AETC AIDS Education & Training Center Program Southeast

Pharmacologic Considerations of HCV Treatment

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Objectives

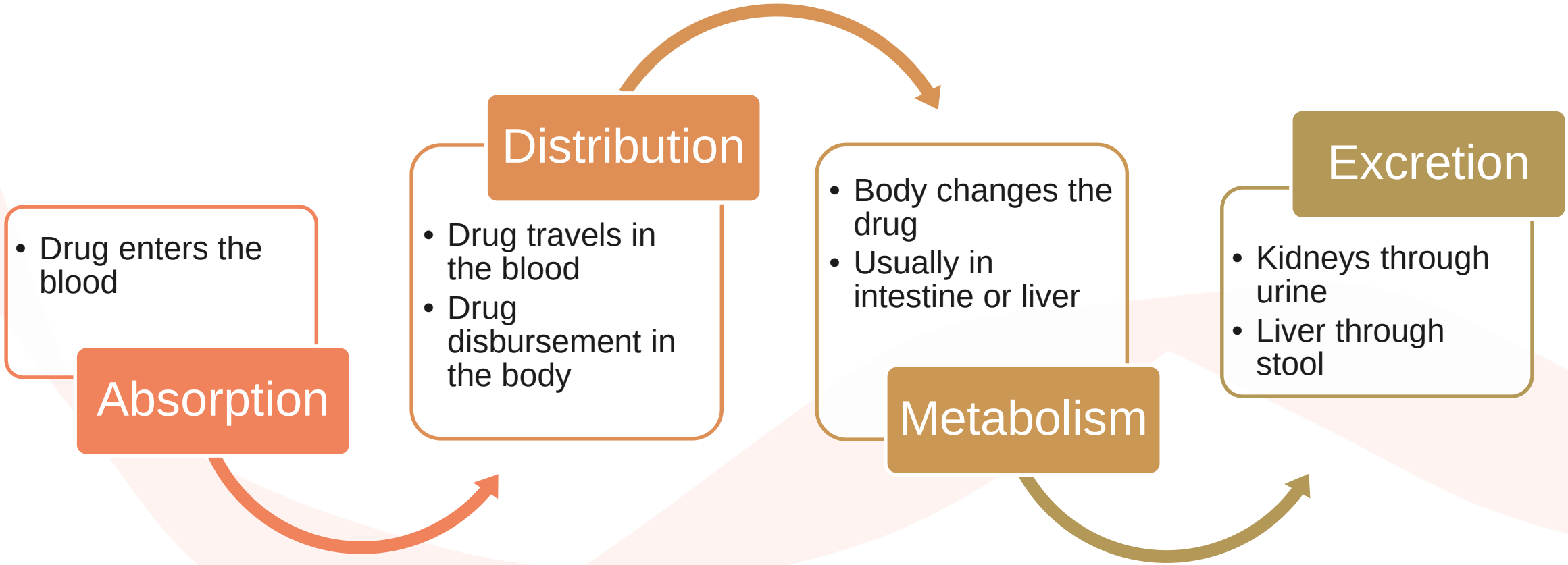
- Review pharmacokinetic properties of currently utilized Hepatitis C medications
- Review drug interactions and drug elimination considerations resulting from pharmacokinetic properties
- Discuss practical management of drug interactions and drug elimination

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



Pharmacokinetics: Quick Review

CYP 3A4 Inhibitors

- Azole antifungals
- Protease inhibitors
- Ritonavir
- Calcium Channel Blockers (CCBs)
- Clarithromycin
- Nefazodone
- Telithromycin

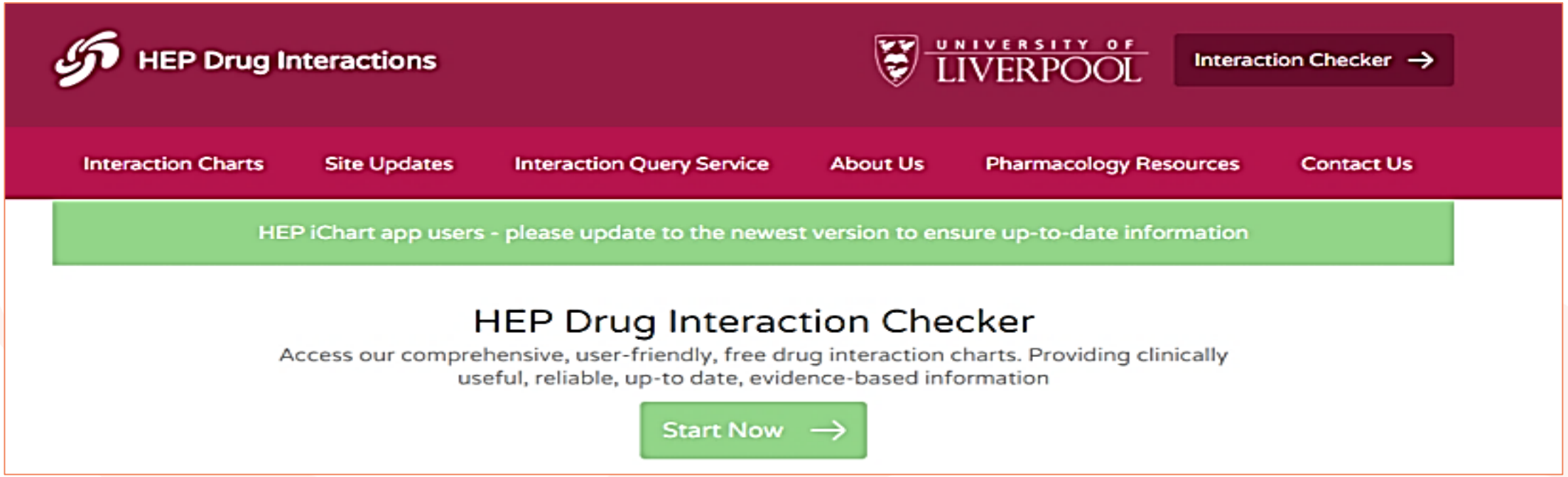
CYP3A4 Inducers

- 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 Johns Wort
- P-gp Substrates: digoxin, loperamide
- OATP1B1 and BCRP substrate: rosuvastatin

HCV Medication Interactions



HEP Drug Interactions

	Simeprevir	Sofosbuvir	Ledipasvir	Daclatasvir	Paritaprevir, ritonavir, ombitasvir plus dasabuvir (PrOD)	Paritaprevir, ritonavir, ombitasvir (PrO)	Grazoprevir/ elbasvir
Ritonavir-boosted atazanavir	No data	No data	Ledipasvir ↑; atazanavir ↑[a] (okay with TAF not TDF)	Daclatasvir ↑[b]	Paritaprevir ↑; atazanavir ↑	Paritaprevir ↑; atazanavir ↔	Grazoprevir ↑ elbasvir ↑; atazanavir ↑
Ritonavir-boosted darunavir	Simeprevir ↑; darunavir ↔	Sofosbuvir ↑; darunavir ↔	Ledipasvir ↑, darunavir ↔[a] (okay with TAF not TDF)	Daclatasvir ↑; darunavir ↔	Paritaprevir ↓/↑; darunavir ↓	Paritaprevir ↑; darunavir ↔	Grazoprevir ↑ elbasvir ↑; darunavir ↔
Ritonavir-boosted lopinavir	No data	No data	No data[a]	Daclatasvir ↑; lopinavir ↔	Paritaprevir ↑; lopinavir ↔	Paritaprevir ↑; lopinavir ↔	Grazoprevir ↑ elbasvir ↑; lopinavir ↔
Ritonavir-boosted tipranavir	No data	No data	No data	No data	No data	No data	No data
Efavirenz	Simeprevir ↓; efavirenz ↔	Sofosbuvir ↔; efavirenz ↔	Ledipasvir ↓; efavirenz ↓[a]	Daclatasvir ↓[b]	No pharmacokinetic data	No data	Grazoprevir ↓ elbasvir ↓; efavirenz ↓
Rilpivirine	Simeprevir ↔; rilpivirine ↔	Sofosbuvir ↔; rilpivirine ↔	Ledipasvir ↔; rilpivirine ↔	No data	Paritaprevir ↑; rilpivirine ↑	No data	Grazoprevir ↔ elbasvir ↔; rilpivirine ↔
Etravirine	No data	No data	No data	Daclatasvir ↓[b]	No data	No data	No data
Raltegravir	Simeprevir ↔; raltegravir ↔	Sofosbuvir ↔; raltegravir ↔	Ledipasvir ↔; raltegravir ↔	No data	PrOD ↔; ↑ raltegravir	PrO ↔; ↑ raltegravir	Grazoprevir ↔ elbasvir ↔; ↑ raltegravir
Cobicistat-boosted elvitegravir	No data	Cobicistat ↑[a]; sofosbuvir ↑ (okay with TAF not TDF)	Cobicistat ↑; ledipasvir ↑[a] (okay with TAF not TDF)	No data	No data	No data	No data
Dolutegravir	No data	No data	Ledipasvir ↔; dolutegravir ↔	Daclatasvir ↔; dolutegravir ↑	Paritaprevir ↓; dolutegravir ↑	No data	Grazoprevir ↔ elbasvir ↔; ↑ dolutegravir
Maraviroc	No data	No data	No data	No data	No data	No data	No data
Tenofovir disoproxil fumarate	Simeprevir ↔; tenofovir ↔	Sofosbuvir ↔; tenofovir ↔	Ledipasvir ↔; tenofovir ↑	Daclatasvir ↔; tenofovir ↔	PrOD ↔; tenofovir ↔	PrO ↔; tenofovir ↔	Grazoprevir ↔ elbasvir ↔; tenofovir ↑

Figure 2. Drug interactions between direct-acting antivirals and antiretroviral drugs. Red, combination should not be used; yellow, use with caution or increased monitoring; and green, suitable for coadministration [7]. [a]Watch renal function, tenofovir levels increased; [b]Decrease daclatasvir (DCV) dose to 30 mg QD, increase DCV dose to 90 mg QD. Up arrow is an increase in the concentration, down arrow is a decrease in the concentration, and a horizontal arrow means no change in the concentration. Abbreviations: TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

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Harvoni®: 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/1.73m^2)
- Avoid amiodarone
- Avoid rosuvastatin

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Epclusa®: 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 equivalent
- CYP3A4 inhibitors/inducers
- Avoid HIV protease inhibitor and tenofovir DF co-administration
- Contraindicated with etravirine, efavirenz, nevirapine
- Avoid in severe renal impairment (<30mL/min/1.73m^2)
- Avoid amiodarone
- Rosuvastatin: 10mg max dose

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Daklinza® + Sovaldi®
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/1.73m^2)
- Avoid amiodarone

http://www.drugdevelopment-technology.com/projects/daklinza-daclatasvir-for-the-treatment-of-chronic-hepatitis-c-genotype-3-infection/

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Viekira Pak® and Viekira XR®
OmbitasvirParitaprevir/Ritonavir + Dasabuvir

https://www.hepmag.com/article/abbvies-viekira-pak-works-just-hepatitis-c-drug-resistance
https://www.hepmag.com/article/fda-approves-oncedaily-hepatitis-c-regimen-viekira-xr

Ombitasvir / Paritaprevir / Ritonavir

- NS5A inhibitor
- A:
  - P-gp substrate
- M:
  - Metabolized via hydrolysis then oxidative metabolism
  - Inhibits CYP2C8, UGT1A1
- E:
  - Biliary elimination

- NS3 protease inhibitor
- A:
  - P-gp substrate
  - Inhibits P-gp, OATP1B1/3, BCRP
- M:
  - Metabolized via CYP3A4 and to a lesser extent by CYP3A5
  - Inhibits CYP2C8, UGT1A1
- E:
  - Metabolism

- Pharmacokinetic enhancer
- A:
  - P-gp substrate
- M:
  - Metabolized by CYP3A4
  - Strong CYP3A4 inhibitor
- 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 Ethiynl 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)

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Zepatier®: 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

- Take with food
- 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

Summary HCV Medication Interactions

- 3A4
  - **Daklinza**® (DCV): substrate
  - **Viekira Pak**® (ritonavir): inhibitor
  - **Zepatier**® (EBV/GZR) : substrates
  - **Olysio** ® (SMV): substrate; mild inhibitor of intestinal CYP3A4
  - **Epclusa**® (VEL): substrate
- P-gp
  - **Harvoni®:** LDV inhibitor; LDV/SOF substrates
  - **Olysio**® (SMV): Inhibitor
  - **Daklinza**® (DCV): inhibitor
  - **Sovaldi**® (SOF): substrate
  - **Zepatier**® (EBV/GZR) : substrates
  - **Epclusa**® (VEL/SOF): substrate, VEL inhibitor
- UGT1A1
  - **Viekira Pak**®(OBV/PTVr/DBV): inhibitor
- OATP 1B1/3
  - **Zepatier**® (GZR): substrate
  - **Olysio**® (SMV): Inhibitor
  - **Daklinza**® (DCV): Inhibitor
  - **Viekira Pak**® (PTV): inhibitor
  - **Epclusa**® (VEL): inhibitor
- BCRP
  - **Daklinza**® (DCV): Inhibitor
  - **Harvoni®:** LDV inhibitor; LDV/SOF substrates
  - **Sovaldi**® (SOF): substrate
  - **Viekira Pak**® (PTVr/DBV): inhibitor
  - **Epclusa**® (VEL): inhibitor

Summary HCV Medication Interactions

- Olysio ® (simeprevir):
  - **3A4:** substrate; mild inhibitor of intestinal CYP3A4
  - **P-gp:** inhibitor
  - **OATP:** Inhibits OATP1B1/3
- Sovaldi® (sofosbuvir):
  - **P-gp:** substrate
  - **BCRP:** substrate
- Harvoni® (ledipasvir/sofosbuvir):
  - **P-gp:** ledipasvir inhibits; ledipasvir/sofosbuvir are substrates
  - **BCRP:** ledipasvir inhibits; ledipasvir/sofosbuvir are substrates
  - **Acid-reducing agents

- Viekira Pak® (paritaprevir, ombitasvir, dasabuvir, ritonavir):
  - **3A4**: ritonavir: inhibitor
  - **UGT1A1**: ombitasvir, paritaprevir, and dasabuvir inhibit
  - **OATP:** paritaprevir inhibits OATP1B1/3
  - **BCRP**: ritonavir, paritaprevir, and dasabuvir inhibit
- Daklinza®(daclatasvir):
  - **3A4** substrate
  - **OATP:** Inhibits OATP1B1/3
  - **P-gp:** inhibitor
  - **BCRP:** inhibitor
- Zepatier® (elbasvir/grazoprevir):
  - **3A4**: substrates (both)
  - **OATP:** grazoprevir substrate of OAT1B1/3
  - **P-gp:** substrates (both)
- Epclusa® (velpatasvir/sofosbuvir):
  - **P-gp:** substrates (both), velpatasvir inhibitor
  - **CYP3A4:** velpatasvir substrate
  - **BCRP:** sofosbuvir substrate, velpatasvir inhibitor
  - **OATP1B1**: velpatasvir inhibitor

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:
- AST 62, ALT 75, Platelets 135,000, INR 1.0
- 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?
  - Epclusa® (VEL/SOF) x 12 weeks
  - Harvoni® (LDV/SOF) x 8 weeks
  - Harvoni® (LDV/SOF) x 12 weeks
  - Epclusa® (VEL/SOF) x 8 weeks
  - 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?

Antacids and DAAs

- Epclusa® and Harvoni®
  - H2 Antagonist: simultaneously or 12 hours apart at a maximum equivalent to famotidine 40mg twice daily
  - Antacids: separate by 4 hours
- Proton pump inhibitors:
  - Harvoni®: administer **simultaneously under fasted conditions** at a maximum equivalent to pantoprazole 40mg
  - Epclusa®: administer VEL/SOF **4 hours before PPI** with food at a maximum equivalent to pantoprazole 40mg

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:
  - AST 35, ALT 65, Platelets 315,000
  - HCV RNA VL 12,500,000
  - GT 1a
  - Elastography consistent with F1-F2 fibrosis
  - Meds: Truvada® (tenofovir DF) + Prezista ® (darunavir) and Norvir ® (ritonavir), oxcarbazepine, quetiapine

Slide adapted from Cody Chastain, MD

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

Concomitant Medications	Daclatasvir	Ledipasvir	Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir	Simeprevir	Sofosbuvir	Elbasvir/ Grazoprevir	Velpatasvir
Acid-reducing agents*		X	X				X
Alfuzosin/tamsulosin			X				
Amiodarone	X	X	X	X	X		X
Anticonvulsants*	X	X	X	X	X	X	X
Antiretrovirals*	See HIV section	See HIV section	See HIV section	See HIV section	See HIV section	See HIV section	See HIV section
Azole antifungals*	X**		X	X		X	
Buprenorphine/naloxone			X				
Calcineurin inhibitors*			X	X		X	
Calcium channel blockers*	X		X	X		X	
Cisapride			X	X		X	
Digoxin	X	X		X		X	
Ergot derivatives			X				
Ethinyl estradiol–containing products			X				
Furosemide			X				
Gemfibrozil			X				
Glucocorticoids*	X		X (inhaled, intranasal)	X		X	
Herbals St. John's wort Milk thistle	X	X	X	X X	X	X X	X
HMG-CoA reductase inhibitors (statins)*	X	X	X	X		X	
Macrolide antimicrobials*	X**			X		X	
Other antiarrhythmics*			X	X		X	
Phosphodiesterase inhibitors*			X	X		X	
Pimozide			X				
Rifamycin antimicrobials*	X	X	X	X	X	X	X
Salmeterol			X				
Sedatives*			X	X		X	

*Some drug interactions are not class specific; see product prescribing information for specific drugs within a class.
**Requires a daclatasvir dose modification.

AASLD/IDSA Guidelines

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Questions?

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