

Clinically Relevant Drug Interactions with Direct Acting Antivirals (DAAs)

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Disclosures

Nothing to disclose

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

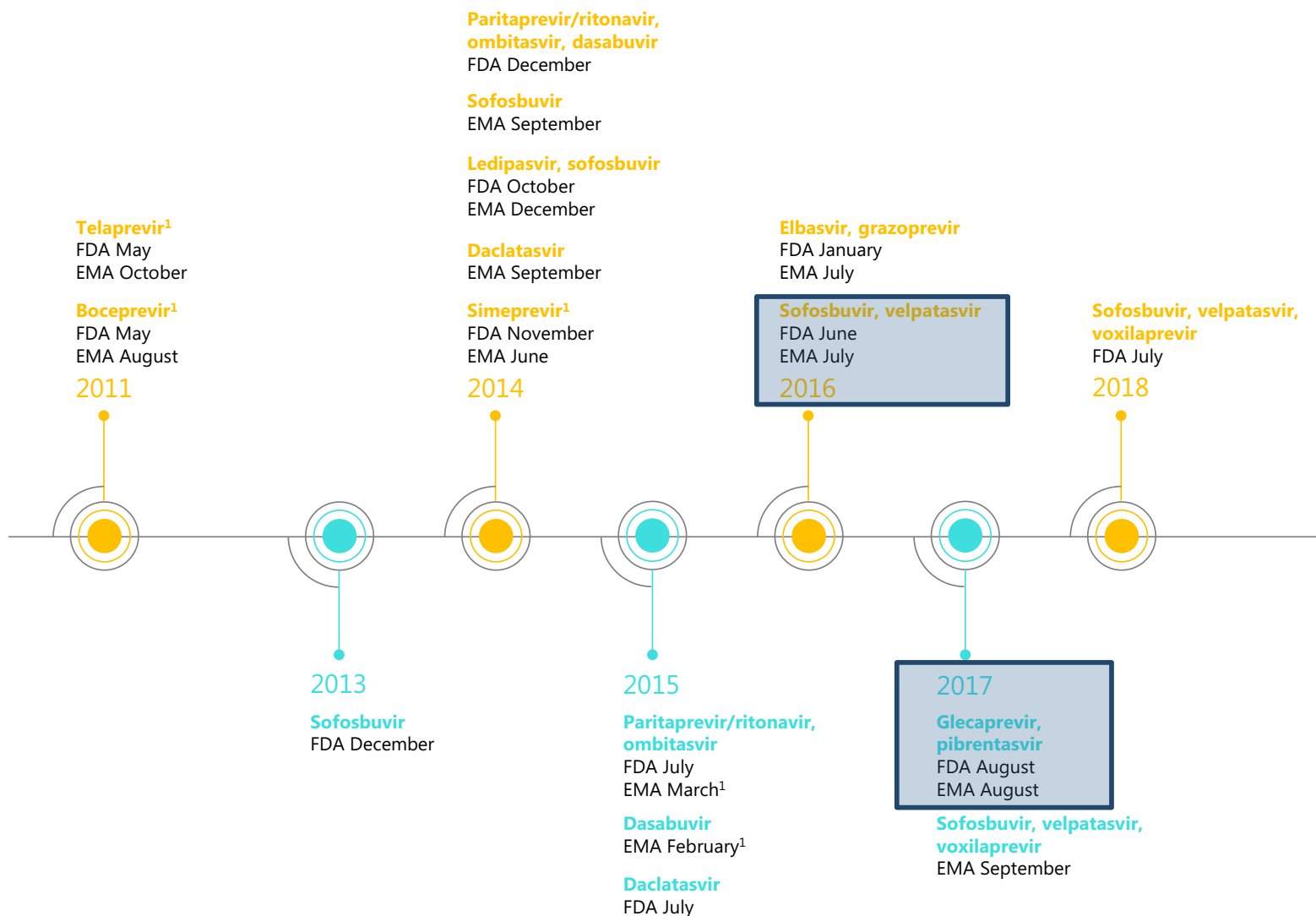
CASE 1

- TC is a 50-year-old male newly diagnosed with HIV (pan-sensitive genotype, CD4 count 350 cells/mm³ 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

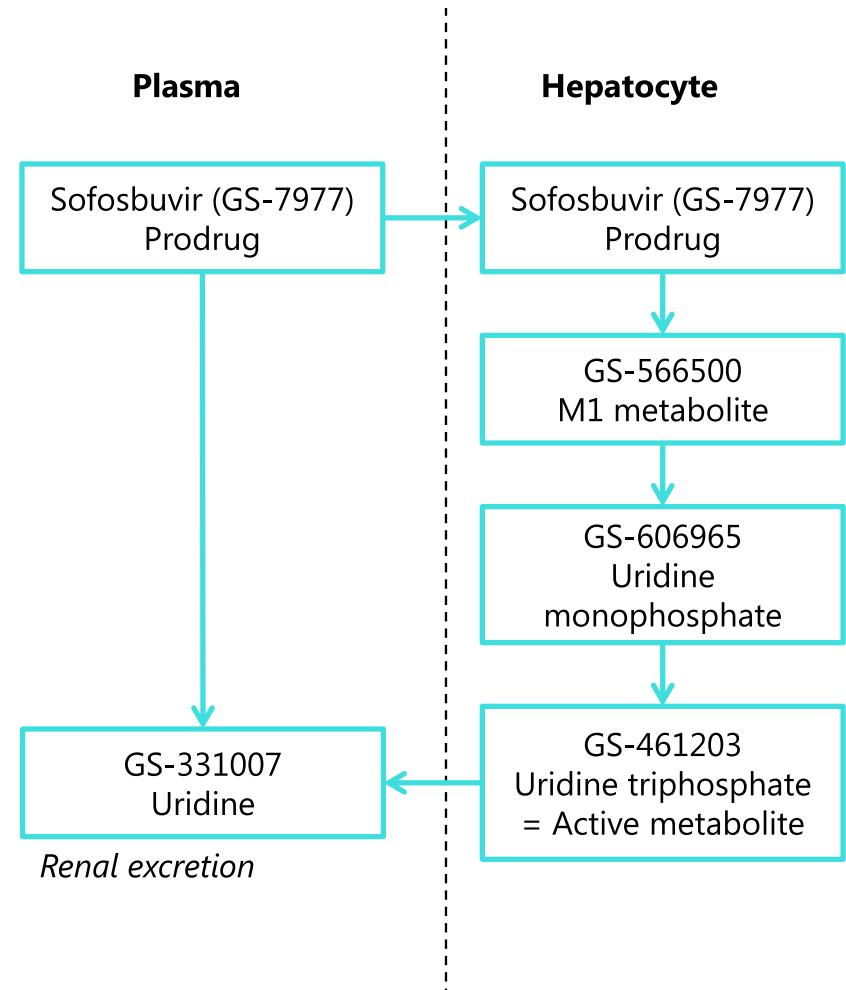
- Keeping in mind you want to treat the HCV in the next 6-12 months, what ART would you select?
 - A. Dolutegravir (Tivicay®) + Emtricitabine/Tenofovir DF (Truvada®)
 - B. Bictegravir/Emtricitabine/Tenofovir AF (Biktarvy®)
 - C. Dolutegravir/Lamivudine (Dovato®)
 - D. Darunavir/Cobicistat/ Emtricitabine/Tenofovir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

Basic PK Properties of DAAs



Pharmacokinetics

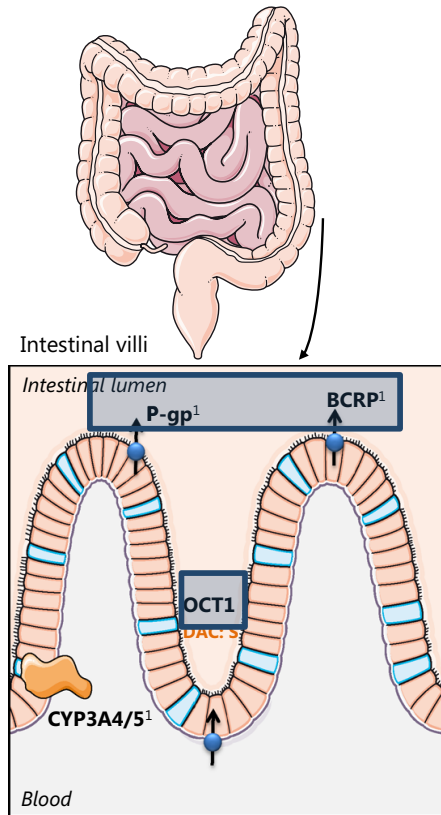
- SOF/VEL (Epclusa®)
 - Absorption
 - VEL has a **pH dependent solubility**
 - Metabolism
 - SOF: Substrate for PgP
 - VEL: **substrate for CYP3A4 (major)**, 2B6 and 2C8
- GLE/PIB (Mavyret®)
 - Absorption
 - Food enhances absorption
 - Metabolism
 - GLE: **substrate for CYP3A4**



Deep Dive

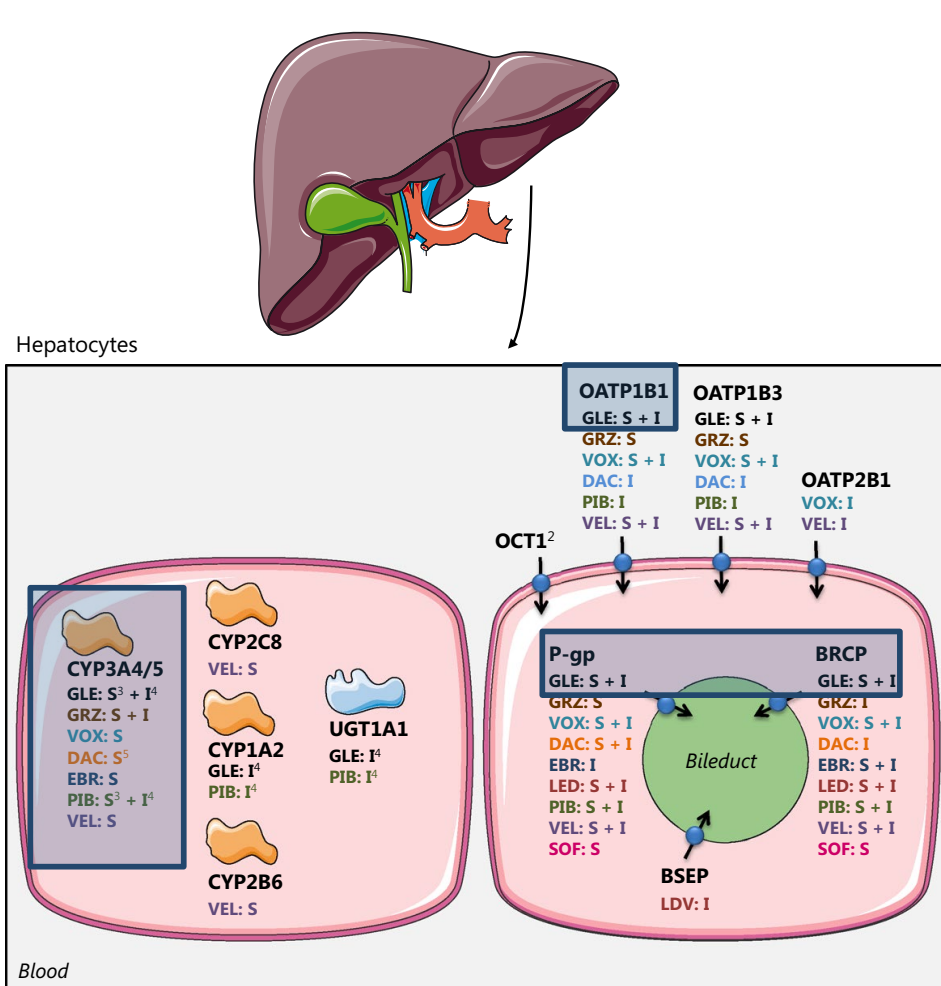
Absorption

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 site logo 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 menu items: 'About Us', 'Interaction Checkers', 'Prescribing Resources', 'Videos', 'Site News', 'Contact Us', and 'Support Us'. A white banner below the menu 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 with a title and a brief description: 'Educational Videos' (mini-lectures on pharmacology, hepatitis, and drug-drug interactions), 'Prescribing Resources' (interaction tables, treatment selectors, clinical prescribing resources, and pharmacokinetic fact sheets), 'Twitter' (@hepinteractions, follow for news and updates), 'Mobile Apps' (available on the App Store and Google Play), 'HIV Website' (HIV Drug Interactions), and 'Cancer Website' (Cancer Drug Interactions).

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

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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

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Navigating Interactions

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.

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"/>	

Navigating Interactions

HEP Drug Interactions  Interaction Checker → Apps ▾

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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
Switch to table view		
Reset Checker		
<input checked="" type="radio"/> A-Z <input type="radio"/> Indication <input type="radio"/> Trade	<input checked="" type="radio"/> A-Z <input type="radio"/> Class	Do Not Coadminister
<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) ⓘ	Look for alternatives →
		More Info ▾
		Potential Weak Interaction
		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_{max} and C_{min} 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_{max}, AUC and C_{min} by 3.09-fold, 4.97-fold and 8.24-fold, respectively. There was no change in pibrentasvir C_{max} or AUC, but C_{min} 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_{max}, AUC and C_{min} increased by 150%, 205% and 358%, respectively. Pibrentasvir C_{max} was unchanged but AUC and C_{min} 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_{max}, AUC and C_{min} increased by 3.09-fold, 4.97-fold and 8.24-fold, respectively. There was no change in pibrentasvir C_{max} or AUC, but C_{min} increased by 66%. Darunavir C_{max} and AUC increased by 30% and 29%, but there was no change in C_{min}. Ritonavir C_{max} and AUC increased by 103% and 87%, but there was no change in C_{min}. Coadministration is not

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HEP Drugs	Co-medications	Drug Interactions
<input type="text" value="sof"/>	<input type="text" value="bic"/>	<input type="checkbox"/> Check HEP/HEP drug interactions
<input type="button" value="X"/>	<input type="button" value="X"/>	<input type="button" value="Switch to table view"/>
<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 checked="" type="checkbox"/> Darunavir/cobicistat ⓘ	<input type="button" value="No Interaction Expected"/>
<input type="checkbox"/> Sofosbuvir ⓘ	<input checked="" type="checkbox"/> Bictegravir/ Emtricitabine/Tenofovir alafenamide (BIC/FTC/TAF) ⓘ	Sofosbuvir/Velpatasvir
<input checked="" type="checkbox"/> Sofosbuvir/Velpatasvir ⓘ	<input checked="" type="checkbox"/> Bictegravir/ Emtricitabine/Tenofovir alafenamide (BIC/FTC/TAF) ⓘ	Bictegravir/ Emtricitabine/Tenofovir alafenamide (BIC/FTC/TAF)
<input type="checkbox"/> Sofosbuvir/Velpatasvir /Voxilaprevir ⓘ		<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
Glecaprevir/pibrentasvir	Efavirenz and etravirine (decrease G/P) Boosted atazanavir and darunavir (increase G/P)	
Sofosbuvir	Tipranavir/ritonavir (decrease SOF through PgP)	
Velpatasvir	Efavirenz, etravirine, tipranavir/ritonavir (decrease VEL)	Avoid TDF if possible (increases TDF), especially with ritonavir or cobicistat (TAF ok)

DAAs 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"> Separate antacids by 4 hours Administer with H2RA OR separate by 12 hours (~40mg famotidine BID) Not recommended with PPIs
Amiodarone	Use with caution	Significant bradycardia
<u>Anticonvulsants:</u> Carbamazepine, phenytoin, PHB	↓ G/P (not recommended)	↓ SOF/VEL (not recommended)
<u>Antimycobacterial:</u> Rifabutin, rifampin, rifapentine	↓ G/P (not recommended)	↓ SOF/VEL (not recommended)
Statins	↑ Lovastatin (Avoid) ↑ Simvastatin (Avoid) ↑ Atorvastatin (Avoid) ↑ 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	↓ G/P (not recommended)	↓ SOF/VEL (not recommended)



Acknowledgment

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