Direct Acting Antivirals for the Treatment of Hepatitis C

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Objectives

- Discuss the evolution of hepatitis C treatment
- Describe the pharmacology of direct acting antivirals agents
- Outline benefits, risks, and characteristics of direct acting antivirals.
- Identify common drug interactions with direct acting antivirals.
Evolving Hepatitis C Treatment
Where we Were...Treatment Recommendations – 2009

<table>
<thead>
<tr>
<th></th>
<th>Genotype 1</th>
<th>Genotypes 2-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegylated interferon alpha-2a + ribavirin*</td>
<td>48</td>
<td>24</td>
</tr>
<tr>
<td>Pegylated interferon alpha-2b + ribavirin*</td>
<td>48</td>
<td>24</td>
</tr>
</tbody>
</table>

*Weight based dosing for genotype 1

Evolving Hepatitis C Treatment
Where we Were...The IDEAL Study - 2009

- Goal: To determine the most effective and best tolerated antiviral combination for the treatment of hepatitis C infection

Evolving Hepatitis C Treatment
Where we are...The Era of Direct Acting Antivirals

2011-2012
- Telaprevir
- Boceprevir

2013
- Daclatasvir
- Sofosbuvir

2014-2015
- Simeprevir
- Sofosbuvir/ledipasvir

2015-2016
- Paritaprevir/ombitasvir/ritonavir = dasabuvir
- Sofosbuvir/velpatasvir

2016-2017
- Grazoprevir/elbasvir

- Complex regimens
- Long duration
- Poor tolerability
- Modest SVR rates
- Combined with IFN and ribavirin

- Simple regimens
- Short duration
- Good tolerability
- High SVR rates
- IFN-and ribavirin-free

SVR=sustained virologic response, IFN=interferon

Hepatitis C Life-Cycle
The Targets of Direct Acting Antivirals

1. Viral attachment and entry in the hepatocyte
2. RNA release and migration to endoplasmic reticulum
3. Translation and production of polyprotein
4. Cleavage of HCV polyprotein by protease enzymes into functional and structural proteins
5. RNA replication with polymerase enzyme
6. Viral assembly, budding, and release
Hepatitis C Life-Cycle
The Targets of Direct Acting Antivirals

HCV Polyprotein Structure

- **Auto-protease** cleaves NS2-NS3 junction
- **Protease enzyme** that cleaves NS4B, NS5A, and NS5B
- **Protease Inhibitors**
  - Simeprevir
  - Paritaprevir
  - Grazoprevir
- **NS4B and NS5A** join to form the RNA replication complex
- **NS5A Inhibitors**
  - Ledipasvir
  - Daclatasvir
  - Ombitasvir
  - Elbasvir
  - Velpatasvir
- **NS5B is the RNA polymerase enzyme**
- **NS5B Inhibitors**
  - Sofosbuvir
  - Dasabuvir

Combination DAA Therapy
Resistance Likely to Develop During Monotherapy

- The high turnover rate and error-prone nature of the HCV polymerase produces potentially resistant viral quasispecies

- Certain quasispecies have a replication advantage over others and become the dominant strains of circulating virus
- Elimination of DAA sensitive virus with monotherapy could open the replication space, allowing resistant variants to proliferate
- Combination therapy increases the likelihood of complete viral suppression and prevents the development of additional resistance
Combination DAA Therapy
Resistance Likely to Develop During Monotherapy

Telaprevir Monotherapy versus Combination Therapy with Pegylated Interferon alfa 2a

Baseline Viral Load

Viral Load Decline (Log10 IU/mL)

Study Time (Days)

Resistance to telaprevir monotherapy developed within 7 days


Combination DAA Therapy
Where we are...Treatment Recommendations – 2017

<table>
<thead>
<tr>
<th>Genotype 1a</th>
<th>No Cirrhosis</th>
<th>Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir/velpatasvir* (400/100 mg qd)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Sofosbuvir/ledipasvir* (90/400 mg qd)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Elbasvir/grazoprevir* (50/100 mg qd)</td>
<td>12†</td>
<td>12†</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/r (25/150/100 mg qd) + dasabuvir (250 mg bid) + ribavirin</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Sofosbuvir (400 mg qd) + simeprevir (150 mg qd)</td>
<td>12</td>
<td>24††</td>
</tr>
<tr>
<td>Daclatasvir (60 mg qd) + sofosbuvir (400 mg qd)</td>
<td>12</td>
<td>24††</td>
</tr>
</tbody>
</table>

*Fixed dose combination tablet administered once daily
†Add ribavirin and extend treatment to 16 weeks when NS5A resistance is detected
††With or without ribavirin

AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org
The Direct Acting Antivirals

Evolving Hepatitis C Treatment
Where we are... The Era of Direct Acting Antivirals


Telaprevir
Boceprevir

Daclatasvir
Simeprevir
Sofosbuvir

Sofosbuvir/ledipasvir
Paritaprevir/ombitasvir/ritonavir + dasabuvir
Grazoprevir/elbasvir

• Complex regimens
• Long duration
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SVR=sustained virologic response, IFN=interferon
Evolving Hepatitis C Treatment
Telaprevir and Boceprevir

TVR – telaprevir, Peg-IFN – Pegylated interferon, RBV – ribavirin, eRVR – early rapid virologic response

Evolving Hepatitis C Treatment
Guideline Recommendations – 2011-2012

<table>
<thead>
<tr>
<th></th>
<th>Genotype 1</th>
<th>Genotypes 2-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir + peg-IFN + ribavirin*</td>
<td>24-48 NR</td>
<td></td>
</tr>
<tr>
<td>Boceprevir + peg-IFN + ribavirin*</td>
<td>28-48 NR</td>
<td></td>
</tr>
<tr>
<td>Pegylated interferon alpha-2a + ribavirin**</td>
<td>48 24</td>
<td></td>
</tr>
<tr>
<td>Pegylated interferon alpha-2b + ribavirin**</td>
<td>48 24</td>
<td></td>
</tr>
</tbody>
</table>

NR – Not recommended
*Response guided therapy
**Weight based dosing for genotype 1


Evolving Hepatitis C Treatment
Telaprevir and Boceprevir

• Limitations
  – Heavy pill burden
    • BOC 4 x 200mg tablets every 8 hours + ribavirin
    • TVR 2 x 375mg tablets every 8 hours + ribavirin
  – Administration with food
    • TVR with 20 grams of fat to increase absorption
  – Poor tolerability
    • TVR – anemia, rash
    • BOC – anemia, dysguesia
  – Limited efficacy and concerns for resistance
Evolving Hepatitis C Treatment
Where we are...The Era of Direct Acting Antivirals

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SVR=sustained virologic response, IFN=interferon

The Direct Acting Antivirals
Sofosbuvir (Sovaldi™)

- Mechanism of action: uridine analogue - competitively inhibits HCV polymerase
- Activity: HCV genotypes 1-6
- FDA Indication: for use in combination for the treatment HCV genotypes 1-4
  - Including those awaiting liver transplantation or those with HIV
- Dose: 400mg once daily with or without food
  - Renal dosing: no adjustment for mild-moderate, no recommendation for severe impairment (CrCl < 30 ml/min)
  - Hepatic dosing: no adjustment for mild, moderate or severe impairment
- Drug Interactions: Not recommended with strong p-glycoprotein inducers; serious symptomatic bradycardia with amiodarone coadministration
- Adverse effects: well tolerated, fatigue, headache most commonly reported

Sofosbuvir (Sovaldi) Prescribing Information. Gilead Sciences.
The Direct Acting Antivirals
Sofosbuvir (Sovaldi™)

Summary of Early, Phase III, Clinical Trials in Hepatitis C, Treatment Naive Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and Intervention</th>
</tr>
</thead>
</table>
| Neutrino      | • Single arm, open-label, GTs 1 and 4-6  
                • SOF + PEG + RBV x 12 wks |
| Fission       | • Randomized, controlled, open-label, GTs 2 and 3,  
                • SOF + PEG + RBV x 12 wks versus PEG + RBV x 24 wks |
| Photon 1 and 2* | • Open label, non-randomized, GTs 1-4  
                     • SOF + RBV x 12 versus 24 weeks |
| Target        | • Longitudinal, cohort study with SOF regimens, including patients with renal disease |

*HIV/HCV Coinfected patients


The Direct Acting Antivirals
Sofosbuvir (Sovaldi™)

Results from the NEUTRINO Study, an open-label, single-arm study of SOF + P/R for 12 weeks in treatment-naive patients with GT 1/4/5/6

The Direct Acting Antivirals
Sofosbuvir (Sovaldi™)

Summary of Adverse Events from the NEUTRINO Trial

<table>
<thead>
<tr>
<th>Event</th>
<th>SOF + PEG + RBV (n=327)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation due to adverse event</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>192 (59%)</td>
</tr>
<tr>
<td>Headache</td>
<td>118 (36%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>112 (34%)</td>
</tr>
<tr>
<td>Rash</td>
<td>59 (18%)</td>
</tr>
<tr>
<td>Hemoglobin &lt; 10 g/dl</td>
<td>74 (23%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>54 (17%)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>51 (16%)</td>
</tr>
<tr>
<td>Depression</td>
<td>31 (9.5%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>81 (41%)</td>
</tr>
</tbody>
</table>


Evolving Hepatitis C Treatment
Where we are...The Era of Direct Acting Antivirals

- Complex regimens
- Long duration
- Poor tolerability
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- Combined with IFN and ribavirin

- Simple regimens
- Short duration
- Good tolerability
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SVR=sustained virologic response, IFN=interferon
The Direct Acting Antivirals
Simeprevir (Olysio™)

- **Mechanism of action:** Blocks the NS3/4A protease enzyme
- **Activity:** HCV – genotypes 1 and 4
- **Indication:** For use in a combination regimen for the treatment HCV genotype 1
  - With sofosbuvir in patients with genotype 1 with or without compensated cirrhosis
  - With Peg-IFN and ribavirin for genotypes 1 or 4 with or without compensated cirrhosis
  - Q80K polymorphism testing may be necessary when treating genotype 1a infection
- **Dose:** 150mg once daily with food
  - Renal dosing: no adjustment for mild-moderate or severe impairment
  - Hepatic dosing: no adjustment for mild, avoid in moderate to severe impairment
- **Drug Interactions:** extensive CYP3A4 metabolism, inhibits P-gp
- **Adverse effects:** rash (including photosensitivity), pruritus and nausea

Simeprevir (Olysio) Prescribing Information. Jansen Therapeutics.

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The Direct Acting Antivirals
Simeprevir (Olysio™)

**Summary of Early, Phase III, Clinical Trials in Hepatitis C, Treatment Naïve Patients**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and Intervention</th>
</tr>
</thead>
</table>
| QUEST - 1 | - Randomized, double-blind, placebo controlled, GT 1  
  - **SIM/PEG/RBV x 24-48 wks (RGT) versus PEG/RBV x 48 wks** |
| QUEST - 2 | - Randomized, double-blind, placebo controlled, GT 1  
  - **SIM/PEG/RBV x 24-48 wks (RGT) versus PEG/RBV x 48 wks** |
| C212* | - Open label, non-randomized, GT 1  
  - **SIM/PEG/RBV x 24-48 wks (RGT)** |
| RESTORE | - Open-label, single arm, GT4, response guided therapy  
  - **SIM/PEG/RBV x 24-48 wks (RGT)** |

RGT = Response Guided Therapy, *HIV/HCV Coinfected patients

The Direct Acting Antivirals
Simeprevir (Olysio™)

Results from QUEST 1 and 2 Randomized Controlled Trials comparing SIM/P/R versus placebo/P/R for 24-48 weeks in treatment-naive patients with GT 1 HCV

The Q80K polymorphism is present in 34% of GT1a patients and can impact treatment response to simeprevir

The Direct Acting Antivirals
Simeprevir (Olysio™)

The Q80K polymorphism is present in 34% of GT1a patients and can impact treatment response to simeprevir.

![Graph showing SVR12 (%) for different GT types with Q80K polymorphism]

- GT1b: 85/228 (SIM/P/R) 53/267 (P/R)
- GT1a no Q80K: 84/138 (SIM/P/R) 43/165 (P/R)
- GT1a + Q80K: 58/49 (SIM/P/R) 52/84 (P/R)

Summary of Adverse Events from the QUEST-2 Trial

<table>
<thead>
<tr>
<th>Event</th>
<th>Simeprevir + PEG/RBV (n=257)</th>
<th>Placebo + PEG/RBV (n=154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation (due to adverse event)</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Grade 3 adverse event</td>
<td>27%</td>
<td>31%</td>
</tr>
<tr>
<td>Grade 4 adverse event</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Headache</td>
<td>38%</td>
<td>37%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37%</td>
<td>42%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>31%</td>
<td>40%</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Rash (any type)</td>
<td>27%</td>
<td>20%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>28%</td>
<td>27%</td>
</tr>
<tr>
<td>Photosensitivity reactions</td>
<td>4%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Anemia</td>
<td>21%</td>
<td>28%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>21%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Evolving Hepatitis C Treatment
Where we are...The Era of Direct Acting Antivirals

2011-2012
Telaprevir
Boceprevir

2013

2014-2015
Daclatasvir

2016-2017
Sofosbuvir/velpatasvir
Grazoprevir/elbasvir

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SVR=sustained virologic response, IFN=interferon

The Direct Acting Antivirals
Sofosbuvir (Sovaldi™) + Simeprevir (Olysio™)

Summary of Phase II and III, Clinical Trials in Hepatitis C, Treatment Naive Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>COSMOS</td>
<td>• Randomized, phase 2a, open-label, GT 1, naive/experienced</td>
</tr>
<tr>
<td></td>
<td>• SOF/SIM ± RBV x 12 or 24 weeks</td>
</tr>
<tr>
<td>OPTIMIST - 1</td>
<td>• Randomized, open-label, GT 1, no cirrhosis</td>
</tr>
<tr>
<td></td>
<td>• SOF/SIM x 8 or 12 weeks</td>
</tr>
<tr>
<td>OPTIMIST - 2</td>
<td>• Open-label, single arm, GT-1, with cirrhosis</td>
</tr>
<tr>
<td></td>
<td>• SOF/SIM x 12 weeks</td>
</tr>
</tbody>
</table>

Lawitz E, et al. 50th EASL, 2015. Abstract LP04
The Direct Acting Antivirals
Sofosbuvir (Sovaldi™) + Simeprevir (Olysio™)

Results from OPTIMIST-1 comparing SIM/SOF for 8 or 12 weeks in treatment-naïve and experienced patients with GT 1 HCV

<table>
<thead>
<tr>
<th>Event n (%)</th>
<th>SOF/SIM x 8 weeks</th>
<th>SOF/SIM x 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td>3 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (9%)</td>
<td>23 (15%)</td>
</tr>
<tr>
<td>Headache</td>
<td>26 (17%)</td>
<td>22 (14%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23 (15%)</td>
<td>19 (12%)</td>
</tr>
<tr>
<td>Rash</td>
<td>12 (8%)</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>9 (6%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>5 (3%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

Evolving Hepatitis C Treatment
Guideline Recommendations - 2014

<table>
<thead>
<tr>
<th>Genotype 1a</th>
<th>No Cirrhosis</th>
<th>Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + peg-IFN + ribavin</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Sofosbuvir + simeprevir +/- ribavin**</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Simeprevir + peg-IFN + ribavin</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Sofosbuvir + ribavin**</td>
<td>24</td>
<td>24</td>
</tr>
</tbody>
</table>

**For IFN ineligible patients, defined as having one or more of the following:
- Intolerance to IFN, autoimmune hepatitis, hypersensitivity to PEG, decompensated hepatic disease, history of depression, or clinical features consistent with depression, a baseline neutrophil count below 1500/μL, a baseline platelet count below 90,000/μL or baseline hemoglobin below 10 g/dL, a history of preexisting cardiac disease.

Evolving Hepatitis C Treatment
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- Sofosbuvir
- Simeprevir
- Daclatasvir
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SVR= sustained virologic response, IFN= interferon
The Direct Acting Antivirals
Daclatasvir (Daklinza™)

- **Mechanism of action**: Blocks the NS5A protein
- **Activity**: Genotypes 1-6
- **FDA Indication**: For use in a combination with sofosbuvir for genotypes 1 or 3
  - GT 1, decompensated cirrhosis or post-transplant, add ribavirin
  - GT 3, any cirrhosis or post-transplant, add ribavirin
- **Dose**: 60 mg orally once daily, with or without food
  - Renal dosing: no adjustment for mild, moderate, or severe impairment
  - Hepatic dosing: no adjustment for mild, moderate or severe impairment
- **Drug Interactions**:
  - Strong CYP3A inhibitors = daclatasvir 30mg daily
  - Strong CYP3A inducers = daclatasvir 90mg daily
- **Adverse effects**: Well tolerated, headache, fatigue, nausea and diarrhea

**Study Design and Intervention**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMMAND 4</td>
<td>• Randomized, placebo-controlled, GT 4, ± cirrhosis</td>
</tr>
<tr>
<td></td>
<td>• DAC + PEG/RBV vs. placebo + PEG/RBV x 24-48 wks (RGT)</td>
</tr>
<tr>
<td>ALLY-1</td>
<td>• Open-label, naïve/exp, GT 1-6, cirrhosis and post-transplant</td>
</tr>
<tr>
<td></td>
<td>• DAC + SOF + RBV x 12 wks</td>
</tr>
<tr>
<td>ALLY-2</td>
<td>• Open label, naïve/exp, GT 1-4, HIV coinfected, ± cirrhosis</td>
</tr>
<tr>
<td></td>
<td>• DAC + SOF x 8-12 wks (naïve), x 12 wks (exp)</td>
</tr>
<tr>
<td>UNITY-1/2</td>
<td>• Open-label, single arm, GT 1, naïve/exp, ± cirrhosis</td>
</tr>
<tr>
<td></td>
<td>• DAC + asunaprevir/beclabuvir ± RBV x 12 wks</td>
</tr>
<tr>
<td>HALLMARK DUAL</td>
<td>• Open-label, multi-cohort, GT 1b, naïve/exp, ± cirrhosis</td>
</tr>
<tr>
<td></td>
<td>• DAC + asunaprevir x 24 weeks</td>
</tr>
</tbody>
</table>

The Direct Acting Antivirals
Daclatasvir (Daklinza™)

Results from ALLY-2 comparing DAC/SOF for 8 or 12 weeks in treatment-naïve and experienced patients with HIV Coinfection

- Treatment naïve x 12 weeks
- Treatment naïve x 8 weeks
- Treatment Exp x 12 weeks

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The Direct Acting Antivirals
Daclatasvir (Daklinza™)

Summary of Adverse Events from the ALLY-1 Trial

<table>
<thead>
<tr>
<th>Event</th>
<th>All Patients (n=203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>34 (17%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>26 (13%)</td>
</tr>
<tr>
<td>Headache</td>
<td>23 (11%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15 (7%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (5%)</td>
</tr>
<tr>
<td>Rash</td>
<td>9 (4%)</td>
</tr>
</tbody>
</table>

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Where we are...The Era of Direct Acting Antivirals

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The Direct Acting Antivirals
Ledipasvir

- Mechanism of action: blocks the NSSA protein
- Activity: HCV genotype 1
- FDA Indication: for use in a combination with sofosbuvir (Harvoni®) for GT 1, 4-6
  - GT 1: 8 weeks can be considered for certain patients
  - Decompensated cirrhosis, add ribavirin or extend to 24 weeks
- Dose: 90mg once daily with or without food
  - Renal dosing: no adjustment for mild-moderate, no recommendation for severe impairment (CrCl < 30 ml/min)
  - Hepatic dosing: no adjustment for mild, moderate or severe impairment
- Drug Interactions: P-glycoprotein substrate and inhibitor, acid dependent absorption
- Adverse effects: well tolerated, headache and fatigue most common

Sofosbuvir/ledipasvir (Harvoni) Prescribing Information. Gilead Sciences.
The Direct Acting Antivirals
Sofosbuvir/Ledipasvir (Harvoni™)

Summary of Phase III, Clinical Trials in Hepatitis C, Treatment Naïve Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and Intervention</th>
</tr>
</thead>
</table>
| ION – 1| • Open-label, randomized, GT 1, ± cirrhosis  
          • LDV/SOF ± RBV x 12 or 24 weeks |
| ION – 3| • Open-label, randomized, GT 1, no cirrhosis  
          • LDV/SOF ± RBV x 8 weeks vs. LDV/SOF x 12 weeks |
| ION – 4| • Open-label, single group, GT 1/4, HIV coinfected, ± cirrhosis  
          • LDV/SOF x 12 weeks |


The Direct Acting Antivirals
Sofosbuvir/Ledipasvir (Harvoni™)

Results from ION-1 and 3, SOF/LED ± RBV x 8, 12 or 24 weeks

<table>
<thead>
<tr>
<th>Study</th>
<th>SOF/LED</th>
<th>SOF/LED + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ION-1</td>
<td>99/211/214</td>
<td>97/211/217</td>
</tr>
<tr>
<td></td>
<td>98/212/217</td>
<td>99/212/217</td>
</tr>
<tr>
<td>ION-3</td>
<td>94/202/215</td>
<td>93/201/216</td>
</tr>
<tr>
<td></td>
<td>95/206/216</td>
<td></td>
</tr>
</tbody>
</table>

### The Direct Acting Antivirals
**Sofosbuvir/Ledipasvir (Harvoni™)**

**Response to Sofosbuvir/ledipasvir for 8 or 12 Weeks of Therapy in ION-3**

<table>
<thead>
<tr>
<th></th>
<th>8 Weeks N=215</th>
<th>12 Weeks N=216</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained Virologic Response</td>
<td>94% (202/215)</td>
<td>96% (206/216)</td>
</tr>
<tr>
<td>Relapse</td>
<td>5% (11/215)</td>
<td>1% (3/216)</td>
</tr>
<tr>
<td>Relapse According to Baseline HCV RNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA ≤6 million IU/mL</td>
<td>2% (2/123)</td>
<td>2% (2/131)</td>
</tr>
<tr>
<td>HCV RNA ≥6 million IU/mL</td>
<td>10% (9/92)</td>
<td>1% (1/85)</td>
</tr>
</tbody>
</table>

- **PI:** Consider 8 weeks in naïve, GT 1, no cirrhosis, HCV RNA <6 million IU/mL
- **AASLD:** Post-hoc, uncontrolled analysis and other studies have conflicting results
- **EASL:** Treatment can be shortened to 8 weeks in naïve, no cirrhosis if HCV RNA level is below 6 million IU/ml

---

### The Direct Acting Antivirals
**Sofosbuvir/Ledipasvir (Harvoni™)**

**Summary of Adverse Events from the ION-1 Trial**

<table>
<thead>
<tr>
<th>Event</th>
<th>LDV/SOF (n=431)</th>
<th>LDV/SOF/RBV (431)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td>19 (4%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>4 (1%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>97 (23%)</td>
<td>161 (37%)</td>
</tr>
<tr>
<td>Headache</td>
<td>107 (25%)</td>
<td>114 (26%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>43 (10%)</td>
<td>92 (21%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>53 (12%)</td>
<td>69 (16%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>48 (11%)</td>
<td>32 (7%)</td>
</tr>
<tr>
<td>Rash</td>
<td>32 (7%)</td>
<td>48 (11%)</td>
</tr>
</tbody>
</table>

Evolving Hepatitis C Treatment
Where we are...The Era of Direct Acting Antivirals

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir</td>
<td>Daclatasvir</td>
<td>Sofosbuvir</td>
<td>Sofosbuvir/ledipasvir</td>
<td>Sofosbuvir/velpatasvir</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>Simeprevir</td>
<td></td>
<td>Paritaprevir/ombitasvir/ritonavir + dasabuvir</td>
<td>Grazoprevir/elbasvir</td>
</tr>
</tbody>
</table>

- Complex regimens
- Long duration
- Poor tolerability
- Modest SVR rates
- Combined with IFN and ribavirin

• Simple regimens
• Short duration
• Good tolerability
• High SVR rates
• IFN-and ribavirin-free

SVR=sustained virologic response, IFN=interferon

The Direct Acting Antivirals
Paritaprevir/r/ombitasvir + dasabuvir (ViekiraPak™, Viekira XR™)

- **Mechanism of action:** NS3/NS4A, NS5A and NS5B inhibition
- **Activity:** HCV genotypes 1 and 4
- **Indication:** With/without ribavirin for patients with genotype 1 HCV infection
  - GT 1α, no cirrhosis, add ribavirin x 12 weeks
  - GT 1β, no cirrhosis, do not add ribavirin
  - GT 1α or 1β, with cirrhosis, add ribavirin x 12 weeks (1b) or 24 weeks (1a)
  - Decompensated cirrhosis – do not use
- **Dose:** Two tablets paritaprevir-ritonavir-ombitasvir once daily (am) with food plus dasabuvir one tablet twice daily with food
- **Drug Interactions:** Contraindicated with drugs that are highly dependent upon CYP3A4, strong CYP3A4 inducers and CYP3A4 inhibitors
- **Adverse effects:** Fatigue, pruritus and insomnia are most common

Paritaprevir/r/ombitasvir + dasabuvir (ViekiraPak) Prescribing Information. AbbVie Inc.
The Direct Acting Antivirals
Paritaprevir/r/ombitasvir + dasabuvir (ViekiraPak™, Viekira XR™)

Summary of Phase III, Clinical Trials in Hepatitis C, Treatment Naïve Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPPHIRE-1</td>
<td>• Randomized, double-blind, placebo-controlled, GT 1, no cirrhosis</td>
</tr>
<tr>
<td></td>
<td>• Paritaprevir/r/ombitasvir + dasabuvir + RBV x 12 weeks</td>
</tr>
<tr>
<td>PEARL-3</td>
<td>• Randomized, open-label, GT 1b, no cirrhosis</td>
</tr>
<tr>
<td></td>
<td>• Paritaprevir/r/ombitasvir + dasabuvir ± RBV x 12 weeks</td>
</tr>
<tr>
<td>PEARL-4</td>
<td>• Randomized, open-label, GT 1a, no cirrhosis</td>
</tr>
<tr>
<td></td>
<td>• Paritaprevir/r/ombitasvir + dasabuvir ± RBV x 12 weeks</td>
</tr>
<tr>
<td>TURQUOISE-2</td>
<td>• Randomized, open-label, GT 1, cirrhosis, naïve/experienced</td>
</tr>
<tr>
<td></td>
<td>• Paritaprevir/r/ombitasvir + dasabuvir + RBV x 12/24 weeks</td>
</tr>
</tbody>
</table>


The Direct Acting Antivirals
Paritaprevir/r/ombitasvir + dasabuvir (ViekiraPak™, Viekira XR™)

Results from PEARL 3 and 4, PrOD ± RBV x 12 weeks for GT 1a and 1b HCV Infection

![SVR12 (%) Graph]

The Direct Acting Antivirals
Paritaprevir/r/ombitasvir + dasabuvir (ViekiraPak™, Viekira XR™)

Summary of Adverse Events from the PEARL 3 and 4 Trials

<table>
<thead>
<tr>
<th>Event</th>
<th>GT1a</th>
<th>GT1b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PrOD + RBV (n=100)</td>
<td>PrOD (n=209)</td>
</tr>
<tr>
<td>Serious adverse events %</td>
<td>3.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Discontinuation due to adverse events %</td>
<td>1.0</td>
<td>0</td>
</tr>
<tr>
<td>Headache %</td>
<td>25.0</td>
<td>28.3</td>
</tr>
<tr>
<td>Fatigue %</td>
<td>46.0</td>
<td>35.1</td>
</tr>
<tr>
<td>Pruritus %</td>
<td>10.0</td>
<td>5.9</td>
</tr>
<tr>
<td>Nausea %</td>
<td>21.0</td>
<td>13.7</td>
</tr>
<tr>
<td>Insomnia %</td>
<td>17.0</td>
<td>7.8</td>
</tr>
<tr>
<td>Diarrhea %</td>
<td>14.0</td>
<td>16.1</td>
</tr>
<tr>
<td>Hemoglobin &lt; 10 g/dl (%)</td>
<td>4.0</td>
<td>0</td>
</tr>
<tr>
<td>Total bilirubin &gt; 3x ULN (%)</td>
<td>3.0</td>
<td>0.5</td>
</tr>
</tbody>
</table>


Evolving Hepatitis C Treatment
Guideline Recommendations - 2015

<table>
<thead>
<tr>
<th>Genotype 1a</th>
<th>No Cirrhosis</th>
<th>Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir/ledipasvir* (90/400 mg qd)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/r (25/150/100 mg qd) + dasabuvir (250 mg bid) + ribavirin</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Sofosbuvir (400 mg qd) + simeprevir (150 mg qd)</td>
<td>12</td>
<td>24††</td>
</tr>
<tr>
<td>Daclatasvir (60 mg qd) + sofosbuvir (400 mg qd)</td>
<td>12</td>
<td>24††</td>
</tr>
</tbody>
</table>

*Fixed dose combination tablet administered once daily
††With or without ribavirin

AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. August 2015
Evolving Hepatitis C Treatment
Where we are...The Era of Direct Acting Antivirals

2011-2012
- Telaprevir
- Boceprevir

2013
- Daclatasvir
- Sofosbuvir

2014-2015
- Simeprevir

2015-2016
- Sofosbuvir/ledipasvir
- Paritaprevir/ombitasvir/ritonavir + dasabuvir

2016-2017
- Grazoprevir/elbasvir
- Sofosbuvir/velpatasvir

- Complex regimens
- Long duration
- Poor tolerability
- Modest SVR rates
- Combined with IFN and ribavirin

- Simple regimens
- Short duration
- Good tolerability
- High SVR rates
- IFN-and ribavirin-free

SVR=sustained virologic response, IFN=interferon

The Direct Acting Antivirals
Elbasvir/Grazoprevir (Zepatier™)

- Mechanism of action: NS5A and NS3/4A inhibition
- Activity: Genotypes 1 and 4
- FDA Indication: For use in a combination for genotype 1 and 4 HCV infection
  - Baseline NS5A polymorphisms: add ribavirin and treat for 16 weeks
- Dose: One tablet, once daily with or without food
  - Renal dosing: no adjustment for any degree of impairment including HD
  - Hepatic dosing: no adjustment for mild; do not use in moderate (no data) or severe impairment (12-fold elevation in grazoprevir levels)
- Drug Interactions: Both agents are P-gp and CYP-3A4 substrates. Coadministration with strong 3A4 inducers or inhibitors is contraindicated
- Adverse effects: Fatigue, headache and nausea. ALT elevation >5x the upper limit of normal in 1% of patients

Elbasvir/grazoprevir (Zepatier) Prescribing Information. Merck.
The Direct Acting Antivirals
Elbasvir/Grazoprevir (Zepatier™)

Summary of Phase III, Clinical Trials in Hepatitis C, Treatment Naïve Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-EDGE TN</td>
<td>• Randomized, placebo-controlled, GT 1, 4 and 6, ± cirrhosis</td>
</tr>
<tr>
<td></td>
<td>• <strong>EBR/GZR x 12 weeks versus placebo</strong></td>
</tr>
<tr>
<td>C-EDGE Coinfection</td>
<td>• Open-label, single-arm, HIV+, GT 1, 4 and 6, ± cirrhosis</td>
</tr>
<tr>
<td>C-EDGE CO-STAR</td>
<td>• Randomized, placebo-controlled, persons who inject drugs</td>
</tr>
<tr>
<td></td>
<td>• EBR/GZR x 12 weeks</td>
</tr>
<tr>
<td>C-SURFER</td>
<td>• Randomized, double-blind, naïve/exp, GT 1, CKD, ± cirrhosis</td>
</tr>
<tr>
<td></td>
<td>• EB/GZR x 12 weeks</td>
</tr>
</tbody>
</table>


---

The Direct Acting Antivirals
Elbasvir/Grazoprevir (Zepatier™)

Results from C-EDGE TN, EBR/GZR x 12 weeks for GT 1, 4 and 6 HCV Infection

<table>
<thead>
<tr>
<th>SVR12 (%)</th>
<th>GT-1a</th>
<th>GT-1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>99</td>
<td>92</td>
</tr>
<tr>
<td>94</td>
<td>11/19</td>
<td>111/131</td>
</tr>
<tr>
<td>99</td>
<td>133/135</td>
<td>129/131</td>
</tr>
<tr>
<td>100</td>
<td>112/112</td>
<td>144/157</td>
</tr>
</tbody>
</table>

*Baseline RAVs with a ≤5-fold shift to elbasvir: SVR12=90% (GT-1a) and 100% (GT-1b)
*Baseline RAVs with a >5-fold shift to elbasvir: SVR12=72% (GT-1a) and 94.1% (GT-1b)

The Direct Acting Antivirals
Elbasvir/Grazoprevir (Zepatier™)

Summary of Adverse Events from the C-EDGE TN Trial

<table>
<thead>
<tr>
<th>Event</th>
<th>All Patients (n=316)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td>12 (3%)</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>4 (1.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>71 (16.9%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>67 (15%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>36 (8.6%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>26 (6.2%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21 (5%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>10 (2.4%)</td>
</tr>
</tbody>
</table>


Evolving Hepatitis C Treatment
Where we are...The ERA of Direct Acting Antivirals

Telaprevir  Daclatasvir  Sofosbuvir/ledipasvir  Sofosbuvir/velpatasvir
Boceprevir  Simeprevir  Paritaprevir/ombitasvir/ritonavir + dasabuvir
Grazoprevir/elbasvir

- Complex regimens
- Long duration
- Poor tolerability
- Modest SVR rates
- Combined with IFN and ribavirin
- Simple regimens
- Short duration
- Good tolerability
- High SVR rates
- IFN-and ribavirin-free

SVR=sustained virologic response, IFN=interferon
The Direct Acting Antivirals

Velpatasvir

- **Mechanism of action:** Blocks the NS5A protein
- **Activity:** Genotypes 1-6
- **FDA Indication:** For use in a combination with sofosbuvir (Epclusa™) for GT 1-6
  - Decompensated cirrhosis, add ribavirin or extend to 24 weeks
- **Dose:** 100mg once daily with or without food
  - Renal dosing: no adjustment for mild-moderate, no recommendation for severe impairment (CrCl < 30 ml/min)
  - Hepatic dosing: no adjustment for mild, moderate or severe impairment
- **Drug Interactions:** pH-dependent absorption, CYP3A4, 2C8, 2B6, P-gp, and BCRP substrate, inhibits P-gp; not recommended with phenytoin, phenobarbital, carbamazepine, rifampin, tipranavir/ritonavir and St. John’s Wort
- **Adverse effects:** Headache and fatigue most common

Sofosbuvir/velpatasvir (Epclusa) Prescribing Information. Gilead Sciences.

---

The Direct Acting Antivirals

Sofosbuvir/velpatasvir (Epclusa™)

**Summary of Phase III, Clinical Trials in Hepatitis C, Treatment Naïve/Exp Patients**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and Intervention</th>
</tr>
</thead>
</table>
| ASTRAL - 1 | • Randomized, placebo-controlled, GT 1, 2, 4-6, ± cirrhosis  
             • SOF/VEL x 12 weeks versus placebo |
| ASTRAL – 2/3 | • Randomized, placebo-controlled, GT 2/3, ± cirrhosis  
               • SOF/VEL x 12 weeks versus placebo |
| ASTRAL - 4  | • Randomized, GT 1-6, decompensated cirrhosis  
              • SOF/VEL ± RBV x 12 weeks or SOF/VEL x 24 weeks |
| ASTRAL - 5  | • Single-arm, open-label, GT 1-6, HIV coinfected, ± cirrhosis  
              • SOF/VEL x 12 weeks |

Wyles D, et al. EASL 2016, Abstract PS104
The Direct Acting Antivirals
Sofosbuvir/velpatasvir (Epclusa™)

Results from ASTRAL-1, VEL/SOF x 12 weeks for GT 1, 2 and 4-6 HCV Infection


---

The Direct Acting Antivirals
Sofosbuvir/velpatasvir (Epclusa™)

Summary of Adverse Events from the ASTRAL-1 Trial

<table>
<thead>
<tr>
<th>Event</th>
<th>SOF/VEL (n=624)</th>
<th>Placebo (n=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td>15 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>1 (&lt;1%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Headache</td>
<td>182 (29%)</td>
<td>33 (28%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>126 (20%)</td>
<td>23 (20%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>75 (12%)</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>50 (8%)</td>
<td>11 (9%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>48 (8%)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>25 (4%)</td>
<td>6 (5%)</td>
</tr>
</tbody>
</table>

Evolving Hepatitis C Treatment
Guideline Recommendations – 2017


The Direct Acting Antivirals
Comparing the Classes and Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Genotypic Coverage</th>
<th>Potency</th>
<th>Barrier to Resistance</th>
<th>Interaction Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS5B</td>
<td>Sofosbuvir</td>
<td>1-6</td>
<td>High</td>
<td>High</td>
<td>Minimal</td>
</tr>
<tr>
<td></td>
<td>Dasabuvir</td>
<td>1</td>
<td>Low</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td>NS5A</td>
<td>Ledipasvir</td>
<td>1</td>
<td>High</td>
<td>Low</td>
<td>Minimal</td>
</tr>
<tr>
<td></td>
<td>Ombitasvir</td>
<td>1, 4</td>
<td>High</td>
<td>Moderate</td>
<td>Minimal</td>
</tr>
<tr>
<td></td>
<td>Elbasvir</td>
<td>1-6</td>
<td>High</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Daclatasvir</td>
<td>1-6</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Velpatasvir</td>
<td>1-6</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>NS3/NS4A</td>
<td>Simeprevir</td>
<td>1, 4</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Grazoprevir</td>
<td>1, 4</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Paritaprevir/</td>
<td>1, 4</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>ritonavir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Fixed dose combination tablet administered once daily
†Add ribavirin and extend treatment to 16 weeks when NS5A resistance is detected
††With or without ribavirin
The Direct Acting Antivirals

Drug Interaction Potential

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Interaction Potential</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS5B</td>
<td>Sofosbuvir</td>
<td>Minimal</td>
<td>Substrate of P-gp and BCRP</td>
</tr>
<tr>
<td></td>
<td>Dasabuvir</td>
<td>Moderate</td>
<td>Substrate of CYP2C8 and 3A, inhibits P-gp</td>
</tr>
<tr>
<td>NS5A</td>
<td>Ledipasvir</td>
<td>Minimal</td>
<td>pH-dependent, P-gp substrate, inhibits P-gp and BCRP</td>
</tr>
<tr>
<td></td>
<td>Ombitasvir</td>
<td>Minimal</td>
<td>pH-dependent, P-gp substrate, inhibits P-gp and BCRP</td>
</tr>
<tr>
<td></td>
<td>Elbasvir</td>
<td>High</td>
<td>Substrate for P-gp and CYP3A4, inhibits P-gp and BCRP</td>
</tr>
<tr>
<td></td>
<td>Daclatasvir</td>
<td>High</td>
<td>Substrate of P-gp and CYP3A4, inhibits P-gp, OATP1B1, BCRP, and OCT1</td>
</tr>
<tr>
<td></td>
<td>Velpatasvir</td>
<td>High</td>
<td>pH-dependent, CYP3A4, 2C8, 2B6, P-gp, and BCRP substrate, inhibits P-gp</td>
</tr>
<tr>
<td>NS3/NS5A</td>
<td>Simeprevir</td>
<td>High</td>
<td>Substrate of CYP3A4, Inhibits OATP1B1 and P-gp</td>
</tr>
<tr>
<td></td>
<td>Grazoprevir</td>
<td>High</td>
<td>Substrate of CYP3A4, P-gp and OATP1B1</td>
</tr>
<tr>
<td></td>
<td>Paritaprevir/</td>
<td>High</td>
<td>Substrate and inhibitor of CYP3A4 and 3A5, P-gp, BCRP and OATP1B1</td>
</tr>
<tr>
<td></td>
<td>ritonavir</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P-gp=P-glycoprotein, BCRP=breast cancer resistance protein, OATP=organic anion transporting polypeptide, OCT=organic cation transporters

The Direct Acting Antivirals

Drug Interaction Resources

  - Available at: [http://www.hcvguidelines.org/](http://www.hcvguidelines.org/)

- EASL Recommendations on Treatment of Hepatitis C
  - Available at: [http://www.easl.eu/](http://www.easl.eu/)

- University of Liverpool, HEP Drug Interactions
  - Available at: [www.hep-druginteractions.org](http://www.hep-druginteractions.org)
Summary

• The treatment of hepatitis C infection has evolved rapidly in recent years with the emergence of DAAs

• Several DAAs are available and are recommended for use as combination therapy

• DAA regimens are very effective, better tolerated and more convenient than historical treatments

• Selecting a DAA regimen depends upon a number of factors including the potential for significant drug interactions