Pharmacologic Considerations of HCV Treatment

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Objectives

- Review pharmacokinetic properties of currently utilized Hepatitis C medications
- Review drug interactions and drug elimination considerations resulting from pharmacokinetic properties
- Discuss practical management of drug interactions and drug elimination
Pharmacokinetics: Quick Review

“Movement of drugs”

Study of the relationship between dose, amount of drug in the body and therapeutic or toxic effects of a drug

Pharmacokinetic data helps us understand:
- Dose and schedule
- Dose adjustments due to drug interactions and other issues

Slide modified courtesy of Ryan Moss, PharmD
Pharmacokinetics: Quick Review

- **Absorption**
  - Drug enters the blood
  - Drug travels in the blood
  - Drug disbursement in the body

- **Distribution**
  - Drug travels in the blood
  - Drug disbursement in the body

- **Metabolism**
  - Body changes the drug
  - Usually in intestine or liver

- **Excretion**
  - Kidneys through urine
  - Liver through stool
### Pharmacokinetics: Quick Review

<table>
<thead>
<tr>
<th>CYP 3A4 Inhibitors</th>
<th>CYP3A4 Inducers</th>
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<tbody>
<tr>
<td>Azole antifungals</td>
<td>Anticonvulsants</td>
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<td>Protease inhibitors</td>
<td>Rifamycins</td>
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<tr>
<td>Ritonavir</td>
<td>St Johns Wort</td>
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<td>Calcium Channel Blockers (CCBs)</td>
<td>Non-Nucleoside Reverse Transcriptase Inhibitors</td>
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<td>Clarithromycin</td>
<td>Modafinil</td>
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<td>Nefazodone</td>
<td>Dexamethasone</td>
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<td>Telithromycin</td>
<td>Bosentan</td>
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<td>Nafcillin</td>
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Pharmacokinetics: Final Review

- **Drug Transporters**
  - Move drug across membranes
  - Affect absorption, excretion, movement into organs
  - Efflux (ex. P-gp)
  - Uptake (ex. OATP)
- **P-gp Inhibitors:** azoles, CCBs, PIs, amiodarone
- **P-gp Inducers:** carbamazepine, rifampin, phenytoin, St Johns Wort
- **P-gp Substrates:** digoxin, loperamide
- **OATP1B1 and BCRP substrate:** rosvastatin
HCV Medication Interactions
## HCV/HIV Medication Interactions

| Drug Interactions Between Direct-Acting Antivirals and Antiretroviral Drugs |
|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
|                              | sofosbuvir (SOF)              | ledipasvir (LDV)              | velpatasvir (VEL)             | daclatasvir (DCV)             | elbasvir + grazoprevir (ELB / GRZ) | paritaprevir + ritonavir (P/R) | paritaprevir + ritonavir + ombitasvir + dasabuvir (P/R/O) |
| Ribavirin–based interferon (IFN) | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            |
| Ribavirin–based interferon (IFN) | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            |
| Ribavirin–based interferon (IFN) | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            |
| Ribavirin–based interferon (IFN) | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            |
| Ribavirin–based interferon (IFN) | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            |
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| ribavirin–based interferon (IFN) | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            |
| ribavirin–based interferon (IFN) | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            |
| ribavirin–based interferon (IFN) | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            | ND                            |

_AASLD/IDSA Guidelines 2017_
Ledipasvir/Sofosbuvir
Ledipasvir / Sofosbuvir

- **NS5A Inhibitor**
  - **A:**
    - Acid increases absorption
    - P-gp substrate
  - **M:**
    - Oxidation/no CYP
    - Inhibits P-gp & BCRP
  - **E:**
    - Biliary elimination

- **NS5B polymerase inhibitor**
  - **A:**
    - P-gp and BCRP substrate
  - **M:**
    - Hydrolyzed to active molecule
    - Does not inhibit or induce any enzymes
  - **E:**
    - Renal clearance of active metabolite
Ledipasvir/Sofosbuvir

- Avoid P-gp Inducers
  - Anticonvulsants
  - Rifamycins
  - St Johns Wort

- Acid suppressing agents
  - Antacids: 4 hours before/after
  - H2 blockers: take with or 12 hour separation; do not exceed equivalent of famotidine 40mg BID
  - PPIs: take simultaneously while fasting; do not exceed omeprazole 20mg

- Avoid HIV protease inhibitors and tenofovir DF co-administration
- Avoid in severe renal impairment (<30mL/min/1.73m²)
- Avoid amiodarone
- Avoid rosuvastatin
Velpatasvir/Sofosbuvir
Velpatasvir / Sofosbuvir

- **NS5A inhibitor**
  - **A:**
    - Acid increases absorption
    - P-gp substrate
  - **M:**
    - Metabolized Via CYP3A4, 2C8, and 2B6
    - Does not inhibit or induce and enzymes
  - **E:**
    - Biliary elimination

- **NS5B polymerase inhibitor**
  - **A:**
    - P-gp and BCRP substrate
  - **M:**
    - Hydrolyzed to active molecule
    - Does not inhibit or induce any enzymes
  - **E:**
    - Renal clearance of active metabolite
Velpatasvir/Sofosbuvir

- Avoid P-gp Inducers
  - Anticonvulsants
  - Rifamycins
  - St Johns Wort

- Acid Suppressing medications
  - Antacids: separate by 4 hours
  - H2 blockers: take with or 12 hour separation; do not exceed equivalent of famotidine 40mg BID
  - PPIs: take 4 hours after VEL; do not exceed omeprazole 20mg

- CYP3A4 inhibitors/inducers
- Avoid HIV protease inhibitor and tenofovir DF co-administration
  - Contraindicated with etravirine, efavirenz, nevirapine
- Avoid in severe renal impairment (<30mL/min/1.73m²)
- Contraindicated with amiodarone
- Rosuvastatin: 10mg max dose
Velpatasvir/Sofosbuvir/Voxilaprevir
Velpatasvir / Sofosbuvir / Voxilaprevir

- NS3/4A Protease Inhibitor
- A:
  - P-gp and BCRP substrate
  - Food increases absorption
- M:
  - CYP3A4 substrate
- E:
  - Biliary elimination
Velpatasvir/Sofosbuvir/Voxilaprevir

- **Take with food**
- Avoid in severe renal impairment (<30mL/min/1.73m²)
- Contraindicated with amiodarone
- Monitor digoxin levels
- Avoid P-gp Inducers
  - Anticonvulsants
  - Rifamycins
  - St Johns Wort
- CYP 3A4 Inducers/inhibitors
  - Contraindicated with atazanavir, lopinavir, tipranavir, and efavirenz
- Acid Suppressing medications
  - Antacids: separate by 4 hours
  - H2 blockers: take with or 12 hour separation; do not exceed equivalent of famotidine 40mg BID
  - PPIs: simultaneously with SOF/VEL/VOX on a fasting stomach; do not exceed omeprazole 20mg
- Statins
  - Pravastatin max dose 40mg
  - Rosuvastatin, pitavastatin not recommended
  - Monitor all others and use lowest recommended dose
Daclatasvir + Sofosbuvir
Daclatasvir + Sofosbuvir

- **NS5A replication complex inhibitor**
  - **A:** P-gp substrate
  - **M:** Primarily metabolized by CYP3A4
    - Inhibits CYP3A4
  - **E:** Biliary elimination

- **NS5B polymerase inhibitor**
  - **A:** P-gp and BCRP substrate
  - **M:** Hydrolyzed to active molecule
    - Does not inhibit or induce any enzymes
  - **E:** Renal clearance of active metabolite

AIDS Education & Training Center Program
Daclatasvir + Sofosbuvir

- CYP3A4 inducers
  - Strong: Avoid
  - Moderate: Increase dose to 90mg
- Strong CYP3A4 inhibitors: reduce daclatasvir dose to 30mg*
- Avoid P-gp Inducers
  - Anticonvulsants
  - Rifamycins
  - St Johns Wort
- Avoid in severe renal impairment (<30mL/min/1.73m²)
- Avoid amiodarone

Glecaprevir/Pibrentasvir

Glecaprevir + Pibrentasvir

- NS3/4A Protease Inhibitor
  - A:
    - P-gp, BCRP substrate
    - OATP 1B1/3 substrate
    - Increased by food
  - M:
    - Secondary metabolism, mild CYP3A4
    - Inhibits p-gp, OATP 1B1/3, BCRP
    - Weak inhibitor of CYP 3A4, 1A2 and UGT1A1
  - E:
    - Biliary elimination

- NS5A replication complex inhibitor
  - A:
    - P-gp, BCRP substrate
  - M:
    - No metabolism
    - Inhibits p-gp, OATP 1B1/3, BCRP
    - Weak inhibitor of CYP 3A4, 1A2 and UGT1A1
  - E:
    - Biliary elimination
Glecaprevir/Pibrentasvir

- Take with food
- No dose modification for renal impairment
- Not recommended in **decompensated cirrhosis**
- Avoid P-gp Inducers
  - Anticonvulsants
  - Rifamycins
  - St Johns Wort
- HIV ART:
  - Atazanavir contraindicated
  - Not recommended: darunavir, lopinavir, ritonavir, efavirenz
- Statins:
  - Not recommended: atorvastatin, lovastatin, simvastatin
  - Pravastatin: decrease by 50%
  - Rosuvastatin: max dose 10mg
- Decrease doses of digoxin
- Not recommended with ethinyl estradiol (increased ALT)
- Not recommended with cyclosporine >100mg daily
Ombitasvir Paritaprevir/Ritonavir + Dasabuvir

### Ombitasvir / Paritaprevir / Ritonavir

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<thead>
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<tbody>
<tr>
<td><strong>NS5A inhibitor</strong></td>
<td><strong>NS3 protease inhibitor</strong></td>
<td><strong>Pharmacokinetic enhancer</strong></td>
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<tr>
<td><strong>A:</strong></td>
<td><strong>A:</strong></td>
<td><strong>A:</strong></td>
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<td>P-gp substrate</td>
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<td>P-gp substrate</td>
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<td><strong>M:</strong></td>
<td><strong>M:</strong></td>
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<tr>
<td>Metabolized via hydrolysis then oxidative metabolism</td>
<td>Metabolized via CYP3A4 and to a lesser extent by CYP3A5</td>
<td>Metabolized by CYP3A4</td>
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<tr>
<td>Inhibits CYP2C8, UGT1A1</td>
<td>Inhibits CYP2C8, UGT1A1</td>
<td>Strong CYP3A4 inhibitor</td>
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<tr>
<td>Biliary elimination</td>
<td>Metabolism</td>
<td>Metabolism</td>
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</table>
Dasabuvir

- Nonnucleoside NS5B polymerase inhibitor
  - **A:**
    - Fat increases absorption
    - P-gp substrate
    - Inhibits BCRP
  - **M:**
    - Metabolism via CYP2C8, and to a lesser extent by CYP3A
    - Inhibits UGT1A1
  - **E:**
    - Metabolism
Ombitasvir/Paritaprevir/ritonavir + Dasabuvir (PrOD)

- Take with food
- Avoid potent CYP3A4 inducers
- Avoid potent CYP3A4 inhibitors
- Avoid Ethinyl estradiol contraceptives
- HMG-CoA Reductase Inhibitors
  - Avoid atorvasatin, simvastatin, and lovastatin
  - Rosuvastatin: max dose 10mg
- Contraindicated HIV medications:
  - Elvitegravir/cobicistat/tenofovir alafenamide or tenofovir disoproxil fumarate
  - Non-Nucleoside Reverse Transcriptase Inhibitors: efavirenz, etravirine, nevirapine
  - Most HIV protease inhibitors
- Quetiapine
- Apixaban
- Contraindicated with moderate to severe hepatic impairment (Child-Pugh B or C)
Elbasvir/Grazoprevir
<table>
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<tr>
<td><strong>NS5A inhibitor</strong></td>
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<tr>
<td><strong>A:</strong></td>
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<td>Fat increases absorption</td>
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<td>P-gp substrate</td>
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<tr>
<td>Inhibits P-gp and BCRP</td>
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<td><strong>M:</strong></td>
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<tr>
<td>Metabolized via CYP3A4</td>
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<td><strong>E:</strong></td>
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<td>Metabolism</td>
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<td><strong>NS3 inhibitor</strong></td>
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<td><strong>A:</strong></td>
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<td>Fat increases absorption</td>
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<td>P-gp substrate</td>
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<tr>
<td>Inhibits UGT1A1 and BCRP</td>
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<td><strong>M:</strong></td>
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<tr>
<td>Metabolism via CYP3A4</td>
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<td><strong>E:</strong></td>
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<tr>
<td>Metabolism</td>
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</table>
Elbasvir/Grazoprevir

- Avoid P-gp inducers
- Avoid CYP3A4 inducers
- Avoid strong CYP3A4 inhibitors
- Contraindicated HIV medications
  - All HIV protease inhibitors
  - Non-Nucleoside Reverse Transcriptase Inhibitors: efavirenz, etravirine, nevirapine
- Contraindicated with moderate to severe hepatic impairment (Child-Pugh B or C)
- Rosuvastatin: do not exceed 10mg
Simeprevir

- NS3 protease inhibitor
- **A:**
  - Food improves absorption
  - P-gp and OATP1B1 inhibitor
- **M:**
  - Metabolized by CYP 3A4
  - Inhibits CYP3A4 (intestinal)
- **E:**
  - Metabolism
Simeprevir

- Avoid in severe hepatic impairment/decompensated cirrhosis
- Avoid strong CYP3A4 inhibitors
- Avoid strong CYP3A4 inducers
- Contraindicated HIV medications
  - All HIV protease inhibitors
  - Non-Nucleoside Reverse Transcriptase Inhibitors: efavirenz, etravirine, nevirapine
- Rosuvastatin: max dose 10mg
Ribavirin

- Purine nucleoside analogue
- **A**: Food improves absorption
- **M**: Minimal metabolism
- **E**: Renal elimination - dose adjust

- Pregnancy category X
Summary/Conclusion

- Due to pharmacokinetic properties of HCV meds, drug interactions are common
- Patients should be screened closely prior to and during treatment for interactions
- Complicated patients (i.e. HIV co-infected, cirrhotic patients, severe renal impairment) require additional considerations
Case 1: Steven

- Steven is a 24 year old white male referred to your clinic for HCV evaluation after a recent hospitalization for endocarditis due to IV drug use. He currently takes **zolpidem 5mg** each evening for sleep, **Adderall 5mg** daily, and **Lisinopril 5mg** daily. He also reports occasional use of **Tums after a spicy meal**. Since his hospitalization, Steven completed rehabilitation and reports that he has not used IV drugs in 6 weeks. He has not received HCV treatment in the past and is eager to be treated. Work up reveals the following:

- HCV RNA 1,004,879 IU/mL
- HCV GT2
- Abdominal ultrasound with transient elastography reveals F1-F2 fibrosis
Case 1: Steven

What treatment strategy do you recommend at this time?

A. VEL/SOF x 12 weeks
B. LDV/SOF x 8 weeks
C. LDV/SOF x 12 weeks
D. VEL/SOF x 8 weeks
E. Delaying treatment until you can confirm drug abstinence for >6 months
Case 1: Steven continued

- Steven is approved for the correct treatment listed above. What counseling regarding his current medications would you provide?
Acid Suppressing Agents and DAAs

- VEL/SOF, VEL/SOF/VOX, LDV/SOF
  - H2 Antagonist: simultaneously or 12 hours apart at a maximum equivalent to famotidine 40mg twice daily
  - Antacids: separate by 4 hours

- Proton pump inhibitors:
  - LDV/SOF: administer simultaneously under fasted conditions at a maximum equivalent to pantoprazole 40mg
  - VEL/SOF: administer VEL/SOF 4 hours before omeprazole 20mg with food. No other PPIs have been studied.
    - 26% reduction in AUC of VEL/SOF
  - VEL/SOF/VOX: administer simultaneously under fasted conditions at a maximum equivalent to omeprazole 20mg
Case 2: Patricia

- Patricia is a 38 y/o female referred for HCV evaluation and treatment, who was diagnosed at time of HIV diagnosis in 2005.
- Her PMH includes HIV (last CD4 950 with HIV viral load <20), bipolar disorder, and prior IVDU.
- Workup reveals:
  - HCV RNA VL 12,500,000
  - GT 1a
  - Elastography consistent with F1-F2 fibrosis
  - Meds: (tenofovir DF/emtricitabine) + darunavir/ritonavir, oxcarbazepine, quetiapine
Case 2: Which medication are concerning for potential drug-drug interactions with DAAs?

A. Tenofovir DF  
B. Darunavir  
C. Ritonavir  
D. Oxcarbazepine  
E. Quetiapine
HCV Medication Interactions

- Acid-reducing agents
- Anticonvulsants
- Amiodarone, digoxin
- Azole antifungals
- Statins

Table: Drug Interactions with Direct-Acting Antivirals and Selected Concomitant Medications

<table>
<thead>
<tr>
<th>Concomitant Medications</th>
<th>DCV</th>
<th>LDV</th>
<th>PrOD</th>
<th>SMV</th>
<th>SOF</th>
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AASLD/IDSA Guidelines
Questions?

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