Hepatitis C in 2016

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Disclosure

• Ad Hoc Advisory Board-Merck, Gilead, BMS, Janssen, Abbvie

• Research support-Merck, Gilead, BMS, Janssen, Abbvie (paid to the University of Pennsylvania)
Outline

• Magnitude and natural history of Hepatitis C
• Screening, diagnosis, and follow up
• Treatment advances in Hepatitis C
• Barriers to successful treatment
Over 5.2 Million People Living With Chronic HCV in the US

*Homeless (n=142,761-337,6100); incarcerated (n=372,754-664,826); veterans (n=1,237,461-2,452,006); active military (n=6805); healthcare workers (n=64,809-259,234); nursing home residents (n=63,609); chronic hemodialysis (n=20,578); hemophiliacs (n=12,971-17,000).

Natural History of HCV

Non-transplant Population

15~40% Resolved

Fibrosis progression 0.1 ~ 0.2 stages / yr
Mean time to cirrhosis 20 ~ 50 yr

HCV infection → Acute hepatitis → Chronic hepatitis → Cirrhosis → Decompensation → Death or LT
50 ~ 85%
~ 20% in 10 ~ 20 yr
70~80% Stable
HCC 5~10%
~ 20% in 10 yr
~ 50% in 5 yr

Liver transplant Population

Acute hepatitis (70 ~ 80%)

Fibrosis progression 0.3 ~ 0.6 stages / yr
Mean time to cirrhosis 7 ~ 12 yr

Liver transplantation → Chronic hepatitis → Cirrhosis → Decompensation → Death or RT
95 ~ 100% HCV-RNA increase after LT, peak at 3 ~ 4 mo
50 ~ 80% at 6 ~ 12 mo
90 ~ 95% at 5 yr
10 ~ 30% at 5 yr
> 40% after 10 yr
~ 50% in 1 yr
~ 60% in 10 yr

Cholestatic hepatitis 2 ~ 9%
> 50% Death or RT in 2 ~ 10 mo

Extrahepatic Manifestations of Chronic HCV Infection

- Arthralgia
- Arthritis
- Behcet’s disease
- Canities
- Cerebral vasculitis
- Cryoglobulinemia
- Diabetes
- Fatigue
- Fibromyalgia
- Hypertrophic cardiomyopathy
- Immune thrombocytopenic purpura
- Insulin resistance
- Lichen myxoedematosus and planus
- Lung abnormalities
- Membranoproliferative glomerulonephritis
- Membrane nephropathy
- Mooren corneal ulceration
- Multiple myeloma
- Neutropenia
- Non-Hodgkin’s lymphoma
- Paresthesia
- Porphyria cutanea tarda
- Pruritus
- Raynaud’s syndrome
- Sialadenitis
- Sjogren’s syndrome
- Spider nevi
- Systemic lupus erthematosus
- Thrombocytopenia
- Thyroid disease
- Vasculitis
- Vitiligo
- Waldenstrom macroglobulinemia
Global Distribution and Prevalence of HCV Genotypes

Progressive Increase in Incidence of HCV-Related Cirrhosis and HCC in US

Annual Prevalence Rates Between 1996 and 2006 Among HCV-Infected Veterans

El-Serag HB. *Gastroenterology* 2012;142:1264–1273.
By 2007, Deaths From HCV Surpassed Those From HIV

Change in Mortality Rates From 1999 to 2007

- HIV: 15,106
- Hepatitis C: 12,734
- Hepatitis B: 1,815

Screening and Diagnosis
HCV Screening: Persons Most Likely to be Infected With HCV

- Adults born between 1945 and 1965
- Past or current injection drug use
- Selected medical conditions
  - Recipients of clotting factors (prior 1987)
  - Chronic hemodialysis
  - Persistently abnormal ALT
- Recipients of transfusions or organ transplants
- Persons with recognized exposures (needle-sticks, mucosal exposures)
- HIV-infected persons
- Birth to an infected mother


Detection of Anti-HCV IgG: Immunoassays

- Diagnostic specificity
  - >99% for 3rd generation assays
- False-negative results
  - Undergoing hemodialysis
  - Immunocompromised patients
- Low positive predictive values in populations with low (10%) prevalence of HCV infection
- Signal-to-cutoff ratios
  - Predict a true antibody positive results >95% of the time, regardless of the anti-HCV prevalence or characteristics of the population tested

### Signal-to-Cutoff Ratios
(FDA-Approved, Screening Assays)
(Detect Anti-HCV IgG)

<table>
<thead>
<tr>
<th>Assay Type</th>
<th>Ratio</th>
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<tbody>
<tr>
<td>Enzyme immunoassay (manual)</td>
<td>≥3.8</td>
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<tr>
<td>Ortho HCV Version 3.0</td>
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<tr>
<td>Abbott HCV EIA 3.0</td>
<td>≥3.8</td>
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<tr>
<td>Chemiluminescence immunoassay</td>
<td>≥8.0</td>
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<tr>
<td>(automated)</td>
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<tr>
<td>Vitros anti-HCV</td>
<td>≥11.0</td>
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<tr>
<td>Advia Centaur HCV</td>
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</tr>
<tr>
<td>Microparticle immunoassay (automated)</td>
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</tr>
<tr>
<td>Architect anti-HCV</td>
<td>≥10.0</td>
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<tr>
<td>Chemiluminescence microparticle immunoassay (automated)</td>
<td>≥5.0</td>
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</table>

# Recommended Laboratory Tests for Chronic HCV Infection

<table>
<thead>
<tr>
<th>Test Application</th>
<th>Hepatitis C antibody by enzyme immunoassay (EIA)</th>
<th>PCR for HCV RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening for past or present HCV infection</td>
<td>Sensitive and inexpensive</td>
<td>Confirmation of positive EIA</td>
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<tr>
<td></td>
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<td>Medical evaluation and management</td>
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</table>

HCV Assays:
What the Results Mean

<table>
<thead>
<tr>
<th>Anti-HCV</th>
<th>HCV RNA</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>Acute or chronic HCV depending on the clinical context</td>
</tr>
</tbody>
</table>
| +        | −       | False positive HCV antibody  
Resolved infection  
Low-level intermittent viremia |
| −        | +       | Early acute HCV infection  
Chronic HCV in setting of immunosuppressed state  
False positive HCV RNA test |
| −        | −       | Absence of HCV infection |

Hold down a patient for liver biopsy
Sampling error of liver biopsy

Fibrosis area: 65%

Courtesy of M. Pinzani, Florence

Fibrosis area: 15%
Noninvasive Methods to Assess Liver Disease in Chronic HCV

- Serum biomarkers
  - Fibrotest
  - Forn index
  - AST to platelet ratio
  - FibroSpect II
  - MP3
  - Enhanced liver fibrosis score (ELF)
  - Fibrosis probability index
  - Hepascore
  - Fibrometers
  - Lok index
  - Goteborg University cirrhosis index
  - Virahep
  - Fibroindex
  - FIB4
  - HALT-C model

- Measurement of liver stiffness
  - Transient elastography
  - Acoustic radiation force impulse imaging
  - Magnetic resonance elastography
Linking HCV-Infected Patients to Treatment

Solid lines: pathways patients follow to treatment; dotted lines: barriers to treatment.

Pathways Patients Follow to be Diagnosed and Treated for HCV

Prior to Developing Symptoms of Liver Failure

Stepwise Barriers to Hepatitis C Treatment

Treatment
SVR is Associated with Reduced Mortality Among HCV-infected Persons

- 530 adults in Europe prospectively followed for median 8.4 years after HCV treatment
- 192 (36%) achieved SVR

Interferon
“Back bone” of HCV Therapy

Recombinant Interferon

An Obituary
Multi-targeted Approach for Treatment: Approved Protease, Polymerase and NS5A Inhibitors

5’ UTR region

9.6 kb RNA

3’ UTR region

Polyprotein

C E1 E2 p7 NS2 NS3 4A NS4B NS5A NS5B

Polyprotein Processing

C Core

E1 Envelope Glycoproteins

E2 Protease

p7 NS2 NS3 NS4A

NS5A Ledipasvir Ombitasvir Daclatasvir Elbasvir Velpatasvir

NS5B RNA-dependent RNA polymerase

No longer used

Telaprevir Boceprevir Simeprevir Paritaprevir Grazoprevir Asunaprevir

NS3-4A protease inhibitors

nucleoside analogs

Sofosbuvir

non-nucleoside analogs

Dasabuvir Beclabuvir

*agents in red are not approved

Adapted from McGovern B, Abu Dayyeh B, and Chung RT. Hepatology. 2008; 48:1700-12
Pill Burden in HCV Therapy

Fixed Dose Combination

- Ledipasvir/Sofosbuvir - approved/available
- Grazoprevir and Elbasvir - approved/available
- Sofosbuvir and Velpatasvir

3 DAA Regimen – approved/available

- Paritaprevir/r/Ombitasvir + Dasabuvir

- Simeprevir plus Sofosbuvir - approved/available
- Daclatasvir and Sofosbuvir - approved/available

Asunaprevir + Daclatasvir

Ribavirin 5-6 pills a day
Genotype 1
# Treatment Duration for Sofosbuvir and Ledipasvir

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Recommended Treatment Duration</th>
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</thead>
<tbody>
<tr>
<td>Treatment-naïve with or without cirrhosis</td>
<td>12 weeks*</td>
</tr>
<tr>
<td>Treatment-experienced** without cirrhosis</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Treatment-experienced** with cirrhosis</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

* Treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA <6 million IU/mL can be treated with **8 weeks** of therapy

** Treatment-experienced patients who previously failed treatment with either PEG/RBV or a PI/PEG/RBV

Sofosbuvir (NUC) + Ledipasvir (NS5A) in G1
Insights on Treatment Duration and Role of Ribavirin

ION-1

Treatment Naïve
~16% w/cirrhosis

- N=214
  - SOF + LDV
  - SVR 99%

- N=217
  - SOF + LDV + RBV
  - SVR 97%

ION-2

Treatment Experienced
~20% w/cirrhosis

- N=109
  - SOF + LDV
  - SVR 94%

- N=111
  - SOF + LDV + RBV
  - SVR 96%

- N=109
  - SOF + LDV
  - SVR 99%

- N=111
  - SOF + LDV + RBV
  - SVR 99%

## Treatment Recommendations for 3 DAA Regimen

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment*</th>
<th>Recommended Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naïve and experienced Genotype 1a without cirrhosis</td>
<td>paritaprevir/ritonavir/ombitasvir and dasabuvir + ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Treatment naïve and experienced Genotype 1a with cirrhosis</td>
<td>paritaprevir/ritonavir/ombitasvir and dasabuvir + ribavirin</td>
<td>24 weeks**</td>
</tr>
<tr>
<td>Treatment naïve and experienced Genotype 1b without cirrhosis</td>
<td>paritaprevir/ritonavir/ombitasvir and dasabuvir</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Treatment naïve and experienced Genotype 1b with cirrhosis</td>
<td>paritaprevir/ritonavir/ombitasvir and dasabuvir + ribavirin</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection

**VIEKIRA PAK administered with ribavirin for 12 weeks may be considered for some patients based on prior treatment history

Paritaprevir/r (PI) + Ombitasvir(NS5A) + Dasabuvir (NNI) + RBV

**SAPPHIRE-1**
Treatment Naïve
0% w/cirrhosis¹

- N=473
- Paritaprevir/r + Ombitasvir + Dasabuvir + RBV
- SVR 96%

**SAPPHIRE-2**
Treatment Experienced
0% w/cirrhosis²

- N=297
- Paritaprevir/r + Ombitasvir + Dasabuvir + RBV
- SVR 96%

Grazoprevir and Elbasvir: Results - SVR12

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>GT1a</th>
<th>GT1b</th>
<th>GT4</th>
<th>GT6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Virologic Failure</td>
<td>299/316</td>
<td>144/157</td>
<td>129/131</td>
<td>18/18</td>
<td>8/10</td>
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<tr>
<td></td>
<td>95%</td>
<td>92%</td>
<td>99%</td>
<td>100%</td>
<td>80%</td>
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<tr>
<td>Breakthrough</td>
<td>12</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Relapse</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>92%</td>
<td>80%</td>
<td>80%</td>
<td>80%</td>
<td>80%</td>
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</table>

# Interactions with CYP enzymes

## Metabolism of DAAs and ritonavir by CYP enzymes

<table>
<thead>
<tr>
<th>DAA</th>
<th>CYP3A4</th>
<th>CYP3A5</th>
<th>CYP2C8</th>
<th>CYP2C19</th>
<th>CYP2D6</th>
<th>CYP1A2</th>
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</thead>
<tbody>
<tr>
<td>Simeprevir†</td>
<td>↓*</td>
<td>-</td>
<td>-</td>
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<td>↓</td>
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<tr>
<td>Paritaprevir†</td>
<td>-</td>
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<td>↓</td>
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<td>-</td>
</tr>
<tr>
<td>Asunaprevir</td>
<td>‡</td>
<td>-</td>
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<tr>
<td>Grazoprevir†</td>
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<tr>
<td>Ombitasvir†</td>
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<tr>
<td>Dasabuvir‡</td>
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<tr>
<td>Ritonavirδε</td>
<td>↓↓↓</td>
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<tr>
<td>Sofosbuvir</td>
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<tr>
<td>Daclatasvir†</td>
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<tr>
<td>Ledipasvir†</td>
<td>-</td>
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<tr>
<td>Elbasvir†</td>
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</tbody>
</table>

† DAA induces enzyme: dose of co-administered CYP inducer should decrease or may remain the same

↓ DAA suppresses enzyme: dose of co-administered CYP inhibitor should increase or may remain the same

* inhibits intestinal CYP3A4 transporters, but not hepatic CYP3A4 transporters

† metabolized by CYP3A4

‡ metabolized by CYP3A4

§ metabolized by CYP3A5

‖ metabolized by CYP2C8

¶ metabolized by CYP2C19

‖‡ metabolized by CYP2C8 > CYP3A4 > CYP2D6

δ metabolized by CYP2D6

ε metabolized by CYP3A
### DAAs & DDIs

#### DDIs between DAAs and cardiovascular drugs

<table>
<thead>
<tr>
<th>Anti-depressants</th>
<th>SIM</th>
<th>DCV</th>
<th>SOF</th>
<th>SOF/LDV</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
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<tr>
<td>Citalopram</td>
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<tr>
<td>Duloxetine</td>
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<tr>
<td>Escitalopram</td>
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<td>Fluoxetine</td>
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<td>Paroxetine</td>
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<tr>
<td>Sertraline</td>
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<tr>
<td>Trazodone</td>
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<tr>
<td>Trimipramine</td>
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<tr>
<td>Venlafaxine</td>
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<table>
<thead>
<tr>
<th>Anti-psychoactives</th>
<th>SIM</th>
<th>DCV</th>
<th>SOF</th>
<th>SOF/LDV</th>
<th>3D</th>
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<tr>
<td>Amantadine</td>
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<tr>
<td>Antipyrine</td>
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<tr>
<td>Chlorpromazine</td>
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<tr>
<td>Clozepine</td>
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<tr>
<td>Fluoxetine</td>
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<td>Haloperidol</td>
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<td>Olanzapine</td>
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<td>Quetiapine</td>
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<tr>
<td>Risperidone</td>
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#### DDIs between DAAs and illicit recreational drugs

<table>
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<tr>
<th>Amphetamine</th>
<th>SIM</th>
<th>DCV</th>
<th>SOF</th>
<th>SOF/LDV</th>
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<tbody>
<tr>
<td>Cocaine</td>
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<td>Diamorphine</td>
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<td>Dextropropam</td>
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<td>Gamma-hydroxybutyrate</td>
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<td>Ketamine</td>
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<td>MDMA (ecstasy)</td>
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<tr>
<td>Methamphetamine</td>
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<tr>
<td>Phencyclidine (PCP)</td>
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<td>Tersoxepam</td>
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#### DDIs between DAAs and ARVs

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<th>Anti-retrovirals</th>
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<tbody>
<tr>
<td>Abacavir</td>
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<td>Didanosine</td>
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<td>Lamivudine</td>
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<td>Stavudine</td>
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<td>Tenofovir</td>
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<td>Zidovudine</td>
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#### DDIs between DAAs and lipid lowering drugs

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<tbody>
<tr>
<td>Atorvastatin</td>
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<tr>
<td>Boclofibrate</td>
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<td>Ezetimibe</td>
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<tr>
<td>Fenofibrate</td>
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<tr>
<td>Fluvastatin</td>
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<td>Gemfibrozil</td>
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<td>Lovastatin</td>
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<td>Pitavastatin</td>
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<td>Pravastatin</td>
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<td>Rosuvastatin</td>
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<td>Simvastatin</td>
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</table>

#### DDIs between DAAs and central nervous system drugs

<table>
<thead>
<tr>
<th>Central nervous system drugs</th>
<th>SIM</th>
<th>DCV</th>
<th>SOF</th>
<th>SOF/LDV</th>
<th>3D</th>
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</thead>
<tbody>
<tr>
<td>Amiodarone</td>
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<td>Digoxin</td>
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<td>Flecaidine</td>
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<td>Venmaklant</td>
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</table>

#### DDIs between DAAs and immunosuppressants

<table>
<thead>
<tr>
<th>Immunosuppressants</th>
<th>SIM</th>
<th>DCV</th>
<th>SOF</th>
<th>SOF/LDV</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
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<td>Cyclosporine</td>
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<td>Etanercept</td>
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<td>Everolimus</td>
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<td>Mycophenolate</td>
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<td>Sirolimus</td>
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<td>Tacrolimus</td>
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</tbody>
</table>

EASLReccommendations for Hepatitis C, 2015
The Future of HCV treatment

- Pangenotypic activity: genotypes 1, 2, 3, 4, 5, and 6
- Shorter and simpler treatment: once daily for 12 weeks
- And, to boot, one size fits all
- Special considerations:
  - safe in decompensated cirrhosis setting
  - safe in transplant setting
  - safe in renal impairment setting
  - fewer drug-drug interactions

- Safe in decompensated cirrhosis setting
- Safe in transplant setting
- Safe in renal impairment setting
- Fewer drug-drug interactions
Sofosbuvir and Velpatasvir (Pan Genotype Activity-single pill): SVR12 by HCV Genotype

SVR12 (%) by HCV Genotype

- Total: 99%
- 1a: 98%
- 1b: 99%
- 2: 100%
- 4: 100%
- 5: 97%
- 6: 100%

Additional notes:
- 1 relapse
- 2 lost to follow-up
- 1 withdrew consent
- 1 relapse
- 1 death

ASTRAL-3: SVR12 By Treatment Arm

![Graph showing SVR12 by treatment arm with comparison between SOF/VEL and SOF+RBV (P=0.001)].

Challenges and Advances in the Future

“CURE” from SIMPLE and TOLERABLE pangenotypic treatment regimens

- 6 weeks (2 or 3 drugs)
- 4 weeks (3 drugs)
- 8 weeks (3 drugs)
- 12 weeks
Barriers to Successful HCV Treatment

- Screening and Diagnosis
- Cost and Payer Resistance
- Acceptance
- Compliance
- Treaters
Demand for HCV Therapy

Patient knocking on my door:” I want the pills to cure my hepatitis C”
Hepatitis C “Miracle Drug” will cost Americans $84,000, Egyptians only $900
Sofosbuvir

Hindi !!

Courtesy of a Brazilian patient and Dr. Hugo Cheinquere
Sofosbuvir

For one month in India

$ 285 !!

For one month in the US

$ 28,000 !!

Courtesy of a Brazilian patient and Dr. Hugo Cheinquer
Data Collection: Definitions of Types of Insurance

- **US Medicaid**: fee-for-service/managed care
  - State-run programs for medical care, drugs
  - Low-income, special-needs individuals

- **US Medicare**:
  - ≥65 years old; <65 years with disabilities

- **Commercial**: employer, private purchase
Incidence of Absolute Denial of DAA Therapy, By Insurance (n=2,321*)

<table>
<thead>
<tr>
<th>Category</th>
<th>Absolute Denial (%)</th>
<th>Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>16%</td>
<td>377/2,321</td>
</tr>
<tr>
<td>US Medicaid</td>
<td>46%</td>
<td>233/503</td>
</tr>
<tr>
<td>US Medicare</td>
<td>5%</td>
<td>40/795</td>
</tr>
<tr>
<td>Commercial Insurance</td>
<td>10%</td>
<td>104/1,023</td>
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</tbody>
</table>

*Excludes 21 patients with incomplete prior authorization after 60 days

p < 0.001
CURE

HCV