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
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

CYP 3A4 Inhibitors
- Azole antifungals
- Protease inhibitors
- Ritonavir
- Calcium Channel Blockers (CCBs)
- Clarithromycin
- Nefazodone
- Telithromycin

CYP3A4 Inducers
- Anticonvulsants
- Rifamycins
- St Johns Wort
- Non-Nucleoside Reverse Transcriptase Inhibitors
- Modafinil
- Dexamethasone
- Bosentan
- Nafcillin
Pharmacokinetics: Quick 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: rosuvastatin
## Table. Drug Interactions Between Direct-Acting Antivirals and Antiretroviral Drugs

<table>
<thead>
<tr>
<th>Sofosbuvir (GS-3)</th>
<th>Ledipasvir (LDV)</th>
<th>Velpatasvir (VEL)</th>
<th>Simeprevir (SMV)</th>
<th>Dasabuvir (DCV)</th>
<th>Gilead's Peginterferonalpha + Dasabuvir (TEL/GID)</th>
<th>Paritaprevir, ritonavir, ombitasvir + dasabuvir (PVC/OD)</th>
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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 amiodarone
- Avoid rosuvastatin
- Avoid in severe renal impairment (<30mL/min/1.73m²)
Velpatasvir/Sofosbuvir
Velpatasvir / Sofosbuvir

- NS5A inhibitor
  - A:
    - Acid increases absorption
    - P-gp substrate
  - M:
    - Metabolized Via CYP3A4, 2C8, and 2B6
      - Inhibits BCRP, OATP1B1, & B3
  - 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**
- 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
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 amiodarone
- Avoid in severe renal impairment (<30mL/min/1.73m²)

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
- 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
OmbitasvirParitaprevir/Ritonavir + Dasabuvir

<table>
<thead>
<tr>
<th>NS5A inhibitor</th>
<th>NS3 protease inhibitor</th>
<th>Pharmacokinetic enhancer</th>
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<tr>
<td><strong>A:</strong></td>
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<tr>
<td>P-gp substrate</td>
<td>P-gp substrate</td>
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<tr>
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<td><strong>M:</strong></td>
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<td>Inhibits CYP2C8, UGT1A1</td>
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<td>Metabolism</td>
<td>Metabolism</td>
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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 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
- Contraindicated with moderate to severe hepatic impairment (Child-Pugh B or C)
Elbasvir/Grazoprevir
Elbasvir / Grazoprevir

- **NS5A inhibitor**
  - **A:**
    - Fat increases absorption
    - P-gp substrate
    - Inhibits P-gp and BCRP
  - **M:**
    - Metabolized via CYP3A4
  - **E:**
    - Metabolism

- **NS3 inhibitor**
  - **A:**
    - Fat increases absorption
    - P-gp substrate
    - Inhibits UGT1A1 and BCRP
  - **M:**
    - Metabolism via CYP3A4
    - Inhibits CYP3A4
  - **E:**
    - Metabolism
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: Michael Scarn

- Michael 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, Michael 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: Michael Scarn

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: Michael Scarn continued

- Michael 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: Bert Macklin

- Bert is a 38 y/o male referred for HCV evaluation and treatment, who was diagnosed at time of HIV diagnosis in 2005.
- 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

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* indicates potential drug interactions; please consult local references for complete clinical advice.
Questions?

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