HIV/HCV Co-infection

John J Faragon, PharmD, BCPS, AAHIV-P
Regional Pharmacy Director,
NY/NJ AIDS Education and Training Center
HIV Pharmacist, Albany Medical Center
Updated AASLD Guidelines

- Optimal therapy for Genotype 1 is the use of boceprevir or telaprevir in combination with peginterferon alfa and ribavirin
- Boceprevir and telaprevir should not be used without peginterferon alfa and weight-based ribavirin
- Response rates improved in genotype 1 with availability of new HCV protease inhibitors

HCV Protease Inhibitors
Boceprevir

- FDA Approved May 2011
- Combined with pegIFN/RBV for genotype 1 patients
- Duration and strategy (fixed vs response-guided duration) evaluated
  - SVR rates of 63% to 66% reported
  - May allow shortening therapy from 48 to 28 weeks in some patients

Boceprevir in Treatment Naïve Patients with Genotype 1

- 800mg three times daily (every 7-9 hours) in combination with peginterferon alfa and weight based ribavirin for 24-44 weeks
- 4 week lead in with peginterferon alfa and ribavirin alone

Boceprevir Administration

- **Timing:**
  - Administer every 7-9 hours

- **Food effect:**
  - Administer with light meal or snack
  - AUC increased 65% relative to fasting state
  - Bioavailability similar regardless of meal type (high-fat vs. low-fat) or whether taken 5 minutes before, with, or immediately after a meal

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Boceprevir (Victrelis™)

How Supplied: 200 mg capsules packaged into a carton with 28 bottles containing 12 capsules (full day supply)

Should be refrigerated until dispensed – then can be stored at room temperature for up to 3 months
HCV Protease Inhibitors
Telaprevir

- FDA Approved May 2011
- Combined with pegIFN/RBV for genotype 1 patients
- Duration and strategy (fixed vs response-guided duration)
  - SVR rates of 69% to 75% reported
  - May allow shortening therapy from 48 to 24 wks in some patients

Telaprevir in Treatment Naïve Patients with Genotype 1

- 750mg three times daily (every 7-9 hours) with food (at least 20g fat) in combination with peginterferon alfa and weight based ribavirin for 12 weeks followed by an additional 12-36 weeks of peginterferon alfa and ribavirin.

Telaprevir Administration

- **Food**
  - Should always be administered with food (not low fat)
  - Meal or snack that contains about 20 grams of fat
  - Take within 30 minutes before the dose

- Systemic exposure (AUC) increases by 237% when administered with standard fat food compared with fasting conditions
  - Low-fat meal (3.6g): exposure increases 117%
  - High-fat meal (56g): exposure increases 330%


Meal/Snack Examples (20 grams fat)

- Bagel with cream cheese
- 1/2 cup nuts
- 3 tablespoons peanut butter
- 1 cup ice cream
- 2 ounces American or Cheddar cheese
- 2 ounces potato chips
- 1/2 cup trail mix
Telaprevir

How supplied: 28-day packer contains 4 weekly cartons of 7 blister strips each (6 tablets per blister strip)

Anorectal Adverse Events

- Incidence was 26.2% versus 5.4% in telaprevir versus placebo arms in studies
  - Usually within first 2 weeks of therapy
  - Reports include hemorrhoids, anal pruritus, anal itching, anal discomfort and rectal burning
  - Mild to moderate, few led to discontinuation
  - Resolved after telaprevir completed
  - Management includes topical anesthetic creams, topical corticosteroids, systemic antihistamines
Telaprevir Induced Rash

- Rash occurs in 56% of patients
  - Often mild or moderate
- Mild rash is maculopapular
- Moderate rash more widespread than mild
- Severe rash covers large part of body
- If rash continues to progress, then telaprevir should be stopped


Telaprevir—Black Box Warning

WARNING: SERIOUS SKIN REACTIONS

See full prescribing information for complete boxed warning.

Fatal and non-fatal serious skin reactions, including Stevens Johnson Syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with INCIVEK combination treatment [see Warnings and Precautions (5.1)]. Fatal cases have been reported in patients with progressive rash and systemic symptoms who continued to receive INCIVEK combination treatment after a serious skin reaction was identified. For serious skin reactions, including rash with systemic symptoms or a progressive severe rash, INCIVEK, peginterferon alfa, and ribavirin must be discontinued immediately. Discontinuing other medications known to be associated with serious skin reactions should be considered. Patients should be promptly referred for urgent medical care.
Despite Pts’ Desires, Futility Rules Must Be Followed

- All therapy should be discontinued in pts with the following:

<table>
<thead>
<tr>
<th></th>
<th>Criteria*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 12 HCV RNA</td>
<td>≥ 100 IU/mL</td>
</tr>
<tr>
<td>Wk 24 HCV RNA</td>
<td>detectable</td>
</tr>
</tbody>
</table>

**Boceprevir[1]**

<table>
<thead>
<tr>
<th></th>
<th>Criteria*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 4 or 12 HCV RNA</td>
<td>&gt; 1000 IU/mL</td>
</tr>
<tr>
<td>Wk 24 HCV RNA</td>
<td>detectable</td>
</tr>
</tbody>
</table>

**Telaprevir[2]**

- Assay should have a lower limit of HCV RNA quantification of ≤ 25 IU/mL and a limit of HCV RNA detection of ~ 10-15 IU/mL.


Treatment Milestones: Educate Pts Early to Avoid Confusion

- Futility rules for HCV treatments define thresholds for virologic response without which SVR is very unlikely to occur
- Stopping treatment for futility limits adverse events, cost, and the risk of resistance
- Ensure pts understand futility rules before starting therapy
### Contraindicated medications with boceprevir and telaprevir

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Contraindicated With BOC[1]</th>
<th>Contraindicated With TVR[2,3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha 1-adrenoceptor antagonist</td>
<td>Alfuzosin</td>
<td>Alfuzosin</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, phenobarbital, phenytoin</td>
<td>Carbamazepine, phenobarbital, phenytoin</td>
</tr>
<tr>
<td>Antimycobacterials</td>
<td>Rifampin</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Ergot derivatives</td>
<td>Dihydroergotamine, ergonovine, ergotamine, methylergonovine</td>
<td>Dihydroergotamine, ergonovine, ergotamine, methylergonovine</td>
</tr>
<tr>
<td>GI motility agents</td>
<td>Cisapride</td>
<td>Cisapride</td>
</tr>
<tr>
<td>Herbal products</td>
<td>St John’s wort</td>
<td>St John’s wort</td>
</tr>
<tr>
<td>HMG CoA reductase inhibitors</td>
<td>Lovastatin, simvastatin</td>
<td>Lovastatin, simvastatin</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Drosiprenone</td>
<td>N/A</td>
</tr>
<tr>
<td>Neuroleptic</td>
<td>Pimozide</td>
<td>Pimozide</td>
</tr>
<tr>
<td>PDE5 inhibitor</td>
<td>Sildenafil or tadalafil when used for tx of pulmonary arterial HTN</td>
<td>Sildenafil or tadalafil when used for tx of pulmonary arterial HTN</td>
</tr>
<tr>
<td>Sedatives/hypnotics</td>
<td>Triazolam; orally administered midazolam</td>
<td>Triazolam; orally administered midazolam</td>
</tr>
</tbody>
</table>

#### Concurrent Medication

<table>
<thead>
<tr>
<th>Concurrent Medication</th>
<th>Boceprevir allowed</th>
<th>Telaprevir allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir/ritonavir (Reyataz®/Norvir®)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Darunavir/ritonavir (Prezista®/Norvir®)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Fosamprenavir/ritonavir (Lexiva®/Norvir®)</td>
<td>No, not studied to date</td>
<td>No</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (Kaletra®)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Efavirenz (Sustiva®)</td>
<td>No</td>
<td>Yes, increase TLV dose to 1125mg Q8H</td>
</tr>
<tr>
<td>Etravirine (Intelence®)</td>
<td>Yes, reduced etravirine levels reported</td>
<td>Yes</td>
</tr>
<tr>
<td>Rilpivirine (Edurant®)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tenofovir (Viread®)</td>
<td>Yes</td>
<td>Yes, monitor renal fx</td>
</tr>
<tr>
<td>Raltegravir (Isentress®)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Elvitegravir (in Stribild®)</td>
<td>??</td>
<td>Yes</td>
</tr>
<tr>
<td>Dolutegravir (Tivicay®)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Maraviroc (Selzentry®)</td>
<td>Yes, MRV 150mg BID</td>
<td>Yes, MRV 150mg BID</td>
</tr>
</tbody>
</table>

Challenges with Current DAA

- **Telaprevir**
  - Rash – Black Box Warning
  - Anemia – Worse than Pegylated interferon + Ribavirin alone
  - Needs interferon and ribavirin – brings all ADRs with it too
  - Anorectal adverse events challenging
  - Only for Genotype 1 – ie not pangenotypic
  - Response guided therapy/stopping rules
  - Drug Interactions complex, especially when treating co-infection
  - Large pull burden (6/day), TID frequency
Challenges with Current DAA

- Boceprevir
  - Dygeusia – Anemia – Worse than Pegylated interferon + Ribavirin alone
  - Needs interferon and ribavirin – brings all ADRs with it too
  - 4 week lead in period
  - Only for Genotype 1 – ie not pangenotypic
  - Response guided therapy/stopping rules
  - Drug Interactions complex, especially when treating co-infection
  - Large pull burden (12/day), TID frequency

ADR More Frequent With TVR and BOC vs PegIFN/RBV

**Telaprevir**[1]

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>TVR-Containing Arms (n = 727)</th>
<th>PegIFN/RBV Arm (n = 361)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>45-50</td>
<td>36</td>
</tr>
<tr>
<td>Nausea</td>
<td>40-43</td>
<td>31</td>
</tr>
<tr>
<td>Rash</td>
<td>35-37</td>
<td>24</td>
</tr>
<tr>
<td>Anemia</td>
<td>37-39</td>
<td>19</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28-32</td>
<td>22</td>
</tr>
</tbody>
</table>

**Boceprevir**[2]

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>BOC-Containing Arms (n = 734)</th>
<th>PegIFN/RBV Arm (n = 363)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>49</td>
<td>29</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>37-43</td>
<td>18</td>
</tr>
</tbody>
</table>

### Select Adverse Effects – PEG-Interferon

- Headaches – 50%
- Low grade fever – 25%
- Chills – 30%
- Fatigue – 60%
- Insomnia – 23%
- Muscle aches – 20%
- Depression – 25%
- Hemolytic anemia (10-13%)
- Fatigue (60-70%)
- Itching (13-29%)
- Rash (5-29%)
- Sinusitis (5-12%)
- Birth defects
  - Strict contraception required during and for a period of 6 months after treatment

### Adverse Effects – Ribavirin

- Hemolytic anemia (10-13%)
- Fatigue (60-70%)
- Itching (13-29%)
- Rash (5-29%)
- Sinusitis (5-12%)
- Birth defects
  - Strict contraception required during and for a period of 6 months after treatment


Future of HCV

- Push for interferon free regimens, likely to happen mid 2014
- Next new medications
  - Simeprevir – once daily HCV PI, less anemia, one pill daily – initially with peg/riba, drug interactions likely
  - Sofosbuvir – NS5b polymerase inhibitor, once daily, minimal ADRs, no drug interactions to date, previous Pharmaset compound
Sofosbuvir (aka GS7977)

- NS5B nucleotide polymerase inhibitor
- Once daily dosing
- Not metabolized VIA CYP450
- Minimal transporter effect
- Low interaction potential
- No major safety signals to date
**NEUTRINO: SVR12 With Sofosbuvir + P/R According to Genotype and Fibrosis Level**


<table>
<thead>
<tr>
<th>FT</th>
<th>No Cirrhosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 1</td>
<td>89/252/273</td>
<td>27/28</td>
</tr>
<tr>
<td>GT 4</td>
<td>96/252/273</td>
<td>92/252</td>
</tr>
<tr>
<td>GT 5.6</td>
<td>100/252/273</td>
<td>80/252</td>
</tr>
</tbody>
</table>

SVR12 According to Fibrosis Level

<table>
<thead>
<tr>
<th>No Cirrhosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>92/252/273</td>
<td>80/252</td>
</tr>
</tbody>
</table>

**ELECTRON: Sofosbuvir/RBV ± Ledipasvir or GS-9669 in GT 1**

- Nonrandomized phase II study in GT 1 noncirrhotics
- AE profile consistent with RBV toxicity profile; one pt discontinued due to AE

<table>
<thead>
<tr>
<th></th>
<th>Wk 12</th>
<th>EOT, %</th>
<th>SVR4, %</th>
<th>SVR12, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naive (n = 25)</td>
<td>Sofosbuvir + RBV</td>
<td>100</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>Null responders (n = 10)</td>
<td>Sofosbuvir + RBV</td>
<td>100</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Treatment naive (n = 25)</td>
<td>Sofosbuvir + Ledipasvir + RBV</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Null responders (n = 9)</td>
<td>Sofosbuvir + Ledipasvir + RBV</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Treatment naive (n = 25)</td>
<td>Sofosbuvir + GS-9669 + RBV</td>
<td>100</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>Null responders (n = 10)</td>
<td>Sofosbuvir + GS-9669 + RBV</td>
<td>100</td>
<td>100</td>
<td>100*</td>
</tr>
</tbody>
</table>

*Only 3 evaluable pts at time of analysis.


Sofosbuvir 400 mg QD; ledipasvir 90 mg QD; GS-9669 500 mg QD; weight-based RBV 1000-1200 mg/day
Sofosbuvir and HIV Medications

- Efavirenz/tenofovir/emtricitabine reduced SOF and GS331007 Cmax by 20-23%
- Rilpivirine, darunavir/ritonavir and raltegravir increased SOF exposure by 21-45%, no effect on GS331007
- SOF increased tenofovir Cmax 25%, decreased RAL AUC 27%, Cmax 43%, but did not affect other medications
- Changes not clinically significant, supports SOF use in wide ranges of subjects on ARV therapy


Sofosbuvir Summary

- Significant CYP450 interactions unlikely
- Studied with wide range of commonly used ARV medications
- Interferon free data with ledipasvir + ribavirin promising
- Likely approved late 2013, PDUFA data December 8, 2013
Sofosbuvir Advisory Panel

- FDA Panel recommended approval October 25, 2013
- Recommendation covers both use with interferon-based therapy for treatment-naive people with HCV genotypes 1 or 4
- Also use in dual therapy with ribavirin for people with easier-to-treat HCV genotypes 2 or 3 - the first approved interferon-free regimen
- Awaiting formal FDA approval


Simeprevir
QUEST-1: Virologic Response to Simeprevir + P/R Treatment

85% of pts in SMV arm met RGT criteria

Virologic Outcomes

HCV RNA Undetectable (%)

Wk 4

Wk 12

Wk 24

Wk 48


SVR12 by RGT Group

85% of pts in SMV arm met RGT criteria

SMV Arm: Total Duration of RGT

C212: Simeprevir + PegIFN/RBV

GT1 HCV/HIV–Coinfected Patients

- Interim analysis of phase III TMC435-C212 trial (N = 106)
  - 82% white; 82% GT1a HCV; 12% not on ART; of those receiving ART, 99% on NRTI (LAM, ABC, FTC, TDF), 87% on RAL, 15% on RPV, 3% on MVC, 3% ENF; boosted PIs and EFV excluded

Noncirrhotic pts with GT1 HCV/HIV coinfection; HCV tx naive or previous relaper

Pts with GT1 HCV/HIV coinfection and previous partial or null response to HCV tx or cirrhosis

*Patients with HCV RNA < 25 IU/mL (either detectable or undetectable) at Wk 4 and undetectable HCV RNA at Wk 12 received 24 total wks of therapy; all other patients received 48 wks of therapy.

Dieterich D, et al. CROI 2013. Abstract 154LB.
Preliminary Outcomes With Simeprevir + PegIFN/RBV in Coinfected Patients

- Triple-therapy AE profile largely consistent with pegIFN/RBV AE profile
- Increased bilirubin in 5% of pts during simeprevir administration period


*Includes only noncirrhotic patients.

Simeprevir/HIV Interactions

- Once daily NS3/4A protease inhibitor
- CYP3A4 inhibitor, weak intestinal PGP inhibitor
- Advantages to current HCV PIs with regards to tolerability, pill burden, frequency
- In co-infection studies
  - 87% were taking raltegravir (Isentress)
  - 15% were taking rilpivirine (Edurant)
  - 3% each were using maraviroc (Selzentry) and enfuvirtide (Fuzeon).
- Plasma concentrations of rilpivirine, tenofovir, efavirenz, and raltegravir did not change significantly, simeprevir levels OK
- Simeprevir levels increased 4.5 fold with darunavir/r (at lower simeprevir dose of 50mg instead of 150mg) not recommended
- Co-administration with efavirenz, however, reduced total simeprevir concentration by about 70%, not recommended

### Effect of ARV on Simeprevir

**TABLE 2. Effect of ARV drugs on PK of simeprevir: LS means ratio (90% CI)**

<table>
<thead>
<tr>
<th>Coadministered HIV drug</th>
<th>simeprevir&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>$AUC_{\text{max}}$ (ng*h/mL)</td>
<td>$C_{\text{ss}}$ (ng/mL)</td>
</tr>
<tr>
<td>NRTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>0.85 (0.73–0.99)</td>
<td>0.86 (0.76–0.98)</td>
<td>0.93 (0.78–1.11)</td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>1.10 (0.97–1.26)</td>
<td>1.06 (0.94–1.19)</td>
<td>0.96 (0.83–1.11)</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>0.49 (0.44–0.54)</td>
<td>0.29 (0.26–0.33)</td>
<td>0.69 (0.08–0.12)</td>
</tr>
<tr>
<td>InSTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>0.93 (0.85–1.02)</td>
<td>0.89 (0.81–0.98)</td>
<td>0.86 (0.75–0.98)</td>
</tr>
<tr>
<td>PI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darunavir/ritonavir&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.79 (1.55–2.06)</td>
<td>2.59 (2.15–3.11)</td>
<td>4.58 (3.54–5.92)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Simeprevir dose was 50mg qd when coadministered with DRV/r and 150mg when used alone.

ARV, antiretroviral; PK, pharmacokinetics; LS, least square; CI, confidence interval; $C_{\text{max}}$, maximum plasma concentration; $AUC_{\text{max}}$, area under time-concentration curve from 0–24 hours; $C_{\text{ss}}$, minimum plasma concentration; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; InSTI, integrase strand transfer inhibitor; PI, protease inhibitor; DRV/r, darunavir/ritonavir

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### Effect of Simeprevir on ARV

**TABLE 3. Effect of simeprevir on PK of ARV drugs: LS means ratio (90% CI)**

<table>
<thead>
<tr>
<th>Coadministered HIV drug</th>
<th>simeprevir&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>$AUC_{\text{max}}$ (ng*h/mL)</td>
<td>$C_{\text{ss}}$ (ng/mL)</td>
</tr>
<tr>
<td>NRTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>1.19 (1.10–1.30)</td>
<td>1.18 (1.13–1.24)</td>
<td>1.24 (1.15–1.33)</td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>1.04 (0.95–1.13)</td>
<td>1.12 (1.05–1.19)</td>
<td>1.25 (1.16–1.35)</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>0.97 (0.89–1.06)</td>
<td>0.90 (0.85–0.95)</td>
<td>0.87 (0.81–0.93)</td>
</tr>
<tr>
<td>InSTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>1.03 (0.78–1.36)</td>
<td>1.08 (0.85–1.38)</td>
<td>1.14 (0.97–1.36)</td>
</tr>
<tr>
<td>PI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darunavir</td>
<td>1.04 (0.99–1.10)</td>
<td>1.18 (1.11–1.25)</td>
<td>1.31 (1.13–1.52)</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>1.23 (1.14–1.32)</td>
<td>1.32 (1.25–1.40)</td>
<td>1.44 (1.30–1.61)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Simeprevir dose was 50mg qd when coadministered with DRV/r and 150mg when used alone.

PK, pharmacokinetics; ARV, antiretroviral; LS, least square; CI, confidence interval; $C_{\text{max}}$, maximum plasma concentration; $AUC_{\text{max}}$, area under time-concentration curve from 0–24 hours; $C_{\text{ss}}$, minimum plasma concentration; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; InSTI, integrase strand transfer inhibitor; PI, protease inhibitor

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Simeprevir Summary

- CYP450 interactions likely
- Studied with commonly used ARV medications, avoid efavirenz and darunavir/ritonavir
- Simeprevir + sofosbuvir in COSMOS study promising +/- ribavirin (CROI 2013)
  - Both given once daily, WITHOUT P/R!
- Likely approved late 2013, PDUFA data late November

Simeprevir Advisory Panel

- FDA Panel recommended approval October 24, 2013
- Recommend approval of simeprevir, an HCV NS3/4A protease inhibitor, in combination with pegylated interferon/ribavirin
- 150 mg once-daily for use by genotype 1 hepatitis C patients, either treatment-naive or prior non-responders, with compensated liver disease including cirrhosis
- Awaiting formal FDA approval
Other Medications/Regimens

AbbVie and HCV

- AbbVie's HCV portfolio
  - NS3/4a protease inhibitor (ABT-450)
  - NS5B Non-Nuke polymerase inhibitor (ABT-333)
  - NS5A inhibitor (ABT-267)
  - ABT450 (protease inhibitor) needs to be boosted with RTV – so expect same RTV drug interactions
  - Contributions of other meds on drug interaction potential not clear yet
  - Likely approval 2014
AVIATOR: SVR24 With Triple DAA + RBV in GT 1 Naive Patients

- Primary endpoint analysis of randomized, open-label phase IIb study

Wk 24
Wk 12
Wk 8

Cohort 1: treatment-naive GT 1 HCV pts (N = 438)


- ABT-450/RTV 150/100 mg QD + ABT-267 + ABT-333 + RBV (n = 80)
- ABT-450/RTV 150/100 mg QD + ABT-333 + RBV (n = 41)
- ABT-450/RTV 100/100 mg QD or 200/100 mg QD + ABT-267 + RBV (n = 79)
- ABT-450/RTV 150/100 mg QD + ABT-267 + ABT-333 (n = 79)
- ABT-450/RTV 100/100 mg QD or 150/100 mg QD + ABT-267 + ABT-333 + RBV (n = 79)
- ABT-450/RTV 100/100 mg QD or 150/100 mg QD + ABT-267 + ABT-333 + RBV (n = 80)

SVR24, %
88
83
89
87
96
90

- ABT-267 dosed at 25 mg QD; ABT-333 dosed at 400 mg BID; weight-based RBV dosed at 1000-1200 mg/day
- Daclatasvir – NS5A inhibitor

- Atazanavir/ritonavir and efavirenz plasma concentrations did not change when co-administered with daclatasvir.
- Daclatasvir AUC was 110% higher when given with atazanavir/ritonavir, daclatasvir AUC reduced by 32% when co-administered with efavirenz
- Required dosage adjustments
  - With Atazanavir/ritonavir, lower daclatasvir dose to 30 mg once-daily
  - With efavirenz, increase daclatasvir dose to 90 mg once-daily
  - Expected to provide exposure similar to that for 60 mg daclatasvir administered alone

Daclatasvir + Sofosbuvir ± RBV in GT 1 Pts With Prior Tx Failure on TVR or BOC

- Primary endpoint analysis of randomized, open-label phase IIa study

- 45% to 48% had TVR/BOC resistance mutations, median 2.4 yrs since previous therapy
  - No difference in response by absence/presence of resistance mutations
  - Both regimens well tolerated; 1 serious AE; no discontinuations due to AEs


Faldaprevir – NS3/4A PI

- CYP3A4 metabolism, inhibitor – increased midazolam by 3-fold
- Studied with darunavir/ritonavir, efavirenz, or tenofovir.
- No effect of faldaprevir on the HIV med PK
  - However, in STARTVerso 4
    - If on darunavir/ritonavir, 120mg dose
    - If on efavirenz, 240mg dose

Faldaprevir

- Regimens in STARTVerso
  - 25% were taking ART regimens containing efavirenz (Sustiva)
  - 20% were taking ritonavir-boosted atazanavir (Reyataz) or darunavir (Prezista)
  - 47% were taking raltegravir or other anti-HIV drugs
  - 4% were not on any ART
- CYP450 interactions likely


STARTVerso1: SVR12 According to ETS, Genotype, and Fibrosis Level

- 23% of pts with GT 1a HCV had Q80K at baseline; not predictive of SVR12

Summary

- HCV is a rapidly evolving field
- Questions
  - Will there be off label use in HCV/HIV co-infection (GT 1), as most will initially have approval with only P/R
  - If so will anyone pay for it off label?
  - On label insurance and 3rd party payment issues?
  - Cost?
  - Best combinations for interferon free regimens in co-infection versus mono infection?
  - Formulations? Combinations?