

Understanding Pharmacokinetic Variability and Managing Drug Interactions

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Learning Objectives

Upon completion of this presentation, learners should be better able to:

1. Identify common mechanisms underlying drug-drug interactions between antiretroviral agents and other medications frequently used by HIV-infected patients.
2. Incorporate management strategies for drug-drug interactions which may present in the care of HIV positive individuals.
3. Analyze the potential for a drug-drug interaction in the setting where pharmacokinetic data are lacking.
4. Appraise emerging drug-drug interaction information with a new pharmacokinetic booster, new protease inhibitors for HCV, and rifabutin dosing with ritonavir-boosted protease inhibitors.

Disclosures

- 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 Merck & Co., in the past 12 months.

Do Drug Interactions Matter?

HAART, Antiepileptics and HIV Response

- US Military HIV Natural History Study cohort
 - ❖ Use of PI or NNRTI-based regimen for ≥ 6 months
 - ❖ AED drug use for ≥ 28 consecutive days during HAART
 - ❖ AEDs grouped as CYP inducers (phenytoin, carbamazepine, or phenobarbital) or other (lamotrigine, levetiracetam, gabapentin).

Outcome	EI AED (N=19)	Other AED (N=85)	Odds Ratio
Virologic Failure	62.5%	26.7%	4.58
VL < 400 cpm at 6 mos.	33.3%	71.4%	0.20
VL < 400 cpm at 12 mos.	36.4%	75.0%	0.19

- Concurrent enzyme inducing AEDs increased the risk of virologic failure and should be avoided.

Pitavastatin

- Pitavastatin is a newer HMG-CoA reductase inhibitor approved for hyperlipidemia.
- The major metabolic pathway in humans is glucuronidation (UGT1A3 and UGT2B7), with marginal metabolism by CYP2C9.

Pitavastatin and Rifampin - Question

- What is the effect of rifampin on the concentrations of pitavastatin?
 1. Rifampin increases pitavastatin concentrations.
 2. Rifampin decreases pitavastatin concentrations.
 3. Rifampin has no effect on pitavastatin concentrations.

Pitavastatin and Rifampin

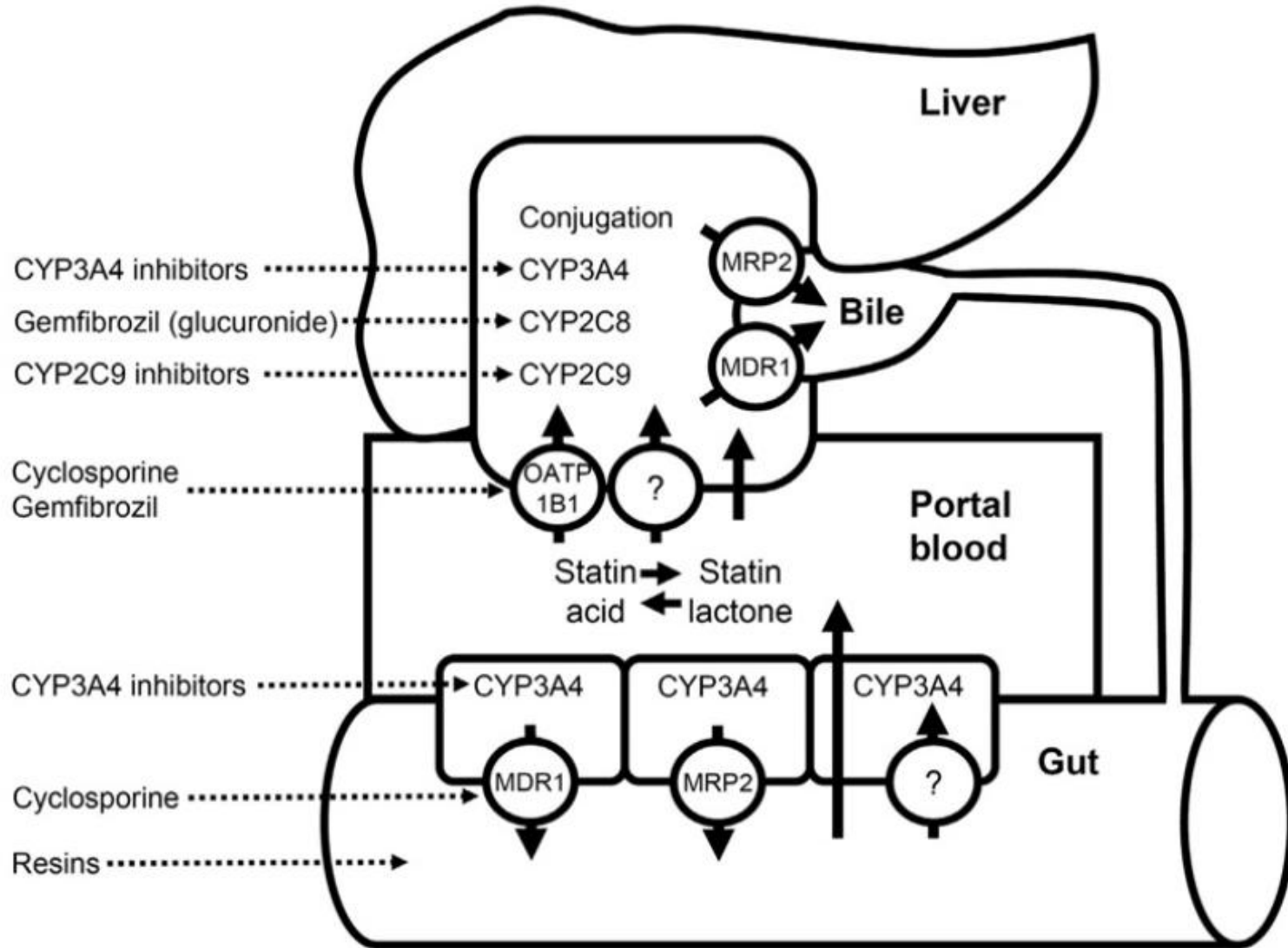
- Rifampin significantly **INCREASES** pitavastatin concentrations and a dose of 2mg once daily should not be exceeded.

Dose Regimen	Change in AUC	Change in Cmax
Pitavastatin 4 mg QD + Rifampin 600 mg QD for 5 days	29% Increase	2-fold Increase

Pitavastatin and LPV/r - Question

- What would you predict is the effect of lopinavir/ritonavir on the pharmacokinetics of pitavastatin?
 1. LPV/r increases pitavastatin concentrations.
 2. LPV/r decreases pitavastatin concentration.
 3. LPV/r has no effect on pitavastatin concentrations.

Sites of Interactions with Statins



Pitavastatin and LPV/r

- LPV/r-pitavastatin interaction study has been completed (NCT01057433, ClinicalTrials.gov); awaiting results.
- Based on data for another HMG-CoA reductase inhibitor [rosuvastatin] LPV/r may significantly increase pitavastatin concentrations. Pitavastatin should not be used with this PI combination.
Pitavastatin prescribing information, 2009.
- Atazanavir increases pitavastatin concentrations.

Dose Regimen	Change in AUC	Change in Cmax
Pitavastatin 4 mg QD + ATV 300 mg QD for 5days	31% Increase	60% Increase

Pharmacokinetic Challenges Along the Continuum of Antiretroviral Therapy

Newborns

- Body composition
- GI, renal and hepatic maturation
- Formulations
- Drug Interactions

Infants & Children

- Hepatic & renal maturation
- Growth and development
- Formulations
- Drug Interactions

Adolescent

- Puberty
- Adherence
- Drug Interactions

Adults

- Pregnancy
- Drug Interactions

Older Adult

- Age related decline in renal and hepatic function
- Concomitant diseases
- Drug Interactions

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

PK Variability and Drug Interactions – What Do We Need to Know

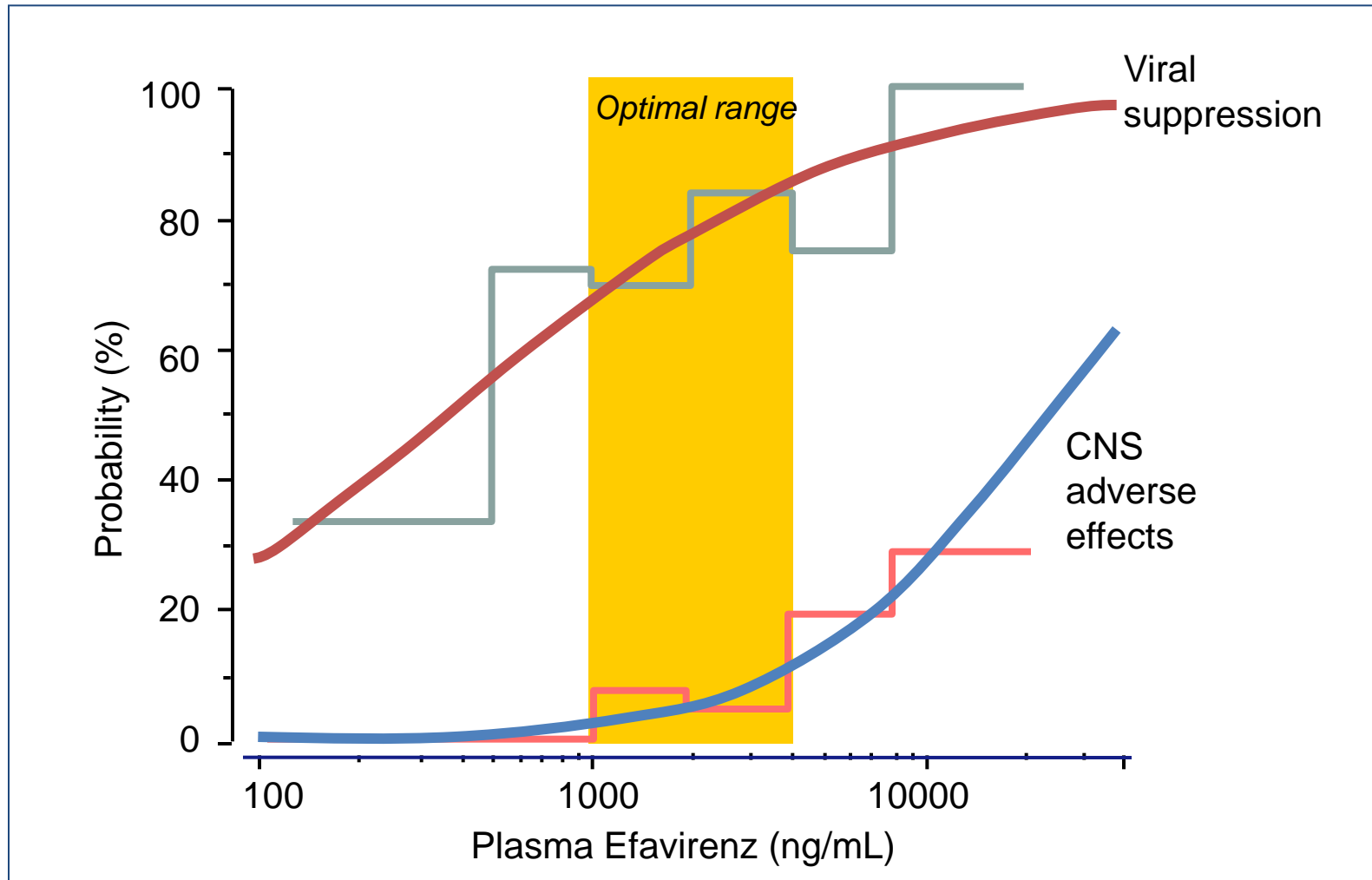
- How much variability is expected?
 - ❖ Inpatient
 - ❖ Outpatient
- What is the magnitude of the effect of the drug interaction on concentrations - - how does it exaggerate variability?
- How much is too much?
 - ❖ Exposure-response relationships
- Can we control for, or accommodate the effects of pharmacokinetic variability?
 - ❖ Pharmacokinetic strategies
 - ❖ Pharmacodynamic strategies

Pravastatin and DRV/RTV

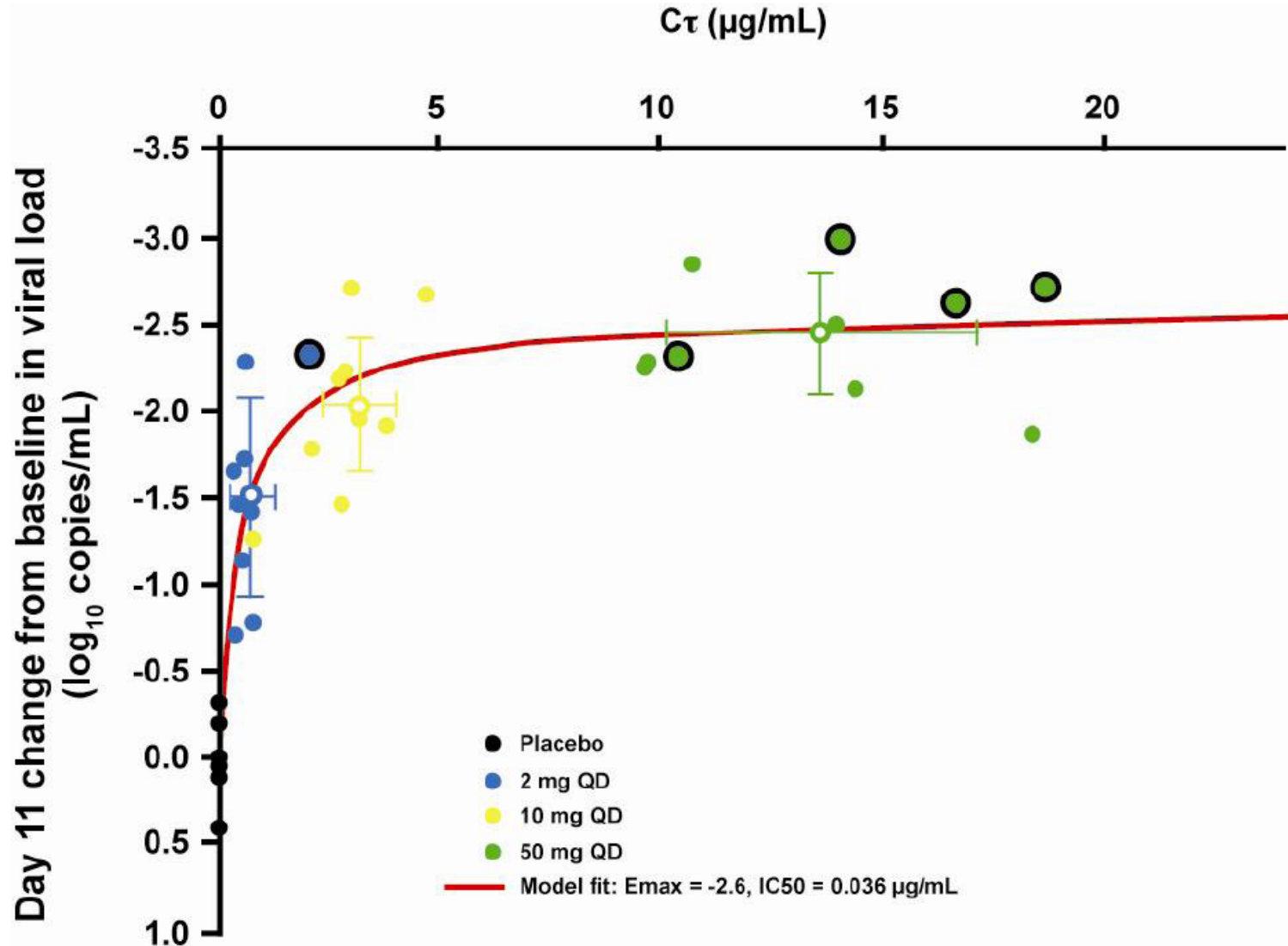
Patient	Pravastatin AUC Ratio (+DRV:-DRV)
1	5.53
2	6.78
3	4.69
4	3.80
5	1.0
6	0.85
7	0.57
8	1.16
9	2.16
10	1.31
11	2.43
12	0.92
13	1.16
14	1.49
Mean, CI	Mean, 1.81; 90% CI, 1.23, 2.66
Range	0.57, 6.78

Sekar VJ, et al.
Pharmacology
Workshop. 2007.
Abstract 55.

Predictive Value of EFV Concentrations for Viral Suppression and CNS Adverse Effects



Pharmacodynamics of GSK'572, an Investigational Integrase Inhibitor



Raltegravir Twice vs. Once Daily Dosing

- QDMRK was a comparison of once vs. twice daily dosing of RAL in 770 treatment-naïve persons.
- Week 48 treatment outcomes:

Regimen	HIV-RNA < 50 cpm (%)	CD4 Change (cells/ μ L)
RAL 800mg QD	83.2	210
RAL 400 mg BID	88.9	196
RAL Once to Twice	-5.7 (-10.7, -0.83)	14 (-7, 34)

- Higher RAL C_{trough} (QD, 40nM vs. BID, 257nM) and C_{all} (QD, 83nM vs. BID, 380nM) were associated with a greater probability of successful treatment outcome.

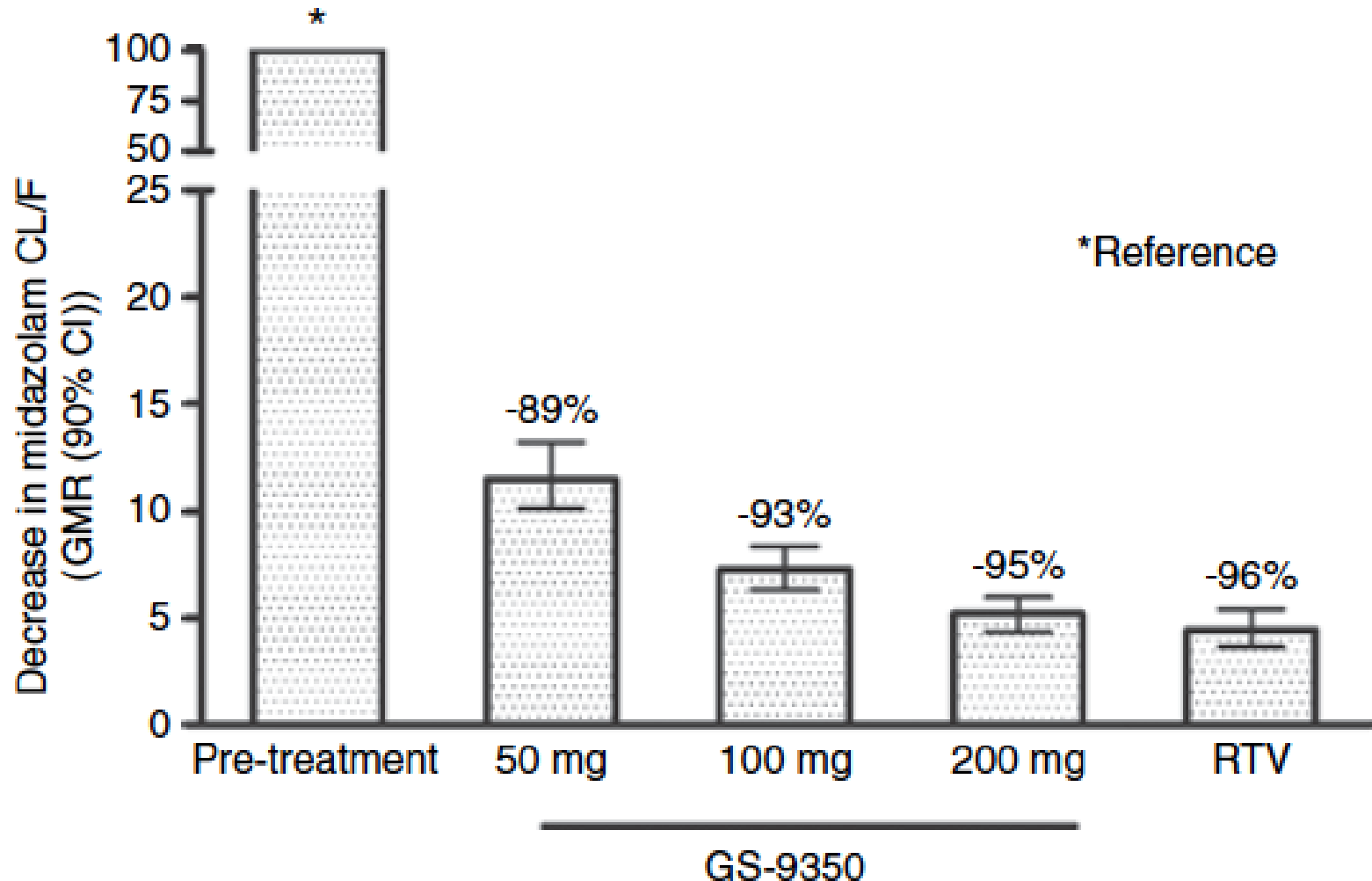
Emerging Issues in the Management of Drug-Drug Interactions

Cobicistat – a new pharmacokinetic enhancer

Boceprevir and Telaprevir – new HCV protease inhibitors

Rifabutin – dosing with boosted protease inhibitors

CYP Inhibitory Potency of Cobicistat



Mathias A, et al. Clin Pharmacol Ther 2010.

Cobicistat vs. RTV Inhibition of Atazanavir and Darunavir

Regimen	AUC Ratio	Cmax Ratio	Cmin Ratio
ATV (300/150 of cobicistat vs. 300/100 with RTV)	101 (94.5-108)	92.3 (85.1-100)	97.6 (88.1-108)
DRV (800/150 of cobicistat vs. 800/100 with RTV)	102 (97.4-106)	103 (100-106)	69.4 (59-81.7)

ICAAC 2009, Abstract A1-1301;

11th International Workshop on Clinical Pharmacology of HIV Therapy, Abstract 28.

Boceprevir (BOC)

- BOC, from preclinical metabolism, is a substrate of aldo keto reductase (AKR) and a substrate and inhibitor of CYP3A4/5 and P-glycoprotein (P-gp).

Regimen	Effect on BOC	Effect on Concom Drug
BOC + midazolam	nr	AUC - 430%
BOC + RTV (100mg QD)	AUC ↑ 19%	nr
BOC + ketoconazole	AUC ↑ 131%	nr
BOC + diflunisal	AUC, no chg; Cmin ↓ 31%	nr
BOC + efavirenz	AUC ↑ 19%; Cmin ↓ 44%	AUC ↓ 20%
BOC + tenofovir	No change	Cmax ↓ 32%
BOC + OC (Yaz®) drospirenone (DRSP) ethinyl estradiol (EE)	nr nr	AUC ↓ 99% AUC ↑ 24%

My Interpretation of Boceprevir Drug Interaction Data

Finding	Interpretation
BOC ↑ Midazolam	BOC is a CYP3A4 inhibitor: will have potential to cause inhibition interactions – – think RTV
RTV ↓ BOC	BOC not CYP3A4 substrate; RTV known to induce other CYPs (2C9, 2C19, 1A2)
Keto ↑ BOC	Keto is inhibitor of CYP3A4 and P-gp; this is likely P-gp inhibition or some other non-CYP pathway
Diflunisal ↑ BOC	Increase in BOC is likely a result of AKR inhibition from diflunisal
EFV ↓ BOC	BOC is susceptible to inducers; interaction with EFV likely to require BOC dose increase
BOC ↑ DRSP & ↓ EE	DRSP increase likely result of CYP inhibition; no obvious mechanism for decrease in EE.

Telaprevir (TVR) and Ritonavir

- Telaprevir is an HCV protease inhibitor that is a substrate and an inhibitor of CYP3A.

Regimen	TVR (LS Ratio)	
	Cmax	Cmin
TVR, 750 q12h + RTV. 100 q12h vs . TVR, 750 q8h (TVR dose redn from 2250 to 1500 mg/day = 33%)	0.85	0.68

- These data indicate there is no boosting effect of RTV on telaprevir; this finding does not support that TVR is a substrate of CYP3A4.

Telaprevir and ARVs

Regimen	TVR Effect (LS Ratio)		ARV Effect (LS Ratio)	
	AUC	Cmin	AUC	Cmin
TVR + ATV/r	0.80	0.85	1.17	1.85
TVR + DRV/r	0.65	0.68	0.60	0.58
TVR + fAPV/r	0.68	0.70	0.53	0.44
TVR + LPV/r	0.46	0.48	1.06	1.14
TVR (1125 q8h) + EFV and TDF	0.82	0.75	0.82 1.10	0.90 1.17

- All RTV-boosted PIs decreased TVR (-20 to -54%).
TVR effect on PIs was mixed (-47 to +17%).
- TVR + ATV/r and increased dose TVR + EFV seem most promising combos based on interaction data.

Rifabutin Dosing - Question

- What dose of rifabutin would you use in a patient who is receiving a ritonavir-boosted protease inhibitor?
 1. Rifabutin 300 mg once daily
 2. Rifabutin 150 mg once daily
 3. Rifabutin 150 mg three times weekly

Rifabutin Dosing with LPV/r in HIV-infected Persons

- Rifabutin (RBT) PK were evaluated in 14 HIV-infected persons established on RBT-containing anti-TB therapy.
- RBT PK were determined after a dose of 300mg QD, and after doses of 150mg TIW and 150mg QD when given with LPV/r (400/100 BID).

Regimen	AUC (ng*h/mL)	Cmax (ng/mL)	Tmax (h)	T1/2 (h)
300mg QD	2920	320	3.5	12.5
150mg TIW with LPV/r	2562	187	3.9	33.5
150mg QD with LPV/r	5172	319	3.6	52.1

- These data indicate Cmax with the RBT 150mg QD dose compares best with 300mg QD.
- Confirmation of safety and efficacy is needed.

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.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.drug-interactions.com
Downloadable drug interaction charts; interactive tools to assess interactions; updated news on published abstracts and papers
- www.hivmedicationguide.com
Interactive drug interaction database
- www.hivpharmacology.com
Updated summary of drug interaction data; guidelines for TDM
- **Micromedex**: comprehensive drug database (subscription required); an app is available

Thank You