Clinical case presentation

Catia Marzolini
University Hospital & University of Basel
University of Liverpool

Workshop on Clinical Pharmacology of HIV, Hepatitis & Other Antiviral Drugs
C. Marzolini has received research funding from Gilead and honoraria for lectures from MSD.
Drug-drug interaction case published in 1999

We present the case of a patient with hepatitis C-induced cirrhosis and concomitant human immunodeficiency virus infection who underwent orthotopic liver transplantation. The patient developed severe, prolonged tacrolimus toxicity in the presence of human immunodeficiency virus protease inhibitors. At various times, the patient received saquinavir, ritonavir, and nelfinavir in conjunction with tacrolimus. In each instance, the tacrolimus concentration rose to toxic levels. We hypothesize that the protease inhibitors' competition for binding to cytochrome P450 isoenzyme system CYP3A induced extreme prolongation of tacrolimus metabolism.

Saquinavir/r + d4T + 3TC
+ tacrolimus 4 mg BID
Patient became lethargic
Tacrolimus level > 120 ng/ml !!!

All medications were stopped. HIV treatment changed to:
Nelfinavir + d4T + 3TC
+ tacrolimus adjusted to 0.5 mg every 3 days
to reach trough levels in the range 4-10 ng/ml

Currently, the nelfinavir package insert does not specifically describe this interaction
Information on drug-drug interactions in 1999

Liverpool printed chart for protease inhibitors

The content of the Liverpool Drug Interaction website has expanded over the years
Drug-drug interactions profiles of ARVs have changed over the years

n ≈ 700 comedications

- **Boosted ARV**
  - Efavirenz: no interaction
  - Etravirine: weak interaction
  - Rilpivirine: potential weak interaction
  - Doravirine: interaction of clinical relevance

- **Raltegravir**
  - Rilpivirine: deleterious interaction

- **Dolutegravir**
  - Bictegravir: deleterious interaction

Presentation #5: S. Gibbons: Changes in DDI profiles for the first-line HIV therapy over the 20 years of the Liverpool Drug Interaction website

www.hiv-druginteractions.org
Better understanding of mechanisms of drug-drug interactions over the years

Drug transporters

Intestine

- CNT1, CNT2, PEPT1, OCT1, OATP1A2, OATP2B1, P-gp, MRP2, BCRP

Intestinal absorption

Liver

- ENT1, OATP1A2, OAT4, PEPT1/2, BCRP, MRPs, MATE1, MATE2, OCT2

Hepatic uptake

Biliary excretion

Kidney

- ENT1, OATP1A2, OAT1, PEPT1/2, BCRP, MRPs, MATE1, MATE2, OCT2

Renal excretion

Blood

- MRPs, MATE1, MATE2, OCT2

Drug transporters

Interactions of HIV drugs with transporters

<table>
<thead>
<tr>
<th>Antiretrovirals</th>
<th>OATP1B1</th>
<th>OAT1</th>
<th>OCT2</th>
<th>MATE1</th>
<th>P-gp</th>
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<th>MRP4</th>
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<td>Efavirenz</td>
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<td>Etravirine</td>
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<td>Rilpivirine</td>
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<td>Zidovudine</td>
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<td>TFV</td>
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<td>Dolutegravir</td>
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<td>Raltegravir</td>
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<td>Maraviroc</td>
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<tr>
<td>Cobicistat</td>
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<tr>
<th>Other</th>
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</tbody>
</table>

Increase in tacrolimus exposure explained by inhibition of CYP3A4 and P-gp by protease inhibitors

Moss D, Siccardi M, Marzolini C In: Drug Interactions in Infectious Diseases 2018
Increasing use of PBPK modelling to simulate drug-drug interactions with ARVs

- *in vitro* drug data
- Mathematical description of ADME integrated in a population physiology model
- Simulation of pharmacokinetics in virtual individuals

- Physicochemical characteristics
- *in vitro* metabolic data
- Apparent intestinal permeability

Simulation of drug-drug interactions
People living with HIV in 1999 have aged since

Aging poses several therapeutic challenges

- Multimorbidity
- Polypharmacy (Inc non-prescription drugs/supplements etc)
- ‘Polydoctory’
- Age-related pharmacokinetic & pharmacodynamic changes

| ↑ Pill burden | Reduced efficacy of HIV agent? |
| ↓ Medication adherence | Reduced efficacy of co-medications? |
| ↑ Prescribing cascade error | Adverse effect? |

DDIs

Perpetrator

ARV

Co-med

Victim

Plenary lecture of Prof. D. Back. CROI 2019
Case: 72-year old man

History:

• 2002: HIV infection

• 2002-2008: lamivudine + zidovudine + efavirenz \( \text{ARV changed to avoid DDI with treatment for Hodgkin's lymphoma} \)

• 2008-2014: FTC + TDF + raltegravir \( \text{NRTI backbone changed due to renal impairment} \)

• since 2014: ABC + 3TC + raltegravir

• VL: < 20 copies/ml; CD4: 457 cells/mm\(^3\)

• other co-morbidities: depression, hypertension, atrial fibrillation (prior stroke), mild asthma, hyperlipidemia, urinary incontinence, constipation, mild renal impairment (CrCl: 54 mL/min)

• medications:
  - raltegravir 400 mg BID
  - lamivudine 300 mg QD
  - abacavir 600 mg QD
  - amlodipine 10 mg QD
  - paroxetine 20 mg QD
  - atorvastatin 20 mg QD
  - bunedoside inh. 200 ug QD
  - rivaroxaban 20 mg QD
  - tolterodine 4 mg QD
  - sterculia 875 mg BID
  - dry eye drops (as needed)

\( \text{ARV} \)

\( \text{antihypertensive} \)

\( \text{antidepressant} \)

\( \text{statin} \)

\( \text{corticosteroid} \)

\( \text{anticoagulant} \)

\( \text{antispamodic (overactive bladder)} \)

\( \text{laxative} \)
Case: 72-year old man

- The patient found by daughter in a state of confusion, agitation
- Clinical examination: BP 130/85 mmHg, heartbeat †, skin red, hot and dry, slight bilateral mydriases
- Daughter reports: patient took diphenhydramine 25 mg in the past few days to help with sleep due to irritating nocturnal cough.

The patient presents the signs of an anticholinergic toxicity, what caused this problem:

Drug-drug interaction between diphenhydramine and raltegravir?
Diphenhydramine overdosed as some drugs not eliminated as well in elderly?
Other problem with the comediations?
Some answers

• Drug-drug interaction between diphenhydramine and raltegravir?

  **NO:** diphenhydramine metabolized by CYP2D6
  raltegravir no inhibitory effect on CYP2D6

  www.hiv-druginteractions.org

• Dosage diphenhydramine (25mg) not adapted for elderly individuals?

  **NO:** usual hypnotic dose: 25-50mg (lower dose to be used in elderly)
  no significant effect on diphenhydramine PK in elderly vs young
  no different effect on mood, memory, heart rate in elderly for
diphenhydramine vs placebo

  **BUT....**

**Some answers**

... the patient is taking several drugs with anticholinergic properties

**Anticholinergic cognitive burden scale** (list of drugs with high anticholinergic burden)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>amitriptyline</td>
<td>clozapine</td>
<td>hydroxyzine</td>
<td>promethazine</td>
</tr>
<tr>
<td>amoxapine</td>
<td>darifenacin</td>
<td>imipramine</td>
<td>propantheline</td>
</tr>
<tr>
<td>atropine</td>
<td>desipramine</td>
<td>meclizine</td>
<td>quetiapine</td>
</tr>
<tr>
<td>benztropine</td>
<td>dicyclomine</td>
<td>methocarbamol</td>
<td>scopolamine</td>
</tr>
<tr>
<td>brompheniramine</td>
<td>dimenhydrinate</td>
<td>nortriptyline</td>
<td>solifenac</td>
</tr>
<tr>
<td>carboxamine</td>
<td>diphenhydramine</td>
<td>olanzapine</td>
<td>thioridazine</td>
</tr>
<tr>
<td>chlorpheniramine</td>
<td>doxepin</td>
<td>orphenadrine</td>
<td>tolterodine</td>
</tr>
<tr>
<td>chlorpromazine</td>
<td>doxylamine</td>
<td>oxybutynin</td>
<td>trifluoperazine</td>
</tr>
<tr>
<td>clemastine</td>
<td>fesoterodine</td>
<td>paroxetine</td>
<td>trimipramine</td>
</tr>
<tr>
<td>clomipramine</td>
<td>flavoxate</td>
<td>perphenazine</td>
<td>trospium</td>
</tr>
</tbody>
</table>

- Anticholinergic drugs are considered as inappropriate for use in elderly.
- Elderly are more sensitive to adverse anticholinergic effects due to significant decrease in cholinergic receptors in the brain.
- Drugs with anticholinergic properties can impair cognition ➔ increase risk of falls, cause constipation, xerostomia, dizziness, blurred vision.

Boustani M et al. Aging Health 2008
Inappropriate drug led to adverse drug events and prescribing cascade

- Overflow urinary incontinence
- Constipation, dry eyes

- Paroxetine
- Tolterodine
- Sterculia & dry eye drops

- Anticholinergic toxicity
  - Diphenhydramine (over-the-counter)

### Treatment
- Raltegravir + 3TC + ABC
- Amlodipine
- Paroxetine ➔ escitalopram
- Atorvastatin
- Budenoside
- Rivaroxaban
- Tolterodine
- Sterculia
- Dry eye drops

### Adverse Drug Events
- Prescribing cascade

### Inappropriate Drugs, DDIs

### Polypharmacy
<table>
<thead>
<tr>
<th>Initial treatment</th>
<th>Adverse drug reaction</th>
<th>Subsequent treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID</td>
<td>↑ BP</td>
<td>Antihypertensive</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>Cough</td>
<td>Cough suppr., antibiotic</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>Gout</td>
<td>Allopurinol, colchicine</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Edema</td>
<td>Diuretic</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>Depression</td>
<td>Antidepressant</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>Dizziness</td>
<td>Prochlorperazine</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Arrhythmia</td>
<td>Antiarrhythmic</td>
</tr>
<tr>
<td>Quinolone</td>
<td>Delirium</td>
<td>Antipsychotic</td>
</tr>
<tr>
<td>Cholinesterase inhibitor</td>
<td>Incontinence</td>
<td>Anticholinergic</td>
</tr>
<tr>
<td>Cholinesterase inhibitor</td>
<td>Rhinorrhea</td>
<td>Diphenhydramine</td>
</tr>
<tr>
<td>SSRI, SNRI</td>
<td>Tremor</td>
<td>Benzodiazepine</td>
</tr>
<tr>
<td>Tricyclic antidepressant</td>
<td>▼ cognition</td>
<td>Cholinesterase inhibitor</td>
</tr>
<tr>
<td>Tricyclic antidepressant</td>
<td>Constipation</td>
<td>Laxative</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Delirium</td>
<td>Antipsychotic</td>
</tr>
<tr>
<td>Lithium</td>
<td>Tremor</td>
<td>Propanolol</td>
</tr>
<tr>
<td>Metoclopramide Antipsychotic</td>
<td>Extrapyramidal effect</td>
<td>Antiparkinsonian agent</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Problem/alternatives</th>
</tr>
</thead>
</table>
| First generation antihistamines | Strong anticholinergic properties  
 Alternatives: cetirizine, desloratadine, loratadine |
| Tricyclic antidepressants    | Strong anticholinergic properties  
 Alternatives: escitalopram, mirtazapine, venlafaxine |
| Benzodiazepines              | Elderly more sensitive to their effect  
 Alternative: non-pharmacological ttt of sleep disorders |
| Atypical antipsychotics      | Increased risk of stroke and mortality  
 Alternatives: aripiprazole, ziprasidone |
| Urological spasmo-lytic agents | Strong anticholinergic properties  
 Alternatives: non-pharmacological ttt (pelvic floor ex.) |
| Stimulant laxatives          | Long term use may cause bowel dysfunction  
 Alternatives: fibers, osmotic laxatives |
| NSAIDS                       | Risk of GI bleeding, renal failure  
 Alternatives: paracetamol, weak opioids |
| Digoxin > 0.125 mg/day       | Risk of toxicity  
 Alternative for AF: beta-blockers |
| Long acting sulfonylureas    | Can cause severe hypoglycemia  
 Alternatives: metformin or other antidiabetic classes |
| Cold medications            | Contain first generation antihistamines with strong anticholinergic properties. Avoid |
Case: 72-year old man

Patient doing better, recalls having problems remembering things notably to take the evening medications

VL measurement: 559’000 copies/mL, development of resistances

➔ **high resistance**: RAL, EVG/c; **intermediate resistance**: DTG needs BID dosing

Patient prefers to have a once daily HIV regimen to prevent the same issue

➔ ABC (600 mg) + 3TC (300 mg) + darunavir/ritonavir (800/100 mg) QD

**Current co-medications**

- Amlodipine 10 mg QD
- Escitalopram 10 mg QD
- Atorvastatin 20 mg QD
- Budenoside 200 ug QD
- Rivaroxaban 20 mg QD

**Which co-medications need to be changed or might require dosage adjustment when switching from raltegravir to darunavir/ritonavir?**
**Metabolic pathways of co-medications**

**Raltegravir**
- CYPs: no induction/inhibition
- Transporters: no induction/inhibition

**Darunavir/ritonavir**
- CYPs: CYP3A4, CYP2D6, CYP1A2, CYP2B6, CYP2C9, CYP2C19
- Transporters: OATP1B1/3, BCRP, MATE1, P-gp

**Legend:**
- strong inhibition
- moderate inhibition
- strong induction
- moderate induction

<table>
<thead>
<tr>
<th>Co-medication</th>
<th>Dose</th>
<th>Elimination pathway</th>
<th>Elderly patients</th>
<th>Reduced renal function</th>
</tr>
</thead>
<tbody>
<tr>
<td>amlodipine</td>
<td>10 mg</td>
<td>CYP3A4</td>
<td>AUC + 50%</td>
<td>no effect</td>
</tr>
<tr>
<td>escitalopram</td>
<td>10 mg</td>
<td>CYP3A4 + CYP2D6 + CYP2C19</td>
<td>AUC + 50%</td>
<td>minor ↑ AUC</td>
</tr>
<tr>
<td>atorvastatin</td>
<td>20 mg</td>
<td>CYP3A4, OATP1B1, P-gp</td>
<td>exposure tend to ↑</td>
<td>no effect</td>
</tr>
<tr>
<td>budenoside</td>
<td>200 ug</td>
<td>CYP3A4</td>
<td>no effect</td>
<td>no effect</td>
</tr>
<tr>
<td>rivaroxaban NTI</td>
<td>20 mg</td>
<td>CYP3A4, CYP2J2 + renal, P-gp, BCRP</td>
<td>exposure ↑ (x 1.5) no dose adj.</td>
<td>CrCl 50-80 (x 1.4) no dosage adj. CrCl 30-49 (x 1.5) 15 mg QD CrCl 15-29 (x 1.6) caution CrCl &lt; 15 not recommended</td>
</tr>
</tbody>
</table>

**How much does darunavir/ritonavir increase amlodipine, escitalopram, budenoside or atorvastatin exposures and how to manage these interactions?**

Approach to predict magnitude of drug-drug interactions with ARVs

Magnitude of drug-drug interaction depends on:

- **Fraction of disposition pathway mediated by the enzyme of interest (DPI)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>DPI&lt;sub&gt;CYP3A4&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>triazolam</td>
<td>0.96</td>
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<tr>
<td>zolpidem</td>
<td>0.26</td>
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</tbody>
</table>

Almost exclusively metabolized by CYP3A4

CYP3A4 contributes to 26% of the overall metabolism

- **Inhibitor (InR) and inducer (IcR) strength**

<table>
<thead>
<tr>
<th>Inhibitor&lt;sub&gt;CYP3A4&lt;/sub&gt;</th>
<th>InR&lt;sub&gt;CYP3A4&lt;/sub&gt;</th>
<th>Inducer&lt;sub&gt;CYP3A4&lt;/sub&gt;</th>
<th>IcR&lt;sub&gt;CYP3A4&lt;/sub&gt;</th>
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<tbody>
<tr>
<td>ritonavir</td>
<td>1.0</td>
<td>rifampicin</td>
<td>0.95</td>
</tr>
<tr>
<td>cimetidine</td>
<td>0.21</td>
<td>efavirenz</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Strong inhibitor CYP3A4

Weak inhibitor CYP3A4

Moderate inducer CYP3A4

These parameters can be derived from available drug-drug interactions studies involving similar drug combinations and reporting the magnitude of drug-drug interaction.

These parameters can then be used to predict the magnitude of drug-drug interactions for **uncharacterized drug combinations involving ARVs** to provide guidance on how to adjust dosage.

Stader F et al. Antimicrob Agent Chemother 2018
Predictive performance and example of calculation

98% and 85% of predicted DDI magnitudes were within 2 fold and 1.5 fold range of observed clinical data

Formula for inhibition

\[
\frac{AUC_{inh}}{AUC} = \frac{1}{1 - DPI_{3A4} \times InR_{3A4}} \Rightarrow \frac{1}{1-0.468 \times 1.000} = 1.9 \text{ fold}
\]

DPI\textsubscript{3A4} of amlodipine: 0.468 \quad InR\textsubscript{3A4} of ritonavir: 1.0

Data from clinical DDI studies

- \approx 2 \text{ fold increase in amlodipine exposure} + IDV/r BID (Glesby M et al. Clin Pharmacol Ther 2005)
- \approx 2 \text{ fold increase in amlodipine exposure} + PTV/r QD (Menon R et al. J Hepatol 2015)

consider a dose reduction for amlodipine of 50%. Monitoring of BP is recommended.

\(\Rightarrow\) decrease amlodipine dosage by half in our patient: 10 mg to 5 mg with monitoring BP

Magnitude drug interaction with escitalopram

DPI of escitalopram: 0.078
InR of ritonavir: 1.0

\[ \frac{AUC_{inh}}{AUC} = 1.1 \text{ fold} \]

Mitigate DDIs magnitude

RTV booster weak inhibitor of CYP2D6

Escitalopram metabolized by CYP3A4, 2C19, 2D6

Desipramine metabolized by CYP2D6

Limited increase in escitalopram exposure. No a priori dosage adjustment is needed.

No change in escitalopram dosage in our patient

Overestimation of drug-drug interaction risk and suboptimal treatment

Larger proportion of PLWH with subtherapeutic antidepressants levels compared to uninfected individuals suggesting deliberate lower dosing of antidepressants as clinicians fear drug-drug interactions with antiretroviral drugs.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Reference range (ng/ml)</th>
<th>PLWH treated with ARV (n = 55)</th>
<th>Uninfected individuals (n = 233)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cmin levels (ng/ml)</td>
<td>Subtherapeutic levels</td>
<td>Cmin levels (ng/ml)</td>
</tr>
<tr>
<td>Citalopram</td>
<td>50-110</td>
<td>65 ± 67</td>
<td>60%</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>30-120</td>
<td>32 ± 35</td>
<td>63%</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>120-500</td>
<td>204 ± 190</td>
<td>50%</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20-65</td>
<td>22 ± 20</td>
<td>54%</td>
</tr>
<tr>
<td>Sertraline</td>
<td>10-150</td>
<td>20 ± 12</td>
<td>20%</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>100-400</td>
<td>223 ± 52</td>
<td>0%</td>
</tr>
</tbody>
</table>

Cattaneo D et al. World J Biol Psychiatry 2018
Magnitudes drug interaction with atorvastatin

\[
\frac{AUC_{\text{inh}}}{AUC} = 3.8 \text{ fold}
\]

Differences in magnitude of drug-drug interactions with statins explained by different metabolic pathways and affinities to drug transporters.

### Atorvastatin + DRV/r

<table>
<thead>
<tr>
<th>ATV/c</th>
<th>ATV/r</th>
<th>DRV/c</th>
<th>DRV/r</th>
<th>LPV/r</th>
<th>EVG/c</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑822%</td>
<td>↑</td>
<td>↑290%</td>
<td>↑</td>
<td>↑490%</td>
<td>↑</td>
</tr>
</tbody>
</table>

### Rosuvastatin + DRV/r

<table>
<thead>
<tr>
<th>ATV/c</th>
<th>ATV/r</th>
<th>DRV/c</th>
<th>DRV/r</th>
<th>LPV/r</th>
<th>EVG/c</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑242%</td>
<td>↑213%</td>
<td>↑93%</td>
<td>↑48%</td>
<td>↑107%</td>
<td>↑38%</td>
</tr>
</tbody>
</table>

**OATP1B1 inhibition:** ATV > LPV > DRV > RTV, Cobi

**Recommendations**

<table>
<thead>
<tr>
<th></th>
<th>ATV/c</th>
<th>DRV/c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>NR/lowest dose</td>
<td>lowest dose</td>
</tr>
<tr>
<td></td>
<td>Max: 10 mg/d</td>
<td>Max: 40 mg/d (US label: 20 mg/d)</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>lowest dose</td>
<td>lowest dose</td>
</tr>
<tr>
<td></td>
<td>Max: 10 mg/d</td>
<td>Max: 20 mg/d</td>
</tr>
</tbody>
</table>

Start atorvastatin at 10 mg at titrate based on clinical response. Consider maximal daily recommended dose.

➔ maintain of atorvastatin and decrease in dose: 20 mg to **10 mg** or alternatively switch to rosuvastatin 5 mg

www.hiv-druginteractions.org
Drug interaction with budenoside

DPI\textsubscript{3A4} of budenoside: 0.865  \quad \text{InR}_{3A4} \text{ of ritonavir: 1.0} \implies \frac{AUC_{\text{inh}}}{AUC} = 7.4 \text{ fold}

- Risk of developing Cushing’s Syndrome, dose reduction does not eliminate risk

**Drug properties that minimize risk of CS** (inhaled/intranasal corticosteroids)

- Low glucocorticosteroid relative receptor binding affinity (RRA)
- Higher plasma protein binding (limits drug diffusion)
- Shorter half-life
- Lower lipophilicity (limits drug diffusion)

<table>
<thead>
<tr>
<th>Corticosteroid/dose form</th>
<th>Relative glucocorticoid receptor binding affinity</th>
<th>Lipophilicity (log P)</th>
<th>Aqueous solubility (µg ml\textsuperscript{-1})</th>
<th>PPB (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone furoate DPI</td>
<td>2989</td>
<td>4.17</td>
<td>0.03</td>
<td>99.7</td>
</tr>
<tr>
<td>Mometasone furoate DPI</td>
<td>2100</td>
<td>4.73</td>
<td>&lt;0.1</td>
<td>99.5</td>
</tr>
<tr>
<td>Fluticasone propionate DPI</td>
<td>1775</td>
<td>3.89</td>
<td>0.14</td>
<td>99.3</td>
</tr>
<tr>
<td>Budesonide dipropionate (BMP) DPI</td>
<td>53 (1345)</td>
<td>4.59 (3.27)</td>
<td>0.13 (15.5)</td>
<td>95.9</td>
</tr>
<tr>
<td>Ciclesonide (des-CIC) MDI</td>
<td>12 (1200)</td>
<td>3.2 (3.0)</td>
<td>&lt;0.1 (7)</td>
<td>98.7</td>
</tr>
<tr>
<td>Budesonide DPI</td>
<td>935</td>
<td>2.32</td>
<td>16</td>
<td>91.4</td>
</tr>
</tbody>
</table>

beclomethasone meets most of the properties

- replacement of budenoside by beclomethasone

Drug interaction with rivaroxaban

What is the magnitude of the interaction between DRV/r and rivaroxaban and is the magnitude of the interaction different in elderly compared to 20-50 year-old individuals?

Simulation using PBPK modelling

![Graph showing rivaroxaban concentration over time with observed and predicted data]

**Impact of age on DDI magnitude**

Similar magnitude of drug-drug interaction in elderly compared to young individuals

**Presentation #15: F. Stader: PBPK modelling to determine pharmacokinetic alterations driving ritonavir exposure changes in aging PLWH**

 DRV/r + etravirine with rivaroxaban 10 mg

 DRV/r + etravirine with rivaroxaban 10 mg

 EVG/c with rivaroxaban 10 mg → CI with boosted ARVs
What about dabigatran

Prodrug substrate of P-gp, eliminated renally
Dosage for AF: 150 mg BID

**PK/PD study for dabigatran + RTV**

**PK**
- dabigatran alone 150 mg
- Dabigatran 150 mg adm 2 h before RTV 100 mg QD
- Dabigatran 150 mg adm together with RTV 100 mg QD

**PD**
- RTV: mixed inhibitory/inducing effect on P-gp

Possible to coadminister with DRV/r

Kumar P et al. AAC 2017

What about our patient who has a mild renal impairment?

**Simulation using PBPK modelling**

- dabigatran alone
- dabigatran + verapamil
- dabigatran 2 h before verapamil
- observed clinical data

Lower limit (28 ng/mL) associated with 50% increased risk of stroke or embolism
Upper limit (210 ng/mL) associated with a doubled risk of major bleeding

dabigatran + verapamil (multiple doses): dabigatran AUC + 50%

Coadministration possible. Caution in case of mild or moderate renal impairment as dabigatran dose might need to be reduced in presence of DRV/r.

⇒ patient switched to dabigatran 110 mg BID

Doki K et al. CPT Pharmacometrics Syst Pharmacol 2019, www.hiv-druginteractions.org
What about apixaban

Substrate of CYP3A4, P-gp, BCRP → drug interaction expected with darunavir/r

Recommendations: SmPC: **not recommended** with dual strong inhibitors of P-gp and CYP3A4
US PI: **avoid** concomitant use or **reduce apixaban dose by 50%** (2.5 mg BID)

Who among you has already used apixaban at a reduced dose with a boosted PI?

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history</td>
<td>HIV, T2DM, HCV, NSTEMI</td>
<td>HIV, HTN, COPD, CKD III</td>
<td>HIV, CAD, AF</td>
<td>HIV, HTN, HCV, T2DM</td>
<td>HIV, HTN, prior VTE, PVD</td>
</tr>
<tr>
<td>ARV</td>
<td>LPV/r +3TC +ABC</td>
<td>DRV/r +3TC +ABC</td>
<td>DRV/r +ETV +RAL</td>
<td>DRV/r +ETV +RAL</td>
<td>EVGc/F/TAF +DRV</td>
</tr>
<tr>
<td>DOAC ind.</td>
<td>Acute VTE</td>
<td>Acute VTE</td>
<td>AF</td>
<td>Acute VTE</td>
<td>Acute VTE</td>
</tr>
<tr>
<td>Apixaban dose</td>
<td>10 mg BID x 4 doses then 2.5 mg BID</td>
<td>5 mg BID x 7 days then 2.5 mg BID</td>
<td>2.5 mg BID indefinitely</td>
<td>10 mg BID x 7 days then 2.5 mg BID</td>
<td>5 mg BID x 7 days then 2.5 mg BID</td>
</tr>
<tr>
<td>Laboratory</td>
<td>Hgb 8.7 g/dL CrCl 35 mL/min</td>
<td>Hgb 11.7 g/dL CrCl 60 mL/min</td>
<td>Hgb 13.3 g/dL CrCl 65 mL/min</td>
<td>Hgb 9.9 g/dL CrCl &lt; 15 mL/min</td>
<td>Hgb 16.1 g/dL CrCl 65 mL/min</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Surgical bleed while on 10 mg BID. No events on 2.5 mg BID</td>
<td>No adverse events</td>
<td>No adverse events</td>
<td>No adverse events</td>
<td>No adverse events</td>
</tr>
</tbody>
</table>

Outcomes of drug-drug interactions in real-life

www.clinicalcasesDDIs.com

The page can be used for:

- **Reporting** new clinical cases on drug combinations
- **Searching** for information on specific combinations.
- **Share information on real-life experience** about drug combinations that may be used in the clinic.

José Molto will present this new website in more details
Available resources to check for drug-drug interactions

- **HIV drugs:** [HIV Drug Interactions](http://www.hiv-druginteractions.org)
- **HIV drugs:** [HIV InSite](http://hivinsite.ucsf.edu)
- **HIV/HCV drugs:** [HIV/HCV Drug Therapy Guide](http://app.hivclinic.ca)
- **HCV drugs:** [HEP Drug Interactions](http://www.hep-druginteractions.org)
- **Cancer drugs:** [Cancer Drug Interactions](http://www.cancer-druginteractions.org)
- **General:** [IBM Micromedex®](http://www.micromedexsolutions.com)
- **General:** [Lexicomp®](http://online.lexi.com/lco/action/home)
Lessons learned

• DDIs are practically unavoidable in HIV care but mostly manageable.

• Potential for DDIs to be considered systematically when selecting an antiretroviral regimen or when adding new medications to an existing HIV treatment with particular attention to adjust dosage or perform clinical monitoring when needed.

• Searchable online drug interactions databases constitute valuable tools to recognise and manage unwanted DDIs in clinical practice.

• Think beyond DDIs in elderly PLWH due to the presence of age related comorbidities and physiological changes which impact the risk-benefit ratio of many drugs ➔ dose carefully; adapt dosage to renal function; check for inappropriate drugs.
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