



NEW YORK STATE
HCV PROVIDER
CLASSIFICATION TRAINING

A grayscale photograph of the New York City skyline, featuring the Empire State Building on the left and the Freedom Tower on the right. A large, semi-transparent red diagonal band runs from the top-left corner towards the bottom-right corner, partially obscuring the buildings and the sky. The sky is filled with soft, grey clouds.

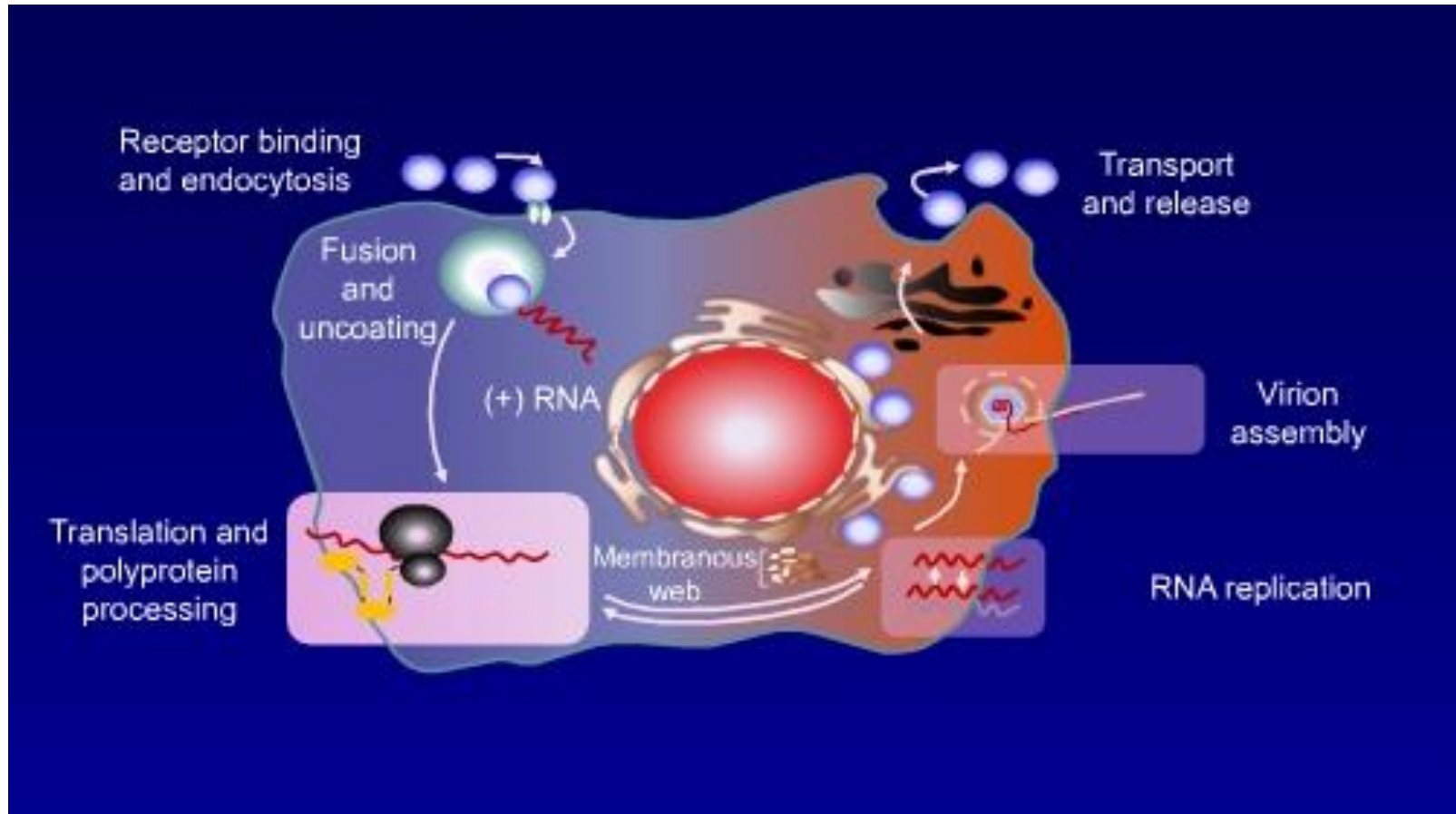
New York State HCV Provider Webinar Series

Drug-Drug Interactions Including PPIs

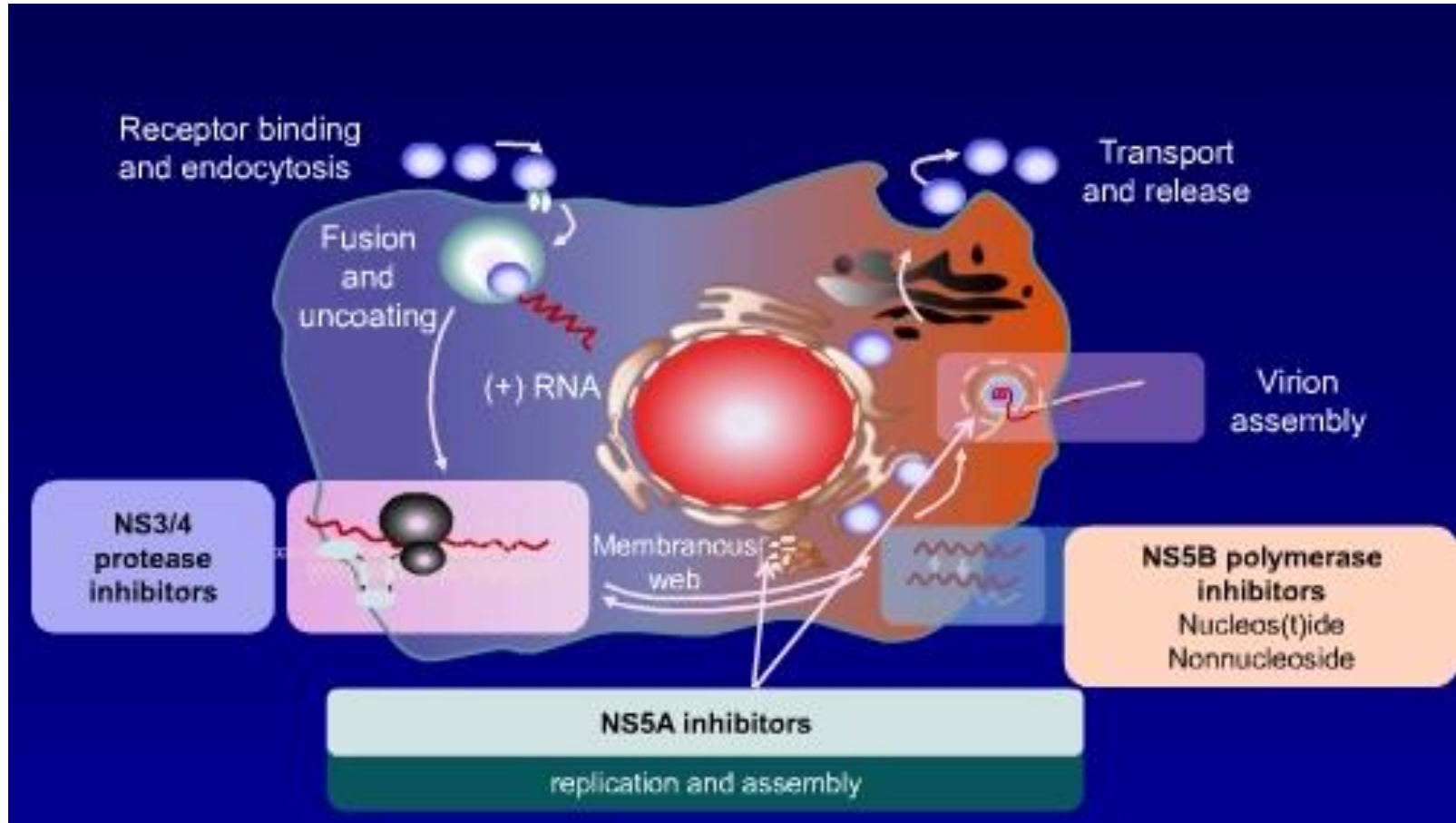
Objectives

- Review all currently approved HCV DAA regimens and the mechanism of action of each anti-HCV drug
- Detail each medication contraindicated with each HCV DAA regimen
- Describe each medication that needs monitoring with current DAA regimens given potential interactions
- Review medications that have no clinically significant interaction with current DAA regimens
- Briefly review drug-drug interactions of the HCV DAA medications with HIV anti-retrovirals

HCV Life Cycle and DAA Targets



HCV Life Cycle and DAA Targets



Classes of Medications Used for Treatment

NS3-4A Protease Inhibitors (“previr”)	NS5A Inhibitors (“asvir”)	NS5B Inhibitors: (“buvir”)		Other
		Nucleoside Analogues	Non-Nucleoside Analogues	
Grazoprevir	Daclatasvir	Sofosbuvir	Dasabuvir	Ribavirin
Paritaprevir	Elbasvir			
Simeprevir	Ledipasvir			
	Ombitasvir			
	Velpatasvir			

Combination Therapies	Trade Name
Grazoprevir/Elbasvir	Zepatier
Paritaprevir/Ombitasvir/Dasabuvir	Viekira XR
Sofosbuvir/Ledipasvir	Harvoni
Sofosbuvir/Velpatasvir	Epclusa

Currently Approved and Recommended Regimens

Genotype	Regimens
1	Paritaprevir/Ombitasvir/Dasabuvir ± RBV Grazeprevir/Elbasvir ± RBV Sofosbuvir/Ledipasvir, Sofosbuvir/Velpatasvir Sofosbuvir/Daclatasvir
2	Sofosbuvir/Velpatasvir, Sofosbuvir/Daclatasvir
3	Sofosbuvir/Velpatasvir, Sofosbuvir/Daclatasvir ± RBV
4	Sofosbuvir/Ledipasvir, Sofosbuvir/Velpatasvir Grazeprevir/Elbasvir ± RBV Paritaprevir/Ombitasvir + RBV
5	Sofosbuvir/Ledipasvir, Sofosbuvir/Velpatasvir
6	Sofosbuvir/Ledipasvir, Sofosbuvir/Velpatasvir

Medications Contraindicated with All Regimens

- P-glycoprotein inducers
 - St John's Wart, rifampin, rifabutin, rifapentine
- Anticonvulsants (strong cytochrome p450 [CYP] inducers)
 - Carbamazepine, oxcarbazepine, phenytoin (CYP3A4, CYP2C19), phenobarbital
 - Levetiracetam and gabapentin are okay—no DDI's

Sofosbuvir Drug-Drug Interactions

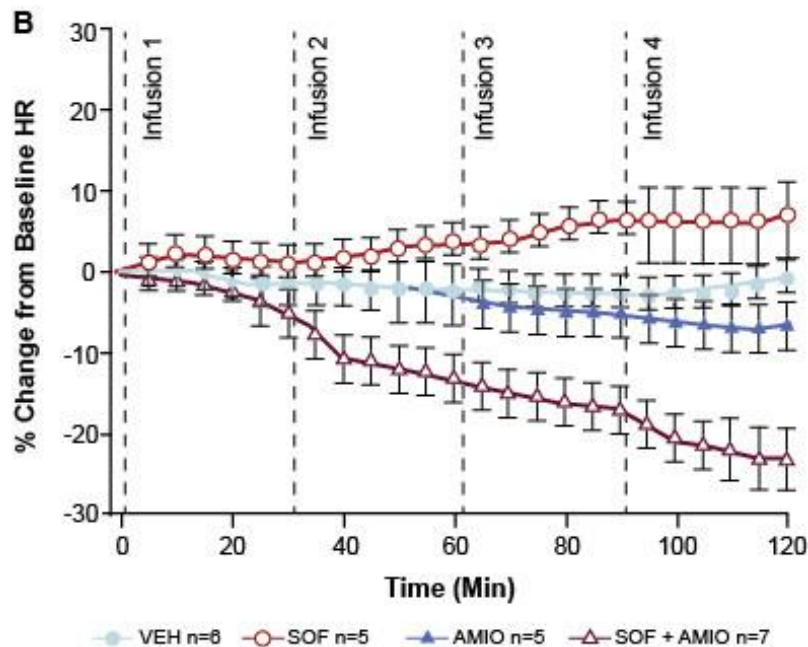
- With all sofosbuvir containing regimens including sofosbuvir alone, ledipasvir/sofosbuvir, and sofosbuvir/velpatasvir
- **Amiodarone**—causes severe symptomatic bradycardia (unclear effect on sofosbuvir concentrations)
- **Tipranivir/ritonavir**-decreases sofosbuvir concentrations

Sofosbuvir + Amiodarone = Bradycardia

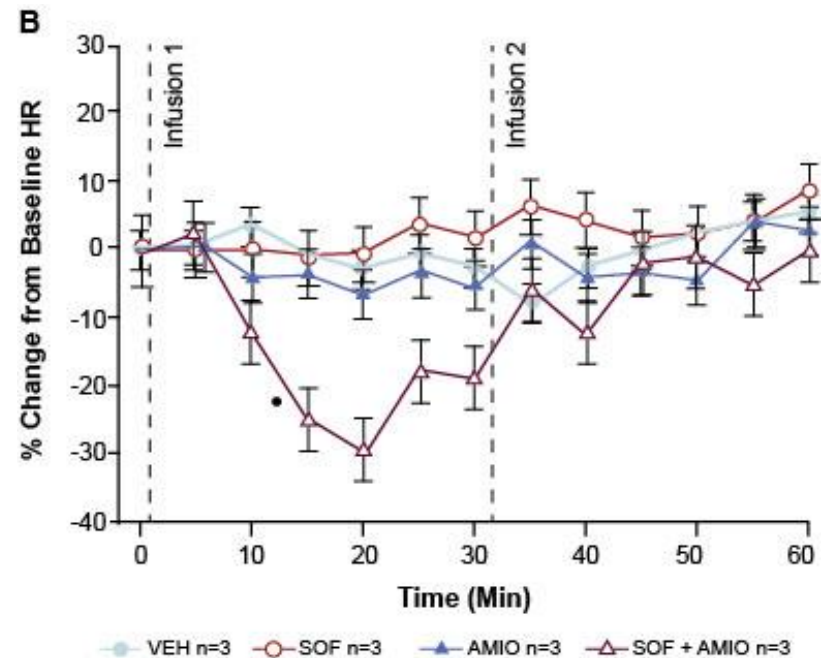
- Described by the French National Agency for Medicines and Health Products Safety in January 2015¹
 - 4 arrhythmias in 1337 patients from compassionate use of daclatasvir and sofosbuvir
- FDA warning issued about sofosbuvir plus another antiviral drug taken with amiodarone can cause serious slowing of the heart rate²
- NEJM November 2015, reported 3 cases of severe symptomatic bradycardia in patients receiving sofosbuvir (2 also had amiodarone exposure)³

Sofosbuvir + Amiodarone = Bradycardia

- Effect is reproducible in Guinea Pigs and Rhesus Monkeys



Guinea Pigs



Rhesus Monkeys

Ledipasvir/Sofosbuvir

- Ledipasvir: NS5a inhibitor
- Sofosbuvir: RNA dependent RNA polymerase inhibitor
- Ledipasvir and sofosbuvir are substrates of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP)

Ledipasvir/Sofosbuvir Drug Interactions

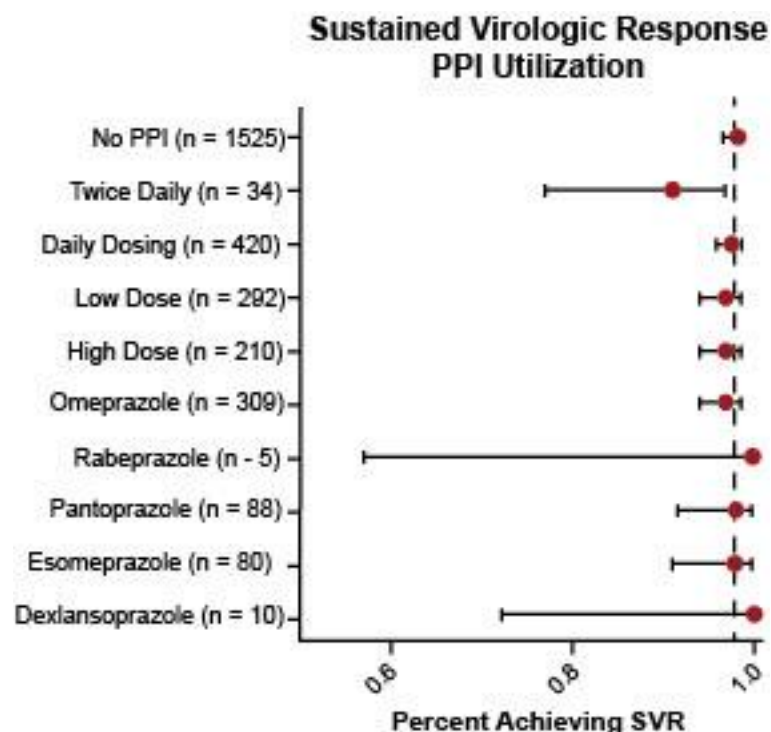
- **Rosuvastatin**—can increase concentration
- **Simeprevir**—increases concentrations of ledipasvir and simeprevir
- Co-formulated **elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate** (Stribild)—due to increased levels of tenofovir
 - Also other HIV regimens with TDF+ PI/ritonavir
 - Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) is safe
- **Digoxin**—can increase digoxin levels, need to monitor levels

Ledipasvir/Sofosbuvir and Acid Suppressors

- Recommendation is no more than **20 mg omeprazole** daily due to reduced levels of ledipasvir
- H2 blockers such as **ranitidine or famotidine** can be taken simultaneously or 12 hours apart, at doses not exceeding 40 mg famotidine twice daily
- **Antacids** (such as aluminum and magnesium hydroxide) must be separated from ledipasvir/sofosbuvir by 4 hours

Real World Data of PPI and LED/SOF

- Published Dec 2016 in Hepatology
- Data collection through Trio Health's Innervation Platform
- 1,566 patients had no PPI vs 468 who had a PPI
 - SVR (ITT analysis): 95.6% w/o PPI vs 94.2% with PPI
 - Completion rate: 98.2% w/o PPI vs 97.1% with PPI
 - Daily PPI (n=410) SVR12 97.8%
 - BID PPI (n=24) SVR12 91.1%



Agents with **No Clinically Significant Interaction** with **Ledipasvir/Sofosbuvir**

- **Antiretrovirals:** Abacavir, atazanavir/ritonavir, darunavir/ritonavir, dolutegravir, efavirenz, emtricitabine, lamivudine, raltegravir, rilpivirine, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
- **Immunosuppressants:** Cyclosporine, tacrolimus
- **Opioids:** Methadone
- **Oral contraceptives:** Including ethinyl estradiol
- **HMG-CoA Reductase inhibitors:** Pravastatin
- **Calcium-channel blockers:** Verapamil

Sofosbuvir/Velpatasvir Drug Interactions

- Drugs that are inducers of P-glycoprotein (P-gp) and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 may decrease plasma concentrations of sofosbuvir and/or velpatasvir
- Velpatasvir is an inhibitor of drug transporters P-gp, BCRP (breast cancer resistance protein), Organic anion transporting polypeptides (OATP) 1B1/3, and OATP2B1
 - Coadministration of velpatasvir with drugs that are substrates of these transporters may increase exposure of such drugs

Sofosbuvir/Velpatasvir Drug Interactions

- **Efavirenz**— Decreases Velpatasvir (CYP3A4, CYP2B6)
- **Topotecan**—Increases topotecan levels (CYP3A4)
 - Binds to topoisomerase I-DNA complexes preventing religation of single-strand breaks (blocks mitosis)
 - Used for treatment of many cancers
- **Tenofovir disoproxil fumarate**—monitor for increased tenofovir levels
- **Rosuvastatin** and **atorvastatin**—can increase levels of statin
- **Digoxin**—can increase digoxin levels, need to monitor levels

Sofosbuvir/Velpatasvir and Acid Suppression

- Co-administration of **omeprazole** or other **proton-pump inhibitors** is not recommended. If medically necessary, sofosbuvir/velpatasvir should be taken with food and 4 hours prior to omeprazole 20 mg. Use with other PPI's has not been studied
- H2 blockers such as **ranitidine** or **famotidine** can be taken simultaneously or 12 hours apart, at doses not exceeding 40 mg famotidine twice daily
- **Antacids** (such as aluminum and magnesium hydroxide) must be separated from sofosbuvir/velpatasvir by 4 hours

Agents with No Clinically Significant Interaction with Sofosbuvir/Velpatasvir

- **Antiretrovirals:** Atazanavir/ritonavir, darunavir/ritonavir, dolutegravir, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, raltegravir, or rilpivirine
- **Immunosuppressants:** Cyclosporine, tacrolimus
- **Oral Contraceptives:** Ethinyl estradiol/norgestimate
- **Opioids:** Methadone
- **Antifungals:** Ketoconazole
- **HMG-CoA Reductase Inhibitors:** Pravastatin

Elbasvir/Grazoprevir Drug Interactions

- Does not contain any sofosbuvir in the regimen
- In some instances will be used with ribavirin
- Grazoprevir (GZR)—protease inhibitor
- Elbasvir (EBR)—NS5A inhibitor
- Contraindicated with OATP 1B1/3 inhibitors and strong inducers of CYP3A

Elbasvir/Grazoprevir Contraindicated Drugs

Drug Class	Drugs Class Examples	Clinical Effects
Anticonvulsants	Phenytoin, carbamazepine	↓ EBR/GZR (CYP3A induction)
Antimycobacterials	Rifampin	↓ EBR/GZR (CYP3A induction)
Herbal Products	St John's Wort	↓ EBR/GZR (CYP3A induction)
HIV Medications	Efavirenz	↓ EBR/GZR (CYP3A induction)
HIV Medications	Atazanavir, darunavir, lopinavir, saquinavir, tipranavir	↑ GZR by OATP1B1/3 inhibition
Immunosuppressants	Cyclosporine	↑ GZR by OATP1B1/3 inhibition

Elbasvir/Grazoprevir Drug Interactions

- **Nafcillin**—decreases EBR/GZR (CYP3A inducer)
- **Ketoconazole**—increases EBR/GZR → increased risk hepatotoxicity
- **Bosentan**—decreases EBR/GZR (CYP3A inducer)
- **Tacrolimus**—increases tacrolimus concentrations
 - Need to monitor levels

Elbasvir/Grazoprevir HIV Drug Interactions

- **Efavirenz**—CYP3A induction reduces EBR/GZR concentrations
- **Etravirine**—CYP3A induction reduces EBR/GZR concentrations
- **Elvitegravir/cobicistat/emtricitabine/tenofovir (both disoproxil fumarate and alafenamide)**
 - Both Stribild and Genvoya
 - Cobicistat increases EBR/GZR concentrations

Elbasvir/Grazoprevir Drug Interactions

- HMG-CoA Reductase Inhibitors
 - **Atorvastatin**—do not exceed 20 mg daily
 - **Rosuvastatin**—do not exceed 10 mg daily
 - **Fluvastatin, lovastatin, and simvastatin**—not studied but interaction likely increases concentrations of these statins
- **Modafinil**—decreases EBR/GZR concentrations (CYP3A inducer)

Agents with No Clinically Significant Interaction with Elbasvir/Grazoprevir

- Acid reducing agents: PPI's, H2 blockers, antacids
- Opioids: buprenorphine/naloxone, methadone
- Antiretrovirals: dolutegravir, raltegravir, rilpivirine, tenofovir disoproxil fumarate, abacavir, emtricitabine, lamivudine
- Digoxin
- Immunosuppressants: mycophenolate mofetil, prednisone
- Oral contraceptive pills
- Phosphate binders
- HMG-CoA reductase inhibitors: pitavastatin, pravastatin
- Antivirals: ribavirin, sofosbuvir, entecavir

Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir (PrOD) Drug Interactions

- Combination of ritonavir with a protease, NS5A inhibitor, and a non-nucleotide NS5B palm polymerase inhibitor
- If treating Genotype 1a, will also use ribavirin
- Contraindicated with drugs highly dependent on CYP3A for clearance
- Contraindicated with strong inducers of CYP3A and CYP2C8 → reduced drug levels of PrOD
- Strong inhibitors of CYP2C8 will increase dasabuvir concentrations and can cause QT prolongation

Drugs Contraindicated with PrOD

Drug Class	Drug Examples	Effects
Alpha1 antagonist	Alfuzosin HCL	Hypotension
Antihyperlipidemic	gemfibrozil	Increase dasabuvir dose → QT prolongation
Ergot derivatives	Ergotamine, methylergonovine, dihydroergotamine	Acute ergot toxicity-vasospasm and ischemia
Oral contraceptives	Ethinyl estradiol containing	ALT elevations (hepatotoxicity)
HMG-CoA reductase inhibitors	Lovastatin, simvastatin	Potential for myopathy
Antipsychotics	Pimozide, Lurasidone	Cardiac arrhythmias, life-threatening reactions
Antiretrovirals	Efavirenz	Hepatotoxicity
PDE5 inhibitor	Sildenafil (Revatio)	Increased sildenafil toxicities

Drugs Contraindicated with PrOD Continued

Drug Class	Drug Examples	Effects
Anti-anginal	Ranolazine	Possible life-threatening reactions
Anti-gout	Colchicine	Possible serious reactions in patients with renal and/or hepatic impairment
GI motility	Cisapride	Possible cardiac arrhythmias
Sedatives	Triazolam and oral midazolam	Increased sedation (CYP3A4)

PrOD Drug Interactions

- Antiarrhythmics: monitor for increased doses of CV med
 - Amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine
- Antifungals:
 - Ketoconazole: maximum dose 200 mg/day
 - Voriconazole: not recommended, decreases dose of voriconazole
- Calcium Channel Blockers: can increase levels of CCB
 - Amlodipine, nifedipine, diltiazem, verapamil
- Corticosteroids
 - Fluticasone: inhaled or nasal spray not recommended

PrOD Drug Interactions Continued

- Diuretics:
 - **Furosemide**: can have increased furosemide levels
- Antiretrovirals
 - Other Ritonavir containing medications not recommended (such as **atazanavir/ritonavir**, **darunavir/ritonavir**, and **lopinavir/ritonavir**), also **rilpivirine**
- HMG-CoA Reductase Inhibitors:
 - **Rosuvastatin**: maximum dose 10 mg/day
 - **Pravastatin**: maximum dose 40 mg/day
- Immunosuppressants:
 - **Cyclosporine** and **tacrolimus**: will need to dose reduce calcineurins, monitor levels closely

PrOD Drug Interactions Continued

- Long Acting Beta-agonists
 - **Salmeterol**: not recommended due to potential cardiac events
- Narcotic analgesics
 - **Buprenorphine/naloxone**: monitor for sedation
 - Acetaminophen/**hydrocodone**: decrease hydrocodone and monitor for sedation
- Proton Pump Inhibitors
 - May need to increase **PPI** dose
- Sedatives
 - **Alprazolam**: increased alprazolam levels
 - **Diazepam**: decreased diazepam levels

PrOD Drug Interactions Continued

- Angiotensin Receptor Blockers: can increase ARB levels
 - **Valsartan, losartan, candesartan**
- Antidiabetic drugs
 - **Metformin**: monitor for signs lactic acidosis
- Antipsychotic
 - **Quetiapine**: increases quetiapine levels, consider alternative HCV therapy or will need to give 1/6 quetiapine dose
- Muscle relaxants
 - **Carisoprodol** and **cyclobenzaprine**: may need to increase dose

Agents with No Clinically Significant Interaction with PrOD

- CV: digoxin and warfarin
- Antiretrovirals: emtricitabine/tenofovir disoproxil fumarate and raltegravir, abacavir, dolutegravir, lamivudine
- Antidepressants: duloxetine, escitalopram
- Opioids: methadone
- Oral contraceptives: progesterone only containing
- Sedatives: zolpidem
- Antivirals: sofosbuvir

Ribavirin Drug Interactions

- Contraindicated: **Didanosine**
 - Risk of hepatic failure, peripheral neuropathy, pancreatitis, lactic acidosis
- Serious, or use alternative
 - **Abacavir**: increases abacavir toxicity, risk of lactic acidosis
 - **Stavudine** and **zidovudine**: competition for thymidine kinase; decreases levels
- Monitor closely
 - **Emtricitabine** and **lamivudine**: increased drug levels, risk lactic acidosis
 - **Inhaled tobramycin**: increase nephrotoxicity and/or ototoxicity
- **Warfarin**: ribavirin can decrease effects of warfarin
- Also is **teratogenic** with pregnancy, must avoid for 6 months after taking

Daclatasvir Drug Interactions

- Only approved stand-alone NS5a inhibitor
- Undergoes CYP3A4 metabolism
- Inhibitor of P-gp, OATP 1B1/3, and BCRP
- Drugs that are contraindicated are the same listed previously (strong CYP3a inducers)
 - **Phenytoin, carbamazepine, rifampin, St John's wort**

Daclatasvir Drug Interactions

- Strong CYP3A inhibitors: increase daclatasvir levels, need to reduce dose to 30 mg once daily
 - Clarithromycin, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, voriconazole
 - HIV protease inhibitors: Atazanavir with ritonavir, indinavir, nelfinavir, saquinavir
 - HIV **cobicistat** containing regimens
- Moderate CYP3a inducers: decrease daclatasvir levels, need to increase dose to 90 mg once daily
 - Bosentan, dexamethasone, modafinil, nafcillin, rifapentine

Daclatasvir Drug Interactions

- Anticoagulants: **dabigatran** etexilate mesylate
 - Increases dabigatran levels
- **Digoxin**: can increase digoxin levels, need to monitor and dose reduce
- HMG-CoA reductase inhibitors: increase levels and risk for myopathy
 - Atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin
- Narcotic analgesic: need to monitor
 - **Buprenorphine ± naloxone**—can increase buprenorphine levels

Agents with No Clinically Significant Interaction with Daclatasvir

- Acid reducing agents: famotidine, omeprazole
- Opioids/sedatives: methadone, midazolam
- Antiretrovirals: dolutegravir, darunavir (with ritonavir or cobicistat), lopinavir (with ritonavir), tenofovir, atazanavir, fosamprenavir
- Immunosuppressants: cyclosporine, tacrolimus
- Antidepressants: escitalopram
- Oral contraceptive pills: ethinyl estradiol/norgestimate
- Antivirals: ribavirin, sofosbuvir
- Antimicrobials: ciprofloxacin, erythromycin, fluconazole
- Calcium channel blockers: diltiazem, verapamil

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www.hiv-druginteractions.org

A comprehensive HIV drug-drug interaction resource, freely available to healthcare workers, patients and researchers. The site is also available in a low graphics version - www.hiv-druginteractionslite.org.

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[German Liver Foundation](#)

[Deutsche Leberstiftung Deutschen Leberstiftung](#)

HCV-trials.com

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HEP iChart – NEW VERSION AVAILABLE

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A new version of the interaction app for mobile devices is now available. The new app includes tablet support for Android devices and is fully compatible with the latest versions of iOS.

Please delete the existing app from your device and download the new version from the App Store or Google Play (search for **HEP iChart**).

This is an "offline" app that is downloaded to your device. An internet connection is not required to use the app, but is needed for downloading updates.

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HCV DAA and Antiretroviral DDI's

		SOF	SOF/LDV	SOF/VEL	3D	GZR/EBR	DCV	SIM
NRTIs	Abacavir	◆	◆	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆	◆	◆
	Tenofovir	◆	■	■	◆	◆	◆	◆
NNRTIs	Efavirenz	◆	■*	●	●	●	■	●
	Etravirine	◆	◆	●	●	●	■	●
	Nevirapine	◆	◆	●	●	●	■	●
	Rilpivirine	◆	◆*	◆*	■	◆	◆	◆
Protease inhibitors	Atazanavir; atazanavir/r; atazanavir/cobicistat	◆	◆*	◆*	■*	●	■	●
	Darunavir/r; darunavir/cobicistat	◆	◆*	◆*	■*	●	◆	●
	Lopinavir/r	◆	◆*	◆*	●	●	◆	●
Entry/Integrase inhibitors	Dolutegravir	◆	◆	◆	◆	◆	◆	◆
	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	◆	■*	■*	●	●	■	●
	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	◆	◆	◆	●	●	■	●
	Maraviroc	◆	◆	◆	■	◆	◆	◆
	Raltegravir	◆	◆	◆	◆	◆	◆	◆

- ◆ No clinically significant interaction expected.
- Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring.
- These drugs should not be co-administered.

SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; SOF/VEL, sofosbuvir plus velpatasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir; grazoprevir plus elbasvir; DCV, daclatasvir; SIM, simeprevir; r, ritonavir.

EASL Recommendations: *Journal of Hepatology*. 2016.

Summary

- St John's Wart, rifampin, carbamazepine, phenytoin, and oxcarbazepine are not safe to use with any HCV regimen
- Amiodarone has a significant interaction with sofosbuvir causing symptomatic bradycardia
- Each HCV regimen has unique drug-drug interactions and a careful review of each patient's medical history and medication list is essential prior to initiating HCV therapy
- It is essential to consult the package insert or the Liverpool website for potential drug interactions
- Withhold any vitamins/herbal supplements and statins during HCV treatment