Role of Drug Interactions in the Management of Hepatitis Virus Infections

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What is the likely impact of pharmacologic drug-drug interactions in viral hepatitis treatment?
Can drug-drug interactions be beneficial?
Ritonavir as a PK Enhancer

Advantages

- Highly potent and specific inhibitor of CYP 3A4
- Extensive safety and tolerability experience with HIV protease inhibitors
- Now available as a 100 mg tablet

Concerns

- Toxicities: GI, lipids, hepatic (?)
- Weak inhibitor of CYP 2D6
- Inducer of several CYP’s and drug transport proteins
- Theoretical anti-HIV activity
Cobicistat (GS-9350): A Pharmacoenhancer Without Anti-HIV Activity

Mathias AA, et al.

*Clin Pharmacol Ther* 2010; 87(3): 322-9

Presented at the 6th International Workshop on HIV & Hepatitis Co-infection,
31 May – 2 June 2010, Tel Aviv, Israel
GS-9350 exhibited time- and dose-dependent PK consistent with mechanism-based inhibition

GS-9350 achieved potent inhibition of CYP3A activity

Near-maximal inhibition achieved at ≥100 mg
Cobicistat as a PK Enhancer

- Cobicistat is a potent, selective, mechanism-based CYP3A inhibitor that lacks anti-HIV activity and has limited effects on adipocyte function *in vitro*.
- Not a CYP inducer.
- Cobicistat boosts CYP3A substrates comparable to low-dose ritonavir in humans.
- EVG/FTC/TDF/cobicistat FDC “Quad” tablet achieves desired exposures of EVG, FTC, and TFV.
  - Effective in Rx-naïve pts. in Phase 3 studies (CROI 2010)
  - One pill, once-a-day
  - Serum creatinine “artifact”?

*Clin Pharmacol Ther 2010; 87(3): 322-9*
Preclinical and Early Clinical Evaluation of SPI-452, a New Pharmacokinetic Enhancer

Gulnik S, Eisenstat M, Afonina E, et al.

CROI 2009
Oral Abstract 41
Study 0452-002:
SPI-452 Enhances Darunavir Exposure

Mean (± SD) Darunavir 600 mg
(with SPI-452 on Day 15)

Day-7 (DRV alone)
25 mg SPI-452
50 mg SPI-452
200 mg SPI-452

Concentration (nM)

Time (h)

Study 0452-002: SPI-452 Enhances Darunavir Exposure

Gulnik S, et al
Oral Abstract 41

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SPI-452 as a PK Enhancer

- SPI-452 is a potent and selective inhibitor of CYP3A4 that lacks inherent antiviral activity.
  - Favorable safety and tolerability profile
  - Favorable metabolic/lipid profile
  - Enhances exposure of co-administered PI’s comparable to ritonavir
    - Darunavir
    - Atazanavir
Is there any reason to worry about standard HCV and HBV treatments, including ribavirin and interferon?
Impact of interferon on other drugs in the regimen?
Effect of IFNα-2b on CYP Metabolism

Islam et al., *Clin Cancer Res* 2002;8:2480

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Interferon and Drug Metabolism

- IFNα-2b inhibits CYP 1A2>>2C19>2D6>2E1 in patients with malignant melanoma.
  - Islam et al., Clin Cancer Res 2002;8:2480
- No inhibition of CYP 1A2, 2D6, or 3A4 discernible in patients with chronic HCV infection treated with IFN α and ribavirin for one month.
  - Becquemont et al., Clin Pharmacol Ther 2002;71:488
  - **But**, low baseline CYP 3A4 and 2D6 activity substantially improved with IFN+RBN
- Leading hypothesis for CYP inhibition by IFN is increased intracellular oxygen free radical concentrations.
  - May be mediated by xanthine oxidase.
Ribavirin Drug Interactions

- Inhibits intracellular phosphorylation of pyrimidine nucleoside analogs like AZT and d4T \textit{in vitro} but not \textit{in vivo}
  - Antagonistic with zidovudine and stavudine \textit{in vitro}
  - Enhanced (synergistic?) anemia with zidovudine
- Increases activity of purine nucleoside analogs like didanosine \textit{in vitro}
  - Possibly related to increased intracellular IMP as a phosphate donor for production of DDI-monophosphate
  - Also may enhance the mitochondrial toxicity of DDI
IFN suppresses compensatory reticulocytosis

De Franceschi et al. *Hepatology* 2000

Presented at the 6th International Workshop on HIV & Hepatitis Co-infection, 31 May – 2 June 2010, Tel Aviv, Israel
How should care providers interpret and manage drug interaction data?
Interpreting drug interaction data: Complex interactions with cholesterol-lowering agents
Differential effects of tipranavir plus ritonavir on atorvastatin or rosuvastatin pharmacokinetics in healthy volunteers.


Effect of Tipranavir/r on Atorvastatin

Pham et al., *AAC* 2009; 53: 4385
Effect of Tipranavir/r on Rosuvastatin

Pham et al., AAC 2009; 53: 4385
Tipranavir/r and Atorvastatin: Individual Subject PK Parameters

Pham et al., AAC 2009; 53: 4385
Tipranavir/r and Rosuvastatin: Individual Subject PK Parameters
Tipranvir/ritonavir effects on statins

- TPV/r increased the mean atorvastatin area-under-the-curve (AUC) by 836%.
  - Mainly clearance effect
  - Mediated by RTV inhibition of CYP 3A4

- TPV/r increased the mean rosuvastatin area-under-the-curve (AUC) by only 37%.
  - Mainly Cmax/absorption effect
  - Probably mediated by drug transporters
Interpreting drug interaction data: Atazanavir plus Raltegravir
**Rationale:** Raltegravir is metabolized by glucuronosyl transferase enzymes (UGT).

- Unboosted atazanavir 400 mg QD inhibits UGT, and modestly increases raltegravir concentrations.
- BID raltegravir and atazanavir represents a promising investigational NRTI-sparing regimen.

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Zhu et al., CROI 2009, Abstract 696
Effect of atazanavir 300 mg BID on raltegravir PK

- Zhu et al., CROI 2009, Abstract 696
Effect of raltegravir on atazanavir PK

- Zhu et al., CROI 2009, Abstract 696
Raltegravir plus Unboosted Atazanavir

- **Results**: Atazanavir 300 mg BID increased the raltegravir AUC by 53%.
  - Probably overall inhibition of UGT 1A1, but effects are inconsistent from patient to patient
- Surprisingly, raltegravir decreased the atazanavir Cmin by 29%.
  - Probably absorption/bioavailability effects.

  Zhu et al., CROI 2009, Abstract 696
How should we manage drug interactions in the future?
“Drug-Drug Interactions in HIV-Infected Patients,”
An Interactive Decision Support Tool
Available at:
http://Clinicaloptions.com/drug-drug,
or for Pocket PC and Palm Devices.
Last Updated March, 2010.
Getting Started: Search Type

Find all interactions for a single antiretroviral drug:
Single Drug

Search for interactions between antiretrovirals and other medications:
Multidrug

Data last updated:
August 17, 2006

Updates will be posted to:
http://clinicaloptions.com/drugdrug
Menu

Find all interactions with a single antiretroviral:

Select Single

Search for interactions between antiretrovirals and other medications:

Select Multidrug

Data last updated:
August 17, 2006

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Selecting Antiretroviral Drugs

Choose One Antiretroviral
Click “Next” to find interactions.
- Display brand names
Class of drugs
- All antiretrovirals
  - Fixed-dose formulations
  - Fusion inhibitor
  - NNRTI
  - NRTI
  - PI
  - PI (ritonavir boosted)

All antiretrovirals
- Abacavir
  - Abacavir/Lamivudine
  - Abacavir/Lamivudine/Zidovudine
  - Amprenavir
  - Amprenavir (liquid)
  - Atazanavir
  - Atazanavir/ritonavir
  - Darunavir/ritonavir
  - Delavirdine
  - Didanosine (buffered)
  - Didanosine EC
  - Efavirenz
  - Efavirenz/Emtricitabine/Tenofovir
  - Emtricitabine
  - Emtricitabine/Tenofovir
  - Enfuvirtide
Categorizing Interactions Found

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Interaction Details

POSSIBLE ADDITIVE TOXICITY
Abacavir + Abacavir/Lamivudine/Zidovudine

Effects:
Excess dosing due to use of more than one formulation containing the same drug.

Recommendation:
Do not combine abacavir/lamivudine/zidovudine (Trizivir) with abacavir (Ziagen) as the products contain the same or similar active ingredients.

References:
To print these details visit:
http://clinicaloptions.com/drugdrug

Step 3 of 3

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Selecting Other Drugs
Interactions Found

Select a result and click "Details".

- **MODERATE INTERACTION**
  - Abacavir + Alcohol

- **MINOR INTERACTION**
  - Abacavir + Lamivudine
  - Abacavir + Methadone

- **POSSIBLE ADDITIVE TOXICITY**
  - Abacavir + Abacavir/Lam
  - Abacavir + Abacavir/Lam

- **NO INTERACTION**
  - Abacavir + Any food
  - Abacavir + Efavirenz/Eml
  - Abacavir + Tenofovir
Drug Interactions and Viral Hepatitis

Conclusions:

- It is important to design regimens that avoid and/or tolerate potential drug-drug interactions.
- New PKE’s may avoid toxicity and resistance concerns that accompany ritonavir use.
- New technologies may provide the most promising means of communicating important information to providers, and assisting with medical decision-making.
  - Interactive web-based compendia
  - Smart phone apps