Clinical Management of Drug-Drug Interactions

Marta Boffito (UK)
Mr Case A

- 34 year old man from NZ
- HIV+ since 2006
- Hx of depression, currently untreated
- CD4 201 (14%), VL 206,000
# Baseline RT

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>FOLD CHANGE</th>
<th>CUT-OFF</th>
<th>RESISTANCE ANALYSIS</th>
<th>CLINICAL NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTI / NtRTI mutations</strong>: 62V, 184V, 365I</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Retrovir®</td>
<td>0.9</td>
<td>1.5</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>Epivir®</td>
<td>49.1</td>
<td>1.2</td>
<td>4.6</td>
<td><strong>MINIMAL RESPONSE</strong></td>
</tr>
<tr>
<td>Videx®</td>
<td>1.1</td>
<td>0.9</td>
<td>2.6</td>
<td><strong>REDUCED RESPONSE</strong></td>
</tr>
<tr>
<td>Zerit®</td>
<td>0.7</td>
<td>1.0</td>
<td>2.3</td>
<td><strong>MAXIMAL RESPONSE</strong></td>
</tr>
<tr>
<td>Ziagen®</td>
<td>0.8</td>
<td>0.9</td>
<td>3.5</td>
<td><strong>MAXIMAL RESPONSE</strong></td>
</tr>
<tr>
<td>Emtriva®</td>
<td>45.6</td>
<td>3.1</td>
<td></td>
<td><strong>RESISTANT</strong></td>
</tr>
<tr>
<td>Viread®</td>
<td>0.6</td>
<td>1.0</td>
<td>2.3</td>
<td><strong>MAXIMAL RESPONSE</strong></td>
</tr>
</tbody>
</table>

| **NNRTI mutations**: 103R, 179D, 225H |
| Viramune®       | 5.1         | 6.0     |                     | **SUSCEPTIBLE**  |
| Sustiva®, Stocrin® | 39.5        | 3.3     |                     | **RESISTANT**    |
| Intelex®       | 0.7         | 1.6     | 27.6                | **MAXIMAL RESPONSE** |

| **PI mutations**: 13V, 63P, 93L |
| Crixivan®       | 0.9         | 0.9     | 4.5                 | **MAXIMAL RESPONSE** |
| Crixivan ®; boosted | 0.9       | 10.6    | 40.1               | **MAXIMAL RESPONSE** |
| Viracept®       | 1.3         | 1.3     | 7.3                 | **MAXIMAL RESPONSE** |
| Invirase®; boosted | 0.6        | 7.1     | 26.5               | **MAXIMAL RESPONSE** |
| Lexiva®, Telzir®; boosted | 0.7    | 1.3     | 11.4               | **MAXIMAL RESPONSE** |
| Kaletra®        | 0.8         | 9.7     | 56.1                | **MAXIMAL RESPONSE** |
| Reyataz®; boosted | 0.7        | 2.7     | 32.9               | **MAXIMAL RESPONSE** |
| Aptivus®; boosted | 0.9        | 1.2     | 5.4                 | **MAXIMAL RESPONSE** |
| Prezista®; boosted | 0.6        | 3.4     | 96.9               | **MAXIMAL RESPONSE** |

Note 1
Note 2
Therefore…

• PI/r plus:
  – TDF plus:
    • ABC (¿ – HIGH VL)
    • RAL
    • ETR
    • MVC (¿ – dose)
    • RPV (¿ – data)
Therefore...

- PI/r plus:
  - TDF plus:
    - ABC (?) – HIGH VL
    - RAL
    - ETR
    - MVC (?) – dose
    - RPV (?) – data
Rilpivirine had no clinically relevant effect on darunavir/ritonavir exposure

Van Heeswijk et al 2007
What do I need to know…

- DDI with current dose (PK data)
- Efficacy at high VL (PD data)
- Toxicity data
Mr Case A - cART

- TDF 300 mg OD
- RAL 400 mg BD
- DRV/r 800/100 mg OD
Mr Case A – few months later…

- Episode of paranoia following recreational drug intake (ecstasy)

- Admitted to psych ward and stopped all his drugs

- Broke both wrists and pain controlled with paracetamol and ibuprofen
Ecstasy

- MDMA metabolized CYP2D6, CYP1A2, CYP2B6, CYP3A4

- RTV inhibits CYP3A4 & CYP2D6 (at higher dose but slow metabolizers may use different pathways for drug metabolism)

- Caution when prescribing PI/r

Oesterheld et al. 2004
CYP2D6  CYP3A4

↑ heart rate
↑ BP
Tremor
Sweating
Bruxism
Hyperthermia
Rhabdomyolysis
Intravasc. coagulation
Acute Renal failure

Systemic circulation

Ecstasy

RTV

Portal vein
Psych ward

- Off cART
- Prescribed olanzapine, as apparently has a past diagnosis of bipolar disorder (?)
- VL up to 100,000 copies/mL
- Restarts same cART 3 weeks later
Olanzapine

- Glucuronidation and CYP450 mediated oxidation are primary metabolic pathways.

- In vitro studies suggest that CYP1A2 and 2D6 (minor *in vivo*), and the flavin-containing mono-oxygenase system are involved in olanzapine oxidation.
Olanzapine and PI/r

- RTV is an inducer of both glucuronidation and CYP1A2

- Coadministration of RTV (500 mg BD) and olanzapine (10 mg single dose) decreased olanzapine AUC (53%) and Cmax (40%)

Penzak et al. 2002
Pain control

• As Mr Case was agitated over night, he hurt his wrists again and complains of severe pain that is not longer controlled by non opioid analgesic

• He is prescribed by Dr X an initial dose of oxycodone of 10 mg every 6 hours to be increased as required to control pain
What did Dr X not check?

1. Drug SPC
2. www.hiv-druginteractions.org
3. Literature
4. Patient preferences
Oxycodone concentrations are greatly increased by concomitant use of RTV or LPV/r

- SPC: Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs, such blockade has not yet been shown to be of clinical significance with this agent.
Oxycodone* concentrations are greatly increased by concomitant use of RTV or LPV/r

Oxycodone half-life was increased from 3.6 h to 5.6/5.7 h

N = 12 healthy volunteers
*10 mg

RTV 300 mg BD
LPV/r 400/100 mg BD

Nieminen et al. 2010
- Involvement of CYP3A4?
- Is it correct to look at effect of other drugs to translate the significance of an interaction?
- Grapefruit juice and voriconazole increase oxycodone exposure
- St John’s wort and rifampicin greatly reduce exposure
Treatment of hypertension…

Why?
Prevalence of poly-pathology is more common in HIV infected than non-infected individuals in any age strata

The following co-morbidities were analysed: Hypertension, Type 2 Diabetes, Cardiovascular Disease and Osteoporosis.
Two thirds of patients in the SHCS received co-medication (1013/1497 patients)

- Cardiovascular/diabetes drugs: 56%
- CNS agents: 31%
- Analgesics: 11%
- Immunosuppressants: 4%
- Hormones: 3%
- Bronchodilators: 3%
- Antihistamines: 2%
- Herbals: 1%

At least 1 drug–drug interaction in 40%
Hypertension

Clinical management of primary hypertension in adults

This guideline partially updates and replaces NICE clinical guideline 34
Available data are scarce...

- Unboosted atazanavir (ATV) and diltiazem (D)

Co-administration of D (180 mg OD) and ATV (400 mg OD)
- No significant effect on ATV concentrations observed
- Increase in the maximum PR interval compared to ATV alone
- Initial dose reduction of D by 50% recommended, with subsequent titration as needed and ECG monitoring

- Co-administration of D and ATV/r has not been studied

Mechanism?
What about other agents?

- **Amlodipine & PI/r:**
  - *Co-administration may increase amlodipine concentrations and a decrease in dose may be necessary*
  - *Caution is warranted and careful monitoring of therapeutic and adverse effects is recommended*
Mr Case B

- 57 y.o. man, recently diagnosed with HIV
- CD4 150 cells/mm³
- VL 70,000 copies/mL
- Hx of depression
- High blood pressure treated by GP with amlodipine 10 mg OD
- Increased ALT (103 U/L)
- Baseline RT = wild type
What cART?

- 2 NRTIs
- PI/r
- Increased risk of AEs

- Amlodipine has been evaluated for safety in more than 11,000 patients in clinical trials
- Treatment is well-tolerated at doses up to 10 mg daily
- The incidence (%) of side effects that occurred in a dose related manner are as follows:

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>2.5 mg</th>
<th>5.0 mg</th>
<th>10.0 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=275</td>
<td>N=296</td>
<td>N=268</td>
<td>N=520</td>
</tr>
<tr>
<td>Edema</td>
<td>1.8</td>
<td>3</td>
<td>10.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.1</td>
<td>3.4</td>
<td>3.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Flushing</td>
<td>0.7</td>
<td>1.4</td>
<td>2.6</td>
<td>0</td>
</tr>
<tr>
<td>Palpitation</td>
<td>0.7</td>
<td>1.4</td>
<td>4.5</td>
<td>0.6</td>
</tr>
</tbody>
</table>
cART?

NRTIs
Third agent...

Do we need more studies to be able to prescribe cART to this patients? If yes, what studies are missing?
Tamsulosin (T) hydrochloride capsules are indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia.

T hydrochloride is extensively metabolized by CYP450 in the liver: mainly CYP3A4 and CYP2D6 as well as via some minor participation of other CYP isoenzymes.

Inhibition of hepatic drug-metabolizing enzymes may lead to increased exposure to T.

Treatment with ketoconazole (a strong inhibitor of CYP3A4) led to increase in Cmax and AUC by 2.2 and 2.8-fold.

Treatment with paroxetine (a strong inhibitor of CYP2D6) led to increase in Cmax and AUC by 1.3 and 1.6-fold.

The metabolites of T hydrochloride undergo extensive conjugation to glucuronide or sulfate prior to renal excretion.

www.hiv-druginteractions.org: Co-administration has not been studied. T is metabolised mainly by CYP3A4 and to a lesser extent by CYP2D6. Ritonavir is predicted to increase tamsulosin exposure which can result in hypotension. Use with caution.

Doses of 0.4 mg OD are used and when insufficient are increased to 0.8 mg OD.

CONCLUSION?
A dedicated clinic for HIV-positive individuals over 50 years of age: a multidisciplinary experience.

Waters L, Patterson B, Scourfield A, Hughes A, de Silva S, Gazzard B, Barton S, Asboe D, Pozniak A, Boffito M.

Department of GU/HIV Medicine, Chelsea & Westminster Hospital, London, UK

The HIV-infected population is ageing. Issues including polypharmacy and co-morbidities led us to develop a dedicated clinic for HIV-infected individuals over 50. We describe our service evaluation after two years. The over 50 clinic commenced in January 2009. The team comprises a registrar, consultant, nurse practitioner and is supported by a pharmacist and mental health services. Patients undergo a full medication and drug interactions review, neurocognitive assessment, adherence self-assessment and investigations including therapeutic drug monitoring (TDM), coronary artery calcium scores (CACS) and bone mineral density. Over two years of activity, 150 patients attended the service. Median (range) age was 58 (50-88), all were on combined antiretroviral therapy and 38% (57/150) were on ≥3 non-HIV drugs. CACS was high (>90th centile) in 14%. Thirty-eight percent had osteopaenia and 18% had osteoporosis requiring treatment. Thirteen out of 125 men had an increased prostate specific antigen, four were diagnosed with prostate cancer. Drug interaction, TDM and neurocognitive assessments were useful for several patients. Asymptomatic patients over 50 in long-term follow-up had new pathologies detected through targeted screening. The clinic has improved general practitioner (GP) liaison and facilitated closer working relationships with other specialties. Patients have reacted positively to the clinic, particularly as many do not routinely access their GP.
Mr Case C

- OVER50 clinic at Chelsea and Westminster Hospital
- 62 y.o. man on Truvada plus nevirapine
- Hx of high cholesterol
- On atorvastatin 20 mg OD
- Currently: tot chol 8.4 mmol/L, TG 3.36 mmol/L, HDL 1.00 mmol/L, LDL 5.87 mmol/L, HDL:chol ratio 8.40
- BP 130/84
- CVR (Framingham) still 28.3% on a statin!
- “… my GP told me that I have untreatable hypercholesterolenemia…”
NNRTIs and statins

• Co-administration (in healthy volunteers) of EFV (600 mg) with simvastatin (40 mg OD), atorvastatin (10mg OD), or pravastatin (40 mg OD) resulted in significant reductions in the $\text{AUC}_{0-24h}$ for all 3 statins:
  - 58% for simvastatin
  - 43% for atorvastatin
  - 40% for pravastatin

• EFV-based ARV regimens with simvastatin (20mg OD) had good but not optimal decreases in LDL and no major adverse effects

• EFV, NVP and ETR have the potential to decrease plasma concentrations of statins and thus lead to a reduced lipid-lowering response

Gerber et al 2005; Rahman et al 2008
NNRTIs and statins

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*PK*

EFV-based ARV regimens with simvastatin (20mg OD) had good but not optimal decreases in LDL and no major adverse effects

*PD*

EFV, NVP and ETR have the potential to decrease plasma concentrations of statins and thus lead to a reduced lipid-lowering response

*Conclusion*

Gerber et al 2005; Rahman et al 2008
Liver and intestines

- CYP3A4
- CYP2C9
- CYP2C19
- Glucuronidation

- Lovastatin
- Simvastatin
- Atorvastatin
- Fluvastatin
- Pitavastatin
- Rosuvastatin
- Pravastatin

Renal

Feces

Role of transmembrane transporters
Potential interaction – may require close monitoring, alteration of drug dosage/timing of administration
No clinically significant interaction expected
These drugs should not be coadministered

<table>
<thead>
<tr>
<th>Lipid Lowering Agents</th>
<th>Atazanavir</th>
<th>Darunavir</th>
<th>Lopinavir</th>
<th>Ritonavir</th>
<th>Efavirenz</th>
<th>Nevirapine</th>
<th>Maraviroc</th>
<th>Raltegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
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<tr>
<td>Ezetimibe</td>
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<tr>
<td>Fluvastatin</td>
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<tr>
<td>Lovastatin</td>
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<tr>
<td>Pravastatin</td>
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<tr>
<td>Rosuvastatin</td>
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<tr>
<td>Simvastatin</td>
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www.hiv-druginteractions.org
www.hiv-druginteractions.org

Potential interaction – may require close monitoring, alteration of drug dosage/timing of administration
No clinically significant interaction expected
These drugs should not be coadministered

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# NNRTIs and statins

<table>
<thead>
<tr>
<th>Medication</th>
<th>NNRTI</th>
<th>Effect</th>
<th>Dosing Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Efavirenz</td>
<td>Atorvastatin AUC ↓ 32-43%</td>
<td>Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose.</td>
</tr>
<tr>
<td></td>
<td>Etravirine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rilpivirine</td>
<td></td>
<td>Atorvastatin AUC ↔ Atorvastatin metabolites ↑</td>
<td>No dosage adjustment necessary.</td>
</tr>
<tr>
<td>Fluvasatin</td>
<td>Etravirine</td>
<td>↑ Fluvasatin possible</td>
<td>Dose adjustments for fluvasatin may be necessary.</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Efavirenz</td>
<td>Simvastatin AUC ↓ 68%</td>
<td>Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If efavirenz used with RTV-boosted PI, simvastatin andLovastatin should be avoided.</td>
</tr>
<tr>
<td>Simvastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Etravirine</td>
<td>↓ Lovastatin possible</td>
<td>Adjust lovastatin or simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If etravirine or nevirapine used with RTV-boosted PI, simvastatin and Lovastatin should be avoided.</td>
</tr>
<tr>
<td></td>
<td>Nevirapine</td>
<td>↓ Simvastatin possible</td>
<td></td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>Efavirenz</td>
<td>No data</td>
<td>No dosage recommendation.</td>
</tr>
<tr>
<td></td>
<td>Etravirine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nevirapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rilpivirine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Efavirenz</td>
<td>Pravastatin AUC ↓ 44%</td>
<td>Adjust statin dose according to lipid responses, not to exceed the maximum recommended dose.</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td></td>
<td>Pravastatin: no data</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Etravirine</td>
<td>No significant effect expected</td>
<td>No dosage adjustment necessary.</td>
</tr>
</tbody>
</table>

Fichtenbaum et al 2002
## PIs and statins

<table>
<thead>
<tr>
<th>Medications</th>
<th>PI</th>
<th>Effect</th>
<th>Dosing Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>ATV +/- RTV</td>
<td>↑ Atorvastatin possible</td>
<td>Titrate Atorvastatin dose carefully and use lowest dose necessary.</td>
</tr>
<tr>
<td></td>
<td>DRV/r, FPV +/- RTV</td>
<td>DRV/r + atorvastatin 10 mg similar to Atorvastatin 40 mg alone; FPV +/- RTV ↑ Atorvastatin AUC 130%-153%; SQV/r ↑ Atorvastatin AUC 79%;</td>
<td>Titrate Atorvastatin dose carefully and use the lowest necessary dose. Do not exceed 20 mg Atorvastatin daily.</td>
</tr>
<tr>
<td></td>
<td>LPV/r</td>
<td>↑ Atorvastatin AUC 488%</td>
<td>Use with caution and use the lowest atorvastatin dose necessary.</td>
</tr>
<tr>
<td></td>
<td>TPV/r</td>
<td>↑ Atorvastatin AUC 836%</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>All PIs</td>
<td>Significant ↑ Lovastatin expected</td>
<td>Contraindicated. Do not coadminister.</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>All PIs</td>
<td>ATV ↑ Pitavastatin AUC 31% and Cmax ↑ 60%; no significant effect on ATV; DRV/↑ Pitavastatin AUC 26%; no significant effect on DRV; LRV/↑ Pitavastatin AUC 20%; no significant effect on LPV</td>
<td>No dosage adjustment necessary.</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>DRV/r</td>
<td>Pravastatin AUC ↑ 81%</td>
<td>Use lowest possible starting dose with careful monitoring.</td>
</tr>
<tr>
<td></td>
<td>LPV/r</td>
<td>Pravastatin AUC ↑ 33%</td>
<td>No dosage adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>SQV/r</td>
<td>Pravastatin AUC ↓ 47-50%</td>
<td>No dosage adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>ATV/↑ Rosuvastatin AUC 213% and Cmax ↑ 600%; LPV/r ↑ Rosuvastatin AUC 108% and Cmax ↑ 366%</td>
<td>Titrate Rosuvastatin dose carefully and use the lowest necessary dose. Do not exceed 10 mg rosuvastatin daily.</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>DRV/r</td>
<td>Rosuvastatin AUC ↑ 48% and Cmax ↑ 139%</td>
<td>Titrate Rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities.</td>
</tr>
<tr>
<td></td>
<td>FPV +/- RTV</td>
<td>No significant effect on rosuvastatin</td>
<td>No dosage adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>SQV/r</td>
<td>No data available</td>
<td>Titrate Rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities.</td>
</tr>
<tr>
<td></td>
<td>TPV/r</td>
<td>Rosuvastatin AUC ↑ 26% and Cmax ↑ 123%</td>
<td>No dosage adjustment necessary.</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>All PIs</td>
<td>Significant ↑ simvastatin level; SQV/r 400 mg/400 mg BID ↑ simvastatin AUC 3059%</td>
<td>Contraindicated. Do not coadminister.</td>
</tr>
</tbody>
</table>
Think DDI in HIV-infected patients when...

- Prescribing new drug therapies
- Switching drugs / drug classes
- Discontinuing drugs with interactive potential
- Prescribing more than 2 interactive drugs
- Caring for patients with multiple providers
- Caring for patients with organ dysfunction