Update on Liverpool Drug Interaction Team Activities

David Back
1. Analytics

2. Expansion of the Interaction Classification

3. Other ongoing projects.

4. New Drugs

5. New Site
HIV annual site visits 2010-16

- 2010: 107,677
- 2011: 135,987
- 2012: 145,686
- 2013: 159,470
- 2014: 181,009
- 2015: 235,990
- 2016: 282,037
HIV average monthly visitors 2010-16
HIV total app downloads 2010-16

Google Analytics
HEP Annual site visits 2010-16

- 2011: 16,444 visits
- 2012: 52,199 visits
- 2013: 54,414 visits
- 2014: 51,910 visits
- 2015: 244,180 visits
- 2016: 394,595 visits

Google Analytics
HEP average monthly visitors 2010-16

- 2011: 949
- 2012: 2,824
- 2013: 3,072
- 2014: 2,961
- 2015: 10,336
- 2016: 17,238

Google Analytics
HEP total app downloads 2010-16

Google Analytics
OUR MISSION IS TO HELP THE WORLD LEARN FROM ITS DATA

We've built the only product analytics platform that lets everyone in your organization deeply understand each user journey. Get instant insights and fast iterations throughout your product development process.

5 TRILLION DATA POINTS EVERY YEAR

99.9% UPTIME

<1 SECOND MEDIAN QUERY SPEED AT SCALE

50,000 AVERAGE EVENTS SCANNED PER QUERY AND AS HIGH AS 10B+
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</table>
MixPanel: Top Co-Med Searches

Interaction:
- primary_drug_name: contains Efavirenz
- Country: contains United Kingdom

By:
- co_drug_name

Segment by another dimension:

Atorvastatin 270 (14.16%)
- Doxycycline
- Ritampicin
- Omeprazole
- Amlodipine
- Clarithromycin
- Amoxicillin
- Simvastatin
- Lansoprazole
- Sildenafile (Erectile Dysfunction)
- Ramipril
- Paracetamol (Acetaminophen)
MixPanel: Top Co-Med Searches
MixPanel – Top Co-med Searches: UK

Amlodipine
Atorvastatin
Ramipril
Simvastatin
Sildenafil

Omeprazole
Lansoprazole

Doxycycline
Rifampicin
Amoxicillin
Clarithromycin

Mirtazipine
Sertraline
Citalopram

www.hiv-druginteractions.org
We have recently expanded our interaction classification to include a new ‘yellow’ classification. In contrast to the existing ‘amber’ interactions, which are ‘potentially clinically significant and likely to require additional monitoring, alteration of drug dosage or timing of administration’, the new yellow classification is for ‘potential interactions likely to be of weak intensity where additional action/monitoring or drug dosage adjustment is unlikely to be required’.
## Examples with 3D* Regimen

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<th>Drug</th>
<th>Interaction Type</th>
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<tr>
<td>Codeine</td>
<td>![Potential Weak Interaction]</td>
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<tr>
<td>Sertraline</td>
<td>![Potential Weak Interaction]</td>
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<tr>
<td>Tramadol</td>
<td>![Potential Weak Interaction]</td>
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*Ombitasvir/Paritaprevir/ritonavir + Dasabuvir
Other Ongoing Projects

1. Translation

2. Linking of DDI database to other platforms/systems, ie electronic prescribing, patient-focused apps etc

3. Charts and Educational Resources

www.hiv-druginteractions.org
Switching to Rezolta®/Prezcobix® (darunavir+cobicistat) or Evotaz® (atazanavir+cobicistat)

- Rezolta/Prezcobix and Evotaz are once daily fixed dose combinations (FDCs) of darunavir (DRV) 800 mg with cobicistat 150 mg, and atazanavir (ATV) 300 mg with cobicistat 150 mg respectively, and are indicated in combination with other antiretroviral medicinal products for the treatment HIV-1 infection in adults aged 18 years or older.

- There are clinical differences between ritonavir (r) and cobicistat boosted protease inhibitors (PIs) which need to be considered prior to switch:
  - Cobicistat drug interactions differ in that, unlike ritonavir, cobicistat does not induce glucuronidation (UGT1A1) or some CYP enzymes. Consequently, switching from PI/r to PI/cobicistat may increase levels of some drugs metabolised via these routes and require monitoring and/or dose modification (see table). Alternatively, consider remaining on ritonavir-boosted PI.
  - Cobicistat decreases estimated creatinine clearance by average 10 ml/min due to inhibition of tubular secretion of creatinine. This does not affect the actual glomerular filtration rate (GFR).
  - Although bioequivalent to DRV+r 800+100 mg, DRV Cmin reduces by 25-30% with cobicistat, but remains above the ICSO for DRV wild type virus. This may be relevant for some cohorts.

- The guidance below addresses key differences when switching from DRV+r or ATV+r to the FDCs and should be used in addition to the Product Labels and www.hiv-druginteractions.org.

### Darunavir-ritonavir to Rezolta/Prezcobix

**ARVs:**
- Efavirenz
- Etiravirine
- Nevirapine

**Anti-convenants:**
- Carafate
- Phenobarbital

**Other:**
- OBP/PTV/r ± DSV (AbbVie *2D/3D)*

**Rezolta/Prezcobix is NOT RECOMMENDED**

- Patient requires DRV 800 mg twice daily.
- Taking any of the following, which are not recommended with Rezolta/Prezcobix but may be used with DRV+r (with dose adjustment to twice daily for some drugs):
  - ARVs: Efavirenz, Etiravirine, Nevirapine
  - Anti-convenants: Carafate, Phenobarbital
  - Other: OBP/PTV/r ± DSV (AbbVie *2D/3D)*

- There are any DRV resistance associated mutations:
  - eGFR <70 ml/min when co-administered with medications that require dose adjustment based on renal function (e.g. tenofovir DF, lamivudine or emtricitabine).
  - Patients aged <18 years where the safety and efficacy of Rezolta/Prezcobix has not been established.

- Rezolta should be used with CAUTION when:
  - There are concerns about lower DRV exposure (compared to DRV+) such as:
    - Pregnancy, including if actively planning to conceive.
  - Where DRV is part of a regimen for patients with HIV encephalopathy or in patients with CSF HIV RNA escape.
  - Taking any other medications, particularly those listed in the table. Conduct full medicines review.
  - Any combinations other than 2 NRTIs + Rezolta/Prezcobix as these have not been studied.

**Specific counselling points for Rezolta/Prezcobix:**

- The recommended dosing regimen is one tablet of Rezolta/Prezcobix taken once daily with food.
- Use up all Prezola (DRV) and ritonavir prior to switch to Rezolta.
- There may be a requirement to switch away from the fixed dose combination when a generic darunavir becomes available.

**Patient factors for Rezolta/Prezcobix:**
- The Rezolta/Prezcobix tablet is larger than other ARVs and may not be acceptable to some. Ensure the patient has seen the tablet prior to leaving clinic.

**Atazanavir-ritonavir to Evotaz**

**ARVs:**
- Efavirenz
- Etiravirine
- Nevirapine

**Anti-convenants:**
- Carafate
- Phenobarbital

**Other:**
- Bosentan
- Hormonal contraceptives

**Evotaz is NOT RECOMMENDED**

- Patient requires ATV 400 mg daily, with or without pharmacokinetic booster.
- Taking hormonal contraceptives, including those containing 30 µg of ethinylestradiol due to potential increase in estrogen exposure. Alternative forms of contraception (non-hormonal) should be considered.
- Taking any of the following, which are not recommended with Evotaz but may be used with ATV+r:
  - ARVs: Efavirenz, Etiravirine, Nevirapine
  - Anti-convenants: Carafate, Phenobarbital
  - Other: Bosentan

- There are any ATV resistance associated mutations:
  - eGFR <70 ml/min when co-administered with medications that require dose adjustment based on renal function (e.g. tenofovir DF, lamivudine or emtricitabine).
  - Patients aged <18 years of age where the safety and efficacy of Evotaz has not been established.

- Evotaz should be used with CAUTION when:
  - Pregnant, including if actively planning to conceive due to a lack of data.
  - Taking any other medicines, particularly those listed in the table. Conduct full medicines review.
  - Any combinations other than 2 NRTIs + Evotaz as these have not been studied.

**Specific counselling points for Evotaz:**

- The recommended dosing regimen is one tablet of Evotaz taken once daily with food.
- Use up all Reyataz (ATV) and ritonavir prior to switch to Evotaz.
- There may be a requirement to switch away from the fixed dose combination when a generic atazanavir becomes available.

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*Consult Product Label for country-specific full indications, cautions, and contraindications.

† 2D = OBP/PTV/r (Viekira®, Technivie®); 3D = OBP/PTV/r + DSV (Viekira® + Evix®, Viekira Pak®, Viekira XR®). Note, OBP/PTV/r + DSV can be administered with DRV or ATV alone (i.e. without cobicistat or additional ritonavir).

**Monitoring considerations for both Rezolta/Prezcobix and Evotaz:**

- Consider additional monitoring post switch for those with identified "cautions" or other clinical indications.
- Serum creatinine is expected to increase with a resulting reduction in eGFR of ~10 ml/min. Typically this plateaus after 4 weeks of cobicistat-based ART. If a further change in eGFR is observed, or other renal markers change, this should prompt review.
Educational Resources

- 3 modules (each of 10, 15 min lectures) on
  - Basic Drug Disposition and Pharmacokinetics
  - Pharmacology of Antiretrovirals
  - Pharmacology in Special Populations

Saye Khoo, David Back, Andrew Owen, Marco Siccardi, Marta Boffito, Catia Marzolini, David Burger
New Drugs 2017-

- Bictegravir (Ph 3)
- Cabotegravir (Ph 3)
- Doravirine (Ph 3)

- Glecaprevir/pibrentasvir (Ph 3)
- Voxilaprevir (Ph 3)
- Grazoprevir/ruzasvir/uprifosbuvir (Ph2)
Combining the internationally recognised drug-drug interactions expertise of the University of Liverpool (UK) with the clinical pharmacology in oncology expertise of Radboud University Nijmegen (the Netherlands), the site will provide a world-leading DDI resource which will inform clinicians, pharmacists and patients about the potential for DDIs with anti-cancer agents.

Both an educational resource and a tool to support better prescribing, the website will improve quality of care and patient outcomes.

Interactions will be described using a simple “traffic light” classification

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The University of Liverpool has been providing drug-drug interaction information since 1999 and the format of this new site will be based on the existing websites for HIV and Hepatitis.

Email k.mcallister@liv.ac.uk to register interest in supporting or sponsoring the site today.
IMPROVE