Review of The Most Common Drug-Drug Interactions in HIV Infected Patients

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The terms of the problem?

✧ The HIV infected patients live longer, but, doing so, they develop earlier some comorbidities, usually observed in the elderly.

✧ Among them we frequently observe:

- Cardiovascular and metabolic diseases
- Cancers
- Neuropsychic problems

✧ Moreover at least one third of these patients are coinfected with HCV hepatitis cirrhosis and fibrosis Liver cancer.

✧ Liver and kidney transplantations are now required and possible.

All these pathologies require a treatment driving the clinician to prescribe several drugs resulting in a high risk of drug-drug interactions.
Drug-drug Interactions

- Occur when either the **pharmacokinetics or the pharmacodynamics** of one drug is altered by another:
  
  - are a source of variability in drug response
  
  - are generally graded responses, that are dependent upon the concentration of the interacting species, and on dose and time
  
  - pharmacokinetic interactions may affect absorption rate, availability, distribution, and hepatic or renal clearance
  
  - pharmacodynamic interactions may be antagonistic, synergistic, or additive
Why are HIV/AIDS patients at risk?

- Use 3 or 4 drugs for antiretroviral drugs
- Multiple agents for treatment/prevention of co-morbidities (infections…)
- Patients living longer must be treated for other chronic diseases
- Most of the ARVs have a profound impact on metabolizing enzymes systems (e.g. CYP450)
Drug-Drug Interactions can result in:

- Therapeutic desired effect
- Negative DDI
- New side effect
- No consequence

- Effect (e.g., ritonavir + saquinavir; ritonavir + simvastatin: rhabdomyolysis)
- Effect (e.g., rifampin + protease inhibitors, indinavir + coumadin)
- New effect (e.g., ritonavir + amitriptyline)
- No consequences
Selected drugs with high potential for drug interactions in HIV patients

- **P450 Substrates / Narrow Therapeutic Window**
  - Statins (esp. simvastatin, lovastatin)
  - Methadone
  - Anticonvulsant drugs
  - Warfarin
  - Sildenafil (Viagra)
  - Oral contraceptives
  - Some benzodiazepines (midazolam, triazolam)
  - Astemizole/terfenadine/cisapride (off the market)
  - Ergot derivatives
  - Antiarrhythmics
Drugs contra-indicated with RTV

- **Antiarrhythmics:** Amiodarone, Bepridil, Flecaïnide, Propafenone, Quinidine
- **Antihistamines:** Astemizole, Terfenadine (off market)
- **Antimigraines:** Dihydroergotamine, Ergotamine
- **GI Motility:** Cisapride (off market)
- **Sedative/Hypnotics:** Midazolam, Triazolam
- **Neuroleptic:** Pimozide
- **Antilipemics:** Simvastatin, Lovastatin
- **St. John’s Wort**
Contraindicated medications
with other PIs

- terfenadine, astemizole
- cisapride
- triazolam, midazolam
- ergot derivatives (DHE, ergotamine)
- rifampin
- Simvastatin, lovastatin
- St. John’s Wort
Psychotropic medications
HIV infected patients have high rates of psychiatric illness.

The effective management of these psychiatric conditions can improve a patient’s quality of life and may improve antiretroviral adherence.

Care providers for patients with HIV infection frequently encounter clinical situations in which psychotropic medications are needed or are being used.

So, it is very important to recognize the many potential interactions based on cytochrome P450 metabolism, which is common to many psychotropics, the protease inhibitors, and the non nucleoside reverse-transcriptase inhibitors.
Of the benzodiazepines, alprazolam, midazolam, and triazolam are dependent on CYP 3A4 for metabolism. Potent inhibitors of this CYP isoform, such as ritonavir, can decrease clearance of these drugs and result in oversedation and possibly death.

Oxazepam, lorazepam, and temazepam are metabolized by glucuronidation. Drugs that increase the activity of glucuronidation, such as ritonavir or nelfinavir, may lower the levels of these drugs.

Eszopiclone is the first drug to be FDA approved for long-term use. Both eszopiclone and zaleplon are metabolized by CYP3A4, leaving them vulnerable to interactions with enzyme inhibitors.
## Benzodiazepines and ARVs

<table>
<thead>
<tr>
<th>Benzo</th>
<th>Metabolism</th>
<th>PIs</th>
<th>NNRTIs</th>
<th>IIs/cobi</th>
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</thead>
<tbody>
<tr>
<td><strong>Bromazepam</strong></td>
<td>Parent: Hydoxylation</td>
<td>Possible ↑ bromazepam concentrations</td>
<td>Possible ↓ bromazepam concentrations and withdrawal</td>
<td>Elvitegravir/cobicistat: possible ↑ bromazepam concentrations. Monitor and reduce benzodiazepine dose if necessary.</td>
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<tr>
<td><strong>Zopiclone</strong></td>
<td>Parent: CYP3A4 &gt; 2C8, 2C9</td>
<td>Possible ↑ zopiclone concentrations. A 50% zopiclone dosage reduction may be warranted when used with potent enzyme inhibitors</td>
<td>Possible ↓ zopiclone concentrations and withdrawal</td>
<td>Elvitegravir/cobicistat: possible ↑ zopiclone concentrations. Monitor and reduce zopiclone dose if necessary.</td>
</tr>
</tbody>
</table>
Antidepressants

Depression is a frequent disorder among HIV patients, with a reported incidence of up to 47.8% in some studies.

Patients are often treated with a variety of antidepressants, including selective serotonin reuptake inhibitors (SSRIs).

The majority of ARVs (PIs and NNRTIs) and antidepressants are substrates for, and can inhibit or induce, the CYP450 system, and they have the potential to cause clinically significant drug interactions including serotonin syndrome, a potentially fatal complication.

Most of these drug-drug interactions are mediated through CYP450 2D6 and 3A4 isoenzymes.

Tseng AL and Foisy MM., 1999; DeSilva KE, 2001
Tricyclic antidepressants

TCAs are indicated for treatment of depression (amitriptyline, imipramine, desipramine, doxepin, nortriptyline, protriptyline, and trimipramine) and obsessive compulsive disorder (clomipramine).

These drugs cause anticholinergic adverse effects, orthostasis, sedation, and weight gain. In overdose, conduction abnormalities (prolonged QT) can be deadly.

Close observation for signs and symptoms of tricyclic toxicity is necessary when combining TCAs with CYP inhibitors (Pis) and risks off treatment failure with inducers (NNRTIs).
Ritonavir has been shown to increase levels of a variety of SSRIs, including fluoxetine, citalopram, paroxetine, and sertraline.

One study reported cases of serotonin syndrome in patients taking concurrent fluoxetine with either ritonavir-saquinavir, or efavirenz-based regimens by either decreasing the daily dose of fluoxetine by half or discontinuing ritonavir.

Monitoring for antidepressant side effects when initiating ritonavir in patients receiving concurrent SSRI therapy is recommended.

SSRIs

**Induction**

**Paroxetine:** in the setting of darunavir showed a decreased paroxetine AUC by 39 %, Cmax by 36 %, Cmin by 37 %, and showed decreased paroxetine effects. In the setting of fosamprenavir, paroxetine had similar results with a decreased AUC by 58 %, Cmax by 60 %, and half-life of 25 % with decreased paroxetine effects. ARVs did not have affected levels.

**Sertaline:** in the setting of darunavir showed decreased AUC by 49 %, Cmax by 44 %, and Cmin by 49 % with decreased sertraline effects. There were no effects on the darunavir levels or efficacy.

**Citalopram:** has been shown to have no interactions with ritonavir
SSRIs effects

Inhibition

- Fluoxetine: in the setting of delavirdine showed that the delavirdine Cmin increased by 50 percent, and there were some increased delavirdine effects. In the setting of ritonavir a ritonavir AUC increased by 19 %, no change to Cmax, and increased ritonavir effects.

- Fluoxetine and fluvoxamine (inhibitors of CYP1A2 /CYP2D6) both increase the levels of the following HIV medications: amprenavir, delarvidine, efavirenz, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, and saquinavir but, considering the magnitude of the changes, no PIs dose adjustment is recommended.

- Sertraline, citalopram, and escitalopram seems to have little effect on the major CYP isoforms and are not expected to affect levels of the ARVs.

Tseng et al, 1999; Otto et al, 2005
Cardiovascular drugs
A side effect of taking HIV protease inhibitors is increased cholesterol and triglyceride (fat) levels. Therefore, some patients taking HIV protease inhibitors may need to take cholesterol-lowering medicines such as statins.

Table 1. Potential and described effects of antiretroviral medications on the metabolism of lipid-lowering agents. The comments are related to the effect of antiretrovirals on lipid-lowering drugs. If there is a potential for an effect of lipid-lowering drugs on antiretrovirals, those will be specifically indicated.

<table>
<thead>
<tr>
<th>Lipid-lowering drug</th>
<th>Ritonavir</th>
<th>Nelfinavir</th>
<th>Other PIs</th>
<th>Nevirapine</th>
<th>Efavirenz</th>
<th>Delavirdine</th>
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<td>HMG-CoA reductase inhibitors</td>
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<td>Simvastatin</td>
<td>Inhibition, ↑↑AUC, contraindicated</td>
<td>Inhibition, ↑↑AUC, contraindicated</td>
<td>Inhibition, ↑↑AUC, contraindicated</td>
<td>Probably no effect</td>
<td>Unknown</td>
<td>Inhibition, ↑↑AUC, contraindicated</td>
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<td>Lovastatin</td>
<td>Inhibition, ↑↑AUC, contraindicated</td>
<td>Inhibition, ↑↑AUC, contraindicated</td>
<td>Inhibition, ↑↑AUC, contraindicated</td>
<td>Probably no effect</td>
<td>Unknown</td>
<td>Inhibition, ↑↑AUC, contraindicated</td>
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<tr>
<td>Atorvastatin</td>
<td>Inhibition, ↑AUC, use with caution</td>
<td>Inhibition, ↑↑AUC, use with caution</td>
<td>Inhibition, ↑↑AUC, use with caution</td>
<td>Probably no effect</td>
<td>Probably no effect</td>
<td>Inhibition, ↑↑AUC, use with caution</td>
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<tr>
<td>Fluvastatin</td>
<td>Possible induction</td>
<td>Possible induction</td>
<td>Probably no effect</td>
<td>Probably no effect</td>
<td>Probably no effect</td>
<td>Inhibition, ↑↑AUC, use with caution</td>
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<td>Pravastatin</td>
<td>Induction of metabolism</td>
<td>Unknown (possible induction)</td>
<td>Probably no effect</td>
<td>Probably no effect</td>
<td>Probably no effect</td>
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<td>Fibric acid derivatives</td>
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<tr>
<td>Gemfibrozil</td>
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<tr>
<td>Fenofibrate</td>
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</table>

AUC = area under the concentration-time curve; PI = protease inhibitor; ↑ = some increase; ↑↑ = marked increase.
Statins and PI/rtv

Fig. 2. Mean effect of ritonavir 400mg/saquinavir 400mg twice daily on the steady-state pharmacokinetics of selected HMG-CoA reductase inhibitors given to HIV-seronegative volunteers (reproduced from Fichtenbaum et al.,[26] with permission from Lippincott Williams & Wilkins). The ordinate shows the percentage change in 24-hour area under the concentration-time curve (AUC$_{24}$) of the HMG-CoA reductase inhibitors after the administration of ritonavir/saquinavir. The abscissa shows the various HMG-CoA reductase inhibitors studied.
## Pravastatin and PIs

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<tr>
<th>Drug Combination</th>
<th>$C_{\text{max}}$</th>
<th>AUC</th>
<th>$C_{\text{min}}$</th>
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</thead>
<tbody>
<tr>
<td>SQV/RTV (400/400 BID) plus pravastatin, 40 mg/day</td>
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<tr>
<td>Effect on PRAV</td>
<td>0.58</td>
<td>0.50</td>
<td>N/A</td>
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<tr>
<td>LPV/RTV (400/100 BID) plus 20 mg/day dose of pravastatin</td>
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<tr>
<td>Effect on PRAV</td>
<td>1.26 (0.87, 1.83)</td>
<td>1.33 (0.91, 1.94)</td>
<td>N/A</td>
</tr>
<tr>
<td>DRV/RTV (600/100 BID) plus 40 mg single dose of pravastatin</td>
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<tr>
<td>Effect on PRAV</td>
<td>1.63 (0.95, 2.8)</td>
<td>1.81 (1.23, 2.66)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Darunavir [package insert].
# Pravastatin and DRV/RTV

<table>
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<tr>
<th>Patient</th>
<th>Pravastatin AUC Ratio (+DRV:-DRV)</th>
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<tr>
<td>1</td>
<td>5.53</td>
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<tr>
<td>2</td>
<td>6.78</td>
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<tr>
<td>13</td>
<td>1.16</td>
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<tr>
<td>14</td>
<td>1.49</td>
</tr>
<tr>
<td>Mean, CI</td>
<td>Mean, 1.81; 90% CI, 1.23, 2.66</td>
</tr>
<tr>
<td>Range</td>
<td>0.57, 6.78</td>
</tr>
</tbody>
</table>

Rosuvastatin and Lopinavir/ritonavir

- In 15 healthy volunteers receiving ROS, 20 mg/d, LPV/r caused a:
  - 4.7-fold increase in ROS Cmax,
  - 2.1-fold increase in ROS AUC;
  - Cmin unchanged
- Half-life unchanged; argues against CYP-mediated interaction
- Is there a role for transporters?

> adverse effects such as myalgias, rhabdomyolysis, elevated creatinine phosphokinase (CPK) (2 patients), and hepatic dysfunction

Hypothesis: Drug transporters

Marzolini C et al. In: Drug Interactions in Infectious Diseases 2011
# Statins

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Equivalence*</th>
<th>Metabolism</th>
<th>OATP1B1</th>
<th>BCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatine</td>
<td>20 mg</td>
<td>CYP3A4/2C8</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Fluvastatine</td>
<td>80 mg</td>
<td>CYP2C9</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10 mg</td>
<td>CYP3A4</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pravastatine</td>
<td>40 mg</td>
<td>no CYP</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Rosuvastatine</td>
<td>5 mg</td>
<td>CYP2C9 (mild)</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td></td>
<td></td>
<td>no elim. changes</td>
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</tbody>
</table>

* Equivalent doses to reduce LDL of 30-40%

In vitro Inhibition of OATP1B1 and BCRP by PIs

<table>
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<tr>
<th>Antiretrovirals</th>
<th>OATP 1A2</th>
<th>1B1</th>
<th>1B3</th>
<th>2B1</th>
<th>OAT 1</th>
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<th>2</th>
<th>PEPT 1</th>
<th>2</th>
<th>Pgp</th>
<th>BCRP 1</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Substrates: Inhibitors: x
Rosuvastatin and LPV/RTV: statin effect

Interaction between atazanavir/r and rosuvastatin

AUC x 3.1
Cmax x 7.0

Busti AJ. J Cardiovasc Pharmacol 2008
## Rosuvastatin - PIs

<table>
<thead>
<tr>
<th>PI</th>
<th>Increase statins (x)</th>
<th>Référence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC</td>
<td>Cmax</td>
</tr>
<tr>
<td>LPV/r</td>
<td>2.1</td>
<td>4.7</td>
</tr>
<tr>
<td>DRV/r</td>
<td>1.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Rosuvastatin +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATZ/r</td>
<td>3.1</td>
<td>7.0</td>
</tr>
<tr>
<td>fAPV/r</td>
<td>no change</td>
<td></td>
</tr>
</tbody>
</table>

Must start at low dose and adapt on the clinical results

(1) Kiser JJ. et al. JAIDS 2008;
(2) Fichtenbaum CJ. et al. 18th Int AIDS Conference 2010, abs. WEPE0101;
Lipid-lowering agents and PIs: drug interactions.

**Yes**
- Fibrates
- Fluvastatin
- Pravastatin
- Ezetimibe

**Low interaction potential**
- Atorvastatin
- Simvastatin
- Pravastatin
- Fosamprenavir

**Use cautiously**
- Nelfinavir
- Lopinavir

**Contraindicated with PIs**
- Saquinavir/Ritonavir

**Possible combination with: pravastatin (bile), rosuvastatin (CYP2C9) and fluvastatin (CYP2C9)**

Chanson N et al. NDT Plus 2008;1:157-161

© The Author [2008]. Published by Oxford University Press on behalf of ERA-EDTA. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org
Lovastatin & simvastatin extensively metabolised by CYP3A4 and plasma levels significantly increased by boosted PI
Contraindicated; use alternative.
# Statins + ARVs

<table>
<thead>
<tr>
<th>Statin</th>
<th>Interacting protease inhibitor(s)</th>
<th>Prescribing recommendation</th>
</tr>
</thead>
</table>
| Atorvastatin | • Tipranavir + ritonavir  
• Telaprevir  
• Lopinavir + ritonavir  
• Darunavir + ritonavir  
• Fosamprenavir  
• Fosamprenavir + ritonavir  
• Saquinavir + ritonavir  
• Nelfinavir | Avoid atorvastatin  
Use with caution and use with the lowest atorvastatin dose necessary  
Do not exceed 20 mg atorvastatin daily  
Do not exceed 40 mg atorvastatin daily |
| Lovastatin   | • HIV protease inhibitors  
• Boceprevir  
• Telaprevir | Contraindicated |
| Pitavastatin | • Atazanavir ± ritonavir  
• Darunavir + ritonavir  
• Lopinavir + ritonavir | No dose limitations |
| Pravastatin  | • Darunavir + ritonavir  
• Lopinavir + ritonavir | No dose limitations |
| Rosuvastatin | • Atazanavir ± ritonavir  
• Lopinavir + ritonavir | Limit rosuvastatin dose to 10 mg once daily |
| Simvastatin  | • HIV protease inhibitors  
• Boceprevir  
• Telaprevir | Contraindicated |
**Effect of etravirine on other drugs**

All studied metabolites are active.

- **Ethinylestradiol**
  - 15% increase
  - 22% decrease

- **TDF**
  - 15% decrease

- **SIL**
  - 15% increase

- **CLAR**
  - 39% decrease

- **Atorvastatin**
  - 37% decrease

- **Rifabutin**
  - 17% decrease

- **S-methadone**
  - 57% decrease

Scholler-Gyure M et al. 4th IAS Conference Sydney Abstract WEPEA 106.

Results: Rosiglitazone PK

- RGZ 4 mg (N = 14)  
  - $t_{1/2} = 5.7$ h

- RGZ 4 mg + ATV 400 mg QD (N = 14)  
  - $t_{1/2} = 4.3$ h

- RGZ 4 mg + ATV/RTV 300/100 mg QD (N = 14)  
  - $t_{1/2} = 3.3$ h
Conclusions

- ATV is a weak inhibitor of CYP2C8
  - CYP2C8 substrates may be modestly increased in the presence of ATV without RTV

- Induction by RTV offsets CYP2C8 inhibition by ATV

- There does not appear to be an *in vivo* relationship between CYP2C8 genotype and RGZ exposure or magnitude of ATV effect
## Other drugs

Table II. Potential effects of antiretroviral medications on the metabolism of antidiabetic agents. The comments are related to the effect of antiretrovirals on antidiabetic drugs. If there is a potential for an effect of antidiabetic drugs on antiretrovirals, those will be specifically indicated.

<table>
<thead>
<tr>
<th>Antidiabetic drug</th>
<th>Ritonavir</th>
<th>Nelfinavir</th>
<th>Other PIs</th>
<th>Nevirapine</th>
<th>Efavirenz</th>
<th>Delavirdine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td></td>
<td></td>
<td></td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>Possible induction</td>
<td>Possible induction</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>Probable inhibition of metabolism</td>
</tr>
<tr>
<td>Glibenclamide (glyburide)</td>
<td>Possible induction</td>
<td>Possible induction</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>Probable inhibition of metabolism</td>
</tr>
<tr>
<td>Glipizide</td>
<td>Possible induction</td>
<td>Possible induction</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>Probable inhibition of metabolism</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Possible induction</td>
<td>Possible induction</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>Probable inhibition of metabolism</td>
</tr>
<tr>
<td>Meglitinides</td>
<td></td>
<td></td>
<td></td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Probable inhibition of metabolism</td>
<td>Probable inhibition of metabolism</td>
<td>Probable inhibition of metabolism</td>
<td>Probable induction of metabolism</td>
<td>Possible induction of metabolic</td>
<td>Probable inhibition of metabolism</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td></td>
<td></td>
<td></td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Troglitazone</td>
<td>Probable induction of PI metabolism</td>
<td>Probable induction of PI metabolism</td>
<td>Probable induction of PI metabolism</td>
<td>Cannot determine</td>
<td>Cannot determine</td>
<td>Probable induction of delavirdine metabolism</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Possible inhibition</td>
<td>Possible inhibition</td>
<td>Possible inhibition</td>
<td>Cannot determine</td>
<td>Cannot determine</td>
<td>Possible induction of delavirdine metabolism</td>
</tr>
</tbody>
</table>

Pi = protease inhibitor.
Antihypertensive drugs

Table III. Potential and described effects of antiretroviral medications on the metabolism of antihypertensive agents. The comments are related to the effect of antiretrovirals on antihypertensive drugs.

<table>
<thead>
<tr>
<th>Antihypertensive drug</th>
<th>Ritonavir</th>
<th>Nelfinavir</th>
<th>Other PIs</th>
<th>Nevirapine</th>
<th>Efavirenz</th>
<th>Delavirdine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-Blockers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Mixed induction/ inhibition</td>
<td>Probably no effect</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Mixed induction/ inhibition</td>
<td>Mild induction</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>Probably no effect</td>
</tr>
<tr>
<td>Timolol</td>
<td>Possible inhibition</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td><strong>Angiotensin receptor antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Losartan</td>
<td>Probable mild induction of active metabolite formation (E-3174)</td>
<td>Probable mild induction of active metabolite formation (E-3174)</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>Probable inhibition of active metabolite formation (E-3174)</td>
</tr>
<tr>
<td>Calcium channel antagonists\textsuperscript{a}</td>
<td>Possible inhibition</td>
<td>Possible inhibition</td>
<td>Possible inhibition</td>
<td>Possible induction</td>
<td>Possible inhibition</td>
<td>Possible inhibition</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Concomitant use of calcium channel antagonists and PIs or NNRTIs should be contraindicated until drug-drug interaction studies establish that the combined use is safe. In addition, verapamil and diltiazem could inhibit the metabolism of PIs and NNRTIs.

NNRTI = non-nucleoside reverse transcriptase inhibitors; PI = protease inhibitor.
Active metabolite production was decreased by 38% ± 15% with 4-(4-chlorobenzyl)pyridine (CYP2B6 inhibitor) and by 45 ± 16% with ketoconazole (CYP3A inhibitor).

Daaly et al, 2011
In the presence of ritonavir, prasugrel AM Cmax and AUC were decreased by 45% (mean ratio: 0.55, CI 90%: 0.40-0.7, p = 0.007) and 38% (mean ratio: 0.62, CI 90%: 0.54-0.7, p = 0.005), respectively, while, T(1/2) and t(max) were not affected.

Midazolam metabolic ratio (MR) dramatically decreased in presence of ritonavir (6.7 ± 2.6 versus 0.13 ± 0.07) reflecting an almost complete inhibition of CYP3A4, whereas omeprazole, flurbiprofen and bupropion MR were not affected.

Therefore ritonavir is able to block prasugrel CYP3A4 bioactivation in vivo. This CYP-mediated drug-drug interaction might lead to a significant reduction of prasugrel efficacy in HIV-infected patients with acute coronary syndrome.
Immunosuppressive drugs
With reductions in AIDS-related mortality, patients with HIV infection are experiencing significant morbidity from end-stage liver and kidney disease and are, thus, potential transplant candidate.

Complex interactions between immunosuppressant and antiretroviral agents has enabled the management of these drugs through careful monitoring and frequent dose adjustments.

It is now recognized that patients with HIV infection should have access to solid organ transplantation.
Immunosuppressive drugs currently used

### Calcineurin inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Enzyme</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciclosporin</td>
<td>CYP3A4/5</td>
<td>Substrate and inhibitor of Pgp</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>CYP3A4/5</td>
<td>Substrate of Pgp</td>
</tr>
</tbody>
</table>

### m-TOR inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Enzyme</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirolimus</td>
<td>CYP3A4/5</td>
<td>Substrate of Pgp</td>
</tr>
<tr>
<td>Everolimus</td>
<td>CYP3A4/5</td>
<td>ND</td>
</tr>
</tbody>
</table>

### Purine synthesis inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Enzyme</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>TPMP</td>
<td>-</td>
</tr>
<tr>
<td>Mycophenolic acid</td>
<td>UGT1A9</td>
<td>-</td>
</tr>
</tbody>
</table>

All these drugs exhibit a narrow therapeutic index.
**Tacrolimus and Sirolimus**

- **T**: macrolide immunosuppressant, calcineurin inhibitor (CNI), which includes cyclosporin
- **S**: macrolide immunosuppressant, mTOR inhibitor

**MOA:**

- **T**: inhibits the activation of T-lymphocytes and the formation of IL-2
- **S**: inhibits immune cell growth and decreasing IL-2 activities

**Narrow therapeutic window**

- Levels too high: toxicities (i.e. nephrotoxicity, mental confusion, hyperglycemia and hypertension)
- Levels too low: transplant rejection
## Metabolism Pathways

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Tacrolimus</th>
<th>Sirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CYP3A4, CYP3A5, CYP2D6, CYP2E1, CYP2A6, UGT2B7, P-gp</td>
<td>CYP3A4 - intestinal, CYP3A5, P-gp</td>
</tr>
<tr>
<td>Inhibitor</td>
<td>CYP3A4 (moderate), UGT1A1, P-gp</td>
<td>CYP3A4, P-gp</td>
</tr>
<tr>
<td>Inducer</td>
<td>NONE</td>
<td>NONE</td>
</tr>
</tbody>
</table>
## Immunosuppressive and antiretroviral drugs as substrates

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>CYP</th>
<th>Transporters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3TC</td>
<td>3A4</td>
<td>P-gp</td>
</tr>
<tr>
<td>D4T</td>
<td>3A4</td>
<td>P-gp</td>
</tr>
<tr>
<td>ddC</td>
<td>3A4</td>
<td>P-gp</td>
</tr>
<tr>
<td>ddl</td>
<td>3A4</td>
<td>P-gp</td>
</tr>
<tr>
<td>ZDV</td>
<td>3A4</td>
<td>P-gp</td>
</tr>
<tr>
<td>ABC</td>
<td>3A4</td>
<td>P-gp</td>
</tr>
<tr>
<td>TFV</td>
<td>3A4</td>
<td>P-gp</td>
</tr>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLV</td>
<td>3A4, 2D6</td>
<td>P-gp</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>3A4, 2D6</td>
<td>P-gp</td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>3A4</td>
<td>P-gp</td>
</tr>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amprenavir (APV)</td>
<td>3A4</td>
<td>P-gp</td>
</tr>
<tr>
<td>Indinavir (IDV)</td>
<td>3A4</td>
<td>P-gp, MRP</td>
</tr>
<tr>
<td>Lopinavir (LPV)</td>
<td>3A4</td>
<td>P-gp</td>
</tr>
<tr>
<td>Nelfinavir (NFV)</td>
<td>3A4</td>
<td>P-gp</td>
</tr>
<tr>
<td>Ritonavir (RTV)</td>
<td>3A4, 2D6</td>
<td>P-gp, MRP</td>
</tr>
<tr>
<td>Saquinavir (SQV)</td>
<td>3A4</td>
<td>P-gp</td>
</tr>
<tr>
<td><strong>Immunosuppressive drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone (GCs)</td>
<td>3A4</td>
<td>P-gp, MRP</td>
</tr>
<tr>
<td>Azathioprine (AZA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine (CsA)</td>
<td>3A4</td>
<td>P-gp, MRP</td>
</tr>
<tr>
<td>Tacrolimus (FK)</td>
<td>3A4</td>
<td>P-gp</td>
</tr>
<tr>
<td>Mycophenolate (MMF)</td>
<td>3A4</td>
<td></td>
</tr>
<tr>
<td>Siroplasmon (Siro)</td>
<td>3A4</td>
<td>P-gp</td>
</tr>
</tbody>
</table>
Blood levels of tacrolimus after allogeneic HSCT
Outpatient monitoring of blood tacrolimus levels

![Graph showing blood tacrolimus levels over days after PBSCT with arrows indicating doses of 0.5 mg given at specific days.]

<table>
<thead>
<tr>
<th>Day after HSCT</th>
<th>Tacrolimus level</th>
<th>Dose of tacrolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>9.9</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>26</td>
<td>12.6</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>29</td>
<td>10.9</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>35</td>
<td>10.8</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>40</td>
<td>9.30</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>9</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>47</td>
<td>5.2</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>64</td>
<td>5.8</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>69</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>71</td>
<td>9</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>77</td>
<td>9</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>85</td>
<td>8.4</td>
<td></td>
</tr>
</tbody>
</table>
Tacrolimus blood levels during 12 or 24 h pharmacokinetic assessment in patients concomitantly treated with different types of HIV therapies. (a) Case 1 was treated with ritonavir, saquinavir and lopinavir when receiving a single dose of 0.5 mg of tacrolimus every 2 weeks (circles) and at a later timepoint with 0.06 mg of tacrolimus once daily (squares). (b) Two patients were treated with 400 mg of riteltegravir and 1 mg (squares, Case 4) or 2 mg (circles, Case 5) of tacrolimus, all given twice daily. (c) Case 3 was treated with ritonavir, darunavir and tacrolimus (0.01 mg in the morning and 0.02 mg in the evening). The horizontal lines show the lower and upper limits of the therapeutic range of tacrolimus blood concentrations, from 5 to 10 ng/mL.

Graphs show tacrolimus *trough levels* from three patients after *orthotopic liver transplant*, treated with

(a) 0.06 mg of tacrolimus once daily (unless otherwise indicated) with ritonavir, lopinavir and saquinavir;

(b) 0.08 mg of tacrolimus once daily with ritonavir and fosamprenavir;

(c) 0.03 mg of tacrolimus daily with ritonavir and darunavir.

The reported data suggest the use of a single dose of 0.5–1 mg of tacrolimus every 1–3 weeks when taken together with ritonavir-containing HAART.

However, this approach requires intensive therapeutic drug monitoring of both immunosuppressants and HAART.

Decreasing the dose of tacrolimus to 0.03–0.08 mg daily in patients with concomitant boosted PI therapy resulted in stable tacrolimus blood levels without alteration of PI drug levels.

Concomitant use of raltegravir and tacrolimus revealed no clinically relevant drug interaction.
HIV – HCV coinfection
Some challenges (in part pharmacological) for HIV/HCV co-infected patients

<table>
<thead>
<tr>
<th>Population</th>
<th>Caveat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver transplantation</td>
<td>Drug–drug interactions; rejection</td>
</tr>
<tr>
<td>Advanced liver disease (cirrhosis)</td>
<td>Impaired DAA metabolism; enhanced toxicity</td>
</tr>
<tr>
<td>Prior IFNα null responders</td>
<td>Lower response; increased risk of selecting HCV drug resistance</td>
</tr>
<tr>
<td>IFNα and/or RBV intolerant</td>
<td>Wait for IFN and/or RBV sparing combinations</td>
</tr>
<tr>
<td>Non-HCV 1 genotypes</td>
<td>Poor or null activity</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>No data</td>
</tr>
<tr>
<td>Children</td>
<td>Dose adjustments</td>
</tr>
<tr>
<td>Acute hepatitis C</td>
<td>No data; added value?</td>
</tr>
<tr>
<td>Inherited hematological disorders: thalasemia, hemophilia</td>
<td>Enhanced toxicities: anemia, bleeding</td>
</tr>
<tr>
<td>Socially dysfunctional groups (i.e. homeless, illegal immigrants)</td>
<td>Difficult-to-reach and keep on satisfactory drug adherence</td>
</tr>
<tr>
<td>Intravenous drug users</td>
<td>Concerns about drug adherence and transmission of drug-resistant HCV mutants</td>
</tr>
</tbody>
</table>
**PK Interactions between PI/r and boceprevir (BOC)**

<table>
<thead>
<tr>
<th>IP/r</th>
<th>BOC → IP/r ($C_{\text{min}}$)</th>
<th>IP/r → BOC ($C_{\text{min}}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r</td>
<td>≪ 49 %</td>
<td>≪ 49 %</td>
</tr>
<tr>
<td>DRV/r</td>
<td>≪ 59 %</td>
<td>≪ 32 %</td>
</tr>
<tr>
<td>LPV/r</td>
<td>≪ 43 %</td>
<td>≪ 45 %</td>
</tr>
</tbody>
</table>

**Conclusions**
- coadministration of BOC and ATV/r or DRV/r or LPV/r decrease significantly the $C_{\text{trough}}$ of these PIs
- but no modification of plasmatique exposure to BOC is observed meanwhile DRV/r and LPV/r reduce clearly the BOC $C_{\text{trough}}$
- these results are obviously in favour of significant PK interactions able to decrease the antiviral therapies.
# Pharmacokinetic Interactions Between ARVs and Telaprevir

<table>
<thead>
<tr>
<th>TVR Dose</th>
<th>ARV</th>
<th>TVR AUC</th>
<th>TVR $C_{\text{min}}$</th>
<th>ARV AUC</th>
<th>ARV$C_{\text{min}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVR 750 mg tid</td>
<td>ATV/r</td>
<td>0.80</td>
<td>0.85</td>
<td>1.17</td>
<td>1.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.76-0.98)</td>
<td>(0.75-0.98)</td>
<td>(0.97-1.43)</td>
<td>(1.40-2.44)</td>
</tr>
<tr>
<td></td>
<td>DRV/r</td>
<td>0.65</td>
<td>0.68</td>
<td>0.60</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.61-0.69)</td>
<td>(0.63-0.74)</td>
<td>(0.57-0.63)</td>
<td>(0.52-0.63)</td>
</tr>
<tr>
<td></td>
<td>FPV/r</td>
<td>0.68</td>
<td>0.70</td>
<td>0.53</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.63-0.72)</td>
<td>(0.64-0.77)</td>
<td>(0.49-0.58)</td>
<td>(0.40-0.50)</td>
</tr>
<tr>
<td></td>
<td>LPV/r</td>
<td>0.46</td>
<td>0.48</td>
<td>1.06</td>
<td>1.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.41-0.52)</td>
<td>(0.40-0.56)</td>
<td>(0.96-1.17)</td>
<td>(0.96-1.36)</td>
</tr>
<tr>
<td>TVR 1125 mg tid</td>
<td>EFV</td>
<td>0.82</td>
<td>0.75</td>
<td>0.82</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.73-0.92)</td>
<td>(0.66-0.86)</td>
<td>(0.74-0.90)</td>
<td>(0.81-1.01)</td>
</tr>
<tr>
<td></td>
<td>TDF</td>
<td>1.10</td>
<td>1.06</td>
<td>1.10</td>
<td>1.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.03-1.18)</td>
<td>(1.06-1.28)</td>
<td>(1.03-1.18)</td>
<td>(1.06-1.28)</td>
</tr>
<tr>
<td>TVR 1500 mg bid</td>
<td>EFV</td>
<td>0.80</td>
<td>0.52</td>
<td>0.85</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.73-0.88)</td>
<td>(0.42-0.64)</td>
<td>(0.79-0.91)</td>
<td>(0.82-0.96)</td>
</tr>
<tr>
<td></td>
<td>TDF</td>
<td>1.10</td>
<td>1.06</td>
<td>1.10</td>
<td>1.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.03-1.17)</td>
<td>(0.98-1.15)</td>
<td>(1.03-1.17)</td>
<td>(0.98-1.15)</td>
</tr>
</tbody>
</table>

Summary of HIV PIs/r and HCV PIs

Effects of BOC or TVR on PIs/r $C_{\text{trough}}$

TVR increase by 85 % ATV $C_{\text{trough}}$

DRV/r decreases by 35 % BOC $C_{\text{trough}}$ and by 32 % TVR $C_{\text{trough}}$
No interaction between BOC and RAL

### Conclusions
- **BOC doesn’t modify RAL exposition**
- Its PK is comparable to historic data
- The absence of interaction provide an interesting alternative for HIV-HCV coinfected patients.
PK Interaction between TMC435 and ARV

• TMC435 new anti-HCV (genotype 1) NS3/4A inhibitor given QD
• TMC435 inhibits OATP1B1 (influx) and MRP2 (efflux) at the origin of hyperbilirubinémies observed at highest doses (Huisman MT, AASLD 2010, Abs. 278)
• TMC435 is a substrate and inhibitor of intestinal CYP3A4 (not in liver) and of hepatic CYP1A2 (Sekar V, EASL 2010, Abs. 1076)

Impact of ARV drugs on TMC 435

<table>
<thead>
<tr>
<th>ARV</th>
<th>$C_{\text{max}}$</th>
<th>$AUC_{24h}$</th>
<th>$C_{\text{min}}$</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>0.85 (0.73 - 0.99)</td>
<td>0.86 (0.76 - 0.98)</td>
<td>0.93 (0.78 - 1.11)</td>
<td>↔</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>1.10 (0.97 - 1.26)</td>
<td>1.06 (0.94 - 1.19)</td>
<td>0.96 (0.83 - 1.11)</td>
<td>↔</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>0.49 (0.44 - 0.54)</td>
<td>0.29 (0.26 - 0.33)</td>
<td>0.09 (0.08 - 0.12)</td>
<td>↓</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>0.93 (0.85 - 1.02)</td>
<td>0.89 (0.81 - 0.98)</td>
<td>0.86 (0.75 - 0.98)</td>
<td>↔</td>
</tr>
</tbody>
</table>
PK Interaction between TMC435 and ARVs

<table>
<thead>
<tr>
<th>ARVs</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;</th>
<th>AUC&lt;sub&gt;24h&lt;/sub&gt;</th>
<th>C&lt;sub&gt;trough&lt;/sub&gt;</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>1,19 (1,10 - 1,30)</td>
<td>1,18 (1,13 - 1,24)</td>
<td>1,24 (1,15 - 1,33)</td>
<td>⇔</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>1,04 (0,95 - 1,13)</td>
<td>1,12 (1,05 - 1,19)</td>
<td>1,25 (1,16 - 1,35)</td>
<td>⇔</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>0,97 (0,89 - 1,06)</td>
<td>0,90 (0,85 - 0,95)</td>
<td>0,87 (0,81 - 0,93)</td>
<td>⇔</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>1,03 (0,78 - 1,36)</td>
<td>1,08 (0,85 - 1,38)</td>
<td>1,14 (0,97 - 1,36)</td>
<td>⇔</td>
</tr>
</tbody>
</table>

- **Conclusions**
  - Good safety
  - **No dose adjustment for TMC435 and RPV, RAL or TDF**
  - But, because of TMC435 metabolism induction by EFV their combination is contra-indicated
    \(C_{\text{max}} \downarrow 51 \%, \text{ASC}_{24h} \downarrow 71 \% \text{ et } C_{\text{min}} \downarrow 91 \%)
Summary of known and anticipated DDIs between ARVs and anti-HCV drugs in current use and the HCV PIs in Phase III development
Table 1. Pharmacokinetic interactions between hepatitis C virus protease inhibitors and common HIV drugs.

<table>
<thead>
<tr>
<th></th>
<th>Telaprevir</th>
<th>Comedication</th>
<th>Boceprevir</th>
<th>Comedication</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF</td>
<td>( \approx )</td>
<td>( \uparrow 30% )</td>
<td>( \uparrow 18% )</td>
<td>( \uparrow 8% )</td>
</tr>
<tr>
<td>EFV</td>
<td>( \downarrow 26% ) (t.i.d.)</td>
<td>( \downarrow 7% ) (t.i.d)</td>
<td>( \downarrow 19% )</td>
<td>( \uparrow 20% )</td>
</tr>
<tr>
<td>ATV/r</td>
<td>( \downarrow 20% )</td>
<td>( \uparrow 17% )</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>DRV/r</td>
<td>( \downarrow 35% )</td>
<td>( \downarrow 40% )</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>FPV/r</td>
<td>( \downarrow 32% )</td>
<td>( \downarrow 47% )</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>LPV/r</td>
<td>( \downarrow 54% )</td>
<td>( \uparrow 16% )</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>RTV (low dose)</td>
<td>( \downarrow 24% )</td>
<td>–</td>
<td>( \downarrow 19% )</td>
<td>–</td>
</tr>
<tr>
<td>R-methadone</td>
<td>( \approx )</td>
<td>( \downarrow 29% )</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Midazolam</td>
<td>–</td>
<td>9-fold</td>
<td>( \uparrow 5)-fold</td>
<td>–</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>( \approx )</td>
<td>( \downarrow 35% )</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>( \approx )</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Contraceptives (estrogen/progestogen)</td>
<td>( \approx )</td>
<td>( \downarrow 28% / \downarrow 11% )</td>
<td>–</td>
<td>( \downarrow 24% / \uparrow 99% )</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>–</td>
<td>( \uparrow 8)-fold</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>( \uparrow 62% )</td>
<td>( \uparrow 46% )</td>
<td>( \uparrow 12.3)-fold</td>
<td>–</td>
</tr>
</tbody>
</table>

Changes reported are for the area under the plasma concentration time curve (AUC). Data for other PK parameters (e.g. \( C_{\text{max}} \) and \( C_{\text{min}} \)) are also available. Refer to www.hep-druginteractions.org for a full and updated list of established and other potentially significant drug interactions. DRV/r, darunavir/ritonavir; EFV, efavirenz; FPV/r, fosamprenavir/ritonavir; LPV/r, lopinavir/ritonavir; RTV, ritonavir; TDF, tenofovir.
# New Anti HCV: STAT-C agents

## Table 1. STAT-C agents in Phase II or III clinical trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Development phase</th>
<th>Potential for interaction with ARVs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telaprevir (Vertex/Tibotec)</td>
<td>NS3/4A HCV protease inhibitor</td>
<td>III</td>
<td>evidence for CYP3A4 metabolism; levels may be increased by ritonavir-boosted ARV PIs, and decreased by NNRTIs; data from Phase II trials show that anaemia was more common in treatment groups than placebo; potential for increased effect if administered with ZDV</td>
</tr>
<tr>
<td>VX-950</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boceprevir (Schering)</td>
<td>NS3/4A HCV protease inhibitor</td>
<td>III</td>
<td>evidence for CYP3A4 metabolism; levels may be increased by ritonavir-boosted ARV PIs, and decreased by NNRTIs; data from Phase II trials show that anaemia was more common in treatment groups than placebo; potential for increased effect if administered with ZDV</td>
</tr>
<tr>
<td>SCH 503034</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMC 435 (Tibotec/Medivir)</td>
<td>NS3/4A HCV protease inhibitor</td>
<td>II</td>
<td>unknown</td>
</tr>
<tr>
<td>MK-7009 (Merck)</td>
<td>NS3/4A HCV protease inhibitor</td>
<td>II</td>
<td>unknown, although Phase I data suggest renal elimination is minor; little potential for interaction with NRTIs via this mechanism</td>
</tr>
</tbody>
</table>

**Polymerase inhibitors**
New Anti HCV: Polymerase inhibitors

<table>
<thead>
<tr>
<th>Drug Code</th>
<th>Type</th>
<th>Phase</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS 9190 (Gilead)</td>
<td>non-nucleoside polymerase inhibitor</td>
<td>III</td>
<td>little potential for inhibition or induction of human CYP450 and lack of recognition by efflux transporter proteins in vitro.</td>
</tr>
<tr>
<td>R7128 (Roche)</td>
<td>nucleoside polymerase inhibitor</td>
<td>II</td>
<td>potential competition for elimination pathways with cytidine analogue NRTIs 3TC and FTC.</td>
</tr>
<tr>
<td>IDX184 (Idenix)</td>
<td>nucleoside polymerase inhibitor (liver targeted pro-drug)</td>
<td>II</td>
<td>unknown</td>
</tr>
<tr>
<td>PF-868554 (Pfizer)</td>
<td>non-nucleoside polymerase inhibitor</td>
<td>II</td>
<td>unknown</td>
</tr>
<tr>
<td>VCH-759 (ViroChem/Vertex)</td>
<td>non-nucleoside polymerase inhibitor</td>
<td>II</td>
<td>unknown</td>
</tr>
<tr>
<td>ANA598 (Anadys)</td>
<td>non-nucleoside polymerase inhibitor</td>
<td>II</td>
<td>unknown</td>
</tr>
</tbody>
</table>

Others

<table>
<thead>
<tr>
<th>Drug Code</th>
<th>Type</th>
<th>Phase</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debio 025</td>
<td>cyclophillin inhibitor</td>
<td>II</td>
<td>hyperbilirubinaemia reported as one of most frequent adverse events in Phase II study, possibly due to inhibition of MRP2 by Debio 025.</td>
</tr>
<tr>
<td>AZD2836/A-831 (Arrow Therapeutics/AstraZeneca)</td>
<td>NS5A inhibitor</td>
<td>II</td>
<td>potential for increased hyperbilirubinaemia risk when co-administered with ATV or IDV.</td>
</tr>
<tr>
<td>ITX5061 (iTherX)</td>
<td>entry inhibitor</td>
<td>II</td>
<td>unknown</td>
</tr>
</tbody>
</table>

ZDV, zidovudine; 3TC, lamivudine; FTC, emtricitabine; MRP2, multidrug resistance protein 2; ATV, atazanavir; IDV, indinavir.
Interaction of Street Drugs with HIV Medications

Prepared by Mark Kinzly & Nabarun Dasgupta, Doug Bruce, MA MD.
Yale School of Epidemiology and Public Health, Yale AIDS Program
# Interactions Between ARVs and Rave Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolism</th>
<th>Actual/Theoretical Interaction</th>
<th>Potential Significance</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>CYP2D6&lt;sup&gt;26-28&lt;/sup&gt;</td>
<td>possible ↑ concentrations with ritonavir</td>
<td>hypertension, hyperthermia, seizures, arrhythmias, tachycardia, tachypnea</td>
<td>avoid combination with ritonavir if possible; alternatively, start with 1/4–1/2 of initial amount of amphetamine used</td>
</tr>
<tr>
<td>GHB</td>
<td>expired breath as CO₂; first-pass metabolism&lt;sup&gt;29,30&lt;/sup&gt;</td>
<td>possible ↑ concentrations/ prolonged effect with antiretrovirals, especially ritonavir</td>
<td>1 case&lt;sup&gt;31&lt;/sup&gt; of GHB toxicity with ritonavir/saquinavir; myoclonic or seizure activity, bradycardia, respiratory depression, loss of consciousness</td>
<td>use cautiously with CYP450 inhibitors (i.e., PIs, delavirdine, efavirenz); become aware of signs/symptoms of GHB toxicity</td>
</tr>
<tr>
<td>Ketamine</td>
<td>CYP2B6 (main), 3A, 2C9 (both to lesser extent)&lt;sup&gt;32-35&lt;/sup&gt;</td>
<td>possible ↑ concentrations with antiretrovirals, especially ritonavir, nelfinavir, and efavirenz</td>
<td>respiratory depression, loss of consciousness, hallucinations</td>
<td>use cautiously with CYP450 inhibitors, especially ritonavir, nelfinavir, and efavirenz; become aware of signs/symptoms of ketamine toxicity</td>
</tr>
<tr>
<td>LSD</td>
<td>unknown&lt;sup&gt;39,40&lt;/sup&gt;</td>
<td>possible ↑ LSD concentrations</td>
<td>hallucinations, agitation, psychosis, flashbacks</td>
<td>use cautiously with CYP450 inhibitors (i.e., PIs, delavirdine, efavirenz); become aware of signs/symptoms of LSD toxicity</td>
</tr>
<tr>
<td>MDMA, Ecstasy</td>
<td>CYP2D6&lt;sup&gt;21-23&lt;/sup&gt; (main), 1A2, 2B6, 3A4 (to lesser extent)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>possible ↑ concentrations with ritonavir, other PIs, efavirenz</td>
<td>1 death reported&lt;sup&gt;18&lt;/sup&gt;; hyponatremia, hyperthermia, arrhythmias, tremor, hyperreflexia, sweating, seizures, tachycardia, rhabdomyolysis</td>
<td>avoid combining with ritonavir if possible; alternatively use ~1/4–1/2 of usual amount and watch for signs of MDMA toxicity; stay well hydrated at party, avoid alcohol, take breaks from dancing</td>
</tr>
<tr>
<td>PCP</td>
<td>CYP3A&lt;sup&gt;36&lt;/sup&gt;, CYP2C11&lt;sup&gt;37&lt;/sup&gt; inhibits CYP2B1&lt;sup&gt;38&lt;/sup&gt;</td>
<td>possible ↑ concentrations with antiretrovirals</td>
<td>seizures, hypertension, rhabdomyolysis, hyperthermia</td>
<td>use cautiously with CYP450 inhibitors (i.e., PIs, delavirdine, efavirenz); become aware of signs/symptoms of PCP toxicity</td>
</tr>
</tbody>
</table>

GHB = γ-hydroxybutyrate; LSD = lysergic acid diethylamide; MDMA = methylenedioxymethamphetamine; PCP = phencyclidine; PI = protease inhibitor.
Methadone and NRTIs

• Methadone may cause nucleosides to build up in the body and lead to toxicity from AZT. Patients should be monitored for toxic reactions to AZT including nausea, vomiting, headaches and low blood platelet levels.

• Methadone may decrease the anti-HIV action of ddi and d4T while taking methadone. This could lead to resistance in the virus. Taking the pill form (and not the syrup) is thought to allow the drugs to pass through the stomach without methadone weakening them.
Methadone

- EFZ and NVP may cause withdrawal if taken while using methadone. People on methadone maintenance may need higher doses of the opiate.
- RTV, and LPV/rtv possibly may also cause similar problems.
<table>
<thead>
<tr>
<th>PI</th>
<th>Effect</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprenavir</td>
<td>Methadone AUC ↓ 35%</td>
<td>Monitor for opiate withdrawal; consider use of other PI</td>
</tr>
<tr>
<td></td>
<td>APV $C_{\text{min}}$ ↓ 25%</td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td>No significant effect on methadone AUC</td>
<td>Combination can likely be safely co-administered</td>
</tr>
<tr>
<td></td>
<td>IDV $C_{\text{min}}$ ↑ 50-100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(AUC unchanged, peak increased)</td>
<td></td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Methadone AUC ↓ 36%</td>
<td>Monitor for symptoms of opiate withdrawal</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Methadone AUC ↓ 40%</td>
<td>Monitor for symptoms of opiate withdrawal</td>
</tr>
<tr>
<td></td>
<td>NFV M8 metabolite AUC ↓ 53%</td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Methadone AUC ↓ 36%</td>
<td>Monitor for symptoms of opiate withdrawal</td>
</tr>
<tr>
<td></td>
<td>APV $C_{\text{min}}$ ↓ 25%</td>
<td></td>
</tr>
<tr>
<td>Saquinavir/ritonavir</td>
<td>Methadone (R) AUC ↓ 32%</td>
<td>Monitor for symptoms of opiate withdrawal</td>
</tr>
<tr>
<td></td>
<td>No effect on unbound methadone levels</td>
<td></td>
</tr>
</tbody>
</table>

Back et al, 2005
Effect of ART on Methadone and Buprenorphine

Methadone

- Methadone levels decreased by PI/r and NNRTIs
- Monitor for withdrawal signs and symptoms
- Some patients may require increase in methadone dose
- Complicated by differential effect on the inactive S(-) and the active R(-) methadone

Buprenorphine (BUP)

- BUP levels decreased by NVP & EFV: Use standard dose BUP and titrate to effect
- For PIs BUP levels increased so may need decrease in BUP dose.
Amphetamines
(dexedrine, amphetamine, methamphetamine, crystal meth)

- Amphetamines work the same way that X does in your body. As with X, Norvir (ritonavir) should be avoided.
  - Norvir is predicted to increase amphetamine levels in the blood by a factor of 2-3.
- The other protease inhibitors should have less of an impact, but strange opposite results are always possible.
PCP (angel dust, morning glory)

- PIs, Delavirdine, and possibly Efavirenz work in the same liver pathway that PCP is broken down in.

- Taking PCP while using these drugs may result in high PCP concentrations and cause toxic shock and/or death.
## ARV Interactions with Recreational Drugs

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Effect</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td><strong>Abacavir AUC ↑ 41%</strong></td>
<td>Clinical significance unknown</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>RTV may ↑ amphetamine levels</td>
<td>Potential amphetamine toxicity</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Potential ↓ levels of PIs and NNRTIs</td>
<td>Potential virologic failure/resistance</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>↑ Midazolam and triazolam levels with PIs and delavirdine (levels of alprazolam and clonazepam may ↑)</td>
<td>Potential benzodiazepine toxicity</td>
</tr>
<tr>
<td>Drug</td>
<td>Effect</td>
<td>Comments</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>----------------------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>( \lambda )-hydroxybutyrate (GHB)</td>
<td>Potential ↑ GHB levels</td>
<td>Potential GHB toxicity</td>
</tr>
<tr>
<td>Heroin</td>
<td>Potential enhanced heroin effect</td>
<td>Clinical significance unknown</td>
</tr>
<tr>
<td>Marijuana</td>
<td>Minimal effect on IDV and NFV</td>
<td>Interaction with ARVs unlikely</td>
</tr>
<tr>
<td>3,4-methylenedioxy-methamphetamine (Ecstasy)</td>
<td>Potential ↑ ecstasy levels</td>
<td>Potential ecstasy toxicity</td>
</tr>
</tbody>
</table>
Anticancer drugs
Multiple interactions possibilities

anticancer/antiretroviral chemotherapy

Efficacy
Toxicity

Between anticancer drugs

Between antiretroviral drugs

Co-medications:
- analgesics,
- antibiotics,
- antacids,
- antifungals…

Interactions between anticancer and antiretroviral drugs
Numerous Similarities

- Polychemotherapy is the rule
- Most of the drugs exhibit a small therapeutic index
- The majority of these drugs interact with metabolic enzymes and/or drug transporters.
- Resistance is an issue
- Comune toxicities are frequent
- Therefore their concomitant use is complicated because of a high risk of pharmacokinetic and/or pharmacodynamic interactions.
Blood-brain barrier

CYP3A4

ABCB1

Oral administration

Liver

Absorption in gut depends on the presence or absence of food and on pH

Stomach

Metabolism in the liver by CYPs (potential site for drug interactions).

Kidney

Excretion in the kidney (potential site for interactions with transporters and proteins)

Intestine

Drug in bloodstream

Transportation in the blood

Chemotherapy

Oral administration

Blood-brain barrier

ABCB1
**P-gp Substrates**

**Antiretrovirals**
- All Protease inhibitors (RTV = booster)
- NNRTIs: *Efavirenz, Nevirapine*? *(at a less extent)*

**Anticancer drugs**
- Chlorambucil
- Cisplatin
- Dactinomycin
- Daunorubicin
- Dexamethasone
- Docetaxel
- Doxorubicin
- Etoposide
- Methylprednisolone
- Mitoxantrone
- Paclitaxel
- Tamoxifen
- Vinblastine
- Vincristine
## Cellular transporters and substrates

<table>
<thead>
<tr>
<th>Transporteur</th>
<th>Classe thérapeutique</th>
<th>Substrats</th>
<th>Exemples</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gp (MDR1/ABCB1)</td>
<td>Anticancéreux</td>
<td>Doxorubicine, daunorucine, vinblastine, vincristine, étoposide, paclitaxel, taxol, docétaxel, méthotrexate, mitoxantrone.</td>
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<tr>
<td></td>
<td>Opioïdes</td>
<td>Méthadone, lopéramide, Fentanyl.</td>
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<td></td>
<td>Psychotrope</td>
<td>Amitriptyline, Midazolam, rispéridone, citalopram.</td>
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<td>Anti-épileptiques</td>
<td>Phénytoïne, Carbamazépine, lamotrigine, phénobarbitral, felbamate.</td>
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<td>Inhibiteurs de protéase du VIH</td>
<td>Amprenavir, indinavir, saquinavir, nelfinavir, ritonavir.</td>
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<td>Antibiotiques</td>
<td>Erythromycine, valinomycine, tétracycline, fluoroquinolones.</td>
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<td>MRP1 (ABCC1)</td>
<td>Anticancéreux</td>
<td>Etoposides, vincristine, Doxorubicine, daunirubicine, méthotrexate.</td>
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<td>Inhibiteurs de protéase du VIH</td>
<td>ritonavir, saquinavir.</td>
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<td>Analogues nucléoïdiques</td>
<td>Zodpvidone, PMEA.</td>
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<td>MRPS (ABCC5)</td>
<td>Anticancéreux</td>
<td>Méthotrexate, 6-mercaptopurine, thioguanine.</td>
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<td>Analogue nucléoïdique</td>
<td>PMEA.</td>
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<td>BCRP (ABCG2)</td>
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<td>Doxorubicine, daunorubicine, étoposide, mitoxantrone, méthotrexate, prazosine, topotécan.</td>
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<td>Analogues nucléoïdiques</td>
<td>Zidovudine, lamivudine.</td>
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Dauchy et col, 2008
Doxorubicin and PI: PK/PD interaction with a PK mechanism

Effect of protease inhibitors on pharmacokinetics parameters of DOX

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<th></th>
<th>C(_{\text{max}}) (µg h(^{-1}))</th>
<th>AUC(_{48}) (µg h(^{-1})1)</th>
<th>AUC(_{0-\infty}) (µg h(^{-1})1)</th>
<th>Cl (1 h(^{-1}) m(^{-2}))</th>
<th>Vd (1 m(^{-2}))</th>
<th>t(_{1/2}) (h)</th>
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<td>DOX</td>
<td>928.03 ± 453.26</td>
<td>458.86 ± 142.33</td>
<td>824.64 ± 220.03</td>
<td>60.26 ± 23.89</td>
<td>3669.75 ± 1241.36</td>
<td>40.14 ± 12.14</td>
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<tr>
<td>DOX + PI (all)</td>
<td>843.21 ± 220.21</td>
<td>436.78 ± 127.08</td>
<td>752.66 ± 219.57</td>
<td>65.03 ± 24.43</td>
<td>3904.44 ± 1533.90</td>
<td>39.14 ± 12.51</td>
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<td>DOX</td>
<td>1061.35 ± 769.61</td>
<td>509.70 ± 216.33</td>
<td>865.59 ± 205.66</td>
<td>52.07 ± 23.98</td>
<td>2996.96 ± 1177.05</td>
<td>34.97 ± 6.46</td>
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<tr>
<td>DOX + SQV-HG</td>
<td>927.35 ± 357.58</td>
<td>543.99 ± 163.68</td>
<td>905.76 ± 281.88</td>
<td>46.51 ± 26.76</td>
<td>2828.27 ± 1380.10</td>
<td>34.81 ± 6.89</td>
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<td>n=6</td>
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<tr>
<td>DOX</td>
<td>904.35 ± 231.80</td>
<td>449.56 ± 84.06</td>
<td>827.59 ± 265.64</td>
<td>62.50 ± 27.31</td>
<td>3994.76 ± 802.98</td>
<td>44.17 ± 14.80</td>
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<tr>
<td>DOX - IDV</td>
<td>776.14 ± 119.82</td>
<td>373.64 ± 48.30</td>
<td>679.86 ± 168.56</td>
<td>73.25 ± 21.50</td>
<td>4419.44 ± 1217.17</td>
<td>41.04 ± 12.13</td>
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<td>n=9</td>
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<tr>
<td>DOX</td>
<td>781.35 ± 190.57</td>
<td>403.50 ± 123.27</td>
<td>756.58 ± 157.02</td>
<td>67.50 ± 16.11</td>
<td>394.70 ± 1972.85</td>
<td>38.80 ± 11.21</td>
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<tr>
<td>DOX + NFV</td>
<td>867.92 ± 106.20</td>
<td>418.04 ± 103.01</td>
<td>686.79 ± 111.80</td>
<td>74.31 ± 12.36</td>
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<td>41.39 ± 20.31</td>
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<td>n=4</td>
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</table>

Results are expressed as mean ± SD.
DOX, doxorubicin; PI, protease inhibitors; SWV-HG, saquinavir hard gel; IDV, indinavir; NFV, nelfinavir; NS, non statistically significant by non parametric Wilcoxon paired test.

No PK interaction based on plasma concentrations but increased toxicity of doxo in patients with HAART + CHOP

Pgp inhibition by Pis increase intracellular penetration of doxo

Probable pharmacodynamique interaction

Toffoli et al, Ann of Oncology, 2004
Impact of ARV and AK drugs on CYPs

**Induit par:** RTV, LPV, EFV, NVP, ETV, TPV

**Inhibé par:** RTV, IDV, APV, SQV, ATV

**Induit par:** RTV, NFV, TPV

**Inhibé par:** EFV, ETV

**Induit par:** RTV, TPV, ATV

**Inhibé par:** ATV

**Induit par:** RTV, TPV

**Inhibé par:** EFV, NVP

Fichtenbaum CJ. *Clin Pharmacokinet.* 2002:41:1195-1211
Antiretrovirals, cytochromes and cytostatics

<table>
<thead>
<tr>
<th>Cytochromes P450</th>
<th>Inhibiteurs (ARVs)</th>
<th>Inducteurs (ARVs)</th>
<th>Substrats (cytostatiques)</th>
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</thead>
<tbody>
<tr>
<td>CYP 3A4</td>
<td>Efavirenz, Ritonavir, Indinavir, Atazanavir, Lopinavir, Tipranavir</td>
<td>Efavirenz, Névirapine, Etravirine, Tipranavir</td>
<td>Paclitaxel, docétaxel, imatinib, sorafénib, sunitinib, vinblastine, vincristine, vinorelbine, cyclophosphamide, ifosfamide, étoposide, téniposide, irinotecan</td>
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<tr>
<td>CYP 2C9</td>
<td>Efavirenz, Ritonavir</td>
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<td>Cyclophosphamide</td>
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<tr>
<td>CYP 2C19</td>
<td>Efavirenz, Amprénavir</td>
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<td>Cyclophosphamide, ifosfamide, thalidomide</td>
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<tr>
<td>CYP 2B6</td>
<td>Efavirenz, Ritonavir</td>
<td>Névirapine</td>
<td>Cyclophosphamide, Ifosfamide</td>
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<tr>
<td>CYP 2D6</td>
<td>Ritonavir</td>
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<td>Tamoxifène</td>
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<tr>
<td>CYP 2E1</td>
<td>Ritonavir</td>
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<td>Etoposide, Teniposide, Dacarbazine</td>
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<td>UGT 1A1</td>
<td>Atazanavir, Raltegravir</td>
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<td>Irinotécan</td>
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<tr>
<td>Chimiothérapie Anticancéreuse</td>
<td>Metabolisme</td>
<td>PK interaction</td>
<td>PD interaction</td>
</tr>
<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td>Agents alkylants (ex : cyclophosphamide)</td>
<td>CYP 2B6, 2C9, 2C19 et 2A4/5</td>
<td>+ IP: AUC ↑ 50%</td>
<td>↗ myélotoxicité, troubles digestifs, arythmie, cystites hémorragiques</td>
</tr>
<tr>
<td>Anthracyclines (ex : doxorubicine)</td>
<td>CYP 3A4, 2D6</td>
<td>Pas de modification AUC plasma par IP</td>
<td>↗ possible de la myélosuppression</td>
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<tr>
<td>Alcaloïdes de la pervenche (ex : vincristine)</td>
<td>CYP 3A4</td>
<td>↗ des concentrations de vinca alcaloïdes</td>
<td>↗ possible de la myélosuppression et des neuropathies autonome/périphérique</td>
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<tr>
<td>Podophyllotoxines (ex : étoposide)</td>
<td>CYP 3A4, 2E1, 1A2</td>
<td>↗ des concentrations d’étoposide avec IP</td>
<td>↗ risque accru de toxicité hépatique et hématologique</td>
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<tr>
<td>Camptothecines (ex : irinotécan)</td>
<td>CYP 3A4 et UGT 1A1</td>
<td>↗ de l’exposition en présence d’un IP</td>
<td>↗ de la myélosuppression CI avec ATV et IDV</td>
</tr>
<tr>
<td>Taxanes (ex : paclitaxel)</td>
<td>CYP 2C8, 3A4</td>
<td>↗ concentrations des taxanes par les IP</td>
<td>↗ myélotoxicité et neuropathies toxicité sévère avec LPV/rtv, réduction de la dose</td>
</tr>
<tr>
<td>Antimétabolites (ex : methotrexate, cytarabine)</td>
<td>Indépendantes des CYPs</td>
<td>Interactions improbables avec IP et INNTI mais possibles avec INTI</td>
<td>Pas de modification de posologie avec IP et INNTI, prudence avec INTIs si voies métaboliques similaires</td>
</tr>
<tr>
<td>Cisplatin, rituximab</td>
<td>Indépendantes des CYPs</td>
<td>Peu probables</td>
<td>RAS sauf potentialité de néphrotoxicité accrue du Cisplatine avec ARV néphrotoxiques (IDV, TDF).</td>
</tr>
</tbody>
</table>

Adapté de Pham et Flexner, JAC 2011
# Interactions between cytotoxics and PIs or NNRTIs: level of risk

<table>
<thead>
<tr>
<th>Cytotoxiques</th>
<th>ATV</th>
<th>DRV</th>
<th>FPV</th>
<th>IDV</th>
<th>LPV</th>
<th>RTV</th>
<th>SQV</th>
<th>TPV</th>
<th>EFV</th>
<th>ETV</th>
<th>NVP</th>
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</table>

Mars 2012 - régulièrement mis à jour sur le site [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org), Liverpool University
### Interactions between cytotoxics and NRTI, MRV or RLV: level of risk

<table>
<thead>
<tr>
<th>Cytotoxiques</th>
<th>ABC</th>
<th>ddl</th>
<th>FTC</th>
<th>3TC</th>
<th>d4T</th>
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</table>

Mars 2012 - régulièrement mis à jour sur le site [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org), Liverpool University
Assess clinical significance/consequence of drug interaction

- Is the interaction consistent and reproducible?
- Study design?
- What is the consequence of the interaction?
- Onset of interaction?
  - Inhibition usually occurs quickly, induction may take days-weeks
- What is a clinically significant change in drug levels?
- At what point does toxicity occur?
- Can toxicity be monitored?
Conclusions

• Drug interactions represent a challenge to clinicians

• Current knowledge is inadequate and constantly changing

• Successful management requires familiarity with a variety of references and vigilant surveillance

• PK data should be critically evaluated

• A systematic approach ensures accurate answers based on available information
Check for documented drug interactions: Internet Resources

- Liverpool Pharmacology Group
  http://www.hiv-druginteractions.org

- Medscape Drug Interaction Calculator
  http://www.medscape.com
  (go to HIV/AIDS specialty page, interaction calculator)

- Toronto General Hospital Immunodeficiency Clinic
  http://www.tthhivclinic.com/interact_tables.html

- Project Inform Drug Interaction Page (good for lay audience)
  http://www.projinf.org/fs/drugin.html