Pharmacologic Considerations of HCV Treatment

Kristen Whelchel, PharmD
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
Schematic representation of drug-metabolizing enzymes and drug transporters demonstrated to be affected by the 3D regimen as perpetrators (A) and important pathways involved in the disposition and elimination of the 3D regimen as victims (B).

Mohamad Shebley et al. Drug Metab Dispos 2017;45:755-764
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: 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 John’s Wort
- **P-gp Substrates**: digoxin, loperamide
- **OATP1B1 and BCRP substrate**: rosvastatin
HEP Drug Interactions

HEP Drug Interaction Checker
Access our comprehensive, user-friendly, free drug interaction charts. Providing clinically useful, reliable, up-to-date, evidence-based information

Start Now
### HCV/HIV Medication Interactions

<table>
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<td>▲ TFV³</td>
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AASLD/IDSA Guidelines 2017
Ledipasvir/Sofosbuvir
Ledipasvir / Sofosbuvir

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

**Sofosbuvir**
- **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 any 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
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

*For genotypes 2 and 3
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

- **NS5A inhibitor**
  - **A:** P-gp substrate
  - **M:** Metabolized via hydrolysis then oxidative metabolism
  - **E:** Biliary elimination

- **NS3 protease inhibitor**
  - **A:** P-gp substrate
  - **M:** Inhibits P-gp, OATP1B1/3, BCRP
  - **M:** Metabolized via CYP3A4 and to a lesser extent by CYP3A5
  - **E:** Biliary elimination

- **Pharmacokinetic enhancer**
  - **A:** P-gp substrate
  - **M:** Metabolized by CYP3A4
  - **E:** Metabolism
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 Ethinyln 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
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
  - **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
COMMON DAA DRUG INTERACTION REVIEW
# Acid Suppressing Agents

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<td>Velpatasvir</td>
<td>Daclatasvir</td>
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<td>Glecaprevir</td>
<td>Sofosbuvir</td>
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<td></td>
<td>Ombitasvir/Dasabuvir/pibrentasvir/ritonavir</td>
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<td>Voxilaprevir</td>
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<td>Pibrentasvir</td>
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H2 Antagonists and Antacids

- Velpatasvir, Ledipasvir
- **H2 Antagonist:**
  - Administration: Simultaneously or 12 hours apart
  - Maximum equivalent to famotidine 40mg twice daily
- **Antacids:** Separate by 4 hours
Proton Pump Inhibitors

- **Ledipasvir/sofosbuvir:**
  - Administer *simultaneously* under fasted conditions
  - Maximum equivalent to pantoprazole 40mg

- **Velpatasvir/sofosbuvir:**
  - Administer *4 hours before PPI*
  - Maximum equivalent to omeprazole 20mg with food. No other PPIs have been studied.

- **Voxilaprevir/velpatasvir/sofosbuvir:**
  - Administer *simultaneously*
  - Maximum equivalent to omeprazole 20mg with food. No other PPIs have been studied.
Glecaprevir/Pibrentasvir

- Pooled analysis of G/P in 2,369 patients (263 on PPI) → mITT SVR12 rate of 97.4%

Flamm, World Congress of Gastroenterology at ACG 2017
Glecaprevir/Pibrentasvir

- Omeprazole 40mg with G/P
  - PIB unaffected
  - GLE AUC 51% lower
- European Medicines Agency (EMA)
  - Concurrently with no more than 20mg of omeprazole
  - 40mg of omeprazole contraindicated

Yu and Forns, The Lancet 2017
Glecaprevir/Pibrentasvir

- AUC values at steady-state were not significantly different with use of acid-reducing agent

Flamm, World Congress of Gastroenterology at ACG 2017
Expert Opinion

- Hold acid reducing agents if possible
- H2 antagonists and antacids:
  - Same as VEL/SOF and LDV/SOF
- PPIs:
  - Omeprazole 20mg equivalent simultaneously
## HMG-CoA Reductase Inhibitors

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<td>↑ prava-Lowest dose, Monitor</td>
<td>↑ lova-Lowest dose, Monitor</td>
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<td>↑ lova-Monitor</td>
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<td>↑ atorva-Lowest dose, Monitor</td>
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<td>↑ simva-Lowest dose, Monitor</td>
<td>↑ pitava-Not rec.</td>
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Diltiazem and DAAs

- Diltiazem is an inhibitor of CYP3A4 and P-gp and P-gp substrate
  - Glecaprevir/pibrentasvir → monitor HR/BP
    - Inhibit P-gp
    - Weak CYP3A4 inhibitor
  - Ledipasvir/sofosbuvir → monitor HR/BP
    - LDV inhibits P-gp
  - Velpatasvir/sofosbuvir → monitor HR/BP
    - VEL inhibits P-gp
  - Voxilaprevir → monitor HR/BP
    - VOX inhibits P-gp (as does VEL!)

- Avoid Amiodarone with sofosbuvir-containing regimens
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>
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<tr>
<th>Concomitant Medications</th>
<th>DCV</th>
<th>LDV</th>
<th>PEGD</th>
<th>SMV</th>
<th>SOF</th>
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Questions?

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kristen.w.whelchel@vumc.org

Acknowledgements: Ryan Moss, PharmD, AAVHIP and Autumn Zuckerman, PharmD, BCPS, AAHIVP