Clinically Relevant Drug Interactions with Direct Acting Antivirals (DAAs)

David Hachey, Pharm.D., AAHIVP
Idaho State University
Department of Family Medicine

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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.
• 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
alterations in $C_{\text{max}}$. GS-331007 was not affected by food. The AUC of SOF and GS-331007 show a near dose-proportional increase in the range of 200–1200 mg. SOF is a substrate of the transporters P-gp and breast cancer resistance protein (BCRP). This is not the case for GS-331007.

### 3.1.2 Distribution

DCV is highly bound to plasma proteins (~99%) and the apparent volume of distribution ($V_d$) is 47.1 L. DCV is passively and actively transported into hepatocytes. In vitro data have shown that DCV is actively transported by organic cation transporter (OCT) and inhibits P-gp, organic anion transporting protein (OATP) 1B1, and BCRP. DCV also in vitro inhibits the renal transporters organic anion transporter (OAT) and OAT3, and OCT2. OCT2 inhibition by DCV is not clinically relevant, as shown in a drug interaction study with metformin (an OCT1 and OCT2 substrate).

SOF is 61–65% bound to plasma proteins and the binding of SOF is independent of drug concentrations (1–20 µg/mL). GS-331007 is minimally bound to plasma proteins.

### 3.1.3 Metabolism

DCV is a substrate of cytochrome P450 (CYP) 3A4; however, 97% of the circulating drug is the parent drug and <5% of metabolites are found in plasma.

SOF has a more complex metabolism (see Fig. 2). SOF is initially metabolized in the liver into the pharmacologically active nucleoside analog triphosphate GS-461203. This is followed by dephosphorylation to the main inactive metabolite GS-331007. GS-331007 accounts for over 90% of the systemic exposure. SOF only accounts for 4% of the systemic exposure.

### 3.1.4 Excretion

DCV is primarily hepatically cleared, as 88% of a radioactive test dose was retrieved in the feces, of which 53% was the parent drug. Only 6.6% of the parent drug was excreted in the urine. The elimination half-life ($t_{1/2}$) is 12–15 h and the clearance is 4.24 L/h.

For SOF, the main route of excretion is via urine (80%); only 14% of a radioactive dose was recovered in feces. The majority was retrieved as GS-331007 (78%) and only 3.5%.
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

Intestinal villi

Blood

Intestinal lumen

BCRP

P-gp

Intestinal villi

Hepatocytes

Hepatic update, metabolism, and biliary excretion
GLE, GRZ, VOX, DAC, EBR, LED, PIB, VEL

Blood

Intestinal lumen

BCRP

P-gp

Intestinal villi

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DAA and ARV Interactions
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

https://www.hep-druginteractions.org/
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<td>Do Not Coadminister</td>
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<td>Gileaprevir/Pibrentasvir</td>
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<tr>
<td>Bictegravir/Emtricitabine/Tenofovir alafenamide (BIC/FTC/TAF)</td>
<td>Look for alternatives</td>
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<td>Bictegravir/Emtricitabine/Tenofovir alafenamide (BIC/FTC/TAF)</td>
<td>Potential Weak Interaction</td>
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</table>

Having trouble viewing the interactions? Click here for the Interaction Checker Lite.

https://www.hep-druginteractions.org/
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.

Description:
- Medicinal products that inhibit OATP1B1/2 (e.g. darunavir) increase systemic concentrations of glecaprevir. Coadministration of darunavir/ritonavir (800/100 mg once daily) and glecaprevir/pibrentasvir increased glecaprevir Cmax, AUC, and Cmin by 3.09-fold, 4.97-fold, and 8.24-fold, respectively. A similar interaction may occur with darunavir/cobicistat.
- Gastrointestinal (GI) motility, 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 pibrentasvir/glecaprevir was studied. Glecaprevir Cmax, AUC, and Cmin increased by 150%, 205%, and 358%, respectively. Pibrentasvir Cmax was unchanged but AUC and Cmin increased by 57% and 89%, respectively. The mechanism is P-gp, BCRP, and OATP inhibition by cobicistat and OATP inhibition by elvitegravir.


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

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**Reset Checker**

- **No Interaction Expected**
- **Sofosbuvir/Velpatasvir**
- **Bictegravir/Emtricitabine/Tenofovir alafenamide (BIC/FTC/TAF)**

More Info

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[https://www.hep-druginteractions.org/](https://www.hep-druginteractions.org/)
## DAA and ARV Interactions

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<tr>
<th>DAA</th>
<th>Avoid/Not Recommended</th>
<th>Use with caution or adjust dose/timing</th>
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</thead>
</table>
| 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
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Glecaprevir/Pibrentasvir (Mavryet®)</th>
<th>Sofosbuvir/Velpatasvir (Epclusa)</th>
</tr>
</thead>
</table>
| Acid Reducing Agents       | No interaction                      | VEL solubility decreases as pH increase  
• 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          |
| **Anticonvulsants:**       | **↓ G/P (not recommended)**         | **↓ SOF/VEL (not recommended)**   |
| Carbamazepine, phenytoin,  |                                     |                                  |
| PHB                        |                                     |                                  |
| **Antimycobacterial:**     | **↓ G/P (not recommended)**         | **↓ SOF/VEL (not recommended)**   |
| Rifabutin, rifampin,       |                                     |                                  |
| rifapentine                |                                     |                                  |
| **Statins**                | **↑ Lovastatin (Avoid)**            | **↑ Rosuvastatin (10 mg max)**   |
|                            | **↑ Simvastatin (Avoid)**           | **↑ Atorvastatin (monitor)**     |
|                            | **↑ Atorvastatin (Avoid)**          |                                  |
|                            | **↑ Rosuvastatin (10 mg max)**      |                                  |
|                            | **↑ Pravastatin (↓ dose 50%)**      |                                  |
|                            | **↑ Pitavastatin (Lowest dose)**    |                                  |
|                            | **↑ Pitavastatin (Lowest dose)**    |                                  |
|                            | **↑ Fluvastatin (Lowest dose)**     |                                  |
| Oral Contraceptives        | **↑ EE levels (avoid or monitor**   |                                  |
|                            | **LFTs)**                           |                                  |
| St Johns Wort              | **↓ G/P (not recommended)**         | **↓ SOF/VEL (not recommended)**   |
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