Treatment of HIV/HCV Coinfection and the Management of Drug-Drug Interactions

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Learning Objectives
At the conclusion of this case, learners will be able to:
• Identify drug-drug interactions with HIV and hepatitis C therapies
• Recognize other therapeutic classes of drugs with the potential for drug interactions with hepatitis C therapies
• Locate reliable resources for screening for drug interactions
• Develop a plan for managing drug interactions
Types of Interactions

- **Pharmacokinetic** – result in a change in the serum/plasma levels of drug
  - Absorption
  - Distribution
  - Metabolism
  - Elimination

- **Pharmacodynamic** – no change in concentrations of drug, but can result in additive, synergistic, or antagonistic effects

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**CYP450 and Drug Metabolism**

- CYP2C
- CYP2D6
- CYP3A4
- CYP1A2
- CYP2E1

**Key points**

- Majority of drugs metabolized by (or substrates for) CYP3A4
- Enzymes can be induced or inhibited

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**Selected Membrane Transporters Relevant for HIV and HCV Therapies**

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Encoded by</th>
<th>Type of Transporter</th>
<th>Tissue Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>OATP1B1</td>
<td>SLCO1B1</td>
<td>Uptake</td>
<td>Primarily liver</td>
</tr>
<tr>
<td>OAT1</td>
<td>SLC22A6</td>
<td>Uptake</td>
<td>Primarily kidney</td>
</tr>
<tr>
<td>P-gp</td>
<td>ABCB1</td>
<td>Efflux</td>
<td>Ubiquitous (gut, liver, kidney, etc.)</td>
</tr>
<tr>
<td>BCRP</td>
<td>ABCG2</td>
<td>Efflux</td>
<td>Ubiquitous (gut, liver, kidney, etc.)</td>
</tr>
</tbody>
</table>
**Patient Case**

- 40 yo female with HIV and HCV genotype 1a both diagnosed in 2010
- ARV - tenofovir disoproxil fumarate 300mg QD/emtricitabine 200mg QD, darunavir 800mg QD/ritonavir 100mg QD x 5 years, CD4 537, HIV TND
- Biopsy 2014 stage 2, recent transient elastography 7.1 kPa
- Labs: HCV RNA 4,530,096 IU/mL, plt 220, Hgb 15.1 g/dL, SCR 0.91 mg/dL (eGFR 66), ALT 184 U/L, AST 114, Alb 4.6, tbil 0.7 mg/dL

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**High SVR Rates in HIV/HCV Coinfected**

- Wyles DL NEJM 2015
- Rockstroh JK Lancet HIV 2015
- Rockstroh JK EASL 2017
- Naggie S NEJM 2015
- Sulkowski MS JAMA 2015
- Wyles DL CID 2017

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**Which DAA regimen would you use to treat this patient?**

1. Elbasvir / Grazoprevir +/- Ribavirin
2. Ritonavir-boosted Paritaprevir, Ombitasvir, Dasabuvir plus Ribavirin
3. Ledipasvir / Sofosbuvir
4. Sofosbuvir / Velpatasvir
5. Glecaprevir / Pibrentasvir
6. Sofosbuvir / Velpatasvir / Voxilaprevir
Elbasvir / Grazoprevir

<table>
<thead>
<tr>
<th>PI Changes and Recommendations</th>
<th>GZR</th>
<th>EBR</th>
<th>ATV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir-boosted atazanavir</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Ritonavir-boosted darunavir</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Ritonavir-boosted lopinavir</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Ritonavir-boosted tipranavir</td>
<td>No data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Etravirine</td>
<td>No data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cobicistat-boosted elvitegravir</td>
<td>GZR</td>
<td>EBR</td>
<td>↑</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>GZR</td>
<td>EBR</td>
<td>RPV</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>GZR</td>
<td>EBR</td>
<td>RAL</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>GZR</td>
<td>EBR</td>
<td>DTG</td>
</tr>
</tbody>
</table>

Comments
- Not recommended for theoretical concern for QTC prolongation.
- Too much RTV.

PrOD with RPV and RAL

<table>
<thead>
<tr>
<th>PI Changes and Recommendations</th>
<th>GZR</th>
<th>EBR</th>
<th>RPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median DRV trough is 3300 ng/mL without PrOD.</td>
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<tr>
<td>Troughs are 1056-1600 with PrOD.</td>
<td></td>
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</tr>
<tr>
<td>Not recommended due to too much RTV.</td>
<td></td>
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</tbody>
</table>

PrOD and HIV PI Interactions

<table>
<thead>
<tr>
<th>PI Changes and Recommendations</th>
<th>GZR</th>
<th>EBR</th>
<th>RAL</th>
<th>DTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir and raltegravir can be safely combined with PrOD.</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Comments
- Drop the ritonavir booster while on PrOD.
- No data with ELV/cobi, but combo is contraindicated.
Ledipasvir / Sofosbuvir with TDF

- TFV exposures are higher when TDF is coadministered with LDV/SOF compared to without LDV/SOF.
- The range of TFV exposures with available safety data:
  - For EFV or RPV: TFV exposures fall within the range.
  - For RTV-boosted PIs: TFV exposures partially exceed the range.

Range of TFV exposures with available safety data

- Data on File, Gilead Sciences.
- Hoetelmans RMW, et al. 6th IWCPHT 2005. Quebec City, Canada. #2.11
- German P, et al. ICPHHT 2014. #O6
- Chittick GE, et al. AAC. 2006; 50(4):1304–10 (SQV+RTV)
- Zhu. 9th IWCPHT. 2008. #023 (ATV+RTV & LPV/r)
- German P, et al. CROI 2015
- Agarwala S, et al. 6th IWCPHT 2005. #16. (ATV+RTV)

In healthy volunteers, TFV increased 40-81% when administered as TDF.
GLSM TFV AUC was 4795 ng*hr/mL with ELV/cobi,
5197 ng*hr/mL with ATV/r, 4427 ng*hr/mL with DRV/r,
and 4314 ng*hr/mL with LPV/r.

Tenofivir PK with SOF/VEL - Volunteers

- In healthy volunteers, TFV increased 40-81% when administered as TDF.
- GLSM TFV AUC was 4795 ng*hr/mL with ELV/cobi,
5197 ng*hr/mL with ATV/r, 4427 ng*hr/mL with DRV/r,
and 4314 ng*hr/mL with LPV/r.

Tenofivir PK with SOF/VEL - Patients

- Phase 3 coinfection trial with SOF/VEL allowed boosted regimens

- By post treatment (PT) week 12, CrCl values were similar to baseline

3 patients with 1 in SCr from baseline of ≥ 0.4 mg/dL.
### Tenofvir PK LDV/SOF vs. SOF/VEL

<table>
<thead>
<tr>
<th></th>
<th>Unboosted Regimens</th>
<th>Boosted Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>TFV AUC (ng/hr/mL), Mean % CV</td>
<td>3839 (31%), n=335</td>
<td>3740 (26%), n=56</td>
</tr>
<tr>
<td>TFV AUC with LDV/SOF in IDN-4</td>
<td>3590 (25%), n=35</td>
<td></td>
</tr>
<tr>
<td>TFV AUC with SOF/VEL in ASTRAL-5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tenofovir AUCs slightly higher with LDV/SOF vs. SOF/VEL. Tenofovir AUCs with SOF/VEL similar to "typical" values in HIV-monoinfected patients on TDF + boosted HIV protease inhibitor.

**Caveats:**
- Exposures were modeled using convenience/sparse samples
- No patients on boosted regimens with LDV/SOF
- Small numbers on SOF/VEL
- Adherence is an unknown factor
- Highly selected patients (good renal function, limited concomitant conditions and medications) in order to qualify for study participation

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### Does this Interaction Translate to an Increased Risk of Nephrotoxicity?

Among 685 HIV/HCV coinfected Veterans on LDV/SOF treatment, no difference in maximum creatinine change during LDV/SOF treatment in those on TDF + HIV protease inhibitor, TDF without an HIV protease inhibitor, and those not on TDF-based ARV.

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### LDV/SOF and SOF/VEL with TDF

- Avoid in those with CrCl < 60 mL/min
- Avoid with boosters pending further data unless the ARV regimen cannot be changed and urgency of treatment is high
- If the combination is used, need frequent renal monitoring
  - Baseline and every 2-4 weeks on treatment
  - Estimated renal function (CKD-EPI equation suggested by CKD in HIV guidelines)
  - Urinary protein and glucose
- If possible, switch to TAF
TAF – An Alternative to TDF with SOF

- Intact TAF transits directly into target cells where it is intracellularly activated to tenofovir diphosphate (TFV-DP)
- TAF has lower circulating plasma TFV levels compared to TDF 300mg
- Basolateral transporters (OAT1, OAT3) effectively transfer TFV, but not intact TAF, into renal proximal tubular cells
- Lower systemic level of TFV; improved renal safety profile

Another Consideration with SOF/VEL

- VEL is metabolized by CYP3A
- Sensitive to potent inducers of CYP3A
- Cannot be used with EFV (or ETV)

Mogalian E, et al. AASLD 11/13-11/17, Boston, MA

Which of the following statements is TRUE regarding use of the new DAA combinations, GP and SOF/VEL/VOX, with ARV?

1. Ritonavir-boosted HIV protease inhibitors are either contraindicated or not recommended with GP
2. Several patients received the combination of GP and ELV/cobi in the EXPEDITION-2 trial, establishing the safety of this combination
3. All ritonavir-boosted HIV protease inhibitors and ELV/cobi can be used with SOF/VEL/VOX
4. Renal monitoring is not necessary with SOF/VEL/VOX and TDF
**Glecaprevir / Pibrentasvir**

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Transporters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Victim</td>
<td>Substrate/GATPs, Pgs</td>
</tr>
<tr>
<td>Perpetrator</td>
<td>Weakly inhibits CYP3A4, CYP1A2</td>
</tr>
<tr>
<td>Inhibitor</td>
<td>Inhibitor of pg, BCRP, OATPs</td>
</tr>
</tbody>
</table>

**PK Changes and Recommendation**

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma exposure</td>
<td>No RTV-boosted PI with GP</td>
<td>Only 1 patient on this combination in EXPEDITION 2, need more safety data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Sofosbuvir / Velpatasvir / Voxilaprevir**

- Tenofovir AUC, Cmax, Ctau increased about 40% with SOF/VEL/VOX
- Absolute tenofovir AUC reportedly ~4600 ng*h/mL
- Avoid TDF if CrCl < 60 mL/min
- If TDF is used, monitor renal function carefully
- Use TAF if possible

**SOF/VEL/VOX with ARV**

Very limited data with DRV/r and ELV/cobi, so monitor for liver toxicity from VOX
Audience Response #2 - ANSWER

Which of the following statements is TRUE regarding use of the new DAA combinations, GP and SOF/VEL/VOX, with ARV?

1. Ritonavir-boosted HIV protease inhibitors are either contraindicated or not recommended with GP √
2. Several patients received the combination of GP and ELV/cobi in the EXPEDITION-2 trial, establishing the safety of this combination X
3. All ritonavir-boosted HIV protease inhibitors and ELV/cobi can be used with SOF/VEL/VOX X
4. Renal monitoring is not necessary with SOF/VEL/VOX and TDF X

Audience Response #1 - ANSWER

Which DAA regimen would you use to treat this patient?

1. Elbasvir / Grazoprevir +/− Ribavirin – not with DRV/r
2. Ritonavir-boosted Paritaprevir, Ombitasvir, Dasabuvir plus Ribavirin – not with DRV/r
3. Ledipasvir / Sofosbuvir - ↑ renal monitoring
4. Sofosbuvir / Velpatasvir ↑ renal monitoring
5. Glecaprevir / Pibrentasvir – not with DRV/r
6. Sofosbuvir / Velpatasvir / Voxilaprevir – limited safety data with DRV/r, not treatment of choice for naïve patient

Patient Case

- 40 yo female with HIV and HCV genotype 1a both diagnosed in 2010
- Medications/PMH include:
  - ARV - tenfovir disoproxil fumarate 300mg QD/emtricitabine 200mg QD, darunavir 800mg QD/ritonavir 100mg QD x 5 years, CD4 537, HIV TND
  - HTN - amlodipine 10mg QD (today bp 122/83)
  - Contraception – levonorgestrel IUD
  - Depression – mirtazapine 15mg po QD
  - GERD – omeprazole 20mg once daily
  - Previously heavy EtOH user, now decreased 1-2 beers few times per week, daily marijuana use, never IDU
How the Top 10 List was Developed

- **Frequency of Concomitant Use**
  - Data from two retrospective analyses which screened concomitant medications against DAA regimens for potential interactions
  - University of Colorado (Langness W J Gastro 2017;23:1618)
    - HCV monoinfected, n=664
  - University of Nijmegen, the Netherlands (Smolders E JAIDS Epub)
    - HIV/HCV coinfected, n=777

- **Frequency of Interaction Screening through University of Liverpool website**
  - Presentation by David Back at Hep C State of the Art Management Meeting "the New York course" May 2017

- **Clinically important interactions (regardless of frequency of concomitant use)**

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# 10 - Amiodarone

- **Sofosbuvir and amiodarone**
  - **9 cases** (3 on SOF/LDV, 5 on SOF/DCV, 1 on S/M/SOF)
    - bradycardia, fatal cardiac arrest, some cases requiring pacemaker insertion
Bradycardia with SOF and Amiodarone – A Pharmacodynamic Interaction

- Amiodarone and SOF concentrations are not increased with the combination
- Studies suggest disruptions in intracellular calcium handling
- Not a class effect
  - MK3682 does not cause bradycardia with amiodarone
  - Depends on diastereochemistry of prodrug


# 10 - Amiodarone

- Avoid amiodarone during HCV treatment if possible
- If it must be used, consider EBR/GZR or GP

For patients taking amiodarone with to:
  - alternatives, inpatient cardiac monitoring for the first 48 hours of DAA treatment is needed, then daily heart rate monitoring x 2 weeks.

# 9 - Antiepileptics

- Carbamazepine, phenytoin, phenobarbital, oxcarbazepine cannot be used with any DAAs due to induction of enzymes/transporters
- Alternatives with the least interaction potential are levetiracetam and topiramate
- Small case series on use of sofosbuvir plus higher doses of daclatasvir (60mg twice or thrice daily) with carbamazepine*
  - Daclatasvir levels still low, but patients did achieve SVR.

*Smolders E, Int Wksp Clin Pharm Antiviral Therapy 2017, P_36
Which DAAs are problematic with hormonal contraceptives containing ethinyl estradiol?

1. LDV/SOF and SOF/VEL
2. PrOD and GP
3. EBR/GZR and DCV/SOF

#8 - Hormonal Contraceptives

- Increasing number of young women of childbearing potential with HCV
  - 22% ↑ between 2011-2014
- Many hormonal contraceptive options
  - Intrauterine devices (IUD) – DDI not as relevant, local hormone delivery
  - Progestin-containing subdermal implants (etnonogestrel)
  - Transdermal patch (ethinyl estradiol/norelgestromin)
  - Vaginal ring (ethinyl estradiol/etnonogestrel)
  - Injectables (medroxyprogesterone acetate)
  - Oral contraceptives (estrogen and progestin or progestin only)

# Effects of DAAs on Contraceptive Hormones

<table>
<thead>
<tr>
<th>DAAs</th>
<th>Ethinyl Estradiol</th>
<th>Levo-norgestrel</th>
<th>Norgestimate</th>
<th>Norethindrone</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOST</td>
<td>• No patch, no hormone-containing pills. • The progestin-only contraceptives can be used. • Can restart estrogen-containing contraceptives 2 weeks after completing.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEAST</td>
<td>• No patch, no hormone-containing pills. • The progestin-only contraceptives can be used. • Can restart estrogen-containing contraceptives 2 weeks after completing.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

References:
#7 - Tacrolimus and Cyclosporine

<table>
<thead>
<tr>
<th>Cyclosporine</th>
<th>Tacrolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir</td>
<td>4.5-fold ↑ in SOF AUC, but GS-331007 metabolite unchanged; no a priori dose adjustment</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>No data; no a priori dose adjustment</td>
</tr>
<tr>
<td>Elbasvir</td>
<td>5.8-fold ↑ in CSA AUC; modeling suggests using 1/5 of CSA dose during PrOD treatment, monitor CSA levels and titrate CSA dose as needed</td>
</tr>
<tr>
<td>Velpatasvir</td>
<td>No interaction observed; no a priori dose adjustment</td>
</tr>
<tr>
<td>GP</td>
<td>5-fold ↑ in GLE AUC with higher doses (400mg) of CSA; not recommended in patients requiring stable CSA doses &gt; 100 mg/day</td>
</tr>
<tr>
<td>SOF/VEL/VOX</td>
<td>9.4-fold ↑ in VOX AUC; combination is not recommended</td>
</tr>
</tbody>
</table>

For all DAAs, even if no a priori dose adjustment is needed, must monitor immunosuppressant levels and titrate dose as needed.

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#6 – Opioids and Opioid Replacement

<table>
<thead>
<tr>
<th>Opioid / Opioid Substitutes</th>
<th>LDV/SOF</th>
<th>SOF/VEL</th>
<th>PROD</th>
<th>GS331007</th>
<th>GP</th>
<th>SOF/VEL/VOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone</td>
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<td>✔</td>
<td>Monitor*</td>
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<td>✔</td>
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<tr>
<td>Fentanyl</td>
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<td>Monitor*</td>
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<td>Hydrocodone</td>
<td>✔</td>
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<td>Monitor*</td>
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<td>Hydrocodone Acetaminophenol</td>
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<td>Methadone Phosphate</td>
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<td>Tapentadol</td>
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</tbody>
</table>

www.hep-druginteractions.org

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#5 - Recreational / ChemSex Drugs

<table>
<thead>
<tr>
<th>LDV/SOF</th>
<th>SOF/VEL</th>
<th>PROD</th>
<th>GS331007</th>
<th>GP</th>
<th>SOF/VEL/VOX</th>
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<td>Ecstasy</td>
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</tbody>
</table>

Site courtesy of David Back (with modification), University of Liverpool, www.hep-druginteractions.org
#4 Statins

Both CYP and transporter mediated interactions to consider with statins

DAAs that inhibit the uptake transporter OATP1B1, the efflux transporter BCRP, and CYP3A result in ↑ plasma concentrations of statin

- Pravastatin
- Rosuvastatin
- Simvastatin
- Lovastatin
- Atorvastatin

Always check for interactions with statins and DAAs

<table>
<thead>
<tr>
<th>Hepatocyte OATP1B1 BCRP CYP3A</th>
<th>pravastatin</th>
<th>rosuvastatin</th>
<th>simvastatin</th>
<th>lovastatin</th>
<th>atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Simvastatin:</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lovastatin:</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Atorvastatin:</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

Always check for interactions with statins and DAAs

#3 - Psychotropics - Antidepressants

<table>
<thead>
<tr>
<th>SSRI/SESR</th>
<th>LCR/SEP</th>
<th>ROH</th>
<th>SOP/VEL</th>
<th>GP</th>
<th>SOP/VEL/VOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Bupropion</td>
<td>√</td>
<td>√</td>
<td>Monitor, reduce if clinically indicated</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Citalopram</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Trazodone</td>
<td>√</td>
<td>√</td>
<td>Dose reduce</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Sertraline</td>
<td>√</td>
<td>√</td>
<td>Monitor, reduce if clinically indicated</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>√</td>
<td>√</td>
<td>Monitor, reduce if clinically indicated</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>√</td>
<td>√</td>
<td>Monitor, reduce if clinically indicated</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

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### #3 – Psychotropics - Antipsychotics

**EBR/GZR**
- **LDV/SOF**
- **PrOD**
- **SOF/VEL**
- **GP**
- **SOF/VEL/VOX**

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>EBR/GZR</th>
<th>LDV/SOF</th>
<th>PrOD</th>
<th>SOF/VEL</th>
<th>GP</th>
<th>SOF/VEL/VOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Monitor</td>
<td>✅</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>√</td>
<td>Monitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>√</td>
<td>Monitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>√</td>
<td>Monitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Use with caution, consider therapeutic drug monitoring and/or EKGs</td>
<td>✅</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>√</td>
<td>Monitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

New category for interactions

yellow - interaction occurs, but no action required

---

### #3 – Psychotropics - Benzodiazepines/Anxiolytics/Sedative Hypnotics

**EBR/GZR**
- **LDV/SOF**
- **PrOD**
- **SOF/VEL**
- **GP**
- **SOF/VEL/VOX**

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>EBR/GZR</th>
<th>LDV/SOF</th>
<th>PrOD</th>
<th>SOF/VEL</th>
<th>GP</th>
<th>SOF/VEL/VOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolpidem</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>√</td>
<td>√</td>
<td>↑34%</td>
<td>Monitor, consider dose reduction if clinically indicated</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>√</td>
<td>√</td>
<td>Monitor</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Diazepam</td>
<td>√</td>
<td>√</td>
<td>Monitor</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Temazepam</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>
#2 - Antihypertensives

- CYP enzymes not involved in metabolism of ACE inhibitors or diuretics
- Carvedilol and nabivolol are metabolized to some extent by CYP3A4
- Contribution of CYP3A to irbesartan and losartan
- Calcium channel blockers are highly reliant on CYP3A for metabolism

---

<table>
<thead>
<tr>
<th>DAA Regimen</th>
<th>HCTZ</th>
<th>GP</th>
<th>LSV/LOX</th>
<th>FTOH</th>
<th>ESP/VEL</th>
<th>ESP/VEL/VOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbasvir/Grzoprevir</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Glecaprevir/Pibrentasvir</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>✓</td>
<td>Monitor</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>Monitor</td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir</td>
<td>✓</td>
<td>Monitor</td>
<td>12 h post, consider dose reduction</td>
<td>Monitor</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

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---

Absorption of which of the following DAA regimens is NOT reduced by proton pump inhibitors?

1. Elbasvir/grazoprevir
2. Glecaprevir/pibrentasvir
3. Ledipasvir/sofosbuvir
4. Sofosbuvir/velpatasvir
#1 - Gastric Acid Modifiers

- Exposures of the following DAAs are reduced with gastric acid modifiers:
  - Ledipasvir
  - Velpatasvir
  - Glecaprevir

- Careful adherence is essential:
  - Appropriate temporal separation of DAA and gastric acid modifier
  - Dosing limitations of the gastric acid modifier

LDV/SOF dosing with gastric acid modifiers

- Separate antacids by 4 hours
- PPI doses comparable to omeprazole 20mg can be administered simultaneously with SOF/LDV under fasted conditions
- H2 blocker doses should not exceed the equivalent of famotidine 40mg BID
- Avoid if possible

<table>
<thead>
<tr>
<th>Equivalent PPI Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole 40mg</td>
</tr>
<tr>
<td>Pantoprazole 40mg</td>
</tr>
<tr>
<td>Lansoprazole 30mg</td>
</tr>
<tr>
<td>Rabeprazole 20mg</td>
</tr>
<tr>
<td>Omeprazole 20mg</td>
</tr>
</tbody>
</table>

PPI Use and SVR with LDV/SOF

- No difference in SVR based on PPI use among 2,034 genotype 1 patients overall.
- PPI type and dose did not affect SVR, but those on twice daily PPI had a lower SVR (92%, p=0.03)

- Afdhal N EASL 2016
SOF/VEL and SOF/VEL/VOX dosing with gastric acid modifiers

- Unlike the current guidance with ledipasvir, recommended to take SOF/VEL in the fed state 4 hours before OME 20mg equivalent
- VEL exposures in the healthy volunteers receiving 20mg OME in the fed state similar to VEL exposures in Phase 3 trials

Mogalian E, et al. ASCPT, 3/8-3/12, 2016, San Diego, CA, #PI-050

GP dosing with gastric acid modifiers

- Unlike with LDV and VEL, this is not an interaction with the NS5A (PIB), it is a reduction in the protease inhibitor (GLE) absorption

<table>
<thead>
<tr>
<th></th>
<th>Effect on GLE (NS5A)</th>
<th>Effect on PIB (NS5A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OME 20mg QD</td>
<td>↑29%</td>
<td>--</td>
</tr>
<tr>
<td>OME 40mg QD 1 hr before GP + breakfast</td>
<td>↑51%</td>
<td>--</td>
</tr>
<tr>
<td>OME 40mg QD in evening</td>
<td>↑49%</td>
<td>--</td>
</tr>
</tbody>
</table>

- The clinical significance and management are unclear
- Do not exceed OME 20mg QD pending further data

SOF/VEL/VOX with gastric acid modifiers

- H2RA: No significant change in SOF, VEL, or VOX with famotidine 40 mg simultaneously or 12-h stagger
- PPI: SOF/VEL/VOX dosed 2 hours after (“worst case”) or 4 hours before (“best case”) omeprazole 20 mg
- Effect is the same; VEL AUC ~50% lower
### Gastric Acid Modifiers - Summary

- Do Not Exceed 20mg omeprazole equivalent with
  - LDV/SOF
  - SOF/VEL
  - GP
  - SOF/VEL/VOX

### Resources for Drug Interaction Screening

- **Specific to Antiretroviral Agents**
  - AASLD/IDSA HCV Guidance
    - [www.hcvguidelines.org](http://www.hcvguidelines.org)
  - DHHS Guidelines Drug Interaction Tables
    - [www.aidsinfo.nih.gov](http://www.aidsinfo.nih.gov)
- **University of Liverpool**
  - [www.hep-druginteractions.org](http://www.hep-druginteractions.org)
  - App: Liverpool HEP iChart

### Hepatic and Renal Impairment

- **Advanced Liver Disease**
  - Exposures of HCV protease inhibitors are increased
  - Increased risk of hepatotoxicity
  - Sofosbuvir and NS5A combinations (with or without ribavirin) are best
- **Renal Impairment**
  - GP and EBR/GZR
- **Both hepatic and renal impairment**
  - Insufficient data
  - Case series are accumulating on use of SOF in renal impairment
  - In Child-Pugh B, glecaprevir AUC is increased 2-fold – FDA accepted a 3-fold increase with ELV/ribi as “safe”, but data are extremely limited
Summary

- Individuals with HIV/HCV coinfection have a high burden of concomitant conditions and medications.
- A critical consideration in the treatment of HCV is the potential for drug interactions.
  - Especially for HIV infected patients where stakes are high for failure.
- A systematic approach to the identification and management of drug interactions is essential.
- In general, current therapies have well-characterized pharmacology and manageable drug interaction profiles, but knowledge gaps remain.

Clinical Pharmacology Knowledge Gaps

- How well do results of interaction studies in healthy volunteers translate to patients?
- Are there renal risks associated with use of TDF and SOF-based HCV therapy?
- What is the therapeutic range of DAAs?
- What antiepileptic medications are safe and effective with DAAs?
- What is the clinical relevance of PPI doses exceeding 20mg omeprazole with GP and SOF/VEL/VOX?
- Which HCV treatment is best for patients with both renal and hepatic impairment?