DHHS Update May 2014 – Highlights of Changes

- New section on cost considerations
- Changes to Frequency of CD4 monitoring
  - Frequent monitoring of CD4 counts in those >300 cells/mm³ with maximally suppressed viral loads is generally not required for patient management.
  - Monitoring CD4 counts in patients who have been on ART for at least 2 years with consistent viral suppression:
    - CD4 count 300–500 cells/mm³ monitor every 12 months (BII).
    - CD4 count >500 cells/mm³: monitoring is optional (CIII).


DHHS Guidelines Update 2014: Recommended Regimens in ARV Naives Regardless of Baseline CD4 and Viral Load

**NNRTI – Based Regimens:**
- Efavirenz/tenofovir/emtricitabine (AI)

**PI – Based Regimens:**
- Atazanavir/ritonavir + tenofovir/emtricitabine (AI)
- Darunavir/ritonavir + tenofovir/emtricitabine (AI)

**INSTI – Based Regimens:**
- Dolutegravir plus abacavir/lamivudine – ONLY if patient HLA-B*5701 negative (AI)
- Dolutegravir plus tenofovir/emtricitabine (AI)
- Elvitegravir/cobicistat/tenofovir/emtricitabine – ONLY if pre-ART CrCl >70ml/min (AI)
- Raltegravir plus tenofovir/emtricitabine (AI)

- Available as Single Tablet Regimen


DHHS Guidelines Initial Recommended Regimens - 2014

**Atripla** → 1/day
**Reyataz/Norvir/Truvada** → 3/day
**Prezista/Norvir/Truvada** → 3/day
HIV/HCV Guideline Updates

HCV Lifecycle


- Receptor binding and endocytosis
- Fusion and uncoating
- Transport and release
- (+) RNA
- Translation and polyprotein processing
- RNA replication
- Virion assembly
- Membranous web
- ER lumen

NS3/4a protease inhibitors
- Boceprevir
- Telaprevir
- Simeprevir
- Asunaprevir
- Faldaprevir
- ABT-450
- ABT-267

NS5A inhibitors
- Ledipasvir
- Ombitasvir
- Daclatasvir

NS5B polymerase inhibitors
- Sofosbuvir
- Dasabuvir
- BMS-791325
- ABT-333

*Role in HCV lifecycle not well defined

HIV Classes and Medications

**NS3/4a Protease Inhibitors**
- Boceprevir
- Telaprevir
- Simeprevir
- Asunaprevir
- Faldaprevir
- ABT-450

**NS5A Inhibitors**
- Ledipasvir
- Ombitasvir
- Daclatasvir

**NS5B Polymerase Inhibitors**
- Sofosbuvir
- Dasabuvir
- BMS-791325
- ABT-333

HCV Classes and Medications

**HIV/HCV Co-Infection, GT1**

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment-naive, prior PEG/RBV relapsers, IFN eligible:</strong></td>
<td><strong>Treatment-naive, prior PEG/RBV relapsers, IFN eligible:</strong></td>
</tr>
<tr>
<td>Sof + PEG/RBV(WB) x 12 weeks</td>
<td>Sof + PEG/RBV(WB) x 24 weeks</td>
</tr>
<tr>
<td><strong>IFN ineligible:</strong></td>
<td><strong>IFN ineligible:</strong></td>
</tr>
<tr>
<td>Sof + SMV ± RBV(WB) x 12 weeks</td>
<td>Sof + PEG/RBV(WB) x 12 weeks</td>
</tr>
<tr>
<td><strong>Treatment experienced, prior PEG/RBV nonresponders:</strong></td>
<td><strong>Treatment experienced, prior PEG/RBV nonresponders:</strong></td>
</tr>
<tr>
<td>Sof + SMV ± RBV(WB) x 12 weeks</td>
<td>Sof + PEG/RBV(WB) x 24 weeks</td>
</tr>
</tbody>
</table>

Not Recommended:
- TVR + PEG/RBV x 24 or 48 weeks (RGT)
- BOC + PEG/RBV x 28 or 48 weeks (RGT)
- PEG/RBV x 48 weeks:
  - Sof + SMV ± RBV(WB) x 12 weeks
  - Sof + PEG/RBV(WB) x 48 weeks

**IFN Ineligible Definitions**

- Intolerance to IFN
- Autoimmune hepatitis and other autoimmune disorders
- Hypersensitivity to PEG or any of its components
- 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

www.hcvguidelines.org

Released January 2014

www.hcvguidelines.org

IFN Ineligible Definitions
COSMOS Study – HCV GT1

<table>
<thead>
<tr>
<th>Arm 1</th>
<th>SMV+SOF+RBV</th>
<th>Post-treatment follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 2</td>
<td>SMV+SOF</td>
<td>Post-treatment follow-up</td>
</tr>
<tr>
<td>Arm 3</td>
<td>SMV+SOF + RBV</td>
<td>Post-treatment follow-up</td>
</tr>
<tr>
<td>Arm 4</td>
<td>SMV+SOF</td>
<td>Post-treatment follow-up</td>
</tr>
</tbody>
</table>

Cohort 1 – Metavir F0-F2, prior null responders
Cohort 2 – Metavir F3-F4, prior null responders or naives
Primary Endpoint: SVR12
Secondary Endpoints: RVR, Tx failure, relapse rate, safety


COSMOS – SVR 12, Cohort 2

SVR12 Among Patients with Genotype 1 HCV and Advanced Liver Fibrosis in Cohort 2 of the COSMOS Study* 12 Weeks of Treatment

<table>
<thead>
<tr>
<th>Regimen</th>
<th>SMV+SOF+RBV (%)</th>
<th>SMV+SOF/RBV + Ribavirin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>Genotype 1a HCV without the Q80K polymorphism</td>
<td>88</td>
<td>93</td>
</tr>
<tr>
<td>Genotype 1a HCV with the Q80K polymorphism</td>
<td>100</td>
<td>88</td>
</tr>
<tr>
<td>Genotype 1b HCV</td>
<td>100</td>
<td>88</td>
</tr>
<tr>
<td>IL28B TT</td>
<td>100</td>
<td>88</td>
</tr>
<tr>
<td>METAVIR F4</td>
<td>86</td>
<td>91</td>
</tr>
</tbody>
</table>


COSMOS, Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SMV+SOF+RBV 24 weeks n=30</th>
<th>SMV+SOF 12 weeks n=27</th>
<th>SMV+SOF + RBV 12 weeks n=28</th>
<th>SMV+SOF 12 weeks n=24</th>
<th>Total n=87</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>70</td>
<td>74</td>
<td>71</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>White/African American</td>
<td>97/3</td>
<td>81/10</td>
<td>93/7</td>
<td>86/14</td>
<td>91/9</td>
</tr>
<tr>
<td>Hispanic, Latino</td>
<td>10</td>
<td>31</td>
<td>19</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Median Age</td>
<td>58</td>
<td>58</td>
<td>57</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Median BMI</td>
<td>29</td>
<td>29</td>
<td>27</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>GT 1a</td>
<td>77</td>
<td>75</td>
<td>82</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>GT 1a, Q80K</td>
<td>48</td>
<td>42</td>
<td>36</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Median HCV VL</td>
<td>6.3</td>
<td>6.6</td>
<td>6.7</td>
<td>6.6</td>
<td></td>
</tr>
<tr>
<td>Null Responders</td>
<td>57</td>
<td>50</td>
<td>56</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>IL28B, non CC</td>
<td>73</td>
<td>88</td>
<td>85</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>


SIM/SOF Drug Interaction Considerations

- **Simeprevir**
  - Mild inhibitor of CYP1A2 activity and intestinal CYP3A4
  - Does not affect hepatic CYP3A4 activity
  - Inhibits OATP1B1/3 and P-glycoprotein
  - Multiple drug interactions expected
- **Sofosbuvir**
  - Substrate for P-glycoprotein and breast cancer resistance protein
  - Intracellular metabolism mediated by hydrolyase and nucleotide phosphorylation pathways
  - Minimal drug interactions expected


Other Drug Interactions with Simeprevir (1 of 2)

<table>
<thead>
<tr>
<th>Medication and/or Class</th>
<th>Interact with Simeprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics – clindamycin, erythromycin, telithromycin</td>
<td>Co-administration with these medications is likely to increase concentrations of either simeprevir or the antibiotic due to CYP3A4 and P-glycoprotein (P-gp) inhibition. Co-administration not recommended.</td>
</tr>
<tr>
<td>Antifungals – fluconazole, itraconazole, voriconazole</td>
<td>Co-administration with these medications is likely to increase concentrations of simeprevir due to CYP3A4 inhibition from the antifungals. Co-administration not recommended.</td>
</tr>
<tr>
<td>Antimicrobials – amoxicillin, trimethoprim, rifampin, rifabutin, rifabutin</td>
<td>Co-administration with these medications is likely to reduce concentrations of simeprevir and lead to reduced simeprevir efficacy. Co-administration not recommended.</td>
</tr>
</tbody>
</table>


www.hcvguidelines.org
### Other Drug Interactions with Simeprevir (2 of 2)

<table>
<thead>
<tr>
<th>Medication and or Class</th>
<th>Rationale for Avoiding with Simeprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-administration with these medications is likely to reduce concentrations of simeprevir leading to reduced simeprevir efficacy. Co-administration not recommended.</td>
<td></td>
</tr>
<tr>
<td>Co-administration with these medications is likely to reduce concentrations of simeprevir leading to reduced simeprevir efficacy due to intestinal P-glycoprotein (P-gp) induction from rifampin.</td>
<td></td>
</tr>
</tbody>
</table>

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### Simprevir and HIV Medications (1 of 2)

<table>
<thead>
<tr>
<th>Concurrent Medication</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Integrase Strand Transfer Inhibitors</td>
<td>Concurrent use at standard doses acceptable. Interactions not expected based upon metabolism of simeprevir.</td>
</tr>
<tr>
<td>Triple (Isentress®)</td>
<td>Concurrent use at standard doses acceptable. Educate the patient to avoid grapefruit products.</td>
</tr>
<tr>
<td>Triple (contained in Stribild®)</td>
<td>Concurrent use at standard doses acceptable. Educate the patient to avoid grapefruit products.</td>
</tr>
<tr>
<td>Triple (isentress®)</td>
<td>Concurrent use at standard doses acceptable. Educate the patient to avoid grapefruit products.</td>
</tr>
<tr>
<td>HIV Entry Inhibitors</td>
<td>Concurrent use at standard doses acceptable. Interactions not expected based upon metabolism of simeprevir.</td>
</tr>
<tr>
<td>Maraviroc (Selzentry®)</td>
<td>Concurrent use at standard doses acceptable. Interactions not expected based upon metabolism of simeprevir.</td>
</tr>
<tr>
<td>HIV Protease Inhibitors</td>
<td>Concurrent use at standard doses acceptable. Interactions not expected based upon metabolism of simeprevir.</td>
</tr>
<tr>
<td>All NRTIs</td>
<td>Concurrent use at standard doses acceptable. Interactions not expected based upon metabolism of simeprevir.</td>
</tr>
</tbody>
</table>

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### Drugs Requiring Monitoring or Dose Limits with Simeprevir

<table>
<thead>
<tr>
<th>Medication and or Class</th>
<th>Rationale for Avoiding with Simeprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease Inhibitors</td>
<td>Increased digoxin levels expected, monitor levels</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>Potential increase in levels, monitor levels if possible</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Potential increase in levels, monitor for hypotension</td>
</tr>
<tr>
<td>Abiraterone</td>
<td>Increased abiraterone levels, use lowest doses, do not exceed 400mg daily</td>
</tr>
<tr>
<td>Lovastatin, pravastatin, rosuvastatin, simvastatin</td>
<td>Increased lovastatin levels, initiate with 5mg daily; do not exceed 10 mg daily</td>
</tr>
<tr>
<td>Oral midazolam, triazolam</td>
<td>Increased levels expected, titrate carefully, use lowest doses</td>
</tr>
</tbody>
</table>

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### Other Drug Interactions with Sofosbuvir

<table>
<thead>
<tr>
<th>Medication and or Class</th>
<th>Rationale for Avoiding with Sofosbuvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-administration with these medications is likely to reduce concentrations of sofosbuvir leading to reduced sofosbuvir efficacy. Co-administration not recommended.</td>
<td></td>
</tr>
<tr>
<td>Co-administration with these medications is likely to reduce concentrations of sofosbuvir leading to reduced sofosbuvir efficacy due to intestinal P-glycoprotein (P-gp) induction from rifampin.</td>
<td></td>
</tr>
<tr>
<td>Co-administration with these medications is likely to reduce concentrations of sofosbuvir leading to reduced sofosbuvir efficacy due to intestinal P-glycoprotein (P-gp) induction associated with St. John’s Wort.</td>
<td></td>
</tr>
</tbody>
</table>

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### Sofosbuvir and HIV Medications (1 of 2)

<table>
<thead>
<tr>
<th>Concurrent Medication</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Protease Inhibitors</td>
<td>Concurrent use at standard doses acceptable. Interactions not expected based upon metabolism of sofosbuvir.</td>
</tr>
<tr>
<td>All HIV PIs, with or without ritonavir, except tipranavir</td>
<td>Concurrent use at standard doses acceptable. Interactions not expected based upon metabolism of sofosbuvir.</td>
</tr>
<tr>
<td>Tipranavir (Aptivus®)</td>
<td>Co-administration not recommended</td>
</tr>
<tr>
<td>HIV Non Nucleoside Reverse Transcriptase Inhibitors</td>
<td>Concurrent use at standard doses acceptable.</td>
</tr>
<tr>
<td>All NNRTIs</td>
<td>Concurrent use at standard doses acceptable.</td>
</tr>
</tbody>
</table>

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**Sofosbuvir and HIV Medications**

<table>
<thead>
<tr>
<th>Concurrent Medication</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Integrase Strand Transfer inhibitors</td>
<td></td>
</tr>
<tr>
<td>Dolutegravir (Tivicay®)</td>
<td>Concurrent use at standard doses acceptable. Interactions not expected based upon metabolism of sofosbuvir.</td>
</tr>
<tr>
<td>Elvitegravir (contained in Stribild®)</td>
<td>Concurrent use at standard doses acceptable. Interactions not expected based upon metabolism of sofosbuvir.</td>
</tr>
<tr>
<td>Raltegravir (Isentress®)</td>
<td>Concurrent use at standard doses acceptable.</td>
</tr>
</tbody>
</table>

**HIV Entry Inhibitors**

<table>
<thead>
<tr>
<th>Concurrent Medication</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc (Selzentry®)</td>
<td>Concurrent use at standard doses acceptable. Interactions not expected based upon metabolism of sofosbuvir.</td>
</tr>
</tbody>
</table>

**HIV Nucleoside/Nucleotide Reverse Transcriptase Inhibitors**

<table>
<thead>
<tr>
<th>Concurrent Medication</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>All NRTIs</td>
<td>Concurrent use at standard doses acceptable. Interactions not expected based upon metabolism of sofosbuvir.</td>
</tr>
</tbody>
</table>

**Short list of Acceptable HIV Regimens with SIM/SOF**

- **NNRTI – Based**
  - Complera
  - If NOT on a proton pump inhibitor
- **INSTI – Based**
  - Isentress + Truvada or Epzicom
  - Tivicay + Truvada
  - Triumeq
- **EI – Based**
  - Selzentry + Truvada or Epzicom

**HIV Regimens to be AVOIDED with SIM/SOF**

- **CAN NOT USE** the following
  - All HIV PIs with or without RTV
  - Strivid
  - Atripla, also Sustiva
  - Viramune
  - Retrovir containing regimens

**HIV/HCV Co-Infection, GT2**

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients, regardless of treatment history: SOF + RBV(WB) x 12 weeks</td>
<td>Treatment naïve and prior PEG/RBV relapers: None</td>
</tr>
<tr>
<td></td>
<td>Treatment experienced, prior PEG/RBV Nonresponders:</td>
</tr>
<tr>
<td></td>
<td>IFN eligible: SOF + PEG/RBV(WB) x 12 Weeks</td>
</tr>
<tr>
<td></td>
<td>IFN ineligible: None</td>
</tr>
</tbody>
</table>

**HIV/HCV Coinfection, GT3**

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients, regardless of treatment history: SOF + RBV(WB) x 24 weeks</td>
<td>Treatment naïve, PEG/RBV relapers: None</td>
</tr>
<tr>
<td></td>
<td>Treatment experienced, prior PEG/RBV Nonresponders:</td>
</tr>
<tr>
<td></td>
<td>IFN eligible: SOF + PEG/RBV(WB) x 12 Weeks</td>
</tr>
<tr>
<td></td>
<td>IFN ineligible: None</td>
</tr>
</tbody>
</table>

**HIV/HCV Coinfection, GT4**

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients, regardless of treatment history: SOF + RBV(WB) x 24 weeks</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Treatment experienced, prior PEG/RBV Nonresponders:</td>
</tr>
<tr>
<td></td>
<td>IFN eligible: SOF + PEG/RBV(WB) x 24 weeks</td>
</tr>
<tr>
<td></td>
<td>IFN ineligible: None</td>
</tr>
<tr>
<td></td>
<td>Treatment naïve, PEG/RBV relapers: None</td>
</tr>
</tbody>
</table>

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HIV/HCV Coinfection, GT 5,6

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients, regardless of treatment history: SOF + PEG/RBV (WB) x 12 weeks</td>
<td>None</td>
</tr>
<tr>
<td>Not recommended: PEG/RBV x 48 weeks, any regimen with TVR, BOC, or SMV</td>
<td></td>
</tr>
</tbody>
</table>

---

HCV Guidelines – When and In Whom to Treat

- Treatment assigned to highest priority
- Resources should be allocated to prioritize patients at highest risk for liver-related complications and severe extra-hepatic HCV complications

---

HCV Guidelines – Highest Priority for Treatment

- Advanced Fibrosis (Metavir F3, compensated cirrhosis (Metavir F4) (IA)
- Organ Transplant (IB)
- Type 2 or 3 essential mixed cryoglobulinemia with end organ manifestations (IB)
- Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis (IIaB)

---

HCV Guidelines – High Priority for Treatment

- Fibrosis (Metavir F2) (IB)
- HIV-1 coinfection (IB)
- HBV coinfection (IIaC)
- Other liver disease (ie NASH) (IIaC)
- Debilitating fatigue (IIaB)
- Type 2 DM (insulin resistant) (IIaB)
- Porphyria cutanea tarda (IIbC)

---

HCV Guidelines – High Transmission Risk, treating may reduce new infections

- MSM with high-risk sexual practices
- Active injection drug users
- Incarcerated persons
- Persons on long-term hemodialysis

---

HCV Guidelines – Factors Associated with Accelerated Fibrosis Progression

- Non Modifiable
  - Fibrosis stage, inflammation grade
  - Older age at time of infection
  - Male sex
  - Organ transplant
  - GT 3 infection
  - HIV or HBV coinfection
- Modifiable
  - Alcohol consumption
  - Nonalcoholic fatty liver disease
  - Obesity
  - Insulin Resistance
HCV Guidelines – Populations unlikely to benefit

- Limited life expectancy, (less than 12 months) due to non liver related comorbid conditions

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PHOTON-2: Sofosbuvir + Ribavirin in GT1-4 HCV Pts Coinfected With HIV

- Ongoing, nonrandomized, open-label phase III study
- Stable ART (HIV-1 RNA < 50 copies/mL for ≥ 8 wks before enrollment); CD4: > 200 cells/mm³ if ART treated; > 500 cells/mm³ if ART naive
- 97% on ART: TDF/FTC, 100%; EFV: 25%; ATV/RTV: 17%; DRV/RTV: 21%; RAL: 23%; RPV: 5%
- 20% of pts with compensated cirrhosis
- Primary endpoint: SVR12

Wk 24

Sofosbuvir
Ribavirin
(n = 200)
Sofosbuvir
Ribavirin
(n = 55)
Sofosbuvir
Ribavirin
(n = 19)

HCV Lifecycle

Receptor binding and endocytosis

Translation and polyprotein processing

NS5A inhibitors

Daclatasvir

Bosudavir

Sofosbuvir

ABT-450

*Role in HCV lifecycle not well defined

Select Investigational Medications

- 3 groups of medications likely by late 2014 include
- All oral, interferon free regimens
  - Ledipasvir combined with sofosbuvir, fixed dosage combination all once daily with or without ribavirin
  - ABT-450/ritonavir/ABT-267 (ombitasvir), fixed dosage combination all once daily, in addition to ABT-333 (dasabuvir), given twice daily with or without ribavirin
- Daclatasvir and asunaprevir
- Other meds moving forward
  - Daclatasvir + asunaprevir + BMS-791325 – early 2015
  - MK-5172, MK-8742
  - GS-9669, GS-9451, GS-5816

HCV Classes and Medications

ION 1 Study
- 4 arms of the study
  - Sofosbuvir/Ledipasvir, FDC, 12 weeks
  - Sofosbuvir/Ledipasvir, FDC + RBV, 12 weeks
  - Sofosbuvir/Ledipasvir, FDC, 24 weeks
  - Sofosbuvir/Ledipasvir, FDC + RBV, 24 weeks
- Treatment naïves, genotype 1, 865 patients
  - SVR rates ranged from 97-99%, even if given without ribavirin.
  - Adverse events were fatigue, headache, insomnia and nausea

ION 2 Study, GT1
- Open label, prior failures on PEG/RBV with or without a HCV Protease Inhibitor
- 440 patients, randomized to either
  - Sofosbuvir/Ledipasvir, FDC, 12 weeks
  - Sofosbuvir/Ledipasvir, FDC + RBV, 12 weeks
  - Sofosbuvir/Ledipasvir, FDC, 24 weeks
  - Sofosbuvir/Ledipasvir, FDC + RBV, 24 weeks
- SVR 12 rates ranged from 94-99%, even if given without ribavirin.
  - Adverse events were fatigue, headache and nausea

ION4, HIV co-infection
- Ledipasvir/Sofosbuvir (90mg/400mg) with
  - Raltegravir + tenofovir/emtricitabine
  - Efavirenz/tenofovir/emtricitabine
  - Rilpivirine/tenofovir/emtricitabine
- Tenofovir exposures increased with ledipsavir, similar to RTV-boosted PIs
- Planned and/or ongoing studies with
  - Ritonavir boosted PIs
  - Stribild and Stribild (with TAF)
  - Dolutegravir

Sapphire I and II – Select Data
- AbbVie Data
  - ABT-450/ritonavir+ABT-267 (ombitasvir) (FDC) plus ABT-333 (dasabuvir) BID with ribavirin
  - Drug interactions an issue (RTV needed for ABT-450)
  - GT1, naïve and prior non-responders
### Sapphire I and II

<table>
<thead>
<tr>
<th>GT1</th>
<th>SAPPHIRE-I SVR12 (n=473)</th>
<th>SAPPHIRE-II SVR12 (n=297)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>96.2% (n=455/473)</td>
<td>96.3% (n=286/297)*</td>
</tr>
<tr>
<td>GT1a</td>
<td>95.3% (n=307/322)</td>
<td>96.7% (n=115/123)</td>
</tr>
<tr>
<td>GT1b</td>
<td>98.0% (n=148/151)</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment-experienced (GT1a and GT1b)**
- Prior null responders: n/a, 95.2% (n=139/146)
- Prior relapers: n/a, 95.3% (n=82/86)
- Prior partial responders: n/a, 100.0% (n=65/65)


### TURQUOISE-I: ABT-450/RTV/Ombitasvir + Dasabuvir + RBV in GT1 HCV/HIV Pts

- **Open-label phase III trial**
- **Inclusion criteria:** GT1; compensated cirrhosis (Child-Pugh A) allowed; DAA naive but pegIFN naïve or experienced; HIV-1 RNA < 40 c/mL on ATV or RAL regimen; CD4 count ≥ 200 or %CD4 ≥ 14%
- **52% on ATV, 49% on RAL in 12-wk arm; 38% on ATV, 63% on RAL in 24-wk arm; 19% with cirrhosis**
- **Primary endpoint:** SVR12

**ABT-450/RTV/Ombitasvir + Dasabuvir + RBV**
- 12 wks (n = 31)
- 24 wks (n = 32)


### Drug Interaction Potential

- **Ritonavir boosting required for ABT-450 to allow once daily administration**
- **RTV has no effect on ABT-267 or ABT-333**
- **Pravastatin – reduce by half, limit ROS to 10mg daily (OATP1B1 inhibition)**
- **2 fold increase in ABT-450 when used with atazanavir (OATP1B1 inhibition), within ranges**
- **Atazanavir levels also in range**


### HCV Classes and Medications

- **NS3/4a Protease Inhibitor:**
  - Asunaprevir
  - Dasabuvir
- **NS5A Inhibitor:**
  - Daclatasvir
- **NS5B Polymerase Inhibitors**
  - Sofosbuvir
  - ABT-333 (dasabuvir)
  - BMS-791325

### Daclatasvir + Asunaprevir

- **HALLMARK-DUAL, Phase 3**
- **GT1b naives, previous non responders or intolerant to PEGIFN RBV**
- **12 week regimen, IFN and RBV free**
- **90% SVR12 for naives**
- **82% SVR12 for non responders**
- **82% SVR12 for intolerance group**

HCV Classes and Medications

<table>
<thead>
<tr>
<th>NS3/4a Protease Inhibitors</th>
<th>NS5A Inhibitors</th>
<th>NS5B Polymerase Inhibitors</th>
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<tr>
<td>Asunaprevir</td>
<td>Daclatasvir</td>
<td>BMS-791325</td>
</tr>
</tbody>
</table>

Daclatasvir + Asunaprevir + BMS 791325, GT1a, BID, 12 week regimen


Daclatasvir and HIV Meds

- Daclatasvir AUC was 110% higher when given with atazanavir/ritonavir
- Daclatasvir AUC reduced by 32% when co-administered with efavirenz.
- Dosage Adjustments
  - With Atazanavir/ritonavir, lower daclatasvir dose to 30 mg once-daily
  - With efavirenz, increase daclatasvir dose to 90 mg once-daily
- Atazanavir/ritonavir and efavirenz plasma concentrations did not change when co-administered with daclatasvir


ION 3 Study, GT1, 8 Week Regimen

- Open label, previously untreated patients
- 647 patients randomized to either
  - Sofosbuvir/Ledipasvir, FDC, 8 weeks
  - Sofosbuvir/Ledipasvir, FDC, + RBV, 8 weeks
  - Sofosbuvir/Ledipasvir, FDC, 12 weeks
- SVR 12 rates ranged from 93-95%, even if given without ribavirin.
- Adverse events were fatigue, headache and nausea
- Supports 8 week regimen for untreated patients, Genotype 1 HCV


What about 3 drugs for 6 Weeks?

SYNERGY Study

- Sofosbuvir (nucleoside NS5B inhibitor) 400 mg / ledipasvir (NS5A inhibitor) 90 mg once-daily
- GS-5808 (non-nucleoside NS5A inhibitor) 360 mg once-daily
- GS-5809 (a protease N804 inhibitor) 360 mg once-daily

Week 0 6 12

Cost Considerations
- Sofosbuvir
  - About $1000 per day
- Simeprevir
  - About $800 per day
- Medicaid restrictions in some states
- Federal and state discount programs in place
- Recent IDSA and HIVMA letter to CMS

www.hcvguidelines.org

Summary
- Rapidly changing HCV landscape, new meds soon
- Does not appear to be differences in efficacy in HCV co-infection
- Interferon free regimens here for majority of patients, ribavirin may not be needed
- Cost and managed care negotiations likely to dictate future regimens

www.hcvguidelines.org

HIV and HCV Update Fall 2014
John J. Faragon, PharmD

www.hcvguidelines.org