

# Understanding Pharmacokinetic Variability and Managing Drug-Drug Interactions

Courtney V. Fletcher, Pharm.D.  
Dean, College of Pharmacy and  
Professor, Department of Pharmacy Practice and  
Division of Infectious Diseases  
University of Nebraska Medical Center  
Omaha, Nebraska USA

# Disclosure

Courtney V. Fletcher, Pharm.D. has disclosed that he will not discuss any off-label indications for drugs used for the treatment of HIV infection. He will discuss drug-drug interaction information that has been presented at scientific meetings or published, which is not included in the FDA approved package insert.

Courtney V. Fletcher, Pharm.D., has disclosed that he has served as a consultant for Bristol-Myers Squibb and Koronis Pharmaceuticals.

# Learning Objectives

1. Identify common mechanisms underlying drug-drug interactions between antiretroviral agents and other medications commonly used by HIV-infected patients.
2. Discuss management strategies for drug-drug interactions.
3. Analyze the potential for a drug-drug interaction in the setting where pharmacokinetic data are lacking.

# Case Study #1

- 45-year-old HIV-infected male, antiretroviral experienced, who has been receiving ZDV/3TC and LPV/RTV for several years. He has had low-level viremia ( $> 400$  to  $< 1000$  copies/mL) for the last 12 months.
- This patient is a long-time smoker; he is overweight (198 lbs); but his blood pressure is within normal limits.
- He has a history of elevated cholesterol and triglycerides, which have responded well to pravastatin (20 mg/day).
- You and he have agreed to a new regimen of TDF/FTC and DRV/RTV (600/100 BID).

# Case Study #1- Increase in Lipids

- 3 months after switch to TDF/FTC + DRV/RTV laboratory results show lipid levels similar to those prior to pravastatin
  - ❖ Fasting cholesterol: 215 mg/dL
  - ❖ Fasting triglycerides: 267 mg/dL
- After an additional 3 months, these values remain unchanged
- The patient denies any adherence problems with pravastatin.
- What is the effect of DRV/RTV on pravastatin concentrations?

# Pravastatin and PIs

	$C_{max}$	AUC	$C_{min}$
SQV/RTV (400/400 BID) plus pravastatin, 40 mg/day			
Effect on PRAV	0.58	0.50	N/A
LPV/RTV (400/100 BID) plus 20 mg/day dose of pravastatin			
Effect on PRAV	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	N/A
DRV/RTV (600/100 BID) plus 40 mg single dose of pravastatin			
Effect on PRAV	1.63 (0.95, 2.8)	1.81 (1.23, 2.66)	N/A

Fichtenbaum C, AIDS 2002;16:569-77. Lopinavir/ritonavir [package insert]. North Chicago, Ill: Abbott Laboratories; 2008. Darunavir [package insert]. Raritan, NJ: Tibotec Therapeutics; 2008.

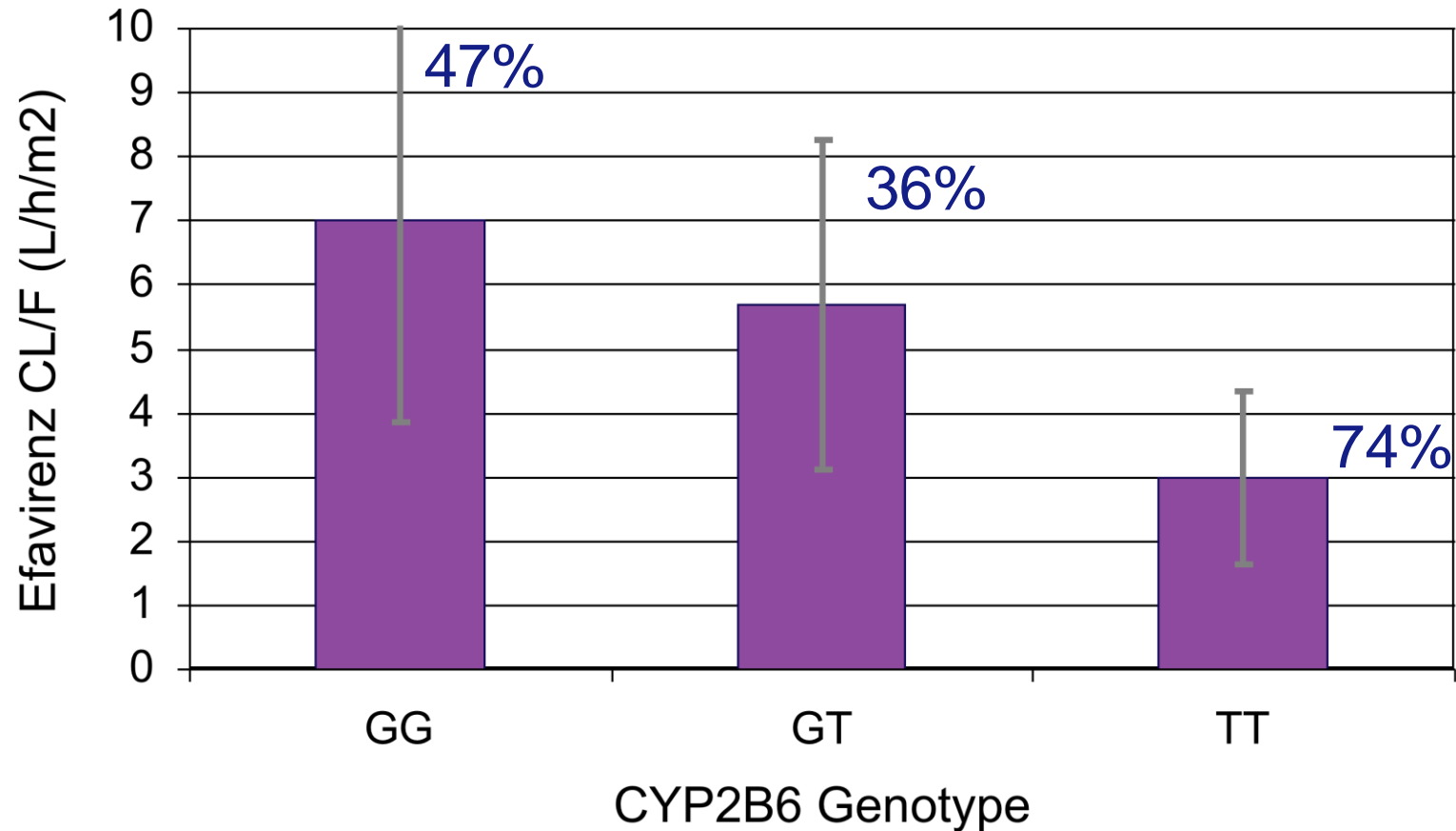
# Pravastatin and DRV/RTV

Patient	Pravastatin AUC Ratio (+DRV:-DRV)
1	5.53
2	6.78
3	4.69
4	3.80
5	1.0
6	0.85
7	0.57
8	1.16
9	2.16
10	1.31
11	2.43
12	0.92
13	1.16
14	1.49
Mean, CI	Mean, 1.81; 90% CI, 1.23, 2.66
Range	0.57, 6.78

# Factors Affecting Pharmacokinetic Variability

- Genetics
- Age
- Sex
- Pregnancy
- Drug-disease interactions
  - ❖ HIV infection (healthy volunteers vs. HIV-infected persons)
  - ❖ Altered GI, renal and hepatic function
- Drug formulation
- Drug-food interactions
- Drug-drug interactions
- Adherence

# Efavirenz Clearance and the Influence of Genetic Variability



# Nomenclature

- *Substrates*

- ❖ Undergo metabolism or transport

- *Inhibitors*

- ❖ Decrease the ability of the isozyme(s) or transporter to metabolize or transport substrates
- ❖ May also be substrates

- *Inducers*

- ❖ Increase the amount or ability of the isozyme(s) or transporter to metabolize or transport substrates
- ❖ May also be substrates

# 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 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

# Drug-Drug Interactions: Management Concepts

- Some interactions are useful
  - ❖ RTV-boosted PIs
- Some interactions can be managed clinically
  - ❖ EFV- and RTV-boosted PIs
- Some interactions are profound, and concomitant administration is contraindicated
  - ❖ Rifampin and all PIs
- Some interactions affect both efficacy and toxicity
  - ❖ TDF and ddl
- Some interactions have unclear clinical significance
  - ❖ TDF and PIs

## Question #2:

# Drug Interaction Challenge

What doses of etravirine, maraviroc, and raltegravir should be used when all 3 drugs are combined?

1. Usual doses of all 3 drugs; no clinically significant interactions
2. Usual doses of etravirine and raltegravir; increase dose of maraviroc to 600 mg BID
3. Usual dose of etravirine; increase dose of maraviroc to 600 mg BID; increase dose of raltegravir to 800 mg BID
4. This combination is contraindicated because of unmanageable competing drug interactions

# Etravirine, Maraviroc and Raltegravir

## ■ ETV

- ❖ substrate: CYP3A, CYP2C9, CYP2C19 and UGT
- ❖ inducer: CYP3A, UGT(1A1); and
- ❖ inhibitor: CYP2C9 and CYP2C19

## ■ MVC

- ❖ substrate: CYP3A and P-gp

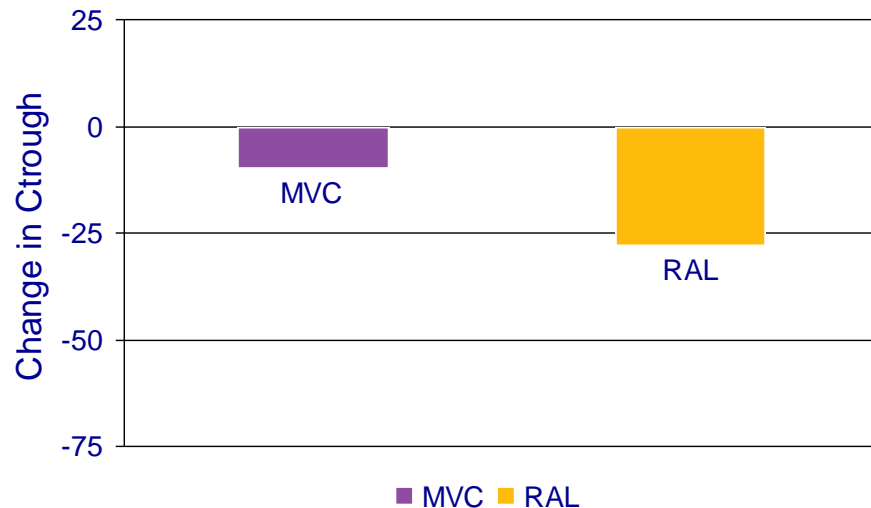
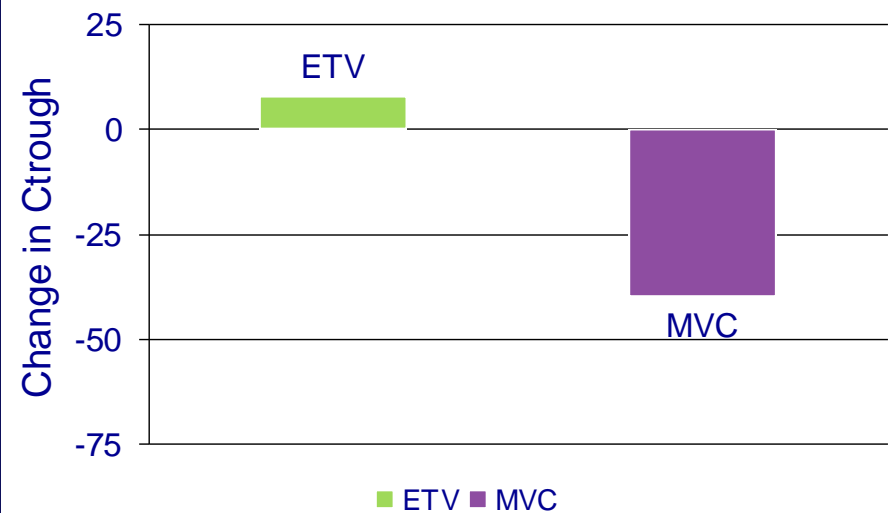
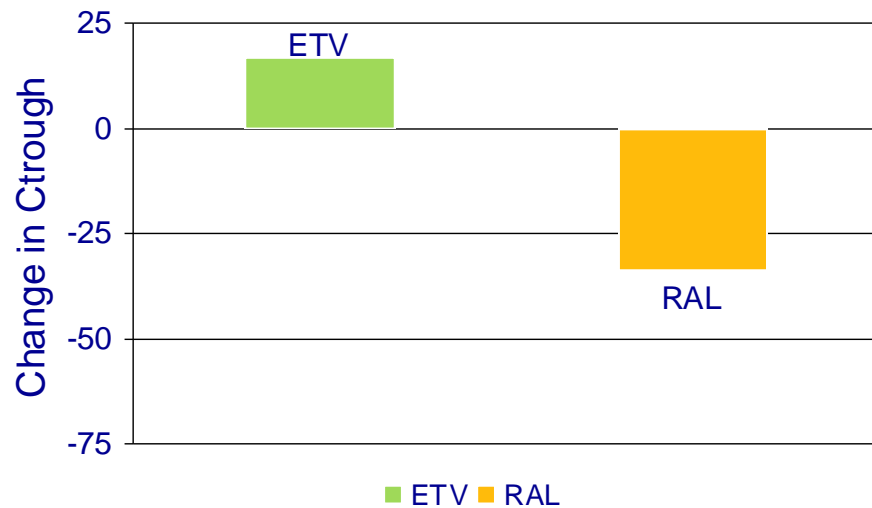
## ■ RAL

- ❖ substrate: UGT1A1 and P-gp

# Etravirine, Maraviroc and Raltegravir

## Effects of Trough Concentration

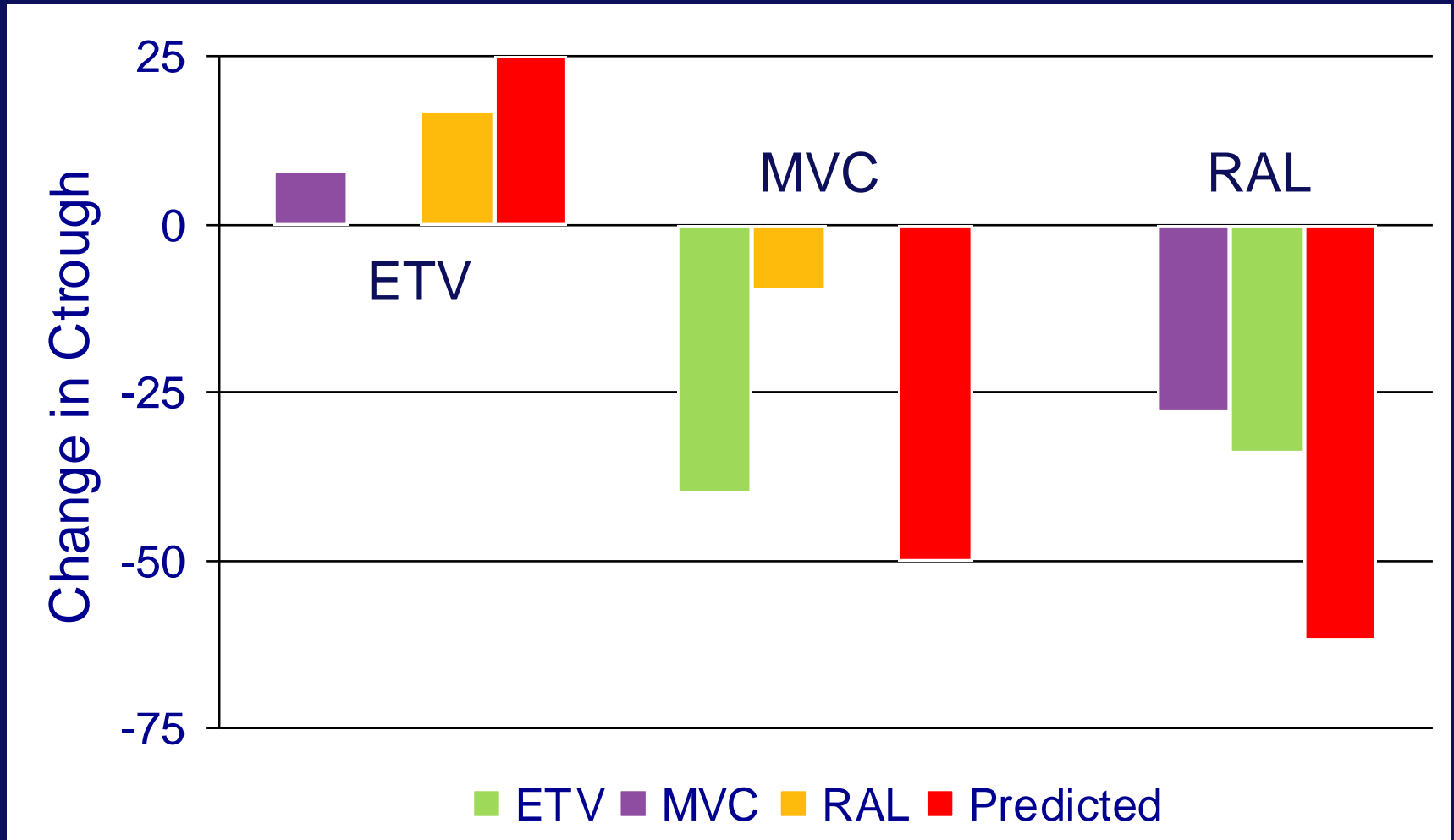
(2 way interaction studies)



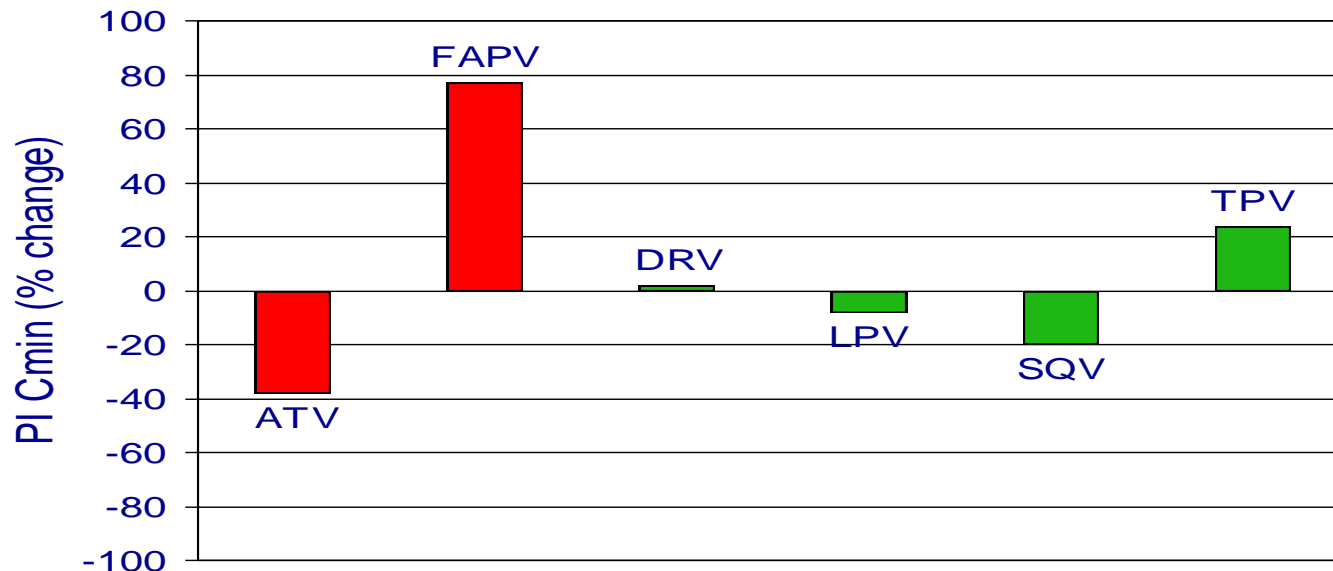
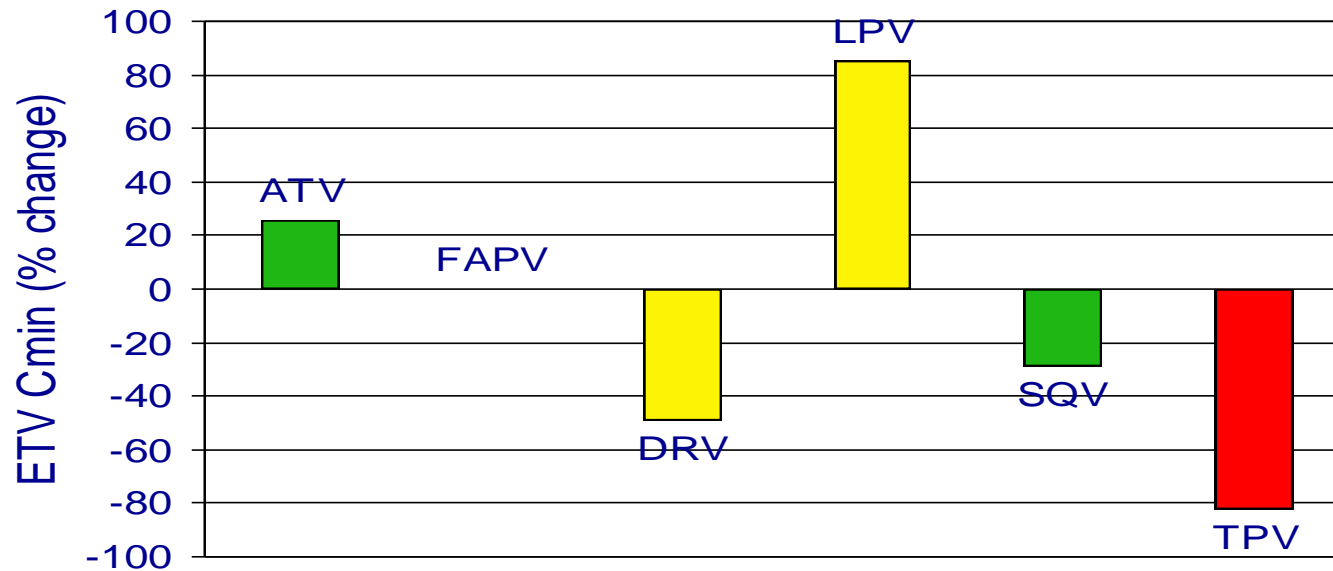
### References:

1. Antimicrob Agents Chemo 2008;52:4228-32.
2. 11<sup>th</sup> EACS, Poster P4.3/02. Madrid, Spain, October 2007.
3. Br J Clin Pharmacol 2010;69:51-7.

# Etravirine, Maraviroc and Raltegravir: predicted effect of all 3 given together

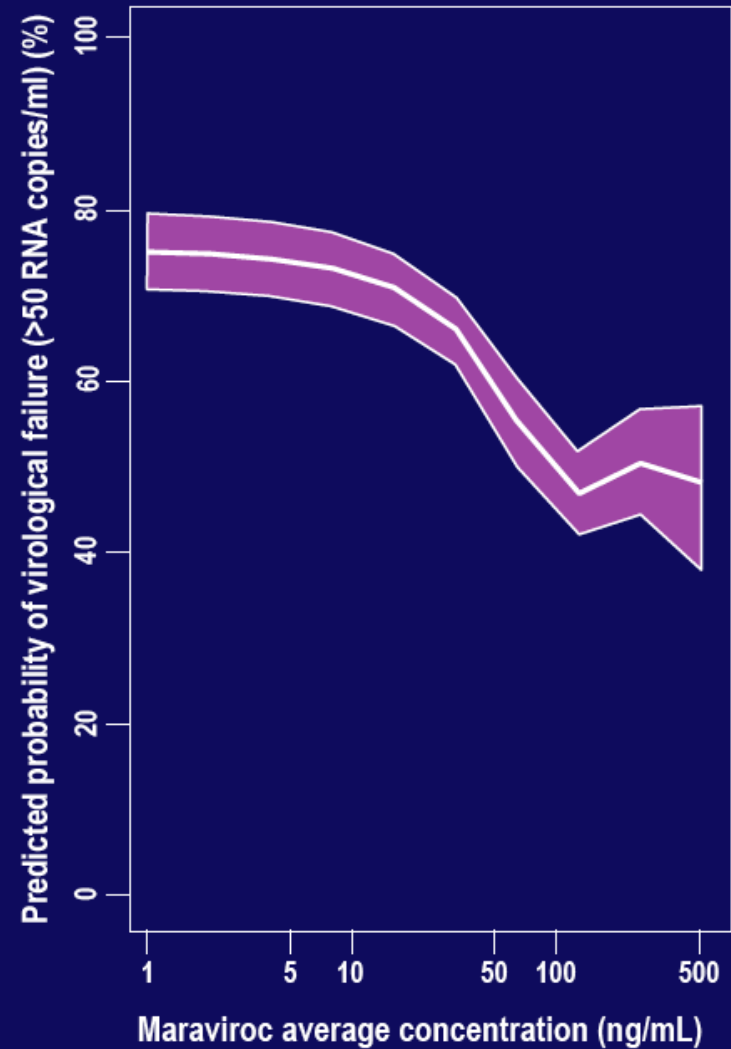
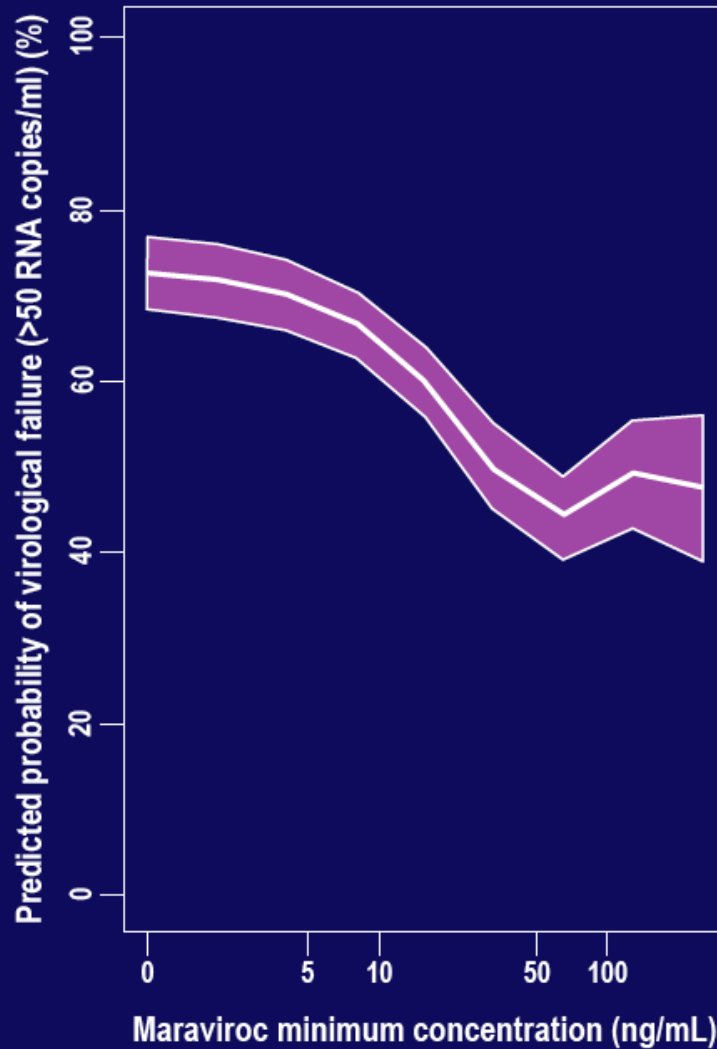


# Etravirine and PI/r Drug Interactions

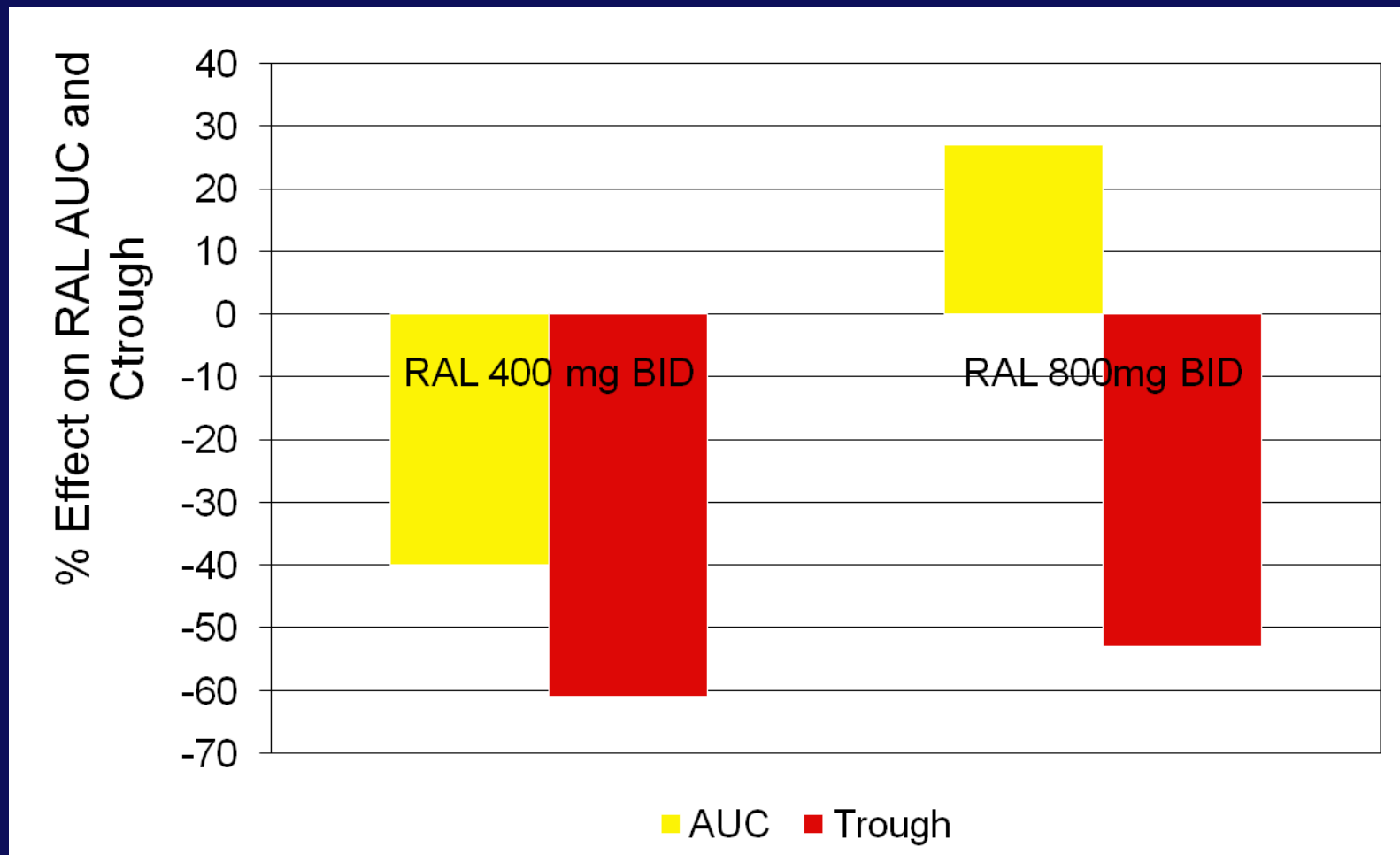


Etravirine  
Prescribing  
Information.  
Tibotec, Inc.  
Feb 23, 2010.

# Median (95% CI) Prediction of Likelihood of Failure as a Function of Cmin and Cavg

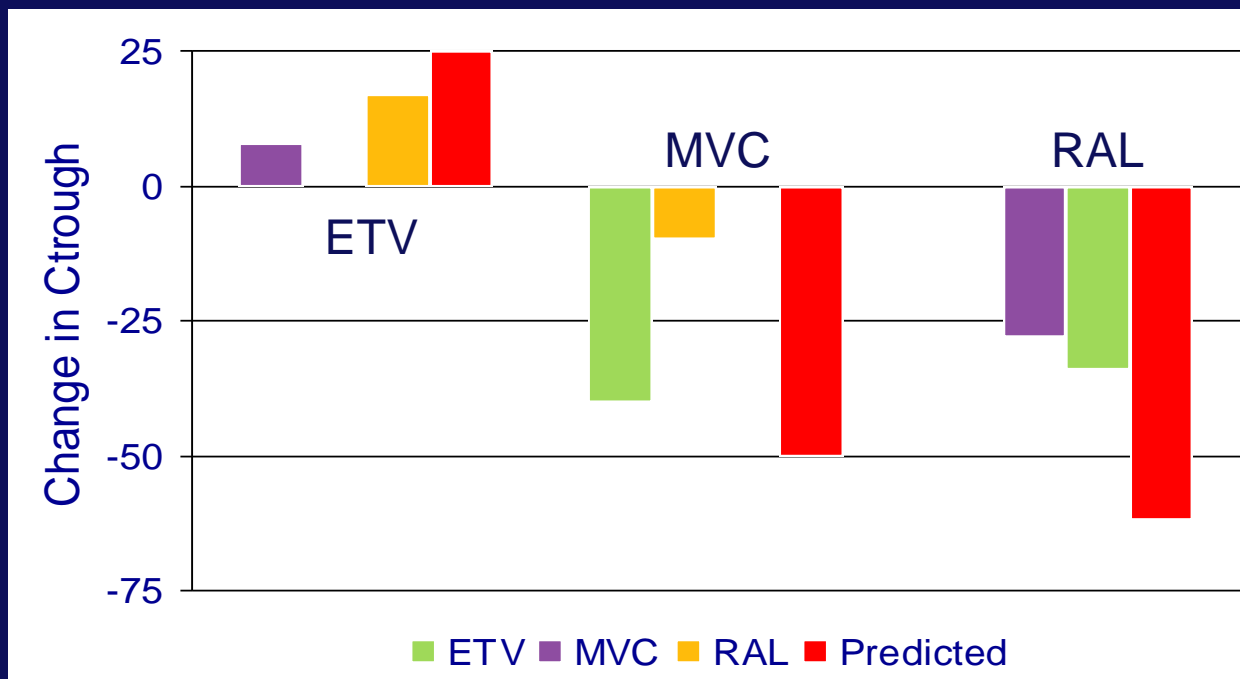


# Raltegravir and Rifampin



If combining RAL with rifampin, increase the RAL dose to 800 mg twice daily.

# Etravirine, Maraviroc and Raltegravir



Best “educated” guess for a combination regimen of ETV, MVC and RAL:

- ETV: usual dose of 200 mg BID
- MVC: increase dose to 600 mg BID
- RAL: consider dose increase to 800 mg BID

# Etravirine, Maraviroc and Raltegravir PK in HIV-Infected Persons

- 37 treatment-experienced persons received:  
ETV, 200 mg twice daily; MVC, 600 mg twice daily;  
and RAL, 400 mg twice daily.
- Mean trough concentrations were:
  - ❖ ETV: 515 ng/mL, 90%CV
  - ❖ MVC: 91.4 ng/mL, 80%CV; trough concentrations were  
< 50 ng/mL in 37% of the samples
  - ❖ RAL: 442 ng/mL, 100%CV
- ETV conc are consistent with the usual dose; MVC conc  
at 2x the usual dose are consistent with the usual dose  
but a high percent of patients had conc below threshold  
value; RAL conc at usual dose are higher than expected  
with lower variability.

# Etravirine-Raltegravir Interaction: 4 Case Reports in HIV-infected persons

	RAL C <sub>trough</sub> (nM)
Case 1: pre ETV	391 - 628
with ETV	10.4 - 20.7
Case 2: with ETV	62
after RAL inc to 1200/d	139
Case 3: with ETV	18.9 - 45.6
Case 4: with ETV	60.1
<b>RAL C<sub>trough</sub> Ratio</b>	<b>0.03 - 0.44</b>

Menard A, et al. AIDS 2009;23:869-71.

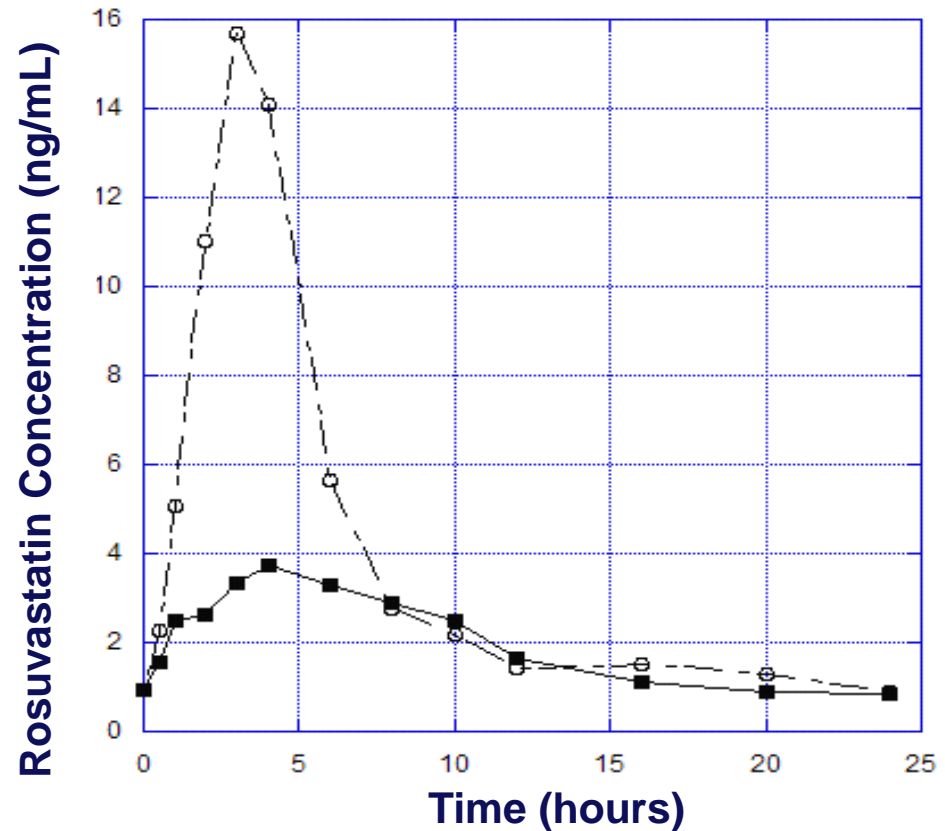
## Question #3

Which of the following is true?

1. Rosuvastatin and LPV/r are not recommended for concomitant administration because of an unmanageable pharmacokinetic and pharmacodynamic interaction.
2. The pharmacokinetic and pharmacodynamic effects of a rosuvastatin and LPV/r interaction are clinically manageable.

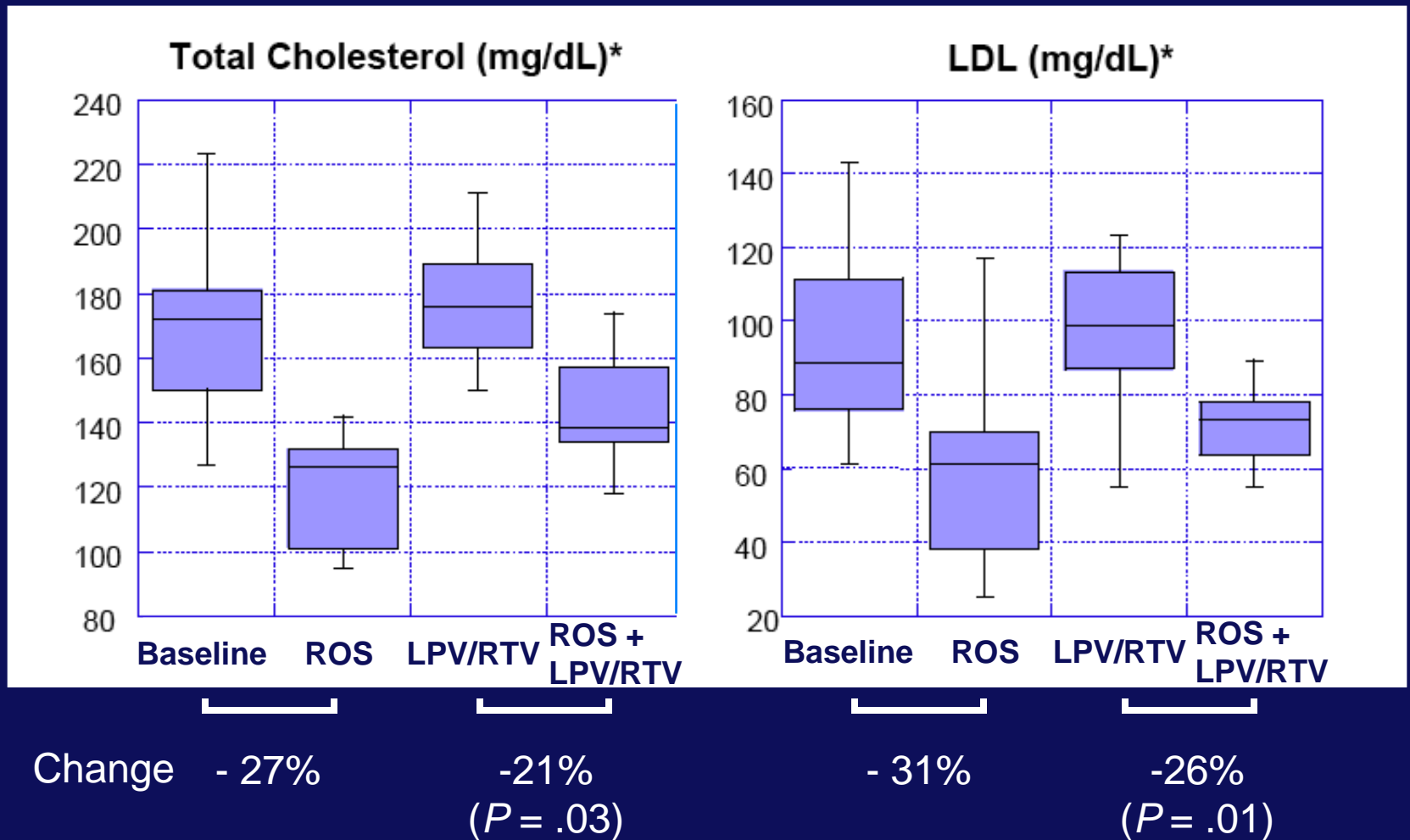
# Rosuvastatin and Lopinavir/ritonavir

- In 15 healthy volunteers receiving ROS, 20 mg/d, LPV/r caused a:
  - 4.7-fold increase in ROS C<sub>max</sub>,
  - 2.1-fold increase in ROS AUC;
  - C<sub>min</sub> unchanged
- Half-life unchanged; argues against CYP-mediated interaction



Closed squares ROS alone,  
Open circles ROS + LPV/RTV

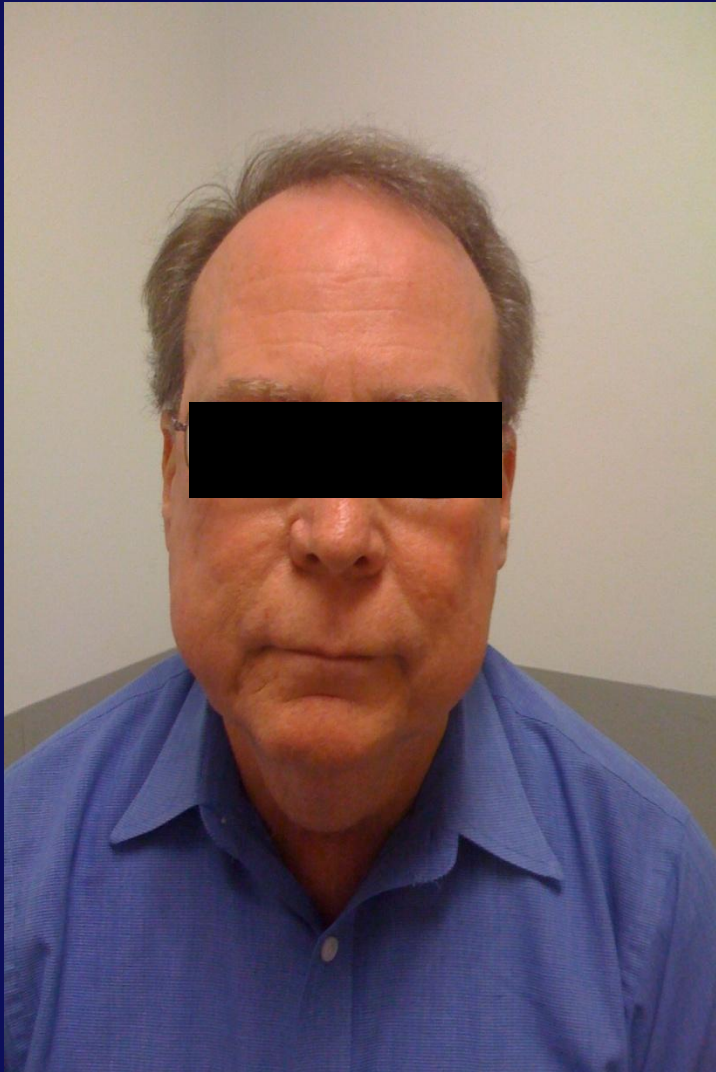
# Rosuvastatin and LPV/RTV: statin effect



# Case Study #4 Pharmacotherapy

- 59 y/o male diagnosed with HIV infection in 6/1987; CD<sub>4</sub> 33%, 370 cells/ $\mu$ L
- 4/00, ARV therapy changed to LPV/RTV, ABC, 3TC.
- 11/08, routine clinic visit: HIV-RNA, < 50 copies/mL; CD<sub>4</sub> 24%, 216 cells/ $\mu$ L. Patient complains of a change in facial appearance (puffiness) and easy bruising.
- Co-morbid conditions include dilated cardio-myopathy, asthma/restrictive lung disease, allergic rhinitis, hypogammaglobulinemia (recurrent bacterial pneumonias), osteoporosis, lipodystrophy, hypothyroidism, onychomycosis, and hypogonadism.
- Medications: LPV/RTV, ABC, 3TC, fluticasone/salmeterol (250/50), testosterone topical, levothyroxine, metoprolol XL, furosemide, atorvastatin, fluconazole, ASA, alendronate, Ca<sup>2+</sup>/Vit D, IVIG.
- What is your assessment and plan?

# Therapy of HIV Infection (cont.)



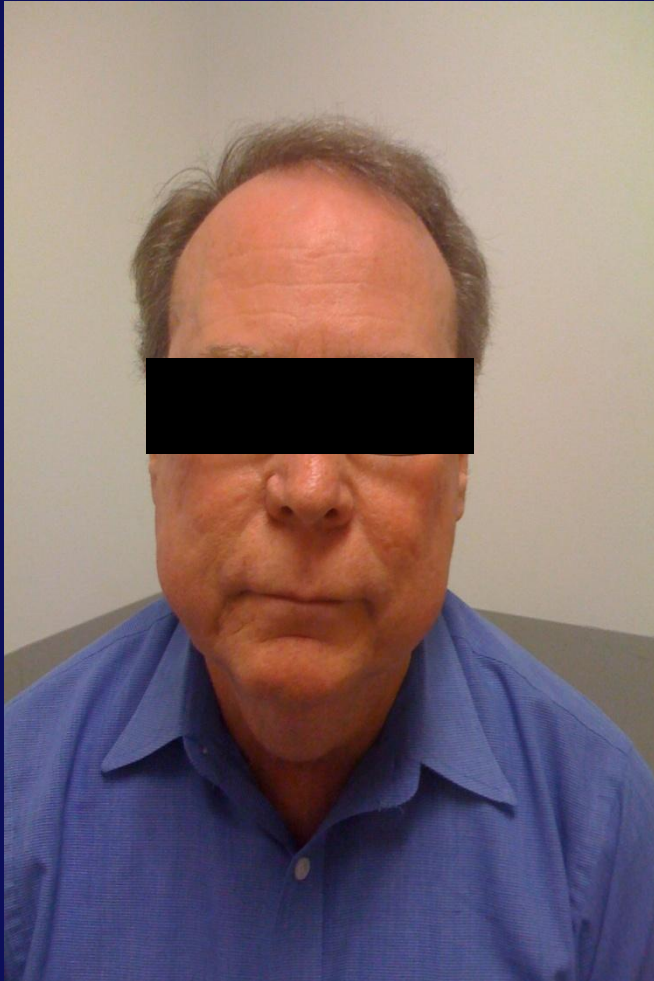
11/08/08



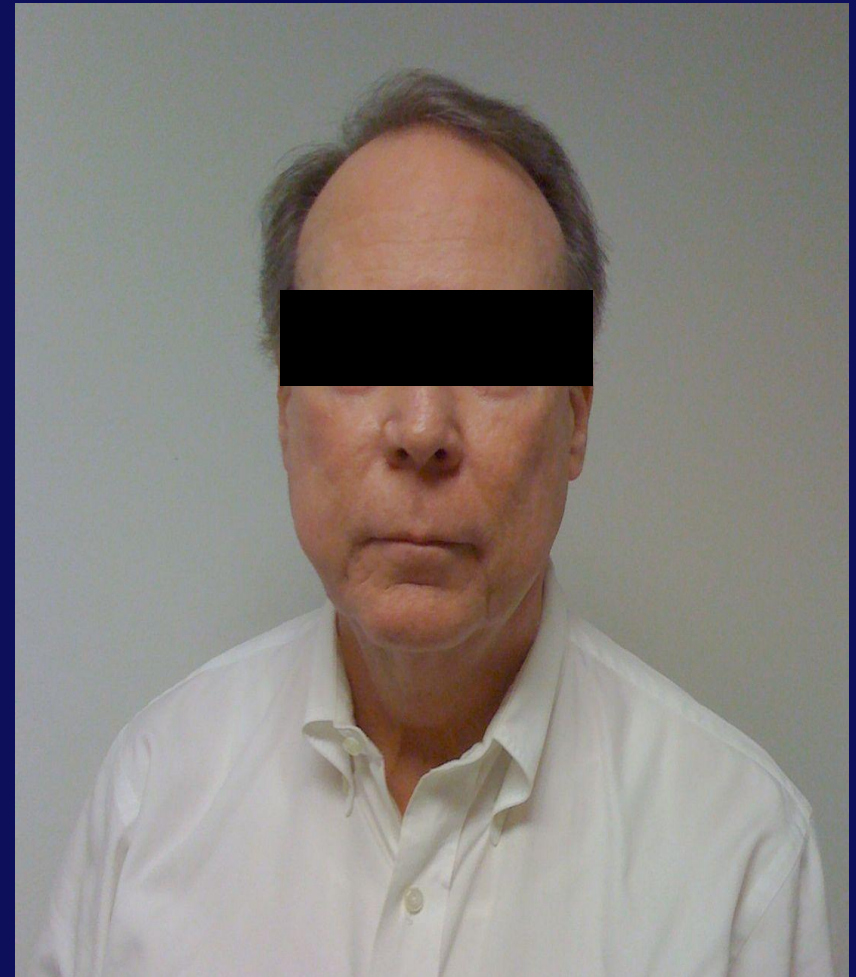
Case courtesy of Harold Kessler, MD, Rush Medical Center, Chicago.

# Therapy of HIV Infection (cont.)

11/08/08



03/02/09



Case courtesy of Harold Kessler, MD, Rush Medical Center, Chicago.

# Clinical Significance of Drug-Drug Interactions

- The clinical significance of a drug-drug interaction can only be determined or confirmed through a clinical study.
- In the absence of (or pending) clinical trial data, well defined exposure-response data provide a basis to predict the significance of a drug-drug interaction; however, there will be settings where the existing data are not informative as to PK and PD of the interaction.
  - ❖ Exercise a measure of caution in managing drug interactions where no confirmatory clinical data exist.

# Drug Interaction Resources

- [www.hivinsite.com](http://www.hivinsite.com)  
Updated drug interaction database with references and interactive tool to assess drug interactions.
- [www.aidsinfo.nih.gov](http://www.aidsinfo.nih.gov)  
DHHS Guidelines for use of antiretroviral agents and updated drug interaction tables.
- [www.drug-interactions.com](http://www.drug-interactions.com)  
Downloadable drug interaction charts; interactive tools to assess interactions; updated news on published abstracts and papers
- [www.hivmedicationguide.com](http://www.hivmedicationguide.com)  
Interactive drug interaction database
- [www.hivpharmacology.com](http://www.hivpharmacology.com)  
Updated summary of drug interaction data; guidelines for TDM
- **Micromedex**: comprehensive drug database; subscription required

*Thank You*

