Pharmacological Challenges in Treating HIV-HCV Co-infected Patients

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University of Liverpool
May 2013
Drug-Drug Interactions

Toxicity

Reduced Efficacy

This is the ‘simple example’! What about combination ARV and multiple co-meds?
HIV Infection
The Magnitude of the Problem
## Risk for ‘clinically significant’ interactions

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Setting</th>
<th>N</th>
<th>CSDI</th>
<th>Screening Tool</th>
<th>VL Effect</th>
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<td>de Maat</td>
<td>2004</td>
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<td>115</td>
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<td>Shah et al</td>
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<td>Liverpool website; Micromedex</td>
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<td>27%</td>
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<td>Patel et al</td>
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<td>190</td>
<td>34%</td>
<td>Lex-interact</td>
<td>N/A</td>
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</tbody>
</table>

References:
- Miller et al. Pharmacotherapy 2007;27:1379
- Marzolini et al. AVT 2010;15:413
- Evans-Jones et al. CID 2010;50:1419
- Kigen et al. Plos One 2010
- Patel Ann Pharmacother 2011;45
Polypharmacy and risk of antiretroviral (ARV)-drug interactions among the aging HIV-positive population: findings from the HIV Outpatient Study (HOPS)

Carol Holtzman¹, Carl Armon², Ellen Tedaldi³, Joan S. Chmiel⁴, Kate Buchacz⁵, Kathy Wood², John T Brooks⁶ and the HOPS Investigators

¹Temple University School of Pharmacy, Philadelphia, PA; ²Cerner Corporation, Vienna, VA; ³Temple University School of Medicine, Philadelphia, PA; ⁴Northwestern University, Feinberg School of Medicine, Chicago, IL; ⁵Centers for Disease Control and Prevention (CDC), Atlanta, GA

RESULTS (N = 3674)

• 261 (7%) were prescribed at least one contraindicated ARV-drug combination, and 1,239 (34%) were prescribed at least one ARV-drug combination with moderate or high evidence of interaction.

• Among patients prescribed a contraindicated ARV-drug combination, 61% were prescribed proton pump inhibitors (PPIs) along with atazanavir or nelfinavir, 19% were prescribed simvastatin or lovastatin along with a PI, and 16% were prescribed benzodiazepines along with a PI (Figure 1).

CONCLUSIONS

• We found a substantial proportion of patients being prescribed ARV-drug combinations with potential for clinically significant interactions among an HIV outpatient cohort in the US, with rates even higher among patients ≥ 50 years of age.
The Mechanisms Involved
Why an **increase** in steady state of a drug?

Possible reasons for increased exposure?

- GI Tract
- Hepatic
- Renal

**Interacting Drug**

```
Drug Conc.

Days

1 2 3 4 5 6 7 8 9 10 11 12
```
Effects of Omeprazole on Plasma Levels of Raltegravir

Marian Iwamoto, Larissa A. Wenning, Bach-Yen Nguyen

Figure 1. Arithmetic mean raltegravir plasma concentration-time profiles in healthy men and women after the single-dose administration of 400-mg raltegravir with or without the administration of 20-mg omeprazole once-daily (Inset: semilog scale).
Dissolution of Raltegravir at different pH

The breakdown of raltegravir 400 mg tablets at pH 1 to 8

Tablet dissolution rate increased at higher pH

[Chart showing dissolution rate vs. pH]
Effect of lopinavir/r on digoxin exposure: transporter mediated

Digoxin AUC ↑1.8-fold

Wyen C et al Clin Pharm Ther; 2008; 84: 75-82
Effect of Boosted PI on intestinal & hepatic CYP3A4

I.V. Midazolam

**Figure 1e.**

- Baseline
- First Dose TPV/r
- Steady State TPV/r

<table>
<thead>
<tr>
<th>Midazolam Concentration (ng/mL)</th>
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<td>Nominal Sampling Time (h)</td>
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</table>

**Hepatic Interaction**

MDZ AUC ↑3-fold

Oral Midazolam

**Figure 1f.**

- Baseline
- First Dose TPV/r
- Steady State TPV/r

<table>
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<tr>
<th>Midazolam Concentration (ng/mL)</th>
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<td>Nominal Sampling Time (h)</td>
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**Intestinal + Hepatic Interaction**

MDZ AUC ↑10-fold

A major cause of drug-drug interaction: inhibition of CYP3A4 enzyme

CYP 3A isozymes are the most abundant in the liver

CYP 3A isozymes are involved in the metabolism of majority of drugs

CYP 3A4
CYP 1A2
CYP 2A6
CYP 2B6
CYP 2C8
CYP 2C9
CYP 2C19
CYP 2D6
CYP 2E1

CYP 3A4

Proportion of drugs that are substrates for major CYP enzymes

CYP: cytochrome P450
All percentages are approximate. For illustrative purposes, hepatic CYP enzymes present at <5% are all represented as 3.3%

Effect of lopinavir/r on rosuvastatin exposure: hepatic transporter mediated

**FIGURE 1.** Rosuvastatin AUCs for subjects on rosuvastatin alone (black squares, solid line) and subjects on rosuvastatin plus lopinavir/ritonavir (open circles, dashed line).
### Drug-drug interactions between HIV drugs and non-HIV drugs

**EACS Guidelines 2012**

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<th>ATV</th>
<th>DRV</th>
<th>LPV</th>
<th>RTV (i)</th>
<th>EFV</th>
<th>ETV</th>
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<td>↔</td>
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</table>

(i) Indicates interaction risk level.
Key Mechanisms of Drug Interactions: Why a decrease in steady state of a drug

Reasons for decreased exposure?
- Gut
- Liver

Interacting Drug

Days
1 2 3 4 5 6 7 8 9 10 11 12
Effect of Omeprazole on plasma levels of Rilpivirine

Co-administration of OMEPRAZOLE 20 mg reduced rilpivirine exposure by 40%

Combination of rilpivirine (25 mg) with PPIs is contraindicated

Effect of H2-blockers can be circumvented with separate intake (12h before, or 4h after)

Van Heeswijk et al. 4th IAS Conference, Sydney, Australia, 22–25 July 2007, abstract TUPDB01

Enzyme Induction

- **Antimycobacterial drugs**
  - Rifampicin (CYP3A, 2C9/19, UGT),
  - Rifabutin (CYP3A)
  - Isoniazid (2E1)

- **Anticonvulsant drugs**
  - Carbamazepine, Phenytoin, Phenobarbital (CYP3A)

- **Herbals**
  - St John’s wort (CYP3A)
Rifampicin Induction and Lopinavir/r

Not Recommended

La Porte CJ et al., AAC 2004; 48: 1553-1560.
“If Sustiva is coadministered with rifampin to patients weighing 50 kg or more, an increase in the dose of Sustiva to 800 mg once daily is recommended.”
CDC 2012 Update

Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis

Department of Health and Human Services
Centers for Disease Control and Prevention

• ‘Efavirenz-based antiretroviral therapy and rifampin-containing TB treatment at standard doses is the preferred treatment for HIV-related tuberculosis in adults’. We consider that data are insufficient to support a definitive statement regarding the need to increase the dose in persons over 50 kg.

Beware – the unexpected!

Lopinavir/ritonavir significantly influences pharmacokinetic exposure of artemether/lumefantrine in HIV-infected Ugandan adults

Pauline Byakika-Kibwika1–3*, Mohammed Lamorde1,2, Violet Okaba-Kayom1, Harriet Mayanja-Kizza1,3, Elly Katabira1,3, Warunee Hanpithakpong4, Nadine Pakker3, Thomas P. C. Dorlo5,6, Joel Tarning4,7, Niklas Lindegardh4,7, Peter J. de Vries6, David Back8, Save Khoo8 and Conetta Merry1–3

(a) Artemether

(b) Lumefantrine

J Antimicrob Chemother 2012; 67: 1217-1223
What Constitutes a Clinically Relevant Drug-Drug Interaction?

20%, 30%, 50%, 70% decrease in PK OR 0.5-fold, 2-fold, 3-fold increase in PK?

- Can be confusing!
- Depends on the individual drug and the exposure – response relationship
Are we only concerned about interactions with oral drugs?
## Corticosteroid metabolism and formulations

<table>
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<th>Drug</th>
<th>Oral</th>
<th>Inhaled</th>
<th>Topical</th>
<th>Eye/ear drops</th>
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</table>

Created from SmPCs for all included drugs. Available at: [http://www.medicines.org.uk/emc/](http://www.medicines.org.uk/emc/).
Iatrogenic Hypercortisolism Complicating Triamcinolone Acetonide Injections in Patients with HIV on Ritonavir-Boosted Protease Inhibitors

David Fessler, MD, MPH, Jennifer Beach, MD, John Keel, MD, and Wendy Stead, MD
HCV Infection
The Magnitude of the Problem
DDIs – an emerging ‘hot topic’ in Hepatitis C

Drug-drug interactions in Hepatitis C
(No of publications)

2012 – 30 publications
2013 - ??

Maasoumy B et al Clinical significance of drug-drug interactions in the era of direct acting antiviral agents against hepatitis C – a real world experience. EASL 2013, Abs 856
The Mechanisms Involved
Telaprevir and Boceprevir interfere with the way the body handles other drugs.
Whereas the major effect of DAAs is to increase concentrations of co-med they may also decrease AND co-meds can interact with DAA
Clinical case: patient characteristics at time of treatment

Description

- 54-year-old male
- Smoker and no alcohol abuse
- Treatment naïve

HCV disease characteristics

- Genotype: HCV G1a
- Fibrosis stage: F3

Other medical information

- BMI: 28
- Type 2 diabetes (taking metformin)
- High cholesterol and cardiovascular risk >20% (taking atorvastatin) – Total Chol: 1.70 g/L; HDL: 0.42 g/L
- Hypertension (taking propranolol)
- Suffering from mild depression (receiving behavioural therapy)
- Hb level: 14 g/dL

BMI: body mass index; Hb: haemoglobin; HCV: hepatitis C virus; HDL: high-density lipoprotein
DDIs: patient’s medications

- Telaprevir
- Propranolol
- Atorvastatin
- Metformin

PR
Which medications are a concern with telaprevir?

- **Metformin**
  - Renal excretion – no interaction expected
  - Not anticipated to cause a problem when combined with DAAs

- **Propranolol**
  - Metabolised by CYP2D6 (major) – no interaction expected

ED: erectile dysfunction

http://www.hep-druginteractions.org
Treatment decision

Because of interactions Atorvastatin was temporarily stopped for 12 weeks after consultation with the cardiologist. No changes were made to the metformin and propranolol prescriptions.
Patient health

- Patient develops an **upper respiratory tract infection** (deemed unrelated to treatment)
- He develops **mild rash**
- His **depression** worsens (becomes moderate)
Management of the patient’s upper respiratory tract infection

Clarithromycin
- CYP 3A inhibitor & substrate
- Concern about increase in telaprevir exposure
- Also concern of increase in CLA – this may warrant ECG monitoring due to the possible risk of QT prolongation

Azithromycin
- Not a CYP 3A inhibitor or substrate
- Drug interactions unlikely
- A 5-day course of azithromycin was chosen due its reduced likelihood of interactions

Choose carefully

ECG: electrocardiogram
http://www.hep-druginteractions.org
Management of mild rash: which corticosteroid?

Systemic corticosteroids

- Not recommended with telaprevir and boceprevir
- Prednisone and methylprednisolone are CYP3A substrates; levels may significantly increase and lead to side effects

Topically applied steroids

- OK to use concomitantly with HCV PIs
- Although not expected to cause significant systemic absorption – be watchful (lessons form HIV)

In this patient, a topically applied corticosteroid (betamethasone) was initiated

Antidepressants and telaprevir

Some Antidepressants are metabolized by CYP 3A4

- Trazodone
- Mirtazapine
- Sertraline

Interaction is likely, caution is advised

Some Antidepressants metabolized primarily by non CYP 3A4

- Paroxetine
- Fluoxetine
- Venlafaxine

Interaction is unlikely*

* Caution – note escitalopram

http://www.hep-druginteractions.org
Treatment outcome: summary

Telaprevir + PR
- Betamethasone
- Fluoxetine

PR
- Rash disappeared; topical steroid stopped
- Depression symptoms improved

Weeks
- 0 12 24 36

HCV RNA (log_{10} IU/mL)
- 0 2 4 6

SVR12
- Restart statin
Drug Interaction Resources

- hivinsite.ucsf.edu
  Updated drug interaction database with references and interactive tool to assess drug interactions.

- www.aidsinfo.nih.gov
  DHHS Guidelines for use of antiretroviral agents and updated drug interaction tables.

- www.hiv-druginteractions.org
  www.hep-druginteractions.org
  Downloadable drug interaction charts; interactive tools to assess interactions; updated news on published abstracts and papers

- www.hivmedicationguide.com
  Interactive drug interaction database

- Micromedex: comprehensive drug database (subscription required); an app is available
Management of Hep Drug-Drug Interactions

LATEST ARTICLES
Meeting Report - 48th EASL, Amsterdam
Meeting Report - 14th HIV Pharmacology Workshop, Amsterdam.
Review - Telaprevir and antiretrovirals.
Drug Interactions - Boceprevir and omeprazole
Review - HCV and transplantation.
Meeting Report - 20th CROI, Atlanta
Click here for previous news items

SITE UPDATES
New Comedications Added
A major update to the comedications list has been completed....

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Please add noreply@hep-druginteractions.org and hivgroup@liv.ac.uk to your address book to assist in uninterrupted delivery and check your SPAM or BULK folder to ensure emails are not being lost.

INTERACTION CHARTS AT YOUR FINGERTIPS
HEP iChart - an interaction app for mobile devices
Available free for Apple and Android devices (search for HEP iChart in the App Store or Google Play).
This is an “offline” app that is downloaded to your device (~350 kb). An internet connection is not required to use the app, but is needed for downloading updates.

NOW OPTIMISED FOR iPADS

VIRAL HEPATITIS CONGRESS 2013
The Viral Hepatitis Congress 2013
26-28 September 2013.
In a co-infected patient we now need to manage the interactions between the HCV and HIV medication as well as other co-meds.