

# Clinically Relevant Drug Interactions with Direct Acting Antivirals (DAAs)

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# Disclosures

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# Objectives

- Describe basic pharmacokinetic properties of DAAs
- Identify clinically important interactions between the DAAs and
  - Antiretroviral medications
  - Non-HIV medications
- Apply outcomes from drug interaction tools to patient care to modify treatment of HCV or HIV

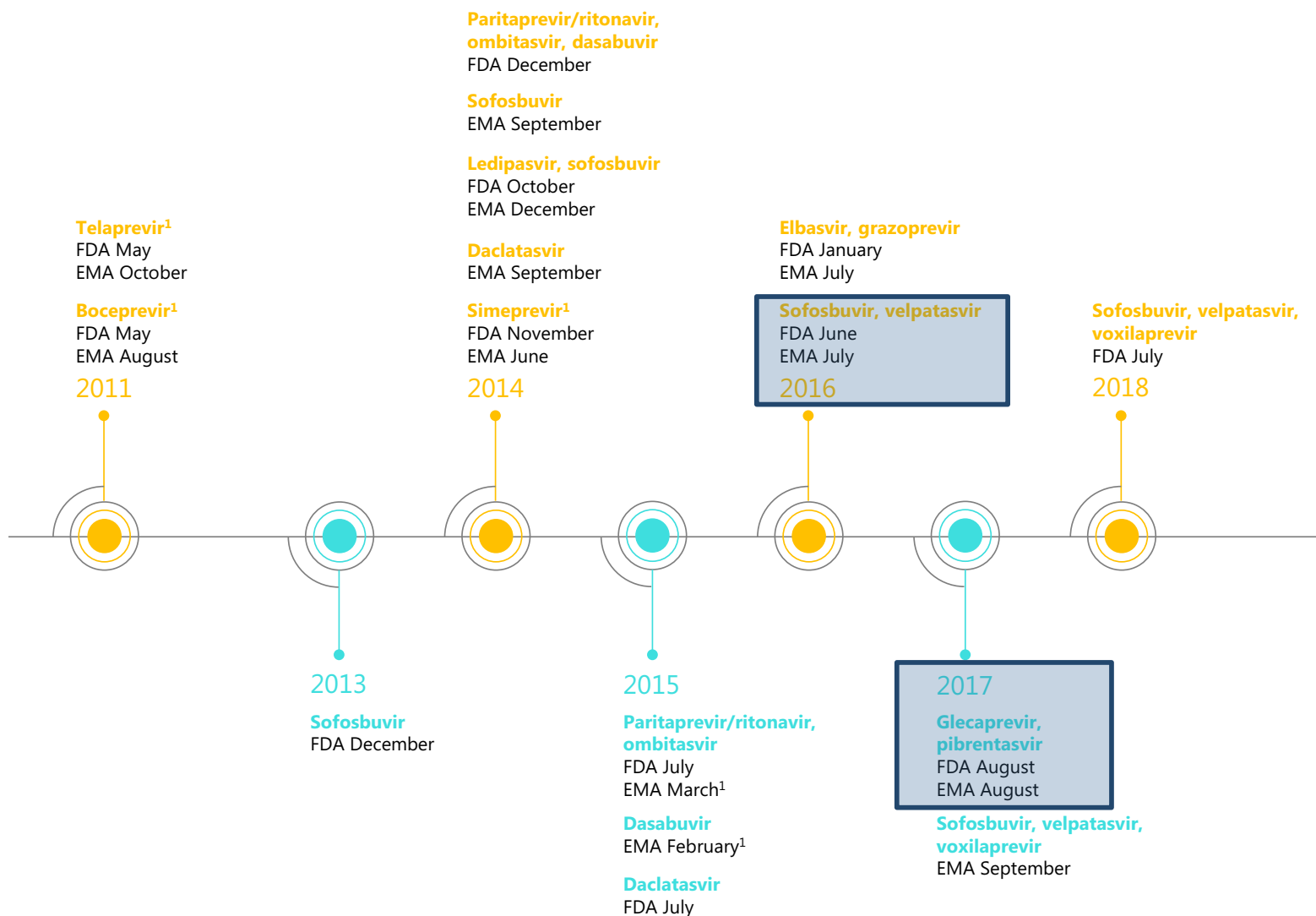
# CASE 1

- TC is a 50-year-old male newly diagnosed with HIV (pan-sensitive genotype, CD4 count 350 cells/mm<sup>3</sup> and VL 50,000). Hepatitis serologies are:
  - HCV Ab positive – GT3 / VL 4,000,000
  - Hepatitis B surface Ab positive / core negative
  - Hepatitis A total Ab positive
- Kidney function is normal, other labs do not indicate the patient has cirrhosis.

# CASE 1

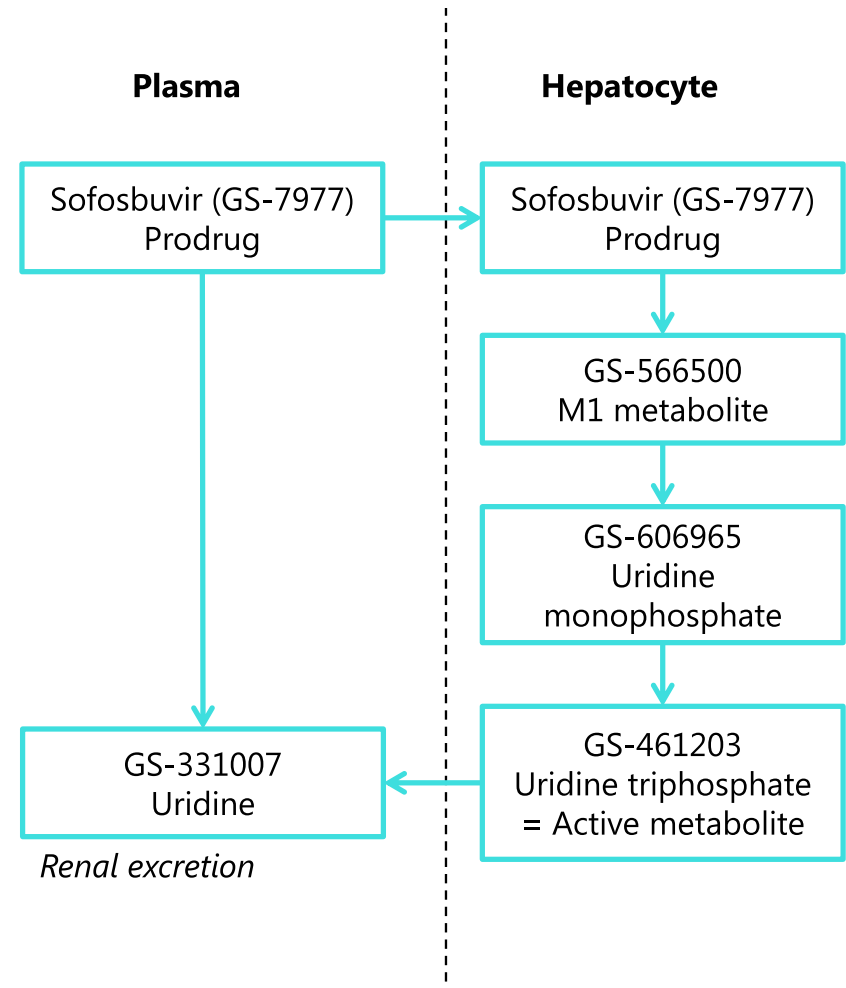
- Keeping in mind you want to treat the HCV in the next 6-12 months, what ART would you select?
  - A. Dolutegravir (Tivicay®) + Emtricitabine/Tenofovir DF (Truvada®)
  - B. Bictegravir/Emtricitabine/Tenofovir AF (Biktarvy®)
  - C. Dolutegravir/Lamivudine (Dovato®)
  - D. Darunavir/Cobicistat/ Emtricitabine/Tenofovir alafenamide (Symtuza®)

# Basic PK Properties of DAAs



# Pharmacokinetics

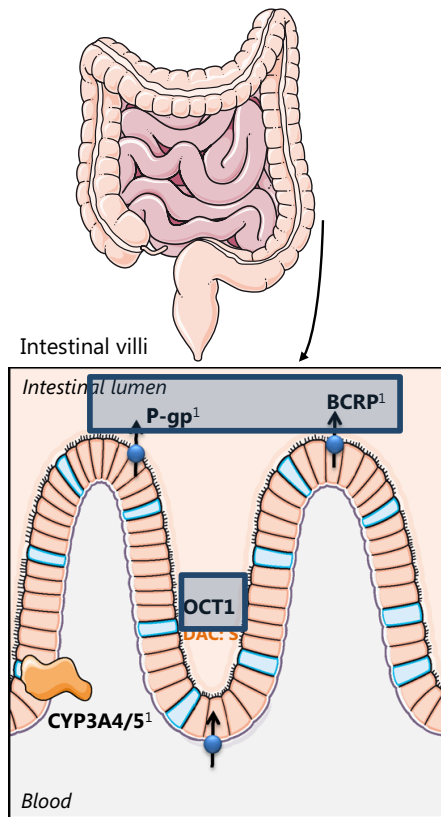
- SOF/VEL (Epclusa®)
  - Absorption
    - VEL has a **pH dependent solubility**
  - Metabolism
    - SOF: Substrate for PgP
    - VEL: **substrate for CYP3A4 (major)**, 2B6 and 2C8
- GLE/PIB (Mavyret®)
  - Absorption
    - Food enhances absorption
  - Metabolism
    - GLE: **substrate for CYP3A4**



# Deep Dive

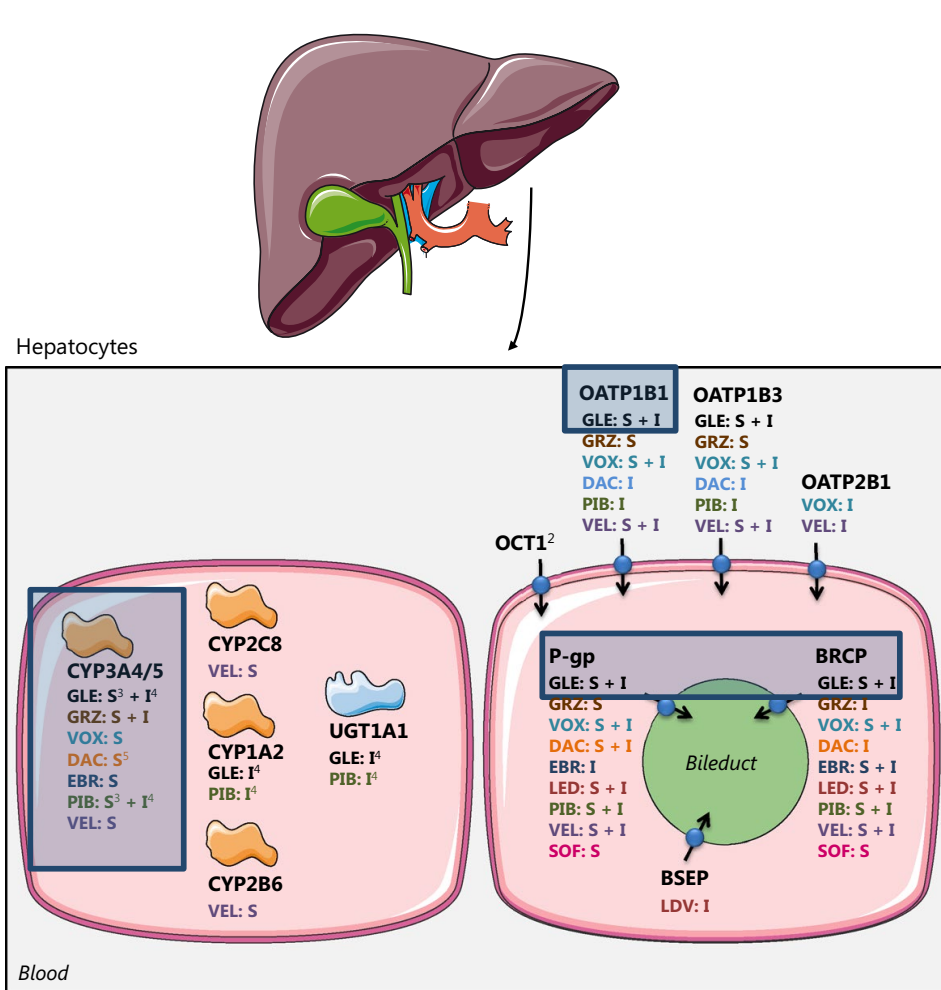
## Absorption

GLE, GRZ, VOX, DAC, EBR, LED, PIB, VEL, SOF



## Hepatic uptake, metabolism, and biliary excretion

GLE, GRZ, VOX, DAC, EBR, LED, PIB, VEL



# DAA and ARV Interactions

# CASE 2

- MT is a 60-year-old male well controlled on a salvage regimen of darunavir/cobicistat (Prezcobix) + Bictegravir/Emtricitabine/Tenofovir AF (Biktarvy®) and needs to be treated for GT 1 (naïve without cirrhosis). Which of the following would be the best treatment option for this patient?
  - A. Glecaprevir/Pibrentasvir (Mavyret®)
  - B. Sofosbuvir/Velpatasvir (Epclusa)
  - C. Something else

# Navigating Interactions

The screenshot shows the homepage of the HEP Drug Interactions website. At the top, there is a dark red header with the logo and name 'HEP Drug Interactions' on the left, the 'UNIVERSITY OF LIVERPOOL' logo in the center, and navigation links for 'Interaction Checker' and 'Apps' on the right. Below the header is a secondary red bar with a list of navigation links: 'About Us', 'Interaction Checkers', 'Prescribing Resources', 'Videos', 'Site News', 'Contact Us', and 'Support Us'. A white banner below this bar contains the text: 'New HCC primaries: Lenvatinib and Sorafenib. New prescribing resource: Antipsychotics & Neuroleptics.' The main content area features a large blue arrow pointing to the 'Interaction Checker' section, which includes the text: 'Access our free, comprehensive and user-friendly drug interaction charts'. Below this are six white boxes arranged in a 2x3 grid, each containing a different resource: 'Educational Videos', 'Prescribing Resources', 'Twitter', 'Mobile Apps', 'HIV Website', and 'Cancer Website'. Each box includes a brief description and a corresponding logo or icon.

HEP Drug Interactions

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Interaction Checker →

Apps ↓

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New HCC primaries: Lenvatinib and Sorafenib. New prescribing resource: Antipsychotics & Neuroleptics.

## Interaction Checker

Access our free, comprehensive and user-friendly drug interaction charts

### Educational Videos

A series of mini-lectures on topics including pharmacology, hepatitis and drug-drug interactions

### Prescribing Resources

Interaction tables, treatment selectors, clinical prescribing resources, and pharmacokinetic fact sheets

### Twitter

@hepinteractions

Follow us on Twitter for interaction news and for the latest additions and changes to the website

### Mobile Apps

Available on the App Store

ANDROID APP ON Google play

### HIV Website

HIV Drug Interactions

### Cancer Website

Cancer Drug Interactions

# Navigating Interactions

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Apps ↓


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New HCC primaries: Lenvatinib and Sorafenib. New prescribing resource: Antipsychotics & Neuroleptics.

Having trouble viewing the interactions? [Click here for the Interaction Checker Lite.](#)

HEP Drugs	Co-medications	Drug Interactions
<input type="text" value="Search HEP drugs..."/>	<input type="text" value="Search co-medications..."/>	<input type="text" value="Check HEP/HEP drug interactions"/>
<input checked="" type="radio"/> A-Z <input type="radio"/> Indication <input type="radio"/> Trade	<input checked="" type="radio"/> A-Z <input type="radio"/> Class	Drug interactions will be displayed here
Selected HEP Drugs will be displayed here.	Selected Co-medications will be displayed here.	
<input type="checkbox"/> Adefovir <input type="button" value="i"/>	<input type="checkbox"/> Abacavir <input type="button" value="i"/>	
<input type="checkbox"/> Daclatasvir <input type="button" value="i"/>	<input type="checkbox"/> Abiraterone <input type="button" value="i"/>	
<input type="checkbox"/> Elbasvir/Grazoprevir <input type="button" value="i"/>	<input type="checkbox"/> Acalabrutinib <input type="button" value="i"/>	
<input type="checkbox"/> Entecavir <input type="button" value="i"/>	<input type="checkbox"/> Acamprosate <input type="button" value="i"/>	
<input type="checkbox"/> Glecaprevir/Pibrentasvir <input type="button" value="i"/>	<input type="checkbox"/> Acarbose <input type="button" value="i"/>	
<input type="checkbox"/> Lamivudine (HBV) <input type="button" value="i"/>	<input type="checkbox"/> Acebutolol <input type="button" value="i"/>	
<input type="checkbox"/> Ledipasvir/Sofosbuvir <input type="button" value="i"/>	<input type="checkbox"/> Aceclofenac <input type="button" value="i"/>	

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HEP Drugs	Co-medications	Drug Interactions
<input type="text" value="gle"/>	<input type="text" value="bic"/>	<input type="checkbox"/> Check HEP/HEP drug interactions
<a href="#">Switch to table view</a>		
<a href="#">Reset Checker</a>		
<input checked="" type="radio"/> A-Z <input type="radio"/> Indication <input type="radio"/> Trade	<input checked="" type="radio"/> A-Z <input type="radio"/> Class	<b>Do Not Coadminister</b>
<input checked="" type="checkbox"/> Glecaprevir/Pibrentasvir ⓘ	<input checked="" type="checkbox"/> Darunavir/cobicistat ⓘ	Glecaprevir/Pibrentasvir
<input checked="" type="checkbox"/> Glecaprevir/Pibrentasvir ⓘ	<input checked="" type="checkbox"/> Bictegravir/ Emtricitabine/Tenofovir alafenamide (BIC/FTC/TAF) ⓘ	Darunavir/cobicistat
	<input checked="" type="checkbox"/> Bictegravir/ Emtricitabine/Tenofovir alafenamide (BIC/FTC/TAF) ⓘ	<a href="#">Look for alternatives</a> →
		<a href="#">More Info</a> ↓
		<b>Potential Weak Interaction</b>
		Glecaprevir/Pibrentasvir
		Bictegravir/ Emtricitabine/Tenofovir alafenamide (BIC/FTC/TAF)



# Navigating Interactions

**Do Not Coadminister**

Glecaprevir/Pibrentasvir


Darunavir/cobicistat

**Summary:**  
Coadministration with darunavir/cobicistat has not been studied and is not recommended as it may substantially increase glecaprevir exposure. Medicinal products that inhibit OATP1B1/3 (e.g. darunavir) increase systemic concentrations of glecaprevir. Coadministration of darunavir/ritonavir (800/100 mg) increased glecaprevir AUC, C<sub>max</sub> and C<sub>min</sub> by 4.97-fold, 3.09-fold and 8.24-fold, respectively. A similar interaction may occur with darunavir/cobicistat.

**Description:**  
Medicinal products that inhibit OATP1B1/3 (e.g. darunavir) increase systemic concentrations of glecaprevir. Coadministration of darunavir/ritonavir (800/100 mg once daily) and glecaprevir/pibrentasvir increased glecaprevir C<sub>max</sub>, AUC and C<sub>min</sub> by 3.09-fold, 4.97-fold and 8.24-fold, respectively. There was no change in pibrentasvir C<sub>max</sub> or AUC, but C<sub>min</sub> increased by 66%. Co-administration with darunavir is not recommended. Co-administration of Maviret with medicinal products that inhibit P-gp and BCRP (e.g. cobicistat) may slow elimination of glecaprevir and pibrentasvir and thereby increase plasma exposure of the antivirals. Coadministration of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide with glecaprevir/pibrentasvir was studied. Glecaprevir C<sub>max</sub>, AUC and C<sub>min</sub> increased by 150%, 205% and 358%, respectively. Pibrentasvir C<sub>max</sub> was unchanged but AUC and C<sub>min</sub> increased by 57% and 89%, respectively. The mechanism is P-gp, BCRP and OATP inhibition by cobicistat and OATP inhibition by elvitegravir. *Maviret Summary of Product Characteristics, AbbVie Ltd., April 2019.*

Coadministration of darunavir/ritonavir (800/100 mg once daily) and glecaprevir/pibrentasvir (300/120 mg once daily) was studied in 8 subjects. Glecaprevir C<sub>max</sub>, AUC and C<sub>min</sub> increased by 3.09-fold, 4.97-fold and 8.24-fold, respectively. There was no change in pibrentasvir C<sub>max</sub> or AUC, but C<sub>min</sub> increased by 66%. Darunavir C<sub>max</sub> and AUC increased by 30% and 29%, but there was no change in C<sub>min</sub>. Ritonavir C<sub>max</sub> and AUC increased by 103% and 87%, but there was no change in C<sub>min</sub>. Coadministration is not

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<input type="text" value="sof"/>	<input type="text" value="bic"/>	<input type="checkbox"/> Check HEP/HEP drug interactions
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<input checked="" type="radio"/> A-Z <input type="radio"/> Indication <input type="radio"/> Trade	<input checked="" type="radio"/> A-Z <input type="radio"/> Class	<input type="button" value="Reset Checker"/>
<input checked="" type="checkbox"/> Sofosbuvir/Velpatasvir <input type="button" value="i"/>	<input checked="" type="checkbox"/> Darunavir/cobicistat <input type="button" value="i"/>	<input type="button" value="No Interaction Expected"/>
<input type="checkbox"/> Sofosbuvir <input type="button" value="i"/>	<input checked="" type="checkbox"/> Bictegravir/ Emtricitabine/Tenofovir alafenamide (BIC/FTC/TAF) <input type="button" value="i"/>	Sofosbuvir/Velpatasvir
<input checked="" type="checkbox"/> Sofosbuvir/Velpatasvir <input type="button" value="i"/>	<input type="checkbox"/> Bictegravir/ Emtricitabine/Tenofovir alafenamide (BIC/FTC/TAF) <input type="button" value="i"/>	Bictegravir/ Emtricitabine/Tenofovir alafenamide (BIC/FTC/TAF)
<input type="checkbox"/> Sofosbuvir/Velpatasvir /Voxilaprevir <input type="button" value="i"/>		<input type="button" value="More Info"/> ↓
		<input type="button" value="No Interaction Expected"/>
		Sofosbuvir/Velpatasvir
		Darunavir/cobicistat
		<input type="button" value="More Info"/> ↓

# DAA and ARV Interactions

DAA	Avoid/Not Recommended	Use with caution or adjust dose/timing
<b>Glecaprevir/pibrentasvir</b>	Efavirenz and etravirine (decrease G/P) Boosted atazanavir and darunavir (increase G/P)	
<b>Sofosbuvir</b>	Tipranavir/ritonavir (decrease SOF through PgP)	
<b>Velpatasvir</b>	Efavirenz, etravirine, tipranavir/ritonavir (decrease VEL)	Avoid TDF if possible (increases TDF), especially with ritonavir or cobicistat (TAF ok)

# **DAA's and Non-ARV Interactions**

# CASE 3

- MH is a 35-year-old female with HIV and well controlled on Bictegravir/Emtricitabine/Tenofovir AF (Biktarvy®). She takes EE/Levonorgestrel (various) and omeprazole 40 QD for control of her Barrett's Esophagus and you are considering treating her HCV with either G/P or SOF/VEL. Which of the following interactions would be the most significant?
  - A. Increase in EE levels from G/P
  - B. Decrease in SOF levels from omeprazole
  - C. Decrease in Glecaprevir levels from omeprazole
  - D. Increase in EE levels from SOF/VEL

Drug Class	Glecaprevir/Pibrentasvir (Mavryet®)	Sofosbuvir/Velpatasvir (Epclusa)
Acid Reducing Agents	No interaction	VEL solubility decreases as pH increase <ul style="list-style-type: none"> <li>Separate antacids by 4 hours</li> <li>Administer with H2RA OR separate by 12 hours (~40mg famotidine BID)</li> <li><b>Not recommended with PPIs</b></li> </ul>
Amiodarone	Use with caution	Significant bradycardia
<u>Anticonvulsants:</u> Carbamazepine, phenytoin, PHB	↓ <b>G/P (not recommended)</b>	↓ <b>SOF/VEL (not recommended)</b>
<u>Antimycobacterial:</u> Rifabutin, rifampin, rifapentine	↓ <b>G/P (not recommended)</b>	↓ <b>SOF/VEL (not recommended)</b>
Statins	↑ <b>Lovastatin (Avoid)</b> ↑ <b>Simvastatin (Avoid)</b> ↑ <b>Atorvastatin (Avoid)</b> ↑ Rosuvastatin (10 mg max) ↑ Pravastatin (↓ dose 50%) ↑ Pitavastatin (Lowest dose) ↑ Fluvastatin (Lowest dose)	↑ Rosuvastatin (10 mg max) ↑ Atorvastatin (monitor)
Oral Contraceptives	↑ EE levels (avoid or monitor LFTs)	
St Johns Wort	↓ <b>G/P (not recommended)</b>	↓ <b>SOF/VEL (not recommended)</b>



# Acknowledgment

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