HIV/HCV CO-INFECTION: RECENT ADVANCES AND NEW OPPORTUNITIES

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Clinical Pharmacy Specialist – HIV and Hepatology

2015 Mountain Plains AETC Faculty Development Conference
Disclosures:

- No Disclosures
Were you at my talk last year?

A. Yes
B. No
HISTORY NEVER LOOKS LIKE HISTORY WHEN YOU ARE LIVING THROUGH IT

John W. Gardner
Objectives

• Review pathogenesis, transmission, and epidemiology of HIV/HCV Co-infection
• Review approved agents and learn current recommendations for treatment of chronic HCV in a patient living with HIV
• Discuss future treatment options for HIV/HCV Co-infection patients, including future medications in the investigational pipeline and estimated approval timelines
What is the most complicated part of Hep C care?

A. Assessment of liver disease
B. Prescribing correct medication/dose; dealing with drug-drug interactions
C. Determining insurance status and accessing coverage for patients
D. Following patients through treatment; dealing with monitoring and side effects
BRIEF BACKGROUND
IN HEPATITIS C
Epidemiology of Hepatitis C

- Estimated 180-200 million people worldwide living with Hepatitis C (HCV) – approximately 3% of the world population
- Leading cause of liver transplantation in America
- From 2010 to 2020:
  - Cirrhosis, hepatic decompensation, and hepatocellular carcinoma are expected to double
  - Liver-related deaths are expected to triple

CDC
HCV-Related Cirrhosis

25% of patients with HCV currently have cirrhosis.

37% of patients with HCV are projected to develop cirrhosis by 2020, peaking at 1 million.

HCV Treatment Cascade (data in millions)

- Americans with Chronic HCV: 3.2
- Diagnosed: 1.6
- Referred to Care: 1.1
- Treated: 0.3
- SVR: 0.18

What is SVR?

- **Sustained Virologic Response (SVR):** as undetectable HCV viral load at least 12 weeks after HCV treatment
  - Usually all oral combination of medications, used for 8-24 weeks
  - SVR4: Measured 4 weeks after treatment
  - SVR12: Standard definition of cure
  - SVR24: Previous standard when peginterferon/ribavirin was used for treatment
- Elimination of virus, not remission
- **NOT** protective against future exposures
  - Reinfection is possible
  - Must address any ongoing risks of exposure
All-Cause Mortality According to Response

Cumulative mortality (%)

- No SVR: 26.0% (95% CI 20.2-28.4)
- SVR: 8.9% (95% CI 3.3-14.5)

Time - years

$p<0.001$
HIV and HCV Co-Infection

- Liver disease associated with HCV infection has become a leading cause of morbidity and mortality among HCV/HIV-coinfected patients
- Higher HCV viral loads in Coinfection
  - Has not been associated with increased fibrosis
- HIV accelerates the natural course of hepatitis C[1]
- Successful HIV suppression can slow fibrosis progression but not back to the rate in HCV monoinfection[2]

HIV/HCV epidemiology

- National-wide, approximately 25% of HIV+ patients are coinfected with HCV\(^1\)
  - UCH IDGP Clinic: ~14%
    - Less IVDU, Less urban
- As many as 80% of HIV+ patients who inject drugs are coinfected with HCV\(^1\)
- Route of transmission can affect sequence of infection
  - IVDU: Generally contract HCV then HIV
  - MSM: Generally contract HIV then HCV\(^2\)
- All patients with HIV infection should be tested for HCV
- HIV+ patients are at 4.1x higher risk to acquire HCV as HIV- patients\(^3\)

Transmission of HCV

- Multiple factors associated with HCV transmission in HIV+ patients
  - Unprotected receptive anal intercourse
  - Online casual sexual partners
  - Sex at sex venues
  - Older age
  - Syphilis
  - Recreational drug use
  - Drinking > 13 alcoholic drinks per week
HIV/HCV Challenges

1. Progression of Liver Disease
   1. Progression to cirrhosis risk 3-fold higher in coinfected vs HCV-monoinfected patients[1]
   2. Relative risk of decompensated liver disease 6-fold higher in coinfected vs HCV-monoinfected patients[2]
   3. Risk of liver cancer is 8x higher in HIV patients than general public[3]
   4. Progression of HCV infection to cirrhosis is 8 years faster in Coinfected patients than HCV mono-infected patients[4]

2. Comorbidities of population
   1. Substance Abuse
   2. Mental Health
   3. HTN, DMII, CVD, etc

3. Drug-Drug Interactions – especially HIV medications

How did Hepatitis C Sneak up on us?
Factors

• Slowly progressive disease
  • Few early symptoms, many infected before virus was identified
• Current guidelines recommend opt-in testing, not opt-out
  • Only test parts of population, not universal
• Actual number of cases in US is unknown
  • Especially in homeless and incarcerated populations
• Increase in acute Hepatitis C Infection
  • Increase in prescription opioid abuse
  • Increase in sexual transmission of HCV
• 62.5% increase in past year heroin use from 2002 – 2013
  • Annual rates of past-year heroin use increased from 1.6 per 1000 in 2002 – 2004 to 2.6 per 1000 in 2011 – 2013
  • Increase in all demographics, including women, privately insured, and persons with higher income
• People who fit criteria of heroin abuse or dependence
  • 90% increase from 2002 – 2013 and 35.7% increase from 2008 – 2013
• Increase in availability of heroin, lower price
  • Higher rates of concurrent prescription opioid abuse
Prescription Opioid Abuse

• In 2008, 562 Coloradans died of prescription opioid overdose, compared to 173 who died of drunk-driving related accidents
• 6% of Coloradans stated they used prescription narcotics for non-medical purposes in 2010-2011, the second highest rate in the nation, According to National Survey on Drug Use and Health
• According to National Institute of Drug Abuse Report in 2014:
  • Marked increase in IV heroin due to switch from prescription narcotic
    • Increase in number of treatment admissions for heroin
    • Heroin increased from being present in 4% of alcohol and drug related deaths in 2004 to 27.9% in 2012
    • Deaths attributed to heroin increased from 1.1 per 100,000 in 2004 to 6.5 per 100,000 in 2012
Sexual Transmission of HCV

- Transmitted through microtears and abrasions in rectal mucosa
- High-Risk sexual behaviors, often accompanied by methamphetamine use
- In NYC, increase in Coinfection whose risk factor was MSM rose from 7% in 2000 to 24% in 2010
  - Suggests an outbreak of HCV as an STI

Treatment in Substance Use

- A meta-analysis in 2013 showed that recovered substance users were able to adhere to HCV treatment and have success rates similar to those without history of substance users.¹
- Little data published in regards to recent DAAs
- Little data in current substance use
- Many private insurance plans and state Medicaid will restrict use in past or current substance users
  - Most do not differentiate between substance use and substance abuse disorder or between different substances such as alcohol or marijuana

HCV Life Cycle and DAA Targets


Receptor binding and endocytosis

Fusion and uncoating

Transport and release

Virion assembly

Translation and polyprotein processing

(+) RNA

Translation and polyprotein processing

NS3/4 protease inhibitors

NS5A* inhibitors

*Block replication complex formation, assembly

NS5B polymerase inhibitors

Nucleoside/nucleotide Nonnucleoside

What Are the Key Elements of an Ideal HCV Regimen?

- Highly Effective
- Safe and Tolerable
- Pan-Genotypic
- Easy Dosing, All Oral
- Few Drug-Drug Interactions
# Approved HCV DAAs

<table>
<thead>
<tr>
<th>Core</th>
<th>Envelope Glycoproteins</th>
<th>Protease</th>
<th>Serine Protease</th>
<th>Serine Protease Cofactor</th>
<th>HCV Replicase</th>
<th>RNA-dependent RNA polymerase</th>
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<tbody>
<tr>
<td>C</td>
<td>E1</td>
<td>p7</td>
<td>NS2</td>
<td>NS3</td>
<td>NS4A</td>
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<table>
<thead>
<tr>
<th>NS3/4A</th>
<th>NS5A</th>
<th>NS5B</th>
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<tr>
<td>Function</td>
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<td>Serine Protease</td>
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<thead>
<tr>
<th>Drugs</th>
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<tr>
<td>Telaprevir</td>
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<td>Non-nucleoside</td>
</tr>
<tr>
<td>Paritaprevir/rit</td>
<td></td>
<td>Dasabuvir</td>
</tr>
</tbody>
</table>
What’s in a name?

- **NS3/4 Protease Inhibitors:**
  - tela\textit{previr}
  - sime\textit{previr}
  - parita\textit{previr}

- **NS5A Inhibitors:**
  - ledip\textit{asvir}
  - ombit\textit{asvir}
  - elb\textit{asvir}

- **NS5B Inhibitors:**
  - sofos\textit{buvir}
  - dasa\textit{buvir}

PRE $\rightarrow$ \textit{Pr}otease Inhibitor

AS $\rightarrow$ NS5\textit{A} Inhibitor

BU $\rightarrow$ NS5\textit{B} Inhibitor
WHERE WE ARE

Non-Direct Acting Antivirals and Improved Direct Acting Antivirals
Telaprevir (INCIVEK™):
- HCV NS3/4A Protease Inhibitor
- Only approved for Genotype 1
- Dosed with peginterferon and ribavirin for 48 weeks
- 3x daily dosing with 20g of fat/dose
- Severe side effects (anemia, rash, anal pain), significant drug interactions

Boceprevir (VICTRELIS™):
- HCV NS3/4A Protease Inhibitor
- Only approved for Genotype 1
- Dosed with peginterferon and ribavirin for 48 weeks
- 3x daily dosing with 400 calories
- Severe side effects (anemia, dysgusia), significant drug interactions
Pegylated Interferon

Mechanism of Action:
- Bind to cell surface initiating signaling, leading to activation of gene transcription. Activated genes inhibit viral replication, cell proliferation, and immunomodulation.
- Interferon covalently bound to polyethylene glycol
  - Slows metabolism, longer half-life
  - Increased serum levels of interferon
  - Improved anti-HCV activity

Formulations (dosing differences between the two):
- Peginterferon Alfa-2a (PEGASYS)
- Peginterferon Alfa-2b (Peg-Intron)

Side Effects:
- Suicide/homicide ideation, increased depression, flu-like symptoms, neutropenia, anemia, thrombocytopenia,
Ribavirin

- **Dose:** Weight-based dosing
  - >75 kg: 1200 mg PO daily in divided doses
  - <75 kg: 1000 mg PO daily in divided doses

- **Mechanism of Action:** Virustatic; alters viral attachment, penetration, and uncoating. Exact mechanism is unknown. Phosphorylated intercellularly to active metabolite.

- Best absorbed with high fat meal

- **Brands:** Copegus, Rebetol, Ribasphere, RibaTab, Virazole

- **Pregnancy Category:** X

- **Side Effects:** rash, hemolytic anemia, fatigue, altered taste, anorexia
## Approved HCV DAAs

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# First In Its Class

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Sofosbuvir (SOVALDI™)

• HCV nucleotide analog NS5B polymerase inhibitor; interrupts HCV replication
• Metabolized to GS-331007 (>90%), predominant PK activity
• 400 mg po daily, taken with or without food
• High barrier to resistance
• Side effects: nausea, insomnia, headache, fatigue
• Renally eliminated; do not use in CrCL <30 ml/min
FDA Cardiovascular Warning – March 24, 2015

• Serious symptomatic bradycardia when coadministered with amiodarone
• Can occur within hours or up to 2 weeks
• Currently mechanism of action is unknown
• Recommend to avoid coadministration of amiodarone and sofosbuvir
• Only consider use if no alternative, monitor closely for symptomatic bradycardia
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Simeprevir (OLYSIO™)

• “Next-generation” HCV NS3/4A protease inhibitor
• 150 mg po daily, with food (no fat or calorie requirement)
• Contains a sulfonamide moiety, no patients experienced a reaction
• No dose adjustment required for patients with mild, moderate, or severe renal dysfunction
• 2-5x increase in plasma levels in decompensated cirrhotic patients, not recommended per Guidelines
• Side effects: photosensitivity, rash, pruritus, nausea, increased bilirubin
Drug Interactions

Simeprevir’s affect on other drugs:
- Mildly inhibits CYP1A2
- Mildly inhibits intestinal CYP3A4
- Inhibits OAT1B1/3 and P-gp transport

Meds to watch: digoxin, antiarrhythmics, erythromycin, HMG CO-A reductase inhibitors, PDE-5 inhibitors, calcium channel blockers, midazolam, triazolam

Affect of other drugs on simeprevir:
- Metabolized through CYP3A
- <1% cleared through urine

Meds to watch: any moderate/strong CYP3A inhibitor/inducer; anti-epileptics, antibiotics, rifampin/rifabutin, antifungals, HMG Co-A reductase inhibitors, cyclosporin
sofofuvir/ledipasvir

- Combination of sofosbuvir 400 mg (nucleoside analog NS5B inhibitor) with ledipasvir 90 mg (NS5A inhibitor)
- First approved combination pill for HCV
- Taking over the world . . . for like another year
Ledipasvir

- First in class HCV NS5A inhibitor
- 90 mg in fixed dose combination
- Half life: 47 hours
- Minimally metabolism, primarily excreted in the feces
  - Oxidative metabolism, not metabolized through CYP pathway
- >99.8% protein bound
- No dose adjustment for renal or hepatic disease (sofosbuvir CrCL <30 ml/min)
- Needs an acidic environment to be absorbed. Drug interaction with all antacids
This is how you do it . . .

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Recommended Treatment Duration</th>
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<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>

*8 weeks can be considered in treatment-naïve patients without cirrhosis who have a pre-treatment HCV RNA less than 6 million IU/mL

- NOT FDA Approved for HIV/HCV Coinfection
Drug Interactions

- Primarily excreted unchanged in feces (98%)
- Not an inhibitor or inducer of CYPP450 enzymes
- Minor substrate of P-gp
- Weak inhibitor of
  - P-gp
  - BCRP (intestinal, not systemic)
  - OATP1B1/1B3
- Monitor drugs that are substrates of p-glycoprotein, such as morphine, nadolol, propranolol, and others

Antacids:
- Ledipasvir best absorbed in an acidic environment
- **PPIs:** Max coadministration of omeprazole 20 mg po daily given simultaneously
- **H2 Blockers:** given with or 12 hours apart from Harvoni at doses not to exceed famotidine 40 mg po BID
- Immediate-acting antacids (calcium carbonate (TUMS), alka seltzer, pepto bismouth, etc)
  - Separate by at least 4 hours
# Phase III Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Geno</th>
<th>Cirrhotic</th>
<th>Past Treatment</th>
<th>Duration</th>
<th>Riba</th>
<th>N</th>
<th>Result (%)</th>
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<td>ION 1</td>
<td>1</td>
<td>15-17%</td>
<td>Naïve</td>
<td>12</td>
<td>N</td>
<td>214</td>
<td>99</td>
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<td></td>
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<td>Y</td>
<td>217</td>
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<td>ION 2</td>
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<td>20%</td>
<td>Experienced</td>
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<td>N</td>
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<td>111</td>
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<td>ION 3</td>
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<td></td>
<td></td>
<td>1952</td>
<td>97</td>
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</tbody>
</table>
ION-4 Study

- Phase III, multicenter, open-label study of Harvoni 12 Week treatment in HIV/HCV Coinfected Patients
- 355 total patients - Genotype 1a (75%), 1b (23%), or 4 (2%)
- 20% cirrhotic
- 55% treatment-experienced

**VIEKIRA PAK™**

- Four drug combination, given with ribavirin, in 2 different fixed dose combinations
- **AV1:** 2 tablets given once daily with food
  - Ombitasvir: 25 mg, NS5A inhibitor
  - Paritaprevir: 150 mg, NS3/4A protease inhibitor
  - Ritonavir: 100 mg, pharmacologic booster
- **AV2:** 1 tablet given twice daily
  - Dasabuvir 250 mg: NS5B inhibitor
Viekira Pak™ Drug Interactions

- **Ombitasvir:**
  - Substrate: metabolized by amide hydrolysis followed by oxidative metabolism
  - Inhibitor: UGT1A1

- **Paritaprevir:**
  - Substrate: metabolized by CYP3A4 and to a lesser extent CYP3A5
  - Inhibitor: UGT1A1, OATP1B1 and 1B3, BCRP

- **Ritonavir:**
  - Substrate: metabolized by CYP3A (major), CYP2B6 (minor), CYP1A2 (minor), p-glycoprotein
  - Inhibitor: CYP3A4 (major), CYP2C8 (major), CYP2D6 (major), p-glycoprotein
  - Inducer: CYP1A2 (moderate), CYP2C9 (moderate).

- **Dasabuvir:**
  - Substrate: metabolized by CYP2C8 (major) and CYP3A (minor)
  - Inhibitor: BCRP
<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Weeks</th>
<th>Riba?</th>
<th>SVR12</th>
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<tbody>
<tr>
<td>Pearl-II</td>
<td>Geno1b experienced</td>
<td>12</td>
<td>Yes n=88</td>
<td>97%</td>
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<td></td>
<td></td>
<td></td>
<td>No n=91</td>
<td>99%</td>
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<td>Pearl-III</td>
<td>Geno1b naive</td>
<td>12</td>
<td>Yes n=201</td>
<td>99%</td>
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<td></td>
<td>No n=209</td>
<td>99%</td>
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<td>Geno1a naive</td>
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<td>Yes n=100</td>
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<td>No n=205</td>
<td>90%</td>
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<td>Turquoise-II</td>
<td>Geno1 compensated cirrhosis</td>
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<td>Yes n=208</td>
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<td>24</td>
<td>Yes n=172</td>
<td>96%</td>
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<td>Geno1 naive</td>
<td>12</td>
<td>Yes n=473</td>
<td>96%</td>
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<tr>
<td>Sapphire-II</td>
<td>Geno1 experienced</td>
<td>12</td>
<td>Yes n=297</td>
<td>96%</td>
</tr>
</tbody>
</table>
TURQUISE-II

12 Weeks: 91.8% SVR12
24 Weeks: 96.5% SVR12

TECHNIVIE™

- Similar to Viekira Pak, but without dasabuvir. Three drug combination, given with ribavirin
- AV1: 2 tablets given once daily with food
  - Ombitasvir: 25 mg, NS5A inhibitor
  - Paritaprevir: 150 mg, NS3/4A protease inhibitor
  - Ritonavir: 100 mg, pharmacologic booster
- Ribavirin: weight based standard dosing
- Approved for 12 weeks in Genotype 4 chronic HCV infection
  - Can consider to exclude ribavirin if patient is not tolerant to ribavirin
- First combination specifically approved for Genotype 4.
  - Most providers feel that GT4 patients are similar to GT1 patients, but the studies had very few numbers
Daclatasvir

- **DAKLINZA™**, approved July 24th, 2015
- NS5A inhibitor
- Pen-genotypic, used for Genotype 2 and 3
  - Limited response in Genotype 3 treatment-experienced cirrhosis
  - Not approved with ribavirin, but many will use ribavirin
- 60 mg tab, once daily used in combination with sofosbuvir
- No dose adjustment per renal or liver function
- Metabolized through CYP3A4
  - Watch for significant drug interactions
  - Dose to 30 mg when coadministered with strong CYP3A4 inhibitors
  - Dose to 90 mg when coadministered with strong CYP3A4 inducers
Ally-2 Study: Sofosbuvir/Daclatasvir in HIV/HCV Coinfection

**Study:**
- Phase III Study of daclatasvir and sofosbuvir for 8-12 Weeks in Genotype 1-6, n=203
- Overall close to 20% cirrhotic
- Must be undetectable on ART and CD4 >100 cells/mL or not on ART with CD4 >350 cells/mL
  - Excluded: coadministration of NNRTIs (except RPV) with ritonavir-boosted Pis
  - Dose adjustments with ritonavir or efavirenz

**Results:**
- Total SVR12: 97%!
- 100% SVR12 in Geno 2-4 (small numbers), no Geno 5-6
- GT 1, 12-week, Naïve: 96% (80/83)
- GT 1, 12-week, Experienced: 98% (43/44)
- GT 1, 8-week, Naïve: 76% (31/41)
- No difference seen in response of cirrhotic patients

DRUG-DRUG INTERACTIONS BETWEEN HIV AND HCV MEDICATIONS
## Kiser ARV Interaction Score Card

<table>
<thead>
<tr>
<th></th>
<th>Simeprevir&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Sofosbuvir&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Ledipasvir&lt;sup&gt;3-6&lt;/sup&gt;</th>
<th>Daclatasvir&lt;sup&gt;7-9&lt;/sup&gt;</th>
<th>3D&lt;sup&gt;10-13&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r</td>
<td>No data</td>
<td>No data</td>
<td>LDV ↑; ATV ↑&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DCV ↑&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ABT450 ↑; ATV ↑</td>
</tr>
<tr>
<td>DRV/r</td>
<td>SIM ↑; DRV ↔</td>
<td>SOF ↑; DRV ↔</td>
<td>LDV ↑, DRV ↔&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DCV ↑;</td>
<td>ABT450 ↓/↑; DRV ↓</td>
</tr>
<tr>
<td>LPV/r</td>
<td>No data</td>
<td>No data</td>
<td>No data&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DCV ↑</td>
<td>ABT450 ↑; LPV ↔</td>
</tr>
<tr>
<td>TPV/r</td>
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<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>EFV</td>
<td>SIM ↓; EFV ↔</td>
<td>SOF ↔; EFV ↔</td>
<td>LDV ↓; EFV ↓&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DCV ↓&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No PK data&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>RPV</td>
<td>SIM ↔; RPV ↔</td>
<td>SOF ↔; RPV ↔</td>
<td>LDV ↔; RPV ↔</td>
<td>No data</td>
<td>ABT450 ↑; RPV ↑</td>
</tr>
<tr>
<td>ETR</td>
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<td>No data</td>
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<td>No data</td>
</tr>
<tr>
<td>RAL</td>
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<td>SOF ↔; RAL ↔</td>
<td>LDV ↔; RAL ↔</td>
<td>No data</td>
<td>3D ↔; ↑ RAL</td>
</tr>
<tr>
<td>EVG/cobi</td>
<td>No data</td>
<td>SOF ↑; cobi ↑&lt;sup&gt;a&lt;/sup&gt;</td>
<td>LDV ↑; cobi ↑&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>DTG</td>
<td>No data</td>
<td>No data</td>
<td>LDV ↔; DTG ↔</td>
<td>DCV ↔; DTG ↑</td>
<td>ABT450 ↓; DTG ↑</td>
</tr>
<tr>
<td>MVC</td>
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<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>TDF</td>
<td>SIM ↔; TFV ↔</td>
<td>SOF ↔; TFV ↔</td>
<td>LDV ↔; TFV ↑</td>
<td>DCV ↔; TFV ↔</td>
<td>3D ↔; TFV ↔</td>
</tr>
</tbody>
</table>

<sup>a</sup>Only problematic when administered with TDF, TFV levels increased, <sup>b</sup>Decrease DCV dose to 30mg QD with ATV, increase DCV dose to 90mg QD with EFV, <sup>c</sup>3D + EFV led to premature study discontinuation due to toxicities


Slide Courtesy of J Kiser Updated 6/12/15
READYING HIV/HCV COINFECTED PATIENTS FOR HCV TREATMENT: OCCURRENCE AND MANAGEMENT OF ANTIVIRAL INTERACTIONS

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Maya Rogers¹, MD
Jennifer Kiser², PharmD

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²Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO USA
Objective

To assess the frequency and degree of potential drug-drug interactions between antiretroviral agents and DAA drug in HIV/HCV co-infected patients receiving care at an academic medical center.
Moderate or Severe Interactions

Percentage of HIV Regimens with Moderate or Severe Interactions

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIM/SOF</td>
<td>70</td>
</tr>
<tr>
<td>SOF/LDV</td>
<td>64</td>
</tr>
<tr>
<td>SOF/DCV</td>
<td>46.6</td>
</tr>
<tr>
<td>3D</td>
<td>61</td>
</tr>
</tbody>
</table>
Subset: 35 of 125 pts prescribed SOF/LDV

Percentage of Patients’ HIV Antiviral Interactions with SOF/LDV

- Severe: 5.7%
- Moderate: 48.6%
- No Significant: 45.7%
17 (48.6%) Patients with Moderate Interactions

10 patients switched their HIV regimen

7 patients did not switch their HIV regimen
- 2 on salvage regimens
- 3 had adherence issues and low viremia
- 2 preferred to stay on their regimen
Challenge for Patients and Providers

• Resistance:
  • Analyzed the resistance profile of all 35 patients
    • All available HIV Genotypes, Phenotypes, and/or PhenoSense
  • 7 (20%) of the 35 patients would not be eligible to change their HIV regimen due to resistance
  • 5 did not have significant drug interactions, but 2 had moderate interactions and switching their regimen was not an option

• Patient Adherence Challenges
  • Switch from once daily regimen to BID (raltegravir)

• Regimen Specific Requirements
  • Food, time of day
Hepatitis C Treatment Guidelines

- www.hcvguidelines.org
- Joint guidelines published by AASLD and IDSA
- Recommends per:
  - Genotype
  - Past treatment experience
  - Degree of liver dysfunction
- Special populations:
  - HIV/HCV Coinfection
  - Post-liver transplant
- Updated regularly
  - Last update: June 30th, 2015
New Information in the Guidelines

1. Stronger wording for whom to treat

   Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies owing to comorbid conditions

   Based on available resources, immediate treatment should be prioritized as necessary so that patients at high risk for liver-related complications are given high priority
New Information in the Guidelines

1. Stronger wording for whom to treat
2. Slightly higher emphasis on HIV/HCV Coinfection

Still do not state that HIV/HCV Coinfection is the highest priority. Reserved for advanced fibrosis (Stage 3-4), post-liver transplant, essential mixed cyroglobulinemia, proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis.

HOWEVER, then lists HIV/HCV Coinfection as a “High Priority of Treatment Owing to high Risk for Complications”
New Information in the Guidelines

1. Stronger wording for whom to treat
2. Slightly higher emphasis on HIV/HCV Coinfection
3. Discuss treating HCV as a way to reduce transmission

Recommend treatment for patients who are at risk of transmission to others: Active IVDU, Incarcerated persons, MSM, Hemodialysis patients, HCV-infected women of childbearing potential, HCV-infected healthcare workers
New Information in the Guidelines

1. Stronger wording for whom to treat
2. Slightly higher emphasis on HIV/HCV Coinfection
3. Discuss treating HCV as a way to reduce transmission
4. Continued emphasis that HIV/HCV Coinfected patients should be use same therapies, doses, and durations as HCV Monoinfected patients.

**HIV/HCV coinfectected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications**
New Information in the Guidelines

1. Stronger wording for whom to treat
2. Slightly higher emphasis on HIV/HCV Coinfection
3. Discuss treating HCV as a way to reduce transmission
4. Continued emphasis that HIV/HCV Coinfected patients should be use same therapies, doses, and durations as HCV Monoinfected patients.
5. Continued emphasis that interferon-based therapy is not recommended as a treatment option for HCV
   *except in certain circumstances in Genotype 3 patients*
Where We Are Going: What is in the Pipeline?
<table>
<thead>
<tr>
<th>Function</th>
<th>NS3/4A</th>
<th>NS5A</th>
<th>NS5B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>Component of HCV Replication Complex</td>
<td>RNA-dependent RNA polymerase</td>
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<tr>
<td>Envelope Glycoproteins</td>
<td></td>
<td>NS5A</td>
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<tr>
<td>E1</td>
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<td>Elbasvir</td>
<td>Nucleoside analogs</td>
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<td></td>
<td>Velpatasvir</td>
<td>Mericitabine</td>
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<td>ACH-3422</td>
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<tr>
<td>Protease</td>
<td>Serine Protease</td>
<td>ACH-2928</td>
<td>ALS-2158</td>
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<tr>
<td>NS2</td>
<td></td>
<td>IDX719</td>
<td>AL-335</td>
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<tr>
<td>Protease Serine</td>
<td></td>
<td>PPI-461</td>
<td>AL-516</td>
</tr>
<tr>
<td>NS3</td>
<td></td>
<td>PPI-668</td>
<td>Non-nucleoside</td>
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<td>Serine Protease Cofactor</td>
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<td>JNJ-56914845</td>
<td>BMS-791325</td>
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<td>NS4A</td>
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<td>Setrobuvir</td>
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<tr>
<td>NS5A</td>
<td></td>
<td></td>
<td>Filibuvir</td>
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<tr>
<td>NS5B</td>
<td></td>
<td></td>
<td>Tegobuvir</td>
</tr>
<tr>
<td>NS5B</td>
<td></td>
<td></td>
<td>VX-222</td>
</tr>
<tr>
<td>RNA-dependent RNA polymerase</td>
<td></td>
<td></td>
<td>TMC647005</td>
</tr>
</tbody>
</table>

Drugs:
- Grazoprevir
- Danoprevir
- ACH-1625
- GS-9451
- GS-9256
- ACH-2684
- Elbasvir
- Velpatasvir
- GSK2336805
- ACH-2928
- IDX719
- PPI-461
- PPI-668
- JNJ-56914845
- Mericitabine
- ACH-3422
- ALS-2158
- AL-335
- AL-516
- BMS-791325
- Deleobuvir
- Setrobuvir
- Filibuvir
- Tegobuvir
- VX-222
- TMC647005
C-EDGE: Phase 3 study of granzoprevir/elbasvir in Coinfected Patients

- Combination of granzoprevir
  - NS3/4A protease inhibitor
  - 100 mg once daily
- With elbasvir
  - NS5A inhibitor
  - 50 mg once daily
- Open-label, single arm, multicenter Phase 3 study
- Genotypes 1, 4, or 6
- Expected Approval date: January 28th, 2016

- 218 patients
- Cirrhotic (16.1%)
- Coinfected:
  - Either naïve to ART with CD4 >500 and VL <50,000 or
  - On stable ART >8 weeks with CD4 >200 and undetectable VL
    - Raltegravir, dolutegravir, rilpiverine

Rockstroh et al. EASL 2015, Vienna, Austria.
C-EDGE: Phase 3 study of granzoprevir/elbasvir in Coinfected Patients

**Figure 2. SVR12 (full analysis set).**

<table>
<thead>
<tr>
<th>Patients, %</th>
<th>All Patients</th>
<th>GT1a</th>
<th>GT1b</th>
<th>GT4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95.0</td>
<td>94.4</td>
<td>95.5</td>
<td>96.4</td>
</tr>
<tr>
<td>207 /218a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| LTFU or discontinued unrelated to VF | 4 | 3 | 1 | 0 |
| Breakthrough | 0 | 0 | 0 | 0 |
| Relapse      | 6 | 4 | 1 | 1 |
| Reinfetion   | 1 | 1 | 0 | 0 |

Rockstroh et al. EASL 2015, Vienna, Austria.
Sofosbuvir/velpatasvir

- Coformulated 1 pill once daily option
- Velpatasvir is a next-generation NS5A inhibitor
  - Replaces ledipasvir
  - Pangentotypic, more potent
- Excellent Phase 2 results with 8 or 12 Weeks +/- riba
  - Studied in variety of genotypes
- Phase 3 data to be presented at AASLD Meeting November 2015
- FDA approval Spring – Summer 2016
The Most Published (and least understood) Topic of This Year: Access to Care
Transparency

1. Who can get coverage?
2. How much is the true cost of the medication?
Lawsuits Against Insurance Companies

1. Plaintiff vs. Anthem Blue Cross in California
   1. Lawsuit: Accuses Blue Cross of withholding a cure for HCV based on cost, forcing patients to wait for eligibility until their liver damage progresses.

2. Plaintiff vs. Connecticut State Medicaid
   1. Lawsuit threatened on behalf of insured patients with F0-F2 fibrosis who would not have been covered under the proposed criteria. This lead to the state Medicaid expanding coverage.
Restrictions for Medicaid Reimbursement of Sofosbuvir for the Treatment of Hepatitis C Virus Infection in US

• Illustrates the complexity of approval process for various state’s medicaid programs
• 69% of states had approval restrictions for advanced liver disease
• 88% of states used drug or alcohol use in their eligibility criteria

Although this creates unique Medicaid programs in each state, states must follow some federal standards. These include covering all FDA-approved drugs, consistent with FDA labeling, whose manufacturers participate in Medicaid’s prescription drug rebate program, and not discriminating in drug coverage.
Cost-Effectiveness

• Much discussion on the price of medications and the cost benefit of treatment
  • Other expensive medications usually were for indications that had less people
    • certain cancers or rare diseases
  • With HCV, the discussion is about a CURE, instead of just management or suppression
• Well done study in Clinical Infectious Disease, Rein and colleagues analyzed the cost of full price Harvoni ($94,500 per treatment) and Viekira PAK ($84,000 per treatment)
  • Compared to no treatment, the incremental cost effectiveness ratio (ICER) was $35,100 and $31,828 per quality adjusted life year (QALY) gained
  • Interventions that cost between $50,000 and $60,000 per QALY are generally considered “Cost Effective”
For years he dreamed of diving into a pool of his own money. I guess he didn’t think it through.
Take Home Points:

1) Huge unmet need for HCV treatment
2) Fast paced, evolving treatment landscape
   a) Improved treatment options from last year
   b) More treatment options in upcoming year
3) Payer sources continue to be a challenge for patients and providers
Questions?

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• Email: jacob.langness@uchealth.org
• Phone: 720-848-0810