Drug Interactions in Managing HIV/HCV Co-Infection
Presenter: Christopher Keeys, Pharm.D., BCPS
28 October 2015
Drug-Drug Interactions between Direct Acting Antiviral (DAA) and Antiretroviral Therapy (ART) in HIV/HCV Co-infected Patients

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PRESENTATION BY:
XIRUI CHEN, PHARM.D., PRACTICE FELLOW
No conflict of interest to disclose by presenters
Objectives

- Identify the basic epidemiology of chronic hepatitis C (CHC) infection and CHC/HIV coinfection in the population
- Recognize the availability and clinical importance of newer direct acting antivirals (DAAs) in the medical management of CHC and CHC/HIV infections
- Identify and discuss the importance of DAA and antiretroviral (ARV) drug drug interactions in the management of CHC and CHC/HIV
- Identify and utilize basic pharmacologic and pharmacokinetic information to minimize drug interactions in care of patients
- Recognize and support medication management strategies that limit drug interactions and adverse health outcomes for patients
Background on HCV

- Epidemiology: An estimated 2.7 million persons in the United States have chronic hepatitis C virus infection (all genotypes). Approximately 75%–85% of people who become infected with Hepatitis C virus develop chronic infection\(^1,2,3\)
- Screening: people with risk factors and all patients with HIV infections\(^3\)
Risk Factors$^{2,3}$

- Recipient of blood transfusions and organ transplants before July 1992 (no screening tools available prior to 1992)
- IV drug use
- Sexual exposure
- Other, including occupational exposure and perinatal exposure
HIV/HCV Co-infection

- Statistics: 50%–90% of HIV IV drug users are co-infected with HCV due to common route of transmission (IV drug use); 25% overall coinfection in population in the USA
- Prognostics of co-infection:
  - Lower rate of spontaneous clearance of virus during acute infection due to low CD4 counts
  - HIV/HCV coinfection accelerates hepatic fibrosis in HCV infected patients, and poor outcomes following transplantation
  - Higher rate of liver decompensation in HIV/HCV co-infected patients, especially in the absence of ART (e.g. ascites, spontaneous bacterial peritonitis, etc.)
  - Higher liver-related mortality rates in HIV-infected patients.
Direct Acting Antivirals (DAAs)\textsuperscript{2,5,6}

2011
- NS3/4A protease inhibitors in combination with PEG-IFN alfa and ribavirin
- Telaprevir (discontinued in Oct 2014)
- Boceprevir (to be discontinued in Dec 2015)

2013
- A third HCV NS3/4A protease inhibitor
- Simeprevir (Nov 2013)
- NS5B polymerase inhibitor: in combination with Ribavirin and/or PEG-IFN alfa
- Sofosbuvir (Dec 2013)

2014
- NS5B polymerase inhibitor in combination with NS5A protein inhibitor: once daily all oral treatment
- Ledipasvir/Sofosbuvir (Oct 2014)
- Ombitasvir/Paritaprevir/ritonavir and dasabuvir (Dec 2014)

2015
- Daclatasvir (Jul 2015)
- Ombitasvir-Paritaprevir-Ritonavir (July 2015)
What’s the Holdup? Evidence?6

- MANY drug interactions between DAA and antiretroviral therapy (ART) limit patient’s choice of treatment options
  - By understanding the basic mechanism of interactions will allow a healthcare provider to choose a therapy that is effective and safe for the patient
- FDA approval
- USPHS, AASLD and IDSA guidance
HCV Life Cycle

Endocytosis
SR-B1
CD81
Uncoating
Host Factors
Translation
Processing
RNA Replication
Viron Assembly
Maturation
Liver Cell
Cytoplasm
ER
Nucleus
New HCV Virion

HCV virion


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HCV Pharmacological Targets

- Simeprevir (OLYSIO®)
- Daclatasvir (DAKLINZA®)
- Ledipasvir / sofosbuvir (HARVONI®)
- Paritaprevir/r ombitasvir Dasabuvir (VIEKIRA PAK®)
- Sofosbuvir (SOVALDI®)
### Oral anti-HCV pharmacological agents

<table>
<thead>
<tr>
<th>Name</th>
<th>Mechanism of Action</th>
<th>Approved Indication</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir (OLYSIO®)</td>
<td>NS3/4A protease inhibitors</td>
<td>CHC genotype 1 or 4 infection in combination with PEG-IFN alfa and ribavirin</td>
<td>150 mg daily with food&lt;br&gt;Not recommended in patients with moderate to severe hepatic impairment</td>
</tr>
<tr>
<td>Sofosbuvir (SOVALDI®)</td>
<td>NS5B polymerase inhibitor</td>
<td>CHC genotypes 1, 2, 3, and 4 infection in combination with ribavirin and/or PEG-IFN alfa&lt;br&gt;HCV/HIV-1 co-infection</td>
<td>400 mg daily&lt;br&gt;No dose adjustment required for mild to moderate renal impairment (eGFR &gt;30 ml/min/1.73m²)&lt;br&gt;No dose adjustment required for any degree of hepatic impairment</td>
</tr>
<tr>
<td>Name</td>
<td>Mechanism of Action</td>
<td>Approved Indication</td>
<td>Dosing</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
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<td>------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir (HARVONI ®)⁹</td>
<td>NS5A protein inhibitor/NS5B polymerase inhibitor</td>
<td>CHC genotype 1 infection</td>
<td>Ledipasvir/Sofosbuvir: 90/400 mg fixed dose, one tablet daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No dose adjustment required for mild to moderate renal impairment (eGFR &gt;30 ml/min/1.73m²)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No dose adjustment required for any degree of hepatic impairment</td>
</tr>
<tr>
<td>Name</td>
<td>Mechanism of Action</td>
<td>Approved Indication</td>
<td>Dosing</td>
</tr>
<tr>
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</tr>
</tbody>
</table>
| Paritaprevir/r Ombitasvir Dasabuvir (VIEKIRA PAK) | NS3/4A protease inhibitor/NS5A protein inhibitor/NS5B polymerase inhibitor | CHC genotype 1 infection with or without ribavirin | • Ombitasvir, paritaprevir, ritonavir: 12.5/75/50 mg fixed dose, one tablet daily in the morning  
• Dasabuvir: 250 mg morning and evening  
No dose adjustment required for any degree of renal impairment  
No dose adjustment required for mild hepatic impairment. Contraindicated in patients with moderate to severe hepatic impairment |
## Oral anti-HCV pharmacological agents

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<th>Name</th>
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</thead>
</table>
| Daclatasvir (DAKLINZA®)

  11                                        | NS5A protein inhibitor                  | CHC genotype 3 infection in combination with sofosbuvir | 60 mg once daily, taken with sofosbuvir no dose adjustment required for any degree of renal impairment |
|                                           |                                         |                                              |                                                                         |
|                                           |                                         |                                              |                                                                         |
|                                           |                                         |                                              |                                                                         |
| Ombitasvir/paritaprevir/ritonavir (TECHNIVIE®)

  12                                        | NS5A protein inhibitor/NS3/4 A protease inhibitor/CYP3A inhibitor | CHC genotype 4 infection in combination with ribavirin | Ombitasvir, paritaprevir, ritonavir: 12.5/75/50 mg fixed dose tablet, 2 tablets once daily in the morning with food no dose adjustment required for any degree of renal impairment |
|                                           |                                         |                                              |                                                                         |
|                                           |                                         |                                              |                                                                         |
|                                           |                                         |                                              |                                                                         |
Why so many DDI?

- Protein (enzyme/transporter) induction and inhibition
Sample Pharmacokinetics Study

[Graph showing the geometric mean ratio and 90% CI for various drugs in relation to Paritaprevir and Ritonavir.]
# Pharmacokinetics of DAA7-18

<table>
<thead>
<tr>
<th>DDA</th>
<th>Substrate of ...</th>
<th>Metabolized by ...</th>
<th>Inhibitor of ...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir (OLYSIO®)</td>
<td>P-gp, BCRP, OATP1B1, MRP2</td>
<td>CYP3A</td>
<td>CYP2A6, CYP2C8, CYP2D6, CYP2C19, CYP3A, P-gp, BCRP, OATP1B1, MRP2</td>
</tr>
<tr>
<td>Sofosbuvir (SOVALDI®)</td>
<td>P-gp, BCRP (active metabolite not affected)</td>
<td>Not metabolized by CYP</td>
<td>P-gp</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir (HARVONI®)</td>
<td>P-gp, BCRP</td>
<td>Not metabolized by CYP</td>
<td>P-gp, BCRP</td>
</tr>
<tr>
<td>Paritaprevir/r Ombitasvir</td>
<td>P-gp, BCRP, OATP1B1/B3</td>
<td>CYP3A</td>
<td>CYP3A (ritonavir), P-gp, BCRP, OATP1B1/B3</td>
</tr>
<tr>
<td>Dasabuvir (VIEKIRA PAK®)</td>
<td></td>
<td>P-gp</td>
<td>Amide hydrolysis antioxidative metabolism</td>
</tr>
<tr>
<td>Daclatasvir (DAKLINZA®)</td>
<td>P-gp, BCRP, OATP1B1/B3</td>
<td>CYP3A</td>
<td>P-gp, BCRP, OATP1B1/B3</td>
</tr>
</tbody>
</table>

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### Summary of DAA and ARV interactions

<table>
<thead>
<tr>
<th>DAA</th>
<th>ARV</th>
<th>Mechanism of Interaction</th>
<th>Effect on DAA</th>
<th>Effect on ART</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir (OLYSIO®)</td>
<td>Efavirenz, Etravirine, Nevirapine</td>
<td>CYP3A4 induction by ARV</td>
<td>↓ Simeprevir</td>
<td>No significant effect on ART</td>
<td>Co-administration not recommended</td>
</tr>
<tr>
<td></td>
<td>Stribild (boosted with COBI)</td>
<td>CYP3A4 Inhibition by COBI</td>
<td>↑ Simeprevir</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ritonavir containing combination</td>
<td>CYP3A4 inhibition by ritonavir</td>
<td>↑ Simeprevir (AUC: ↑159%, Cmax: ↑79%, Cmin: ↑358%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In general, not recommended to coadminister with moderate to severe CYP3A inhibitors (e.g. anticonvulsants, dexamethasone,azole antifungals, macrolide antibiotics etc.) of CYP3A inhibitors (e.g. phenytoin, carbamazepine, rifampin, St. John’s Worts). No significant interactions with tacrolimus or cyclosporine, therefore, it may be a good choice for patients who underwent liver transplants.
## Summary of DAA and ARV interactions

<table>
<thead>
<tr>
<th>DAA</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir (SOVALDI®)</td>
<td>Tipranavir/r</td>
<td>P-gp induction by tipranavir/r</td>
<td>↓ sofosbuvir</td>
<td>No significant effect on ART</td>
<td>Co-administration not recommended</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir (HARVONI®)</td>
<td>Tenofovir</td>
<td>P-gp inhibition by ledipasvir</td>
<td>No significant effect on DAA</td>
<td>↑ Tenofovir</td>
<td>Co-administration with Stribild® not recommended</td>
</tr>
<tr>
<td></td>
<td>Atazanavir/r</td>
<td>P-gp inhibition by Atazanavir/r</td>
<td>↑ Ledipasvir</td>
<td>↑ Atazanavir</td>
<td>Consider alternative therapy</td>
</tr>
<tr>
<td></td>
<td>Tipranavir/r</td>
<td>P-gp induction by tipranavir</td>
<td>↓ Ledipasvir/sofosbuvir</td>
<td>No significant effect on ART</td>
<td>Co-administration not recommended</td>
</tr>
</tbody>
</table>

In general, not recommended to coadminister with P-gp inducers (e.g. rifampin, St. John’s wort). SOVALDI® has relatively few significant interactions with ART, may be a good choice for HIV/HCV co-infected patients receiving ART. No significant interaction with tacrolimus or cyclosporine, therefore, it may be a good choice for patients who underwent transplants.

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## Summary of DAA and ARV interactions

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<thead>
<tr>
<th>DAA</th>
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<th>Effect on DAA</th>
<th>Effect on ART</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paritaprevir/r Ombitasvir Dasabuvir (VIEKIRA PAK®)</td>
<td>Protease Inhibitors (Atazanavir/r, Darunavir, Lopinavir/r)</td>
<td>CYP3A inhibition by Ritonavir</td>
<td>↑ Paritaprevir ↑ or ↓ Ombitasavir ↓ Dasabuvir</td>
<td>↑ Atazanavir ↑ Lopinavir</td>
<td>Dose Atazanavir alone without COBI or Ritonavir boost</td>
</tr>
<tr>
<td></td>
<td>NNRTIs (Rilpivirine)</td>
<td>3A4 induction</td>
<td>Predicted ↓ DAA</td>
<td>↑ Rilpivirine</td>
<td>Co-administration not recommended</td>
</tr>
<tr>
<td></td>
<td>Elvitegravir, Stribild</td>
<td>3A4 inhibition by Ritonavir</td>
<td></td>
<td>Predicted ↑ ART</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maraviroc</td>
<td>3A4 inhibition by Ritonavir</td>
<td></td>
<td>Predicted ↑ ART</td>
<td></td>
</tr>
</tbody>
</table>

In general, not recommended to co-administer with CYP3A inducers (e.g. Phenytoin, Carbamazepine, Rifampin, etc.) or substrates. Co-administration with strong CYP2C8 inhibitor (e.g. Gemfibrozil) is contraindicated.
### Summary of DAA and ARV interactions

<table>
<thead>
<tr>
<th>DAA</th>
<th>ARV</th>
<th>Mechanism of Interaction</th>
<th>Effect on DAA</th>
<th>Effect on ART</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclatasvir (DAKLINZA®)</td>
<td>Atazanavir/r</td>
<td>CYP3A4 inhibition</td>
<td>↑ Daclatasvir</td>
<td></td>
<td>↓ Raclatasvir dose to 30 mg daily</td>
</tr>
<tr>
<td></td>
<td>Efavirenz, Etravirine</td>
<td>CYP3A4 induction</td>
<td>↓ Daclatasvir</td>
<td></td>
<td>↑ Raclatasvir dose to 90 mg daily</td>
</tr>
</tbody>
</table>

In general, dose modification recommended when co-administering with strong CYP3A4 inhibitors/inducers. Monitor signs and symptoms of myopathy when co-administered with HMG-CoA reductase inhibitors.
### Commonly co-preserved drugs

- Oral contraceptives: metabolized by CYP3A, CYP2C9
- Cyclosporine/Tacrolimus: metabolized by CYP3A, substrate for P-gp
- Selective Serotonin Reuptake Inhibitors: CYP2D6 inhibition
- Methadone: CYP3A4 substrate
- Digoxin: P-gp substrate
- “Statins”: CYP3A4 substrate
- Antimicrobials: CYP3A4 inhibitor P-gp inhibitor (e.g. azithromycin, azole antifungal)
Prescribing (Selection of Agents)  

- Efficacy- genotype (FDA, USPHS, guidelines)
- Comorbidities and HIV treatment status
- Prior Treatment
- Stage of fibrosis
- Route (e.g. injections vs oral/ both)
- Duration
- Contraindications/ Precautions/Warnings
- Adverse Drug Events
- Drug-Drug Interactions
- Access (Formulary status; insurance) and Cost
Dispensing

- Pharmacist play pivotal role in evaluating the appropriateness of selection of agents, patient access and continuum of care
  - Record and review COMPLETE and UP-TO-DATE list of patient’s medication, including OTC products; especially at transitions in care (medication reconciliation)
  - Timely communication with prescribers and other healthcare providers
  - Patient education on adverse drug events and adherence
  - Continuing education on newly approved DAA agents with better efficacy, safety and fewer DDIs
• DDI may alter oral absorption; check for ........
  o Avoidance of concomitant medication administrations
  o Spacing of medications
  o Taking with or without meals; special dietary adjustments
  o Daily timing of medication administration to maximize treatment benefit
  o Daily timing of medication administration to minimize adverse effects
  o Special administration needs e.g., young children, tube feeding, impaired swallowing, poor vision (look- alike/side alike medications)
Monitoring

- **Adherence**
  - HCV RNA quantitative testing at week 4
  - Re-evaluate at week 6 if level was detectible at week 4
  - Week 12 level (end of therapy) level is unnecessary since most patients will achieve sustained virologic response (SVR); exception is patients needing ≥ 24 weeks
  - Prescription fills, refills, mean possession rate (MPR), direct observation, etc.

- **Toxicity**
  - Lab work at baseline (CBC, BMP, liver enzyme and bilirubin levels)
  - Routinely throughout the treatment (weeks 2,4,8,12 or more often if abnormal/concerning lab results)
  - Recommend treatment discontinuation for serious adverse effects, e.g., if AST >10x baseline, or hyperbilirubinemia
### Common Adverse Drug Reactions

<table>
<thead>
<tr>
<th>DAA</th>
<th>ADR (&gt;5%)</th>
<th>Labeled Warning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir (OLYSIO\textsuperscript{a})\textsuperscript{7}</td>
<td>Rash, pruritus, nausea, myalgia, dyspnea</td>
<td>Hepatic decompensation and hepatic failure. Usually within 1-4 weeks in therapy initiation. Not recommended in patients with severe cirrhosis. Serious photosensitivity reactions resulting in hospitalization have been observed with OLYSIO in combination with Peg-IFN-alfa and RBV. Simeprevir contains sulfa-moiety, use caution in patients with sulfa allergy.</td>
</tr>
<tr>
<td>Paritaprevir/r Ombitasvir/ Dasabuvir (VIEKIRA PAK\textsuperscript{a})\textsuperscript{10}</td>
<td>Fatigue, nausea, pruritus, skin reactions, insomnia, asthenia</td>
<td>Hepatic decompensation and hepatic failure. Usually within 1-4 weeks in therapy initiation. Not recommended in patients with severe cirrhosis.</td>
</tr>
<tr>
<td>Sofosbuvir (SOVALDI\textsuperscript{a})\textsuperscript{8}</td>
<td>Headache, fatigue, diarrhea, nausea, insomnia, pruritus, decreased appetite</td>
<td>Serious symptomatic bradycardia has been reported in patients taking amiodarone who initiate treatment with sofosbuvir in combination with another HCV direct-acting antiviral.</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir (HARVONI\textsuperscript{a})\textsuperscript{9}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daclatasvir (DAKLINZA\textsuperscript{a})\textsuperscript{11}</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{7} DAA ADR (>5%) Labeled Warning

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Study Design: Cross sectional study among HIV/HCV co-infected patients

Method:
1. Medications lists were collected from medical records
2. Medication lists were entered into Lexi-Interact drug interaction software
3. Documented contraindicated DDI (XDDI) before/after the addition of either simeprevir or sofosbuvir containing therapy

Results:
- Before the addition of any HCV therapy: 20% patients had XDDIs
- Addition of simeprevir containing therapy: 88.4% (p<0.001) patients had XDDIs
- Addition of Sofosbuvir containing therapy: 24.5% (p<0.001) patients had XDDIs

NNRTI regimen (PR: 1.62; 95% CI: 1.38-1.91, p<0.001), PI regimen (PR: 1.64; 95% CI: 1.40-1.93, p<0.001), and ≥7 non-HIV medications (PR: 1.06; 95% CI: 1.00-1.14, p=0.09) were all associated with higher prevalence of XDDs.
Many interactions can be predicted if healthcare professionals taking care of patients have an understanding of the mechanism of proposed interaction.

<table>
<thead>
<tr>
<th>DAA</th>
<th>ART</th>
<th>Mechanism of Interaction</th>
<th>Predicted Result</th>
<th>Actual Result</th>
<th>Recommend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclatasvir 60 mg daily</td>
<td>Atazanavir/ Ritonavir</td>
<td>CYP3A4 inhibition</td>
<td>↑ Daclatasvir</td>
<td>↑ 3x AUC</td>
<td>↓ Daclatavir to 30 mg daily</td>
</tr>
<tr>
<td>Daclatasvir 60 mg daily</td>
<td>Efavirenz</td>
<td>CYP3A4 induction</td>
<td>↓ Daclatasvir</td>
<td>↓ 2x AUC</td>
<td>↑ Daclatavir to 90 mg daily</td>
</tr>
<tr>
<td>Daclatasvir 60 mg daily</td>
<td>Tenofovir</td>
<td>No effect on CYP3A4</td>
<td>No DDI</td>
<td>No clinical significant DDI</td>
<td></td>
</tr>
</tbody>
</table>
Sofosbuvir has labeled warning regarding severe bradycardia when administered in combination with amiodarone.

Patient was on amiodarone and propranolol; 2 hours after the patient had received Sofosbuvir and Daclatasvir, the patient experienced severe bradycardia, heart rate was recorded as 27 beats/min. Amiodarone and propranolol were subsequently stopped, but DAA were continued for 3 days. Each time patient received DAA, he would demonstrate bradycardia. Upon discontinuation of Sofosbuvir and Daclatasvir, no bradycardic events were observed. Thirteen days after patient has stopped amiodarone and atenolol, patient was challenged with DAA, bradycardia was again recorded after 2 days. No bradycardic events were observed following a challenge 8 weeks after discontinuation of amiodarone.
Database of Antiretroviral Drug Interactions

Ian R. McNicholl, PharmD, UCPS, Editor

Search by Antiretroviral Drug
Select an FDA-approved antiretroviral and view interactions with other drugs specified by drug name or drug class, or view "all interactions".

Search by Interacting Drug
Select any drug in the database and view all interactions with FDA-approved antiretrovirals.

Search by Interacting Drug Class
Select any drug class in the database and view all interactions with FDA-approved antiretrovirals.

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References


