Real Life Experience And Available Tools To Manage Drug–Drug Interactions

Rachel Therrien
Clinical Pharmacist
Centre Hospitalier de l’Université de Montréal

Vienna, November 2012
2 clinical cases:
- Discussion of the management
- Presentation of the tools to help in decision making.
Case 1

- Male 44 years old.
- HIV + 1999.
- Allergies:
  - tazocin, levofloxacin, ampicillin.
- Medical history:
  - severe osteoporosis, splenectomy
- Antiretroviral therapy:
  - highly experienced to antiretroviral therapy.
Case 1

2008 (December)
- Darunavir (Prezista)/r (600/100 BID) + 3TC + Raltegravir (Isentress) BID
- Viral load became undetectable

2010 (April) : Hodgkin Lymphoma
- CD4 = 760 cells/mm³
- Ratio CD4/CD8 = 0.43     CD4% : 20%
- CV < 50 copies/mL
Case 1

**Antiretroviral**
- Darunavir/r (BID)
- Raltegravir (Isentress) BID
- 3TC BID

**Chemotherapy (ABVD)**
- Doxorubicin
- Bleomycin
- Vinblastine
- Dacarbazine
- Dexamethasone

If we look at the treatments the patient is receiving and will receive. We have this scenario.

In the best of situations, we wish to:
- Avoid drug toxicity
- Preserve HIV and chemotherapy efficacy
What I like to do first?

Discuss with the oncology team

- Expected efficacy
- Expected side effects and their usual management
- The number of chemotherapy cycles and how long it will last

Efficacy:

- 70-80% of HIV negative patients can be cured.

Side effects:

- Hematologic, digestive
- Neuropathy, lung and cardiotoxicity
- Major concern: febrile neutropenia and clinical infections

Side effects management:

- Dose reduction
- Treatment breaks – delays
- CSF

CSF : colony stimulating factor
Which of the following options would you select?

- Stop the antiretroviral therapy (ARV).
- Omit PI and switch to a non PI-ARV combination.
- Reduce the dose of the vinblastine.
- Consider G-CSF systematic administration.
- Nothing special.
Early data reported poor outcomes with HL chemotherapy when used without ARV.

More recent analyses suggest that ARV use with chemotherapy is important in the treatment of HIV-HL.

The currently recommended treatment for HIV-associated HL is chemotherapy given concurrently with ARV therapy.

Recommendations for initiation of ART in HIV-positive persons without prior ART exposure

Recommendations are graded while taking into account both the degree of progression of HIV disease and the presence of or high risk for developing various types of (co-morbid) conditions.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Current CD4+ lymphocyte count (x10^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>350-500</td>
</tr>
<tr>
<td></td>
<td>&gt; 500</td>
</tr>
<tr>
<td>Asymptomatic HIV infection</td>
<td>C</td>
</tr>
<tr>
<td>Symptomatic HIV disease (CDC B or C conditions) incl. tuberculosis</td>
<td>R</td>
</tr>
<tr>
<td>Primary HIV infection</td>
<td>C</td>
</tr>
<tr>
<td>Pregnancy (before third trimester)</td>
<td>R</td>
</tr>
<tr>
<td>Conditions (likely or possibly) associated with HIV, other than CDC stage B or C disease:</td>
<td></td>
</tr>
<tr>
<td>HIV-associated kidney disease</td>
<td>R</td>
</tr>
<tr>
<td>HIV-associated neurocognitive impairment</td>
<td>R</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>R</td>
</tr>
<tr>
<td>HPV-associated cancers</td>
<td>R</td>
</tr>
<tr>
<td>Other non-AIDS-defining cancers requiring chemo- and/or radiotherapy</td>
<td>C</td>
</tr>
<tr>
<td>Autoimmune disease – otherwise unexplained</td>
<td>C</td>
</tr>
<tr>
<td>High risk for CVD (&gt; 20 % estimated 10-yr risk) or history of CVD</td>
<td>C</td>
</tr>
<tr>
<td>Chronic viral hepatitis</td>
<td></td>
</tr>
<tr>
<td>HBV requiring anti-HBV treatment</td>
<td>R</td>
</tr>
<tr>
<td>HBV not requiring anti-HBV treatment</td>
<td>C/R (iv)</td>
</tr>
<tr>
<td>HCV for which anti-HCV treatment is being considered or given</td>
<td>R (v)</td>
</tr>
<tr>
<td>HCV for which anti-HCV treatment not feasible</td>
<td>R</td>
</tr>
</tbody>
</table>

R = use of ART is recommended.

EACS guidelines 2012
## Case 1

### Antiretroviral
- Darunavir/r BID (CYP3A4/2D6 inh)
- Raltegravir BID
- 3TC BID

### Chemotherapy (ABVD)
- Doxorubicin
- Bleomycin
- Vinblastine
- Dacarbazine
- Dexamethasone

In this scenario we have, antiretrovirals with mainly an inhibitory effect combined with chemotherapy which has a narrow therapeutic index.

**We have to find**
1. Metabolism of each drug
2. Pharmacokinetic studies
3. Case reports

**Where**
1. Hiv drug-drug interactions site
2. Drug Monograph
3. Literature search (Pubmed.)
4. As many references as I can find
Click on the antiretroviral

Search by drug class
<table>
<thead>
<tr>
<th>Antiretrovirals (Protease Inhibitors)</th>
<th>Cytotoxics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>Asparaginase</td>
</tr>
<tr>
<td>Darunavir</td>
<td>Bleomycin</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Carboplatin</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Chlorambucil</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Cytarabine</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Decarbazine</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Daunorubicin</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>Docetaxel</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
</tr>
<tr>
<td></td>
<td>Etoposide</td>
</tr>
<tr>
<td></td>
<td>Fluorouracil</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide</td>
</tr>
<tr>
<td></td>
<td>Irinotecan</td>
</tr>
<tr>
<td></td>
<td>Mercaptopurine</td>
</tr>
<tr>
<td></td>
<td>Mesna</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Procarbazine</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Vinblastine</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Vincristine</td>
</tr>
</tbody>
</table>
**Key to symbols:**

- ![ ] These drugs should not be coadministered
- ![ ] Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration
- ![ ] No clinically significant interaction expected
- ![ ] There are no clear data, actual or theoretical, to indicate whether an interaction will occur
- n/a Data not available

To generate a personalised report in PDF format enter a report ID and click 'Get Report'.

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<table>
<thead>
<tr>
<th>Antiretrovirals (Protease Inhibitors)</th>
<th>Darunavir</th>
<th>Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir</td>
<td>![ ]</td>
<td>n/a</td>
</tr>
<tr>
<td>Ritonavir</td>
<td></td>
<td>![ ]</td>
</tr>
<tr>
<td>Cytotoxicics</td>
<td>![ ]</td>
<td>![ ]</td>
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<tr>
<td>Bleomycin</td>
<td>![ ]</td>
<td>![ ]</td>
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<tr>
<td>Docetaxel</td>
<td>![ ]</td>
<td>![ ]</td>
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<tr>
<td>Doxorubicin</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
</tbody>
</table>

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## Drug Interaction Details

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>HIV Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxics</td>
<td>Vinblastine</td>
<td>Darunavir</td>
</tr>
</tbody>
</table>

- Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration

### Quality of Evidence: Low

### Summary

Coadministration of vinblastine with protease inhibitors was independently associated with WHO grade III-IV neutropenia. For boosted PIs, an inverse correlation between dosage of ritonavir and mean nadir neutrophil count was found.

### Description

In order to better define the interaction between combination antiretroviral therapy and vinblastine (a substrate of CYP3A4), clinical charts were reviewed of all HIV infected patients in a centre in Rome who received a diagnosis of Hodgkin’s lymphoma as coadministration of potent inhibitors of CYP3A4, such as ritonavir, may decrease vinblastine metabolism and consequently increase vinblastine-related myelosuppression. It was found that the use of protease inhibitors was independently associated with WHO grade III-IV neutropenia. Moreover, an inverse correlation between dosage of ritonavir and mean nadir neutrophil count was found. The concomitant administration of vinblastine-containing chemotherapy regimens with protease inhibitors can lead to higher levels of neutropenia than those of different classes of drugs such as NNRTIs or integrase inhibitors.


View all known interactions with Darunavir

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Last Reviewed: 06 November 2012

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Interaction Report from www.hiv-druginteractions.org

Report ID: Rachel
Date Produced: 24 November 2012

<table>
<thead>
<tr>
<th>Antiretroviral treatment</th>
<th>Co-medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir</td>
<td>Bleomycin</td>
</tr>
<tr>
<td></td>
<td>Dacarbazine</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
</tr>
<tr>
<td></td>
<td>Vinblastine</td>
</tr>
<tr>
<td>Ritonavir</td>
<td></td>
</tr>
</tbody>
</table>

This report lists the potentially clinically significant interactions (i.e. “red” and “amber” classifications) for the drugs in the table above. Interactions with a “green” classification (i.e. no clinically significant interaction expected) have been checked but are not shown on this report.

For full details of all interactions, see www.hiv-druginteractions.org.

Description of the interactions

Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration (AMBER)

- **Darunavir** and **Dacarbazine**: Coadministration has not been studied. Dacarbazine undergoes activation to MTIC primarily via CYP1A2 and to a lesser extent by CYP2E1, with CYP1A1 having a role in extrahepatic metabolism. In vitro data indicate that ritonavir induces CYP1A2. Darunavir/ritonavir may increase the conversion to MTIC and thereby increase the efficacy and toxicity of dacarbazine. Monitor side effects.

- **Darunavir** and **Ritonavir**: Darunavir should only be used in combination with 100 mg of ritonavir as a pharmacokinetic enhancer. Increasing the dose of ritonavir did not significantly affect darunavir concentrations and is not recommended.

- **Darunavir** and **Vinblastine**: Coadministration of vinblastine with protease inhibitors was independently associated with WHO grade III-IV neutropenia. For boosted PIs, an inverse correlation between dosage of ritonavir and mean nadir neutrophil count was found.

- **Ritonavir** and **Dacarbazine**: Coadministration has not been studied. Dacarbazine undergoes activation to MTIC primarily via CYP1A2 and to a lesser extent by CYP2E1, with CYP1A1 having a role in extrahepatic metabolism. In vitro data indicate that ritonavir induces CYP1A2 and may increase the conversion to MTIC and thereby increase the efficacy and toxicity of dacarbazine. Monitor side effects.

- **Ritonavir** and **Vinblastine**: Coadministration may increase vinblastine concentrations, resulting in the potential for increased incidence of adverse events. Coadministration of vinblastine with protease inhibitors was independently associated with WHO grade III-IV neutropenia in a clinical cohort. For boosted PIs, an inverse correlation between dosage of ritonavir and mean nadir neutrophil count was found.

Information supplied and monitored by The Liverpool HIV Pharmacology Group. This report is provided for information only. It is not intended to replace a consultation with an appropriately qualified health professional. We aim to ensure that the information published in this report is accurate and consistent with current knowledge and practice. However, medical knowledge and practice is constantly evolving and individual cases may require specific advice that cannot be addressed through this report. The University of Liverpool, eMedFusion and their servants or agents shall not be responsible or in any way liable for the continued currency of the information or for any errors, omissions or inaccuracies in this publication whether arising from negligence or otherwise howsoever or for any consequences arising therefrom. The University of Liverpool and eMedFusion expressly exclude liability for errors, omissions or inaccuracies to the fullest extent permitted by law.
Drug Information for Healthcare Professionals

Drug Interaction Tables

Pharmacokinetic Properties of Antiretrovirals
Pharmacologic Properties of Hepatitis C Antivirals
Additional Information for Pharmacists and Physicians
Medication Fact Sheets for Patients
Reimbursement Information

News
We are very proud to announce that [www.hivclinic.ca](http://www.hivclinic.ca) has recently received awards from two prestigious Canadian pharmacy organizations for excellence in pharmacy practice. We are honoured and humbled to be recognized by our colleagues and peers. Thank you to everyone for your continued support and use of the website!

2010 Commitment to Care Disease Management Initiative Award

E. Amy Eck Award

The website was presented as a poster at the 2011 Canadian Association for HIV Research (CAHR) conference, held April 14-17, 2011 in

Editorial Information

The Toronto General Hospital website has been in operation since 2000, initially as [www.tghhivclinic.com](http://www.tghhivclinic.com), and since 2009 as [www.hivclinic.ca](http://www.hivclinic.ca). The main objectives of the drug information portion of the website are to provide a comprehensive and centralized repository of current data on HIV drug therapy for health care professionals with a main focus on drug interactions, and to promote safe and rational prescribing of antiretrovirals. The website content is updated regularly, and includes information from key international HIV conferences and recent publications in the medical/pharmacy literature. The chief editors of the website content are Alice Tsang, Pharm.D., and Michelle Foxey, Pharm.D.

Disclaimer
The information in this website is intended for use by and with experienced physicians and pharmacists. The information is not intended to replace sound professional judgment in individual situations, and should be used in
Drug Interaction Tables

Antiretroviral Interactions

CCRS Inhibitors

Integrase Inhibitors

Nucleoside Reverse Transcriptase Inhibitors

Non-nucleoside Reverse Transcriptase Inhibitors

Protease Inhibitors

Protease Inhibitors - Secondary agents (amprenavir, indinavir, nelfinavir, saquinavir)

Tenofovir

Interactions with Other Drug Classes

Anticonvulsants

Antihyperglycemics

Antihypertensives

Antimalarials

Antineoplastic Agents

Azoled Antifungals

Hepatitis C Directly Acting Antivirals

Antiretroviral Treatment Options for Patients with DAAs - Summary

Lipid-lowering Drugs

Methadone

Narcotics

Oral Contraceptives

Osteoporosis Medications

Psychotropics

Pulmonary Arterial Hypertension Drugs

Recreational Drugs

Inclusive updates from:

- 7th International Workshop on Clinical Pharmacology of Hepatitis Therapy, Boston, MA, June 27-28, 2012
- 13th International Workshop on Clinical Pharmacology of HIV Therapy, April 16-18th, 2012, Barcelona
- 19th Conference on Retroviruses and Opportunistic Infections, Seattle, WA, March 5-8, 2012
- HELP DART 2011, December 4-5, 2011, Koloa, Hawaii

Additional Information:


Understanding and Managing Drug Interactions in HIV Disease

Disclaimer

The information in this site is intended for use by and with experienced physicians and pharmacists. The information is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and...
<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Metabolism</th>
<th>Actual/Theoretical Interaction</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altretamine¹</td>
<td>Alkylating Agents</td>
<td>Hepatic microsomal oxidation to active and cytotoxic derivatives. Exact isoenzyme unknown.</td>
<td>Potential for ↓ efficacy with P-450 inhibitors.</td>
<td>May need to hold antiretroviral regimens with 3A4 inhibiting drugs, or change to agents that do not inhibit 3A4 when concurrent therapy with altretamine needed.</td>
</tr>
<tr>
<td>Anastrozole²⁻³</td>
<td>Endocrine Therapies</td>
<td>Metabolized by N-dealkylation, hydroxylation and glucuronidation. Metabolites inactive. Exact isoenzymes unknown (3A4 possible).</td>
<td>Induction of glucuronidation may ↓ levels of drug and subsequently affect efficacy. CYP450 inhibitors may ↑ levels of anastrozole; inducers may do opposite.</td>
<td>Monitor for ↓ efficacy with ritonavir or nelfinavir (↑ glucuronidation) and nevirapine or efavirenz (induce 3A4) Possible ↑ risk and severity of side effects with PIs, delavirdine, or elvitegravir/cobicistat (e.g. hot flushes, peripheral edema, constitutional symptoms etc.).</td>
</tr>
<tr>
<td>Bexarotene⁴</td>
<td>Synthetic retinoid analog</td>
<td>Metabolized by CYP3A4 to oxidative metabolites, which are active (degree of activity unknown). Oxidative metabolites may be glucuronidated. Auto-induction occurs with chronic administration, particularly with doses &gt;300 mg/m2/day.</td>
<td>Inhibition or induction of CYP3A4 may affect levels of bexarotene and subsequently affect efficacy or toxicity. Induction of glucuronidation may promote clearance of active metabolites and possibly impact efficacy. Bexarotene may induce metabolism of CYP3A4 substrates, including PIs and NNRTIs. Virological failure was reported in a 70-year old man on efavirenz, 3TC and abacavir (VL&lt;50 for 12 years) 2 months after starting bexarotene 300 mg QD for a neoplastic disorder. Efavirenz plasma concentration was 595 ng/mL compared to 1478 ng/mL prior to initiation of bexarotene. Bexarotene concentrations were approximately 50% lower vs. steady-state reference pharmacokinetic data.⁵</td>
<td>Potential for ↓ bexarotene concentrations with NNRTIs, and ↑ concentrations with PIs and elvitegravir/cobicistat; bexarotene may ↓ concentrations of NNRTIs, PIs, and elvitegravir/cobicistat. Consider TDM of bexarotene and antiretrovirals if available, and monitor closely for efficacy/response. May wish to consider using ARV agents that do not impact CYP450 system if possible.</td>
</tr>
</tbody>
</table>

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¹ Preparations: 100 mg, 300 mg, 600 mg capsules, 100 mg tablets, 100 mg/100 mg tablets.
² Preparations: 1 mg, 10 mg tablets, 1 mg/10 mg tablets.
³ Takeda Pharmaceuticals, Osaka, Japan.
⁴ Preparations: 300 mg, 600 mg tablets.
⁵ Preparations: 30 mg, 60 mg capsules, 90 mg tablets.
Interactions with one drug in particular

Select Drug To View Interactions
N.B. Be careful not to forget ritonavir if also present in the regimen (e.g., with tipranavir).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valacyclo</td>
<td>Valganciclovir</td>
<td>Vapenic acid</td>
</tr>
<tr>
<td>Venclear</td>
<td>Vardenafil</td>
<td>Varenflit</td>
</tr>
<tr>
<td>Vesicuzine</td>
<td>Varenamid</td>
<td>Virensec</td>
</tr>
<tr>
<td>Venustat</td>
<td>Vincristine</td>
<td>Vindions</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Vitamin E</td>
<td>Vornicosce</td>
</tr>
</tbody>
</table>

www.guidetherapeutiquevih.com
www.hivmedicationguide.com
Interactions with one drug in particular

Atazanavir/Omeprazole 40 mg

Significance: Contraindicated.

Mechanisms: Omeprazole 40 mg by increasing gastric pH may decrease the solubility, absorption, and plasma concentration of Atazanavir.

<table>
<thead>
<tr>
<th></th>
<th>Atazanavir</th>
<th>Omeprazole 40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic Substrate: 3A4 (major) transporters: BCRP, MRP1, MRP2, P-gp</td>
<td></td>
<td>Metabolic Substrate: 2C19, 2C8 3A4, 2D6</td>
</tr>
<tr>
<td>Metabolic Inhibitor: 3A4 (strong), 2C8 (moderate when taken alone without ritonavir), UGT1A1 (moderate) transporters: BCRP, MRP1, MRP2, CYP1B1, CYP3A4, CYP3A5, P-gp</td>
<td>Metabolic Inducer: 1A2, 3A4</td>
<td>Metabolic Inhibitor: 2C9, 2C19</td>
</tr>
</tbody>
</table>

Pharmacokinetic parameters:

<table>
<thead>
<tr>
<th>Reference #</th>
<th>1000</th>
<th>1000</th>
</tr>
</thead>
<tbody>
<tr>
<td># patients</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>HIV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dose</td>
<td>400 mg</td>
<td>400 mg*</td>
</tr>
<tr>
<td>Frequency</td>
<td>QD</td>
<td>QD</td>
</tr>
<tr>
<td>Food</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Duration (days)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>AUC</td>
<td>- 94%</td>
<td>- 97%</td>
</tr>
<tr>
<td>Cmax</td>
<td>- 96%</td>
<td>- 94%</td>
</tr>
<tr>
<td>Cmin</td>
<td>- 95%</td>
<td>- 95%</td>
</tr>
</tbody>
</table>

Pharmacodynamic Effects:

Recommendations:

Avoid. Use alternative.

Alternatives:

Tests:

Atazanavir

Comments:

* Plus 8 ounces of cola. The addition of a cola did not mitigate the reduction in atazanavir exposure. Ref(1034). The dosage was 400mg of Atazanavir and 40mg of Omeprazole. Omeprazole was given 2 hours before Atazanavir. The 43% increase in omeprazole in not clinically significant. Ref(1039). Atazanavir exposures were largely unaffected at intra-gastric pH less or equal to 4 but decreased substantially above that threshold. Atazanavir could be used with Omeprazole only if Omeprazole is potentized with ritonavir, if the patient is not resistant to the antiretrovirals and it is suggested to not exceed a dosage of 20 mg of Omeprazole. See atazanavir/ritonavir/omeprazole 20 mg.
HIV and Cardiology

Pamphlet description
This pamphlet provides information on interactions between antiretrovirals and medication used in cardiology, such as: anticoagulant and antiplatelet drugs, angiotensin II AT1 receptor antagonists (ARA), antiarrythmic drugs, beta-blockers, calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI). The literature currently available on the subject appears in interactions tables. We can also find an extrapolation of interactions in the light of the pharmacokinetics of every agent.

Author: R. Therrien
Pharmacists, UFRSS3

Download
HIV and Cardiology

Atazanavir (Reyataz) and gastric acid-reducing agents
Other sites

- www.interaccionesvih.com
- www.hopkins-hivguide.org
- www.hivinsite.com (Drug interaction database)
- www.medscape.com/druginfo/druginterchecker
- www.clinicaloptions.com (Drug-drug interactions tool)
# ABVD: proposed metabolism

<table>
<thead>
<tr>
<th></th>
<th>1A2</th>
<th>2B6</th>
<th>2C19</th>
<th>2E1</th>
<th>3A4</th>
<th>Non CYP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intracellular metabolism</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>Substrate (AM)</td>
<td></td>
<td>Substrate (AM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
<td></td>
<td>Substrate</td>
<td>Inducer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td></td>
<td></td>
<td>Aldoketo reduction</td>
<td>Carboxyl reduction</td>
<td>Transporters: P-gp</td>
<td>Expression of the cardiac cytochrome P450 (P450) enzymes (related to cardiotoxicity)</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Substrate</td>
<td>Inducer (?)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Vinca levels may ↑ risk and severity of autonomic, peripheral neuropathy and myelosuppression

Cardiotoxicity
Dacarbazine

- Use of concurrent ritonavir (CYP 1A2 induction) may cause formation of active metabolites.
  - May ↑ efficacy
  - May cause nausea, vomiting and myelosuppression

Doxorubicin

- Metabolised to Doxorubicinol (cardiotoxic):
  - Aldoketoreductase, aldehyde and carbonyl reductase.
- Transporters and CYP450 are involved:
  - Cancer cells and cardiomyocytes
- Canadian Monograph (March 2012):
  - Doxorubicin p-gp: verapamil ↑ 2 x doxorubicin.
  - Cyclosporine: ↑ 55% doxorubicin and 443% metabolite
- Literature reports suggest that adding cyclosporine to doxorubicin results in:
  - More profound and prolonged hematologic toxicity than that observed with doxorubicin alone.
  - Coma and seizures with fatal outcome have also been described with concomitant administration of cyclosporine and doxorubicin.
What do we know?

Pharmacokinetic interactions
HIV drug interactions websites
Cases studies
Case reports
Kaletra + vinblastine

Severe digestive and hematological toxicities and moderate renal failure. Dose reductions were well tolerated.\(^1\)

Kaletra + vinblastine

ABVD for Hodgkin’s lymphoma

Report of 3 patients who experienced severe vinblastine-associated neurotoxicity.
2 had early-onset autonomic neuropathy with severe medical ileus requiring hospitalization
One had late-onset with severe and painful peripheral neuropathy\(^3\)

Kaletra + vinblastine

One case report of a profound life-threatening febrile neutropenia at each cycle. Interaction was managed with lopinavir-ritonavir interruption around chemotherapy administration.\(^4\)

Retrospective study (Hodgkin’s Lymphoma)

PI (N= 7) and non PI (N=9)
More grade III or IV neutropenia with PI
An inverse correlation between dosage of ritonavir and mean nadir neutrophil count.\(^2\)


\(^4\)Makinson A et al. Profound neutropenia resulting from interaction between antiretroviral therapy and vinblastine

### Internet sites and literature review.

#### Vinblastine

<table>
<thead>
<tr>
<th>Phase II study</th>
<th>59 patients received (doxorubicin, vinblastine, mechlorethamine, etoposide, prednisone, bleomycin). 54% developed neurotoxicity, with 29% of patients experiencing grade 3 toxicity. 83% patients (D4T/DDI/DDC)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadien retrospective study</td>
<td>Review of 32 patients (HIV-HL). 90% ABVD, 10% MOPP/ABV and 63% HAART. They looked at 17 potential risk factors and 18 individual ARVs.  • Ritonavir or lopinavir use was associated with significant toxicities.  • Ritonavir and lopinavir use were associated with grade 3–4 neurotoxicity.  • Ritonavir was associated with any king of hematologic toxicities²</td>
</tr>
</tbody>
</table>

---

## Internet sites and literature review.

### Vincristine

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaletra + vincristine</td>
<td>Cyclophosphamide, doxorubicin, methotrexate and vincristine for Burkitt lymphoma. At day 12 the patient developed a paralytic ileus lasting 10 days. For the subsequent cycles of chemotherapy, vincristine was replaced with etoposide and this regimen was well tolerated.¹</td>
</tr>
<tr>
<td>Retrospective study (Non Hodgkin’s Lymphoma)</td>
<td>In NHL patients, 24 (CHOP + ARV) were compared to 80 (CHOP alone). Grade 3-4 autonomic neuropathy (17% vs 0%) Anemia : 33% vs 7% Colony stimulating factor use: 92% vs 66%.²</td>
</tr>
<tr>
<td>Retrospective study (Large B-cell lymphoma)</td>
<td>81 HIV-infected patients with diffuse large B-cell lymphoma under antiretroviral therapy (with at least one PI) and treated with 3 weekly CHOP-rituximab grade 3 to 4 neutropenia (43% of all 426 cycles) infections (10% of all cycles).³</td>
</tr>
</tbody>
</table>

---

Little definitive information is available regarding how individual antiretroviral medications may interact with chemotherapy agents.

But it seems that we have enough information to believe that a PI/r combination can increase side effects (GI, neuro and hematotoxicity).
Case report with one patient reports good tolerance.
A case series from my hospital (N=7) reports good tolerance with Raltegravir and CHOP

Marcotte. XVII IAS; Vienna, Austria; 2010.
# Case 1

<table>
<thead>
<tr>
<th>Antiretroviral</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir/r</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Bleomycin</td>
</tr>
<tr>
<td>3TC</td>
<td>Vinblastine</td>
</tr>
<tr>
<td></td>
<td>Darcarbazine</td>
</tr>
<tr>
<td></td>
<td>Decadron</td>
</tr>
</tbody>
</table>

We chose to stop the Darunavir/r. We changed Darunavir/r to ?
### NRTIs
- Abacavir (ABC) - Ziagen
- Didanosine (ddI) - Videx
- Lamivudine (3TC) - 3TC
- Stavudine (d4T) - zerit
- Tenofovir (TDF) - Viread
- Zidovudine (ZDV) - Retrovir
- 3TC/ABC - Kivexa
- 3TC/ABC/ZDV - Trizivir
- 3TC/ZDV - Combivir
- FTC/TDF - Truvada

### NNRTIs
- Delavirdine (DLV) - Rescriptor
- Efavirenz (EFV) - Sustiva
- Nevirapine (NVP) - Viramune
- **Etravirine (ETV)** - Intelence
- Rilpivirine (RPV) - Edurant

### Protease Inhibitors
- Atazanavir (ATV) - Reyataz
- Darunavir (DRV) - Prezista
- Fosamprenavir (f-APV) - Telzir
- Indinavir (IDV) - Crixivan
- Lopinavir/ritonavir (LPV/r) - Kaletra
- Nelfinavir (NFV) - Viracept
- Ritonavir (RTV) - Norvir
- Saquinavir (SQV) - Invirase
- Tipranavir (TPV) - Aptivus

### Entry Inhibitors
- Enfuvirtide (ENF) - Fuzeon
- Maraviroc - Celsentri

### Integrase Inhibitors
- Raltegravir (Isentress)

### Combination classes
- 2 NRTIs (Truvada) + 1 NNRTI (Efavirenz or Rilpivirine)

### Combination Drugs
- Atripla
- Complera
Case 1

- Darunavir (Prezista)/r

  Etravirine (Intelence)
  CYP 3A4 inducer (weak ?)
  CYP 2C9/2C19 inhibitor

Could potentially decrease vinblastine exposure?
No available information.
We do not know if it is significant or not.
Case 1

- 05/04/10: Darunavir (Prezista)/r ➔ Etravirine (Intelence)
- 15/04/10: Rash (blister) + respiratory distress
  
  All antiretroviral therapy was stopped.

What would you do?

1. Chemo without antiretroviral therapy
2. Chemo + Darunavir/3TC/Raltegravir
   1. Oncology pharmacist was reluctant because he was confronted with a case of cardiotoxicity between Kaletra and a chemo agent, just the month before.
3. Chemo + Fuzeon/3TC/Raltegravir
   1. Patient was highly reluctant to accept the Fuzeon

16/04/11: first cycle (of 8) of chemotherapy was started.
He had his first chemotherapy cycle without antiretroviral therapy

What do you think happened?
## Case 1

**First cycle:** 16 April  
**ARV stop:** 15 April

<table>
<thead>
<tr>
<th>Date</th>
<th>CD4</th>
<th>% CD4</th>
<th>Ratio CD4/CD8</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/03/10</td>
<td>760</td>
<td>20%</td>
<td>0.43</td>
</tr>
<tr>
<td>26/04/10</td>
<td>120</td>
<td>18%</td>
<td>0.51</td>
</tr>
<tr>
<td>14/05/10</td>
<td>430</td>
<td>16%</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Viral load had increased to 844 220 copies/mL
## Case 1

<table>
<thead>
<tr>
<th>Date</th>
<th>CD4</th>
<th>% CD4</th>
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<td>16%</td>
<td>0.37</td>
</tr>
</tbody>
</table>

We decided to do the CCR5 tropism.

VL: 844 220 copies/mL

**CCR5 tropism: positive**
Case 1

**Antiretroviral**
- Raltegravir (Isentress)
- 3TC
- Maraviroc (Celsentri) (CYP3A4 substrate)
- + Enfuvirtide (Fuzeon)

**Chemotherapy**
- Doxorubicin
- Bleomycin
- Vinblastine (CYP 3A4 induction ?)
- Dacarbazine
- Decadron (CYP 3A4 too short for induction ?)

This gave me time to convince the patient to accept the switch to Fuzeon.
We therefore switched the PI to maraviroc and Fuzeon. And I suggested to keep maraviroc at the usual dose.
Case 1

**Antiretroviral**
- Raltegravir (Isentress)
- 3TC
- Maraviroc (Celsentri) 300 mg BID
- + Enfuvirtide (Fuzeon)

**Chemotherapy**
- Doxorubicin
- Bleomycin
- Vinblastine
- Darcarbazine
- Decadron

Can you tell me the end of the story?
## Case 1

<table>
<thead>
<tr>
<th>Antiretroviral</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir (Isentress)</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>3TC</td>
<td>Bleomycin</td>
</tr>
<tr>
<td>Maraviroc (Celsentri) 300</td>
<td>Vinblastine</td>
</tr>
<tr>
<td>+ Enfuvirtide (Fuzeon)</td>
<td>Darcarbazine</td>
</tr>
<tr>
<td></td>
<td>Decadron</td>
</tr>
</tbody>
</table>

1. He developped a PjP (Septra had not been introduced).
2. But after that, he received his chemo without any serious side effects and his viral load became and stayed undetectable until the end his chemotherapy.
The day he finished his last cycle of chemotherapy, he asked me to stop Fuzeon.

We stopped Fuzeon and maraviroc and we reintroduced his old therapy with:

- Darunavir/r (inh CYP 3A4/p-gp, ind 1A2)
- Raltegravir
- 3TC

What do you think happened?
CASE 1

<table>
<thead>
<tr>
<th>Antiretroviral (Changed)</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir/r (inh CYP 3A4)</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Bleomycin</td>
</tr>
<tr>
<td>3TC</td>
<td>Vinblastine</td>
</tr>
<tr>
<td></td>
<td>Darcarbazine</td>
</tr>
<tr>
<td></td>
<td>Decadron</td>
</tr>
</tbody>
</table>

He experienced a significant fall in his neutrophil count, which had not occurred until then.

Lesson: Now I wait longer if I have to reintroduce the PI.
Case 2

- JCV ♂, 48 years old

- Was admitted to the hospital for:
  - N/V for the last 3 weeks,
  - Could not eat for the last 3 days,
  - Severe gastroesophageal reflux.
    - CV: ↑10 700 copies/mL (previously: <50)
    - CD4+: ↓290 cells/mm³ (previously: 600)

- Medical history:
  - Hepatitis B, PJP, Herniated disc (chronic back pain)

Recent hospitalization (3 months ago) with similar symptoms.
Case 2

- **Antiretroviral therapy:**
  - Lamivudine + tenofovir
  - Atazanavir/ritonavir (300/100)

- **Others:**
  - Pantoprazole 40 mg DIE
  - Fentanyl 75mg/h every 3 days + morphine 15mg q4h PRN
  - Baclofen 10mg TID
  - Sildenafil 25 mg q 48h PRN and Tadalafil 10mg q48h PRN

Same therapy for the last 5 years and VL undetectable

Same medication for the last 3 years
Case 2

- Patient was started on
  - Dimenhydrinate, metoclopramide

- I was asked because attending physician wanted to stop atazanavir:
  - It was felt that the interaction with pantoloc induced the virologic/immunologic failure.

What do you think?
Case 2

Patient has been on Atazanavir + Pantoloc for the last 3 years and has remained undetectable all this time.

CV : ↑ 10 700 copies/mL (before: < 50)
CD4+: ↓ 290 cells/mm³ (before: 600)

I thought that the vomiting of the last weeks could explain the results.

At the hospital, with the dimenhydrinate and metoclopramide he has no vomiting.
**Atazanavir (Reyataz) or Atazanavir (Reyataz)/Ritonavir (Norvir) and Gastric Acid-Reducing Agents.**

<table>
<thead>
<tr>
<th>Proton Pump Inhibitor</th>
<th>Atazanavir</th>
<th>Atazanavir/Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg of omeprazole (Losec) or equivalent</td>
<td>Contraindicated</td>
<td>An increase in the dose of atazanavir (Reyataz)/ritonavir (Norvir) 400/100 mg is recommended with food QD</td>
</tr>
<tr>
<td>40 mg of omeprazole (Losec) or equivalent</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

[www.hivmedicationguide.com](http://www.hivmedicationguide.com)
**Atazanavir (ATZ) 300 mg / ritonavir (rtv) 100 mg DIE**

<table>
<thead>
<tr>
<th>Valeurs visées selon le statut du patient</th>
<th>Cmin visée (mg/L)</th>
<th>Rapport de concentration (RC) visé</th>
<th>Quotient Inhibiteur Génotypique (GIQ) visé</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avec ou sans échec antérieur aux IP</td>
<td>0.15</td>
<td>0.125</td>
<td>0.1</td>
</tr>
<tr>
<td>Précaution: très peu d'études cliniques de qualité sont disponibles avec ATZ pour guider les seuils thérapeutiques.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Courbe de population ATZ 300mg / rtv 100 mg DIE**

**Courbe min. visée, patient avec ou sans échec antérieure aux IP**

**AVIS PHARMACOLOGIQUE (du dernier échantillon)**

La concentration plasmatique d’atazanavir est difficile à interpréter car l’heure du prélèvement et l’heure et la date de la dernière prise d’atazanavir n’a pas été inscrite sur la feuille de collect de données. Selon l’information du laboratoire de biochimie du CHUM (Hôtel Dieu) et la pharmacienne de l’UHRESS (Hôtel Dieu) le temps post-dose est environ 22 heures.

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**AVERTISSEMENT**: La qualité de l’avis pharmacologique est limitée par les données disponibles sur le patient. Il est de la responsabilité du médecin traitant de considérer toutes les données du patient et d'adopter une décision thérapeutique éclairée.

Signature du pharmacien: [Signature]

Date (aa/mm/jj): [Date]

Information supplémentaire:

(514) 934-1934, ext 32168
Case 2

- He is still at the hospital and we do not know what is making him sick.

- Many tests were performed during his hospitalization without any specific diagnosis being made.

- At one point, the gastroenterologist came and increased the Pantoloc BID. •Pantoprazole 40 mg BID

- And the microbiologist suggested once more to change the atazanavir.

- I didn’t argue this time and we switched atazanavir/r to darunavir/r
We changed the ARV therapy to:
- Emtricitabine + Tenofovir (Truvada)
- Darunavir /ritonavir (Prezista + Norvir)

Fentanyl 75mg/h q 3 days + morphine 15mg q4h PRN
Baclofen 10 mg TID
Sildenafil 25mg q 48h PRN or Tadalafil 10mg q48h PRN

Do you see any existing or new potential interactions?
Case 2

Fentanyl (Duragesic)
- Substrate CYP 3A4 (inactive metabolite)
  - Case of death with Kaletra + fentanyl

Morphine (Statex)
- Conjugated : UGT2B7, UGT1A3

Sildenafil (Viagra) or Tadalafil (Cialis)
- Substrate CYP 3A4 (inactive metabolite)

Because atazanavir combined with ritonavir has a similar drug interaction profile to darunavir/ritonavir combination.

I did not really expect new interactions. But I usually remain alert for new sides effects or lost of efficacy.
Case 2

- During rounds at some point, a physician felt the patient had a moon face.
  - We did not know the patient previously and this may have helped us notice it.
- We questioned the patient and he told us that he gained weight and that he had noticed that he had a big belly for the last month.
- The physician asked for cortisol and ACTH levels.
Case 2

Both were low

- Cortisol AM : 40 nmol/L
- ACTH : ↓

- A diagnosis of secondary adrenal insufficiency was made
Case 2

- I went back to the patient and asked questions regarding his back pain management and found out that he had 3 times a year triamcinolone injections (5 times the current year).
- With the last injection 6 weeks ago.

Triamcinolone: CYP 3A4
### Key to symbols:
- ☑/☑ These drugs should not be coadministered
- ☑/☒ Potential interaction — may require close monitoring, alteration of drug dosage or timing of administration
- ☑/☒ No clinically significant interaction expected
- ♦/☒ There are no clear data, actual or theoretical, to indicate whether an interaction will occur
- n/a Data not available

### Antiretrovirals (Protease Inhibitors)

<table>
<thead>
<tr>
<th>Antiretrovirals (Protease Inhibitors)</th>
<th>Atazanavir</th>
<th>Darunavir</th>
<th>Lopinavir</th>
<th>Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>n/a</td>
<td>☑</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Darunavir</td>
<td>☑</td>
<td>n/a</td>
<td>☑</td>
<td></td>
</tr>
<tr>
<td>Lopinavir</td>
<td>☑</td>
<td>☑</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>☑</td>
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<td></td>
</tr>
</tbody>
</table>

### Steroids

<table>
<thead>
<tr>
<th>Steroids</th>
<th>Atazanavir</th>
<th>Darunavir</th>
<th>Lopinavir</th>
<th>Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclometasone</td>
<td>☑</td>
<td>☑</td>
<td></td>
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<tr>
<td>Budesonide</td>
<td>☑</td>
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<tr>
<td>Dexamethasone</td>
<td>☑</td>
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<tr>
<td>Fluticasone</td>
<td>☑</td>
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<tr>
<td>Hydrocortisone (oral)</td>
<td>☑</td>
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<tr>
<td>Hydrocortisone (topical)</td>
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<tr>
<td>Mometasone</td>
<td>☑</td>
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<tr>
<td>Prednisolone</td>
<td>☑</td>
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<td></td>
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<tr>
<td>Tramcinolone</td>
<td>☑</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

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## Trimacainolone injection

| 3 Cases | Three HIV-infected patients treated by a ritonavir-boosted protease inhibitor (PI) regimen received a single intra-articular injection of 40 mg triamcinolone.  

The three patients (lopinavir/r or indinavir/r) rapidly (2 weeks) developed signs and symptoms of iatrogenic Cushing's syndrome (swollen face, weight gain, hyperexitability, insomnia, hypertension, hyperglycemia) followed (5-6 weeks) by secondary adrenal insufficiency (severe fatigue, abdominal pain, nausea/vomiting and anorexia).  

The blood tests showed a low morning plasma cortisol and a low ACTH concentration.  
**Diagnosis**: secondary adrenal insufficiency.  
**Treatment with hydrocortisone replacement for two of them (x 5-8 months)**.

---

## Trimacainolone injection

<table>
<thead>
<tr>
<th>1 Case</th>
<th></th>
</tr>
</thead>
</table>
| **Lopinavir/r + Triamcinolone** | **The patient received two epidural injections one week apart. One month later, he developed Cushing syndrome (swollen face, weight gain, buffalo hump, hypertension, hyperglycemia).**  

A high triamcinolone plasma concentration.  

Low morning plasma cortisol, a low ACTH concentration and inadequate cortrosyn response. Resolution after 5 months.  

Eleven months later: **avascular necrosis** of the femoral head\(^2\) |  |

---

## Trimacinolone injection

<table>
<thead>
<tr>
<th>Two cases</th>
<th>2 Atazanavir/r + Triamcinolone</th>
</tr>
</thead>
<tbody>
<tr>
<td>One male with transforaminal epidural injection 3 and 2 months before. Abdominal bruising, weight gain (15kg), acneiform lesions, high blood pressure, notable truncal weight and a cushinoid facies. Low AM cortisol and ATCH. Height triamcinolone level. One month later, he developed avascular necrosis of the femoral head. 4 months later cortisol and ACTH were back to normal.(^1)</td>
<td></td>
</tr>
<tr>
<td>One female with a 40 mg triamcinolone subacromial space injection. Two weeks after: weight redistribution around the neck and upper thighs, weakness, heat intolerance, blurry vision, heart palpitations, fatigue, hyperexcitability, insomnia, and increased appetite. Low AM cortisol and ATCH and inadequate cortrosyn response. Resolution after two months.(^1)</td>
<td></td>
</tr>
</tbody>
</table>

---

Case report of Cushing’s syndrome and adrenal suppression with PI/r and

- Fluticasone/budenoside inhalation\(^1\)
- Dexamethasone 0.1% eye drops\(^2\)

1. [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org) and [www.gudetherapeutiquevih.com](http://www.gudetherapeutiquevih.com)
Avoid combination of CYP 3A4 corticosteroid and boosted PI.

Beclomethasone could be an alternative.

Replace the PI regimen by NNRTI regimen or raltegravir.

If not possible, use a low dose and for a short period of time and

Teach the patient about cushingnoid syndrome.
If ICS, reduce gradually the exposure to the corticosteroids.

Test for morning cortisol and ACTH. Perform cortrosyn test and reactive hyperglycemia test.

If secondary adrenal insufficiency occurs, substitution with a low physiological dose of hydrocortisone (10–20 mg/day) is recommended and complete recovery of adrenal function will usually take a few months.
Case 2

- Truvada + Prezista /Norvir

  Truvada + Raltegravir + Etravirine

- Fentanyl 75mg/h q 3 days + morphine 15mg q4h PRN
- Baclofen 10mg TID
- Triamcinolone (epidural injection 3X/yr)
- Sildenafil 25mg q 48h PRN or Tadalafil 10mg q48h PRN
Conclusion: Drug–drug interactions management

- Review the literature
  - HIV drug-drug interactions sites
  - Monograph
  - Pubmed etc

- Discuss with colleagues from other specialities

- TDM

- Switch to ARV with less interaction potential (Raltegravir, NNRTI, maraviroc, enfuvirtide)
  - Cardiology (plavix, antiarythmic)
  - Oncology
  - Triamcinolone
  - Transplant
  - HCV