Management of Drug-Drug Interactions

David Back
University of Liverpool
June 2015
Disclosures

- Honoraria received for Advisory Boards, lectures from Abbvie, Gilead, Merck, Viiv, Janssen, Teva.


- **Molecular Virology**
  Deciphered the viral replication cycle and identified targets.

- **Structural Biology**
  Provided structures of viral targets – allowing modelling of drug-target interactions.

- **Multiple Clinical Trials**
  Efficacy and AEs.

- **Molecular & Clinical Pharmacology**
  Shown disposition of compounds and developed strategies to optimise therapies – in particular for *drug-drug interactions*. 
Drug–Drug Interaction Studies: Regulatory Guidance and An Industry Perspective

**Preclinical**

New Drug:

i) How is it metabolised and transported?

ii) Is it an inhibitor or inducer?

---

**Healthy Volunteers**

Targeted DDI studies

To predict the nature and extent of a DDI ie increase or decrease in exposure

---

**Patient Population**

HCV - Differential fibrosis stage:

Altered expression and function of hepatic enzymes and/or transporters!
Q: Drug-Drug Interactions are:

1. Straightforward to manage
2. Something I worry about
3. Something I try not to think about
4. For my pharmacist or nurse practitioner or someone else to worry about!
Protease Inhibitor Drug Interactions

Non-nucleoside reverse transcriptase inhibitor drug interactions
March 2000

Potential interactions amongst antiretroviral agents used to treat HIV infection
Updated February 1998
Now on the Web!
http://www.liv.ac.uk/hivgroup

This chart is designed to indicate how one ant-HIV drug may affect the pharmacokinetics (and activation by phosphorylation, if applicable) of another drug when given in combination. Before prescribing any medication, please consult the full prescribing information of the product concerned.
**LATEST ARTICLES**

- **Meeting Report** - 54th ICAAC, Washington
- **Case Report** - Atazanavir/ritonavir and telaprevir.
- **Meeting Report** - AIDS 2014, Melbourne
- **Drug Interactions** - Etravirine and rifabutin or clarithromycin
- **Drug Interactions** - Rifabutin dosage with boosted protease inhibitors

[Click here for previous news items]

**SITE UPDATES**

- **Interactions with Cobicistat**
  Cobicistat (Tybost®) as a single agent is licensed for the pharmacokinetic enhancement of atazanavir.

- **Empty Green Project**
  We have started a new project reassessing the empty/theoretical green interactions and providing met...

[>>more]

**EDITORIAL SPONSORSHIP**

We are pleased to announce Editorial Sponsorship from BHIVA, EACS and the International Congress on Drug Therapy in HIV (Glasgow).

**ASSOCIATED SITES**

- **HIV Drug Therapy**
  Portal providing emerging data, clinical updates and meeting reviews.
- **British Society for Nanomedicine**
  Website of the British Society of Nanomedicine with sections for scientists.

**DRUG INTERACTION CHARTS**

- **Now Includes Cobicistat**
  Access our comprehensive, user-friendly, free, drug interactions charts

[CLICK HERE]

- **To view low bandwidth version click here**

**TREATMENT SELECTOR TABLES**

- **Treatment Selector Tables** - now with dolutegravir

**INTERACTION CHARTS FOR YOUR SMART PHONE AND TABLET**

- **HIV iChart** - an interaction app for mobile devices

  **iOS 7/8** - We are aware that the update function on the app may not work properly with iOS 7 on some devices and have recently become aware of further problems with iOS 8 on iPhones. An update for the app is in development.

  Free for Apple and Android devices.

  The interaction charts are available as an app which can be downloaded free of charge from the App Store or Google Play (search for HIV iChart).
Drug- Drug Interactions

Perpetrator

HIV drug

Victim

Co-med

D Back – Personal Communication
## Antiretrovirals and Interaction Potential

<table>
<thead>
<tr>
<th>Highest potential</th>
<th>Moderate Potential</th>
<th>Low Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boosted PIs</strong></td>
<td><strong>Rilpivirine</strong></td>
<td><strong>Raltegravir</strong></td>
</tr>
<tr>
<td>Perpetrators – enzyme and transporter inhibition</td>
<td>Victim of enzyme inhibition and induction. Also absorption.</td>
<td>Victim of few induction and absorption interactions</td>
</tr>
<tr>
<td>Victim - absorption (ATV); induction</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EVG/cobi</strong></td>
<td><strong>Maraviroc</strong></td>
<td><strong>Most NRTIs</strong></td>
</tr>
<tr>
<td>Perpetrator – enzyme and transporter inhibition</td>
<td>Victim of enzyme inhibition and induction.</td>
<td>Some transporter mediated</td>
</tr>
<tr>
<td>Victim - absorption; induction</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Efavirenz, nevirapine, etravirine</strong></td>
<td></td>
<td><strong>Dolutegravir</strong></td>
</tr>
<tr>
<td>Perpetrators – enzyme and transporter induction</td>
<td></td>
<td>Victim of enzyme induction and absorption interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Drug-Drug Interactions

Perpetrator

DAA

Co-med

Victim
Telaprevir (TVR) and Boceprevir (BOC) Interactions: What have we learned?

- TVR and BOC are perpetrators of many interactions primarily by inhibition of CYP3A4 but also transporters.
- The magnitude of interaction; TVR > BOC but both have MARKED interaction potential

Concomitant outpatient meds including OTC and herbals assessed in 261 HCV-monoinfected pts evaluated for antiviral treatment at Hannover Med School 2011-2014.

DDI between the outpatient med and DAAs evaluated using www.hep-druginteractions.org and prescribing information.
### Some key points to note

#### The symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>🔴 / 🔴</td>
<td>These drugs should not be coadministered</td>
</tr>
<tr>
<td>🔴 / 🔴</td>
<td>Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration</td>
</tr>
<tr>
<td>📈 / 🔴</td>
<td>No clinically significant interaction expected</td>
</tr>
<tr>
<td>🔸 / 🔴</td>
<td>This interaction has not been assessed</td>
</tr>
<tr>
<td>n/a</td>
<td>Data not available</td>
</tr>
</tbody>
</table>

If a drug is not listed it cannot automatically be assumed it is safe to coadminister.
Clinical significance of drug-drug interactions during therapy with novel DAAs against HCV

Hoener Zu Siederdissen C, et al EASL-ILC 2015; Poster presentation P0754
Clinical significance of drug-drug interactions during therapy with novel DAAs against HCV

Hoener Zu Siederdissen C, et al EASL-ILC 2015; Poster presentation P0754

Classification not possible due to lack of information
Patient (GT1; tx experienced; F4) currently on 16 different prescribed medications for complex comorbidities hears about new DAAs!

- Aspirin 75 mg
- Amlodipine 10 mg
- Gliclazide 80 mg
- Paroxetine 20 mg
- Atenolol 50 mg
- Amitriptyline 25 mg
- Digoxin 125 mcg
- Omeprazole 40 mg bid
- Levothyroxine 100 mcg
- Levocetirizine 5 mg
- Co-codamol 2 qds
- Pravastatin 20 mg
- Movicol (as needed)
- Senna (as needed)
- Beclomethasone 250 mcg inhaler
- Salbutamol 100 mcg inhaler

We clearly need help!
Numerous and complex drug-drug interactions are possible with the HCV DAAs, especially when they are used in IFN-free combinations. Strict rules should thus be applied. As the data accumulate, guidance for contra-indications and dose adjustments can be found in Tables 4A to 4F of these Recommendations and at www.hep-druginteractions.org where they are regularly updated (B1).
DDIs between HCV DAAs and HIV antiretrovirals

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>SIM</th>
<th>DAC</th>
<th>SOF</th>
<th>LDV/SOF</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>♦</td>
<td>♦</td>
<td>♦️</td>
<td>♦️</td>
<td>♦️</td>
</tr>
<tr>
<td>Didanosine</td>
<td>♦</td>
<td>♦</td>
<td>♦️</td>
<td>♦️</td>
<td>♦️</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>♦</td>
<td>♦</td>
<td>♦️</td>
<td>♦️</td>
<td>♦️</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>♦</td>
<td>♦</td>
<td>♦️</td>
<td>♦️</td>
<td>♦️</td>
</tr>
<tr>
<td>Stavudine</td>
<td>♦</td>
<td>♦</td>
<td>♦️</td>
<td>♦️</td>
<td>♦️</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>♦</td>
<td>♦</td>
<td>♦️</td>
<td>♦️</td>
<td>♦️</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>♦</td>
<td>♦</td>
<td>♦️</td>
<td>♦️</td>
<td>♦️</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NNRTIs</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
</tr>
<tr>
<td>Etravirine</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>♦️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protease Inhibitors</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir; atazanavir/ritonivir</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
</tr>
<tr>
<td>Darunavir/ritonavir; darunavir/cobicistat</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry/Integrase inhibitors</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir</td>
<td>♦️</td>
<td>♦️</td>
<td>♦️</td>
<td>♦️</td>
<td>♦️</td>
</tr>
<tr>
<td>Elvitegravir/cobicistat</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
<td>♦️️</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>♦️</td>
<td>♦️</td>
<td>♦️</td>
<td>♦️</td>
<td>♦️</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>♦️</td>
<td>♦️</td>
<td>♦️</td>
<td>♦️</td>
<td>♦️</td>
</tr>
</tbody>
</table>

*Known or anticipated increases in tenofovir with boosted regimens and efavirenz and rilpivirine when given LDV/SOF: caution and frequent renal monitoring needed.

No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs (A2)

However that does not mean that Sofosbuvir has no drug interactions.
Recommendations

The fixed-dose combination of sofosbuvir and ledipasvir can be used with all antiretrovirals. However, this regimen should not be used with the combination of tenofovir/emtricitabine with atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir or elvitegravir/cobicistat when possible, or used with caution with frequent renal monitoring (B1).
Effect of LDV/SOF on HIV Protease Inhibitors

<table>
<thead>
<tr>
<th>Perpetrator</th>
<th>Object*</th>
<th>AUC</th>
<th>$C_{\text{max}}$</th>
<th>$C_{\tau}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDV/SOF</td>
<td>ATV</td>
<td>↔</td>
<td>↔</td>
<td>↑63%</td>
</tr>
<tr>
<td></td>
<td>RTV</td>
<td>↔</td>
<td>↔</td>
<td>↑45%</td>
</tr>
<tr>
<td></td>
<td>FTC</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td>TFV</td>
<td>↑40%*</td>
<td>↑47%</td>
<td>↑47%</td>
</tr>
<tr>
<td>LDV/SOF</td>
<td>DRV</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td>RTV</td>
<td>↔</td>
<td>↔</td>
<td>↑48%</td>
</tr>
<tr>
<td></td>
<td>FTC</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td>TFV</td>
<td>↑50%</td>
<td>↑64%</td>
<td>↑59%</td>
</tr>
</tbody>
</table>

Similar results observed when LDV/SOF and ATV/RTV+FTC/TDF or DRV/RTV+FTC/TDF were administered simultaneously or following a 12-hour stagger.

* Within pre-set intervals

Similar results observed when LDV/SOF and ATV/RTV+FTC/TDF or DRV/RTV+FTC/TDF were administered simultaneously or following a 12-hour stagger.

* Within pre-set intervals
LDV/SOF and ARV Regimen-based DDIs

♦ Possible differences between healthy volunteer and HCV patient data

♦ Need to understand the implications of the increase in TFV exposure particularly with a
  – Boosted-PI regimen
    • Remember that TFV exposure is higher with boosted PI-regimens relative to TFV with NNRTI-based regimens
Recommendations

The use of cobicistat-based regimens, efavirenz, etravirine, nevirapine, ritonavir, and any HIV protease inhibitor, boosted or not by ritonavir, is not recommended in HIV-infected patients receiving simeprevir (A1)
## Permitted Antiretrovirals with Simeprevir

<table>
<thead>
<tr>
<th>1st Agent</th>
<th>NRTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir</td>
<td>Tenofovir</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Emtricitabine</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Lamivudine</td>
</tr>
<tr>
<td><strong>Dolutegravir</strong></td>
<td><strong>Abacavir</strong></td>
</tr>
</tbody>
</table>

*Not studied but not expected to interact*

- DRV/r increased SIM exposure by 7-fold
- EFV decreased SIM exposure by 70%

[www.hcvguidelines.org](http://www.hcvguidelines.org), Olysio SmPC Aug 2014
Due to a **increase** in daclatasvir exposure with ATV/r and a **decrease** in daclatasvir exposure with EFV

The daily daclatasvir dose should be adjusted to 30 mg daily in HIV-infected patients receiving atazanavir/ritonavir and to 90 mg daily in those receiving efavirenz (B2)
Effect of DRV/r or LPV/r on DCV PK: AI444-093 Study Design

A phase 1, non-randomized, open-label, one-way drug interaction study (AI444-093) in healthy volunteers

- Eligible subjects were healthy adults aged 18–49 years; body mass index 18.0–32.0
- Subjects received DCV 60 mg once daily for 4 days, then DCV 30 mg once daily with either DRV/r (800/100 mg once daily) or LPV/r (400/100 mg twice daily) on Days 5–14
- 24-hour PK sampling was conducted on Days 4 (DCV alone) and 14 (DCV + PI/r)

D, study discharge; PK, 12-hour or 24-hour intensive PK assessment; S, screening visit.
AI444-093: DCV Concentration–Time Profiles

AUC GMR = 0.703

DCV (QD) ± DRV/r (QD)

AUC GMR = 0.577

DCV (QD) ± LPV/r (BID)
SVR12 by Baseline Factors: 8-Week Group

- **Race**
  - White: 71%, 20/28
  - Black: 79%, 15/19

- **HCV RNA, IU/mL**
  - < 2 M: 63%, 20/32
  - ≥ 2 M: 79%, 27/34
  - < 6 M: 69%, 11/16
  - ≥ 6 M: 77%, 34/44

- **Cirrhosis**
  - Yes: 60%, 3/5
  - No: 88%, 14/21

- **cART regimen**
  - DRV: 67%, 14/21
  - Other NNRTI: 80%, 7/8
  - Other: 82%, 8/10

---

*RAL, n=8; DTG, n=1; no cART, n=2. *DCV dose was reduced to 30 mg/day with ritonavir-boosted PI regimens in ALLY-2; based on recent data, DCV 60mg/day is recommended when used with DRV/r or LPV/r regimens [Eley et al. HIVDART 2014; Poster 63]*
Recommendations

The combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir should not be used with efavirenz, etravirine or nevirapine, and rilpivirine should be used cautiously with repeat ECG monitoring. Atazanavir and darunavir should be taken without ritonavir and other protease inhibitors are contraindicated with this combination. Elvitegravir/cobicistat should not be used with this regimen because of the additional boosting effect (B1)
# Recommendations for ART with the AbbVie 3-DAA Regimen

<table>
<thead>
<tr>
<th>Regimen evaluated</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside Reverse Transcriptase Inhibitor</td>
<td></td>
</tr>
<tr>
<td>Emtricitabine/Tenofovir Abacavir/lamivudine</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td></td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td>Integrase Inhibitors</td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td>Elvitegravir/cobicistat</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Protease Inhibitors</td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td>No dose adjustment required*</td>
</tr>
<tr>
<td>Darunavir</td>
<td>No dose adjustment required*</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>Not recommended/Contraindicated**</td>
</tr>
<tr>
<td>Non-Nucleoside Reverse Transcriptase Inhibitor</td>
<td></td>
</tr>
<tr>
<td>Efavirenz/Emtricitabine/Tenofovir</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Not recommended***</td>
</tr>
</tbody>
</table>

*Dose PI at the same time as OBV/PTV/RTV without additional RTV
** Not recommended (USPI) or contraindicated.(EU SPC). Coadministration of the 3D or 2D was tolerated in over 100 subjects for 14 days.
***EU SPC: Rilpivirine should be used cautiously, in the setting of repeated ECG monitoring. Please refer to the SPC for additional details.
Results and Recommendations: Darunavir with and without RTV

- Darunavir $C_{\text{trough}}$ is lower when coadministered with the 3D regimen.
- Similar $C_{\text{trough}}$ and $C_{\text{max}}$ results were observed for darunavir though AUC increased by 34% when darunavir/ritonavir (PM) was administered with the 3D regimen.

![Graph showing Central Value Ratio with 90% CI for Darunavir QD (AM) and BID](image-url)
Can Darunavir be dosed with the 3D regimen?

- There is up to a 50% lower DRV Ctrough

- This is unlikely to negatively impact HIV treatment efficacy (in the maintenance of plasma HIV-1 RNA suppression for patients on a stable DRV-based ART regimen during treatment with 3D). This is currently being verified in the M14-004 study in HCV-HIV co-infected subjects

- USPI: Coadministration not recommended

- EU SPC: DRV 800 mg once daily administered at the same time as ombitasvir/paritaprevir/ritonavir + dasabuvir can be used in the absence of extensive PI resistance

Ref:
PK-PD analyses of darunavir from two Phase 3 trials (ODIN and ARTEMIS) (Sekar V et al., 2008, 15th Conference on Retroviruses and Opportunistic Infections (CROI); Sekar V et al., 2010, 10th International Conference on Drug Therapy in HIV)

Molto J, Valle M, Ferrer E, et al. Reduced darunavir dose is as effective in maintaining HIV suppression as the standard dose in virologically suppressed HIV-infected patients. 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy. 19-21 May 2014. Washington, DC. Abstract O_02
### GZR/EBR DDI RESULTS WITH COMMONLY USED HIV ART


<table>
<thead>
<tr>
<th>HIV ARV</th>
<th>Effect on GZR AUC</th>
<th>Effect on EBR AUC</th>
<th>Effect on Interacting Drug AUC</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>tenofovir disoproxil fumarate</td>
<td>↔ 0.9x</td>
<td>↔ 0.9x</td>
<td>↑1.2x with GZR ↑1.3x with EBR</td>
<td>No adjustment</td>
</tr>
<tr>
<td>raltegravir</td>
<td>↔ 0.9x</td>
<td>↔ 1.0x</td>
<td>↑1.4x with GZR ↔1.0x with EBR</td>
<td>No adjustment</td>
</tr>
<tr>
<td>dolutegravir</td>
<td>↔ 1.0x</td>
<td>↔ 1.0x</td>
<td>↑1.2x with GZR+EBR</td>
<td>No adjustment</td>
</tr>
<tr>
<td>rilpivirine</td>
<td>↔ 0.9x</td>
<td>↔ 1.1x</td>
<td>↔ 1.1x with GZR+EBR</td>
<td>No adjustment</td>
</tr>
<tr>
<td>efavirenz</td>
<td>↓ 0.2x</td>
<td>↓ 0.5x</td>
<td>↔ 1.0x with GZR ↓0.8x with EBR</td>
<td>Not recommended</td>
</tr>
<tr>
<td>darunavir/ritonavir</td>
<td>↑ 7.5x</td>
<td>↑ 1.7x</td>
<td>↔ 1.1x with GZR ↔1.0x with EBR</td>
<td>Not recommended</td>
</tr>
<tr>
<td>atazanavir/ritonavir</td>
<td>↑ 10.6x</td>
<td>↑ 4.8x</td>
<td>↑1.4x with GZR ↔1.1x with EBR</td>
<td>Not recommended</td>
</tr>
<tr>
<td>lopinavir/ritonavir</td>
<td>↑ 12.9x</td>
<td>↑ 3.7x</td>
<td>↔ 1.0x with GZR ↔1.0x with EBR</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

Etravirine also not recommended – not studied.

Talaty et al., AASLD 2013; Caro et al., AASLD 2013; Yeh et al., CROI 2014; Yeh et al., CROI 2014; Yeh et al., CROI 2015; Yeh et al., IWCPHHT 2015
## DDIs between HCV DAAs and cardiovascular drugs

<table>
<thead>
<tr>
<th></th>
<th>SIM</th>
<th>DAC</th>
<th>SOF</th>
<th>LDV/SOF</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-arrhythmics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Digoxin</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Flecanide</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Vernakalant</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td><strong>Anti-platelet and anti-coagulants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Warfarin</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td><strong>Beta blockers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Propranolol</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td><strong>Hypertension and heart failure agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aliskiren</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Candesartan</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Enalapril</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
</tr>
</tbody>
</table>

Mechanism of action of the Amiodarone – SOF/DAA interaction

1. Gut efflux transporter blocked – with increase in amiodarone exposure?

2. Local effect of SOF/DAA on cardiomyocyte with accumulation of amiodarone in the heart?

3. Protein binding displacement of amiodarone by the SOF/DAA – increase in ‘active, unbound’ amiodarone?

Or

4. Are there some genetic factors that give a large increase in SOF
Classification of DDIs in Liverpool database

Data taken from www.hep-druginteractions.org
Remember our patient
Can we treat with OBV/PTV/r + DSV?

Aspirin 75 mg
Amlodipine 10 mg – ↑ levels. Consider dose reduction to 5 mg (as per SPC)
Gliclazide 80 mg – ↓ levels. Monitor blood glucose & consider increase if clinically indicated
Paroxetine 20 mg
Atenolol 50 mg
Amitriptyline 25 mg
Digoxin 125 mcg – Very small changes seen, no dose changes required. Consider levels
Omeprazole 40 mg – ↓ levels. Monitor for decreased efficacy and dose if req. (max 40 mg)
Levothyroxine 100 mcg – Exposure may be increased, limited data. Monitor TSH levels
Levocetirizine 5 mg
Co-codamol 2 qds – No dose adjustment required, theoretical interaction, monitor side effects
Pravastatin 20 mg – Consider dose reduction by 50%
Movicol (as needed)
Senna (as needed)
Beclomethasone 250 mcg inhaler
Salbutamol 100 mcg inhaler

TSH = Thyroid-stimulating hormone.
What about LDV/SOF?

Aspirin 75 mg
Amlodipine 10 mg – ↑ levels possible via P-gp inhibition. Monitor heart rate & blood pressure
Gliclazide 80 mg
Paroxetine 20 mg
Atenolol 50 mg
Amitriptyline 25 mg
Digoxin 125 mcg – ↑ concentration possible via P-gp inhibition. Consider levels
Omeprazole 40 mg – ↓ LDV concentrations, max 20mg daily
Levothyroxine 100 mcg
Levocetirizine 5 mg
Co-codamol 2 qds
Pravastatin 20 mg – May increase levels due to P-gp/BRCP inhibition. Consider dose ↓
Movicol (as needed)
Senna (as needed)
Beclomethasone 250 mcg inhaler
Salbutamol 100 mcg inhaler

BRCP = Breast cancer resistance protein; LDV = ledipasvir; P-gp = P-glycoprotein; SOF = sofosbuvir.
Conclusion

• Despite a complex drug history, drug interactions with both regimens would largely be manageable and either regimen (if available) would be suitable.
A stepwise approach to DDI management

1. Is co-medication necessary?
   - NO → Stop
   - YES → Can interaction be managed?

2. Can interaction be managed?
   - NO → Are there alternatives?
     - NO → - Accept risk and proceed with care
       - Be aware of likely off license use of combination; look for toxicities and side effects associated with combined use
       - Establish robust clinical monitoring plan
     - YES → Change to another clinically appropriate medicine
       - Consult pharmacy to advise new dose
       - Establish monitoring plan
       - Change dose back on completion of treatment
   - YES → NO → Establish monitoring plan
   - Establish monitoring plan
   - Change dose back on completion of treatment
Thank You

Grateful to colleagues involved in www.hiv-druginteractions.org and www.hep-druginteractions.org and to colleagues involved in the EACS and EASL Guidelines

Grateful for slides from Dr Wendy Yeh (Merck), Dr Rajiv Menon (Abbvie) and Dr Tim Eley (BMS)