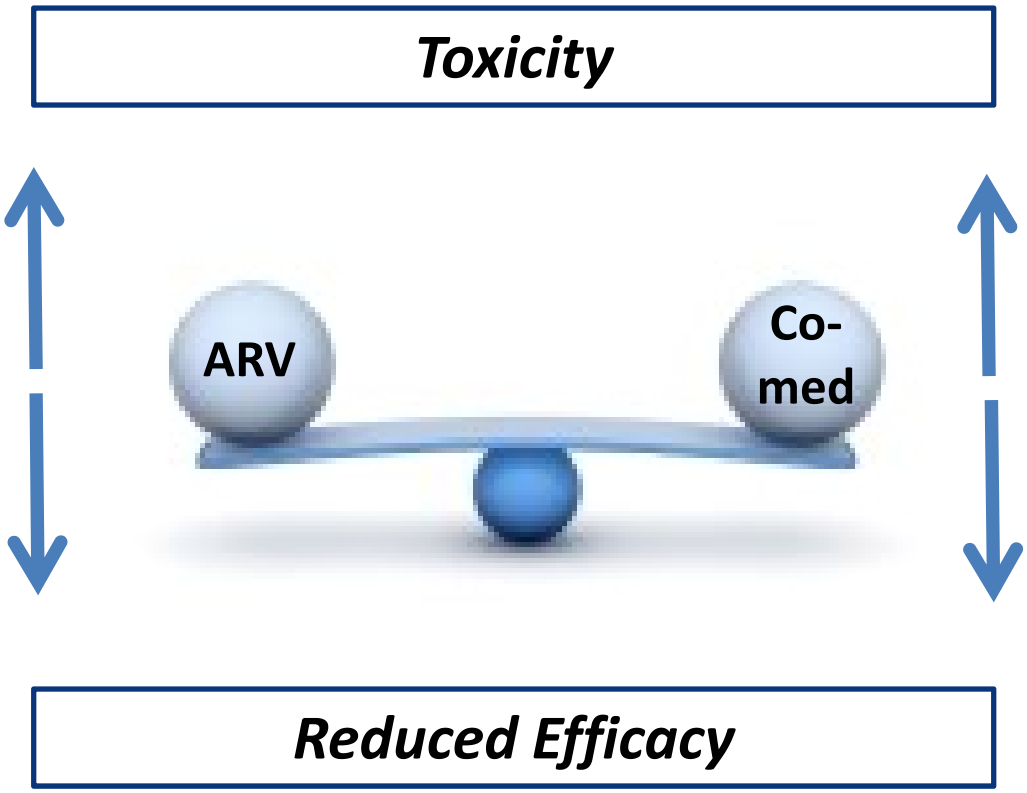
Mechanisms of Drug-Drug Interactions: What do we know?

David Back

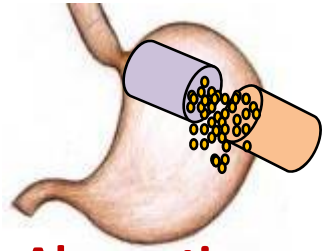
University of Liverpool

November 2012



This is the 'simple example'! What about combination ARV and multiple co-meds?

ADME



Absorption

Drug Concentration in Systemic Circulation

Tissues Reservoirs

Distribution

Elimination

Metabolism

Google Images.com

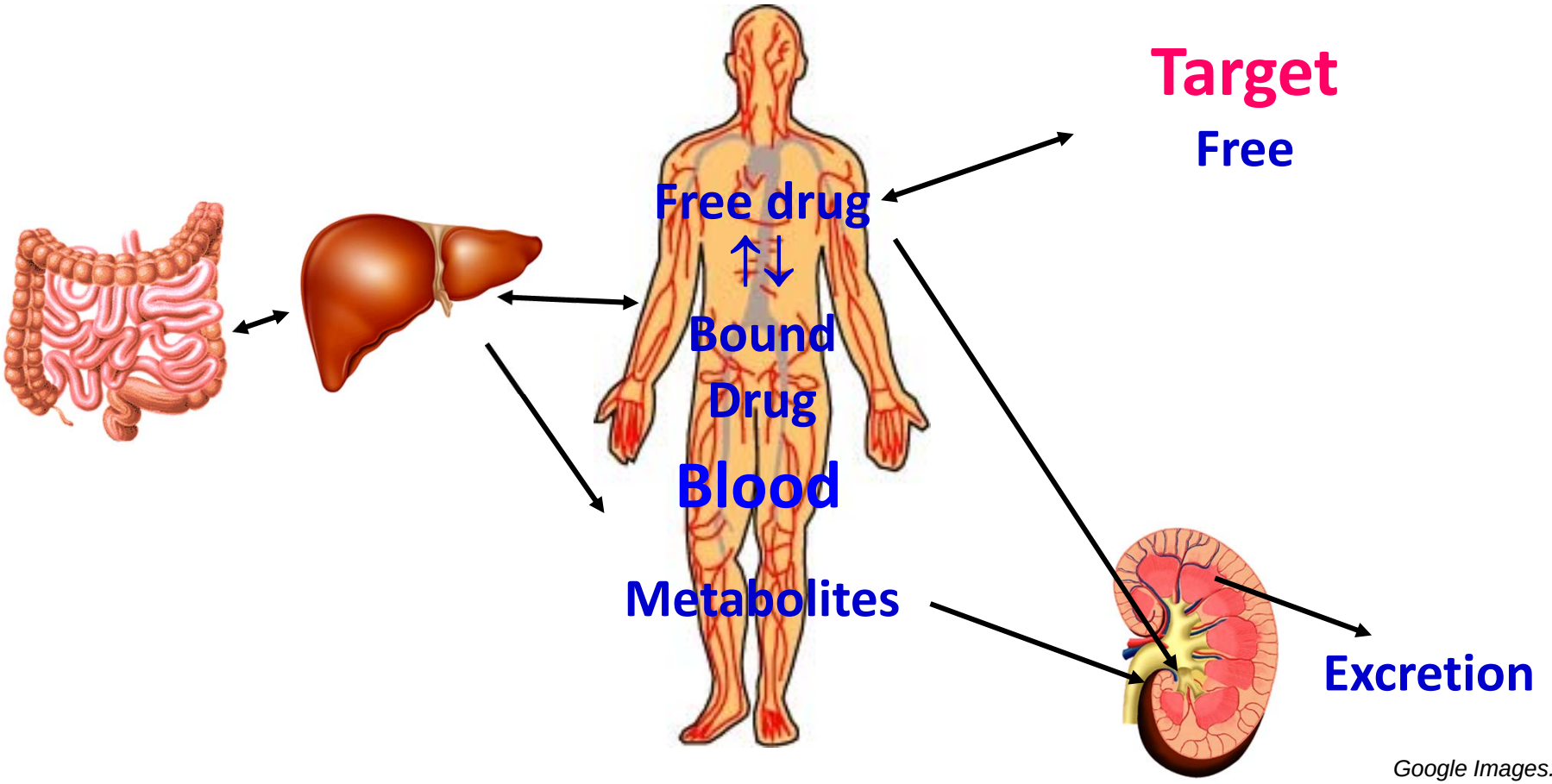
ADME

Tissues Reservoirs

⇄

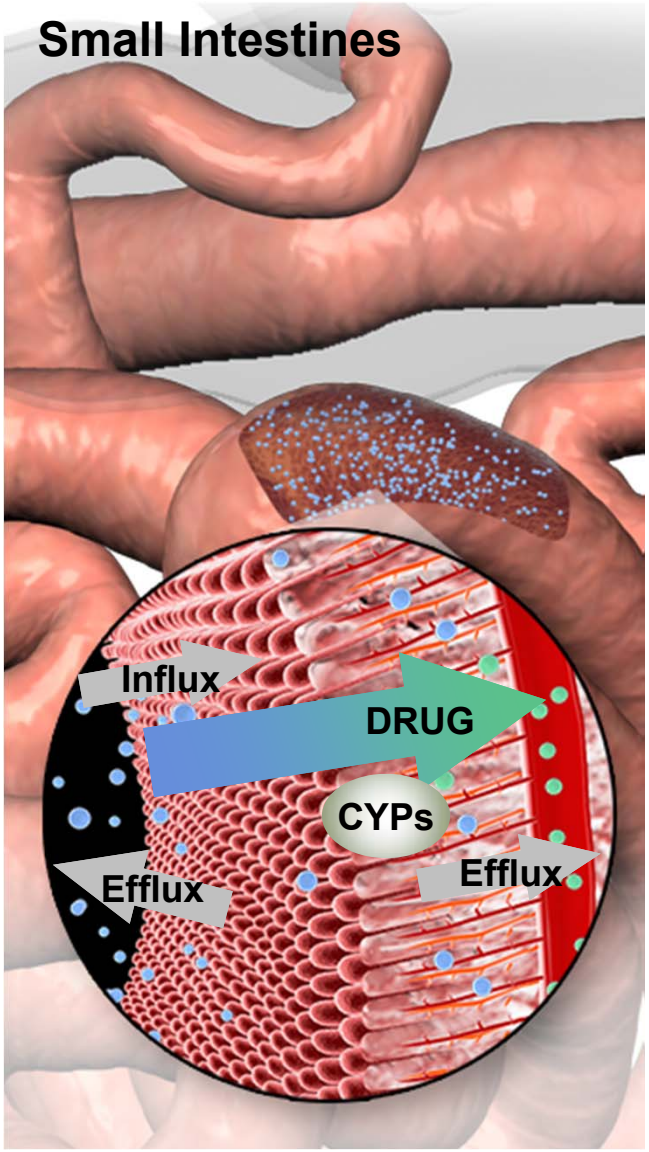
Drug Concentration in Systemic Circulation

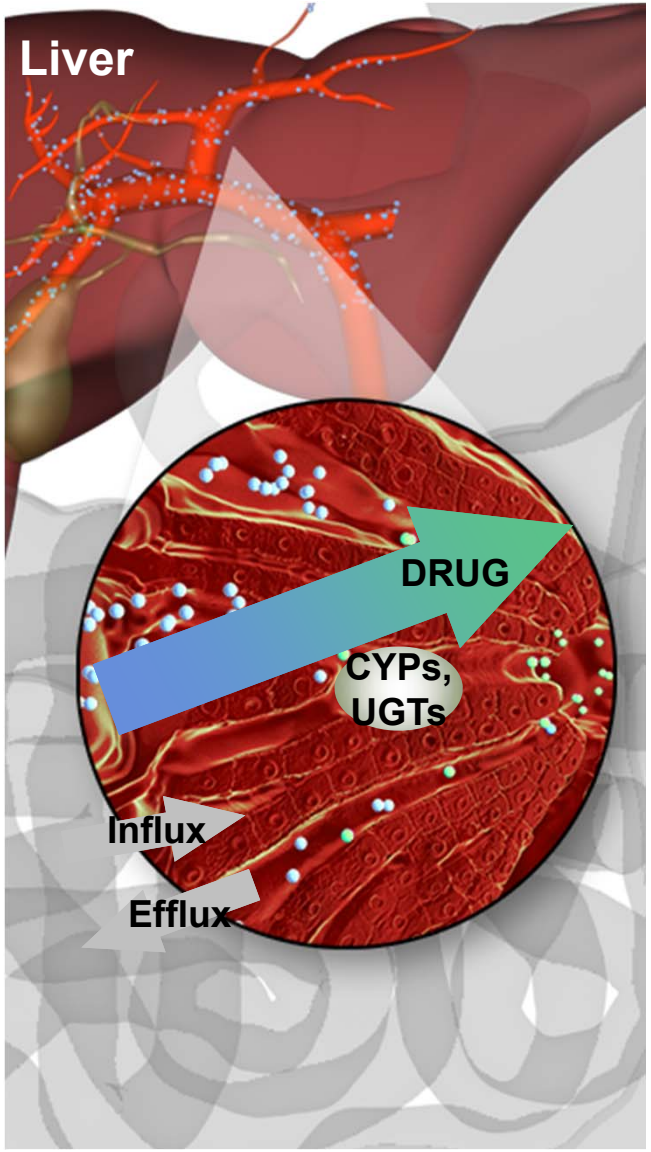
Distribution



Google Images.com

Importance of transport and metabolism in relation to systemic drug levels

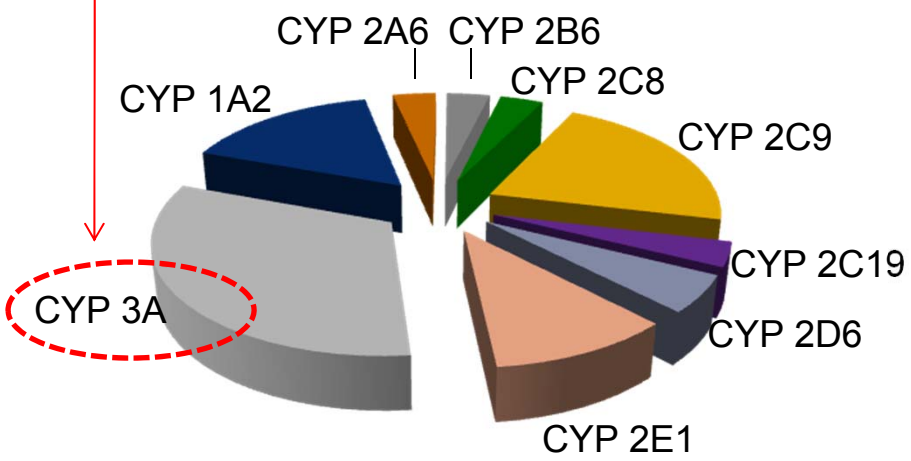




Adapted from Bailey DG, et al. Br J Clin Pharmacol. 1998:46:101–10

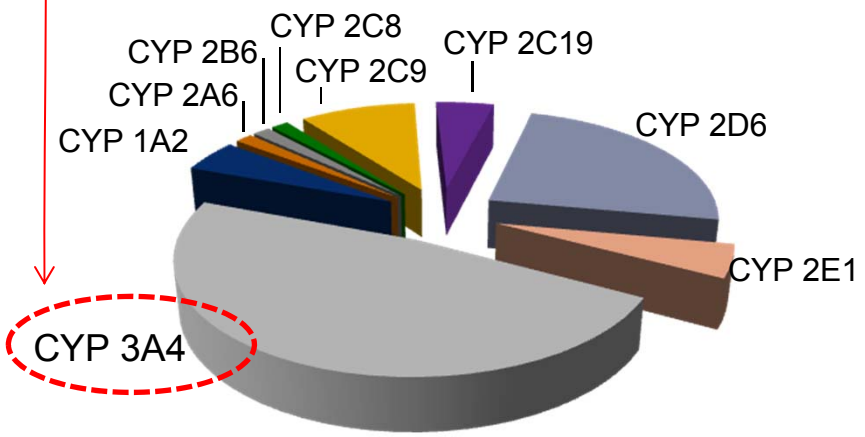
CYP Enzymes

CYP 3A is the most abundant CYP isozyme



Proportion of total CYP enzymes present in human liver

CYP 3A 4 involved in the metabolism of majority of drugs

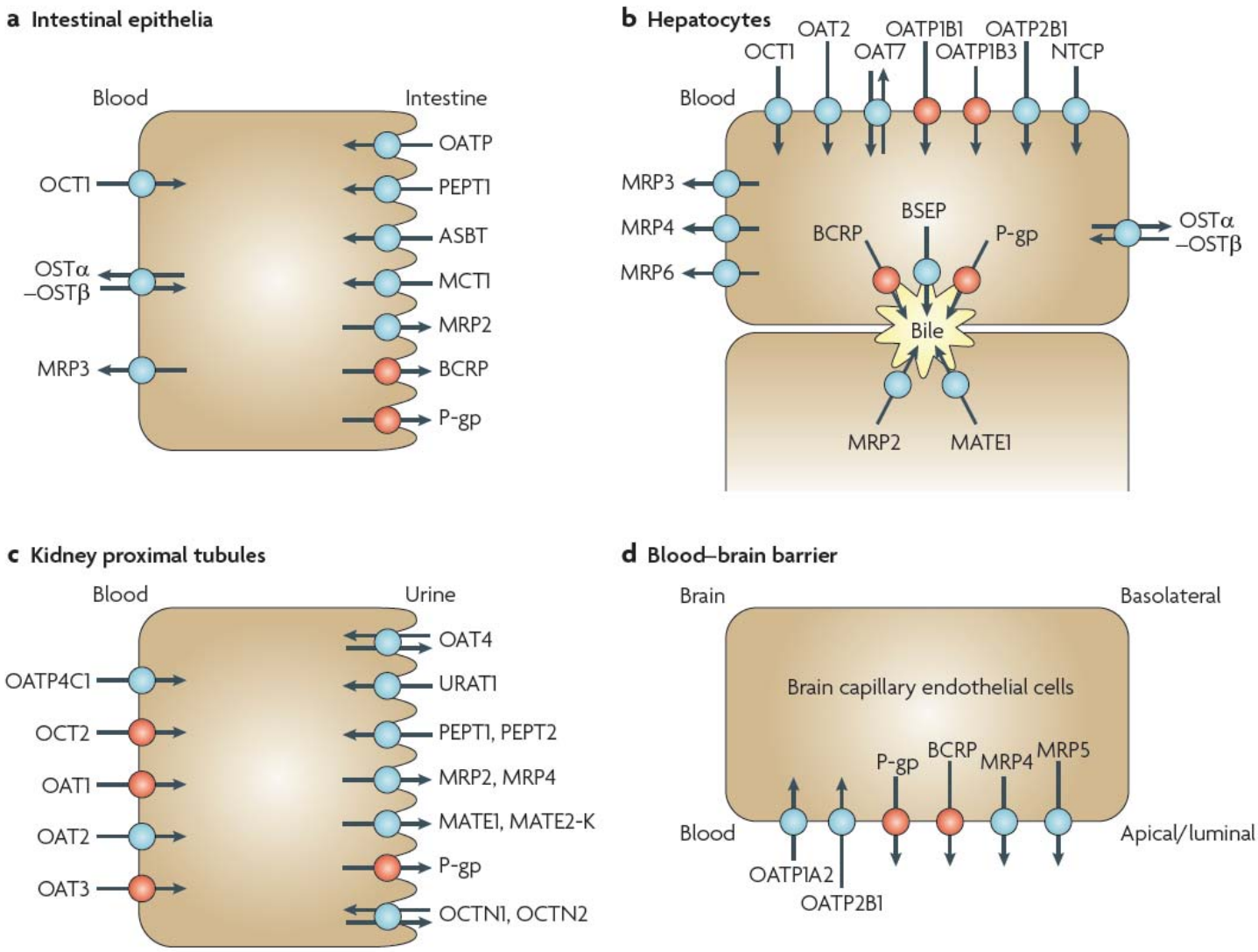


Proportion of drugs that are substrates for major CYP enzymes

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

Hacker MP, et al. Pharmacology: Principles and Practice. Academic Press 2009

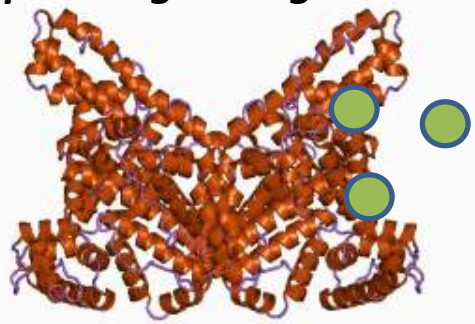
Transporters



Nature Reviews; Drug Discovery. 2010; 9: 215-236

Protein binding displacement

Example: Single drug



Albumin

PK

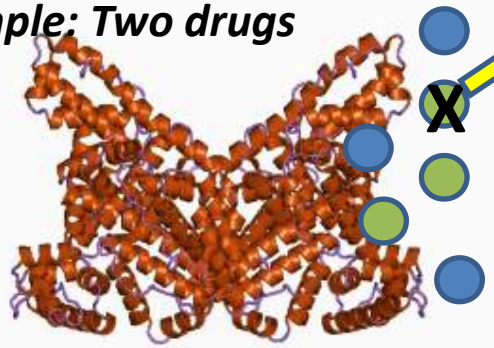
Total drug concentration: 3
Free concentration: 1
Free fraction: 33%

Key message

Free drug responsible for pharmacologic activity (PD), and subject to systemic clearance (PK)

Initial ↑ in free drug leads to increase in systemic clearance

Example: Two drugs



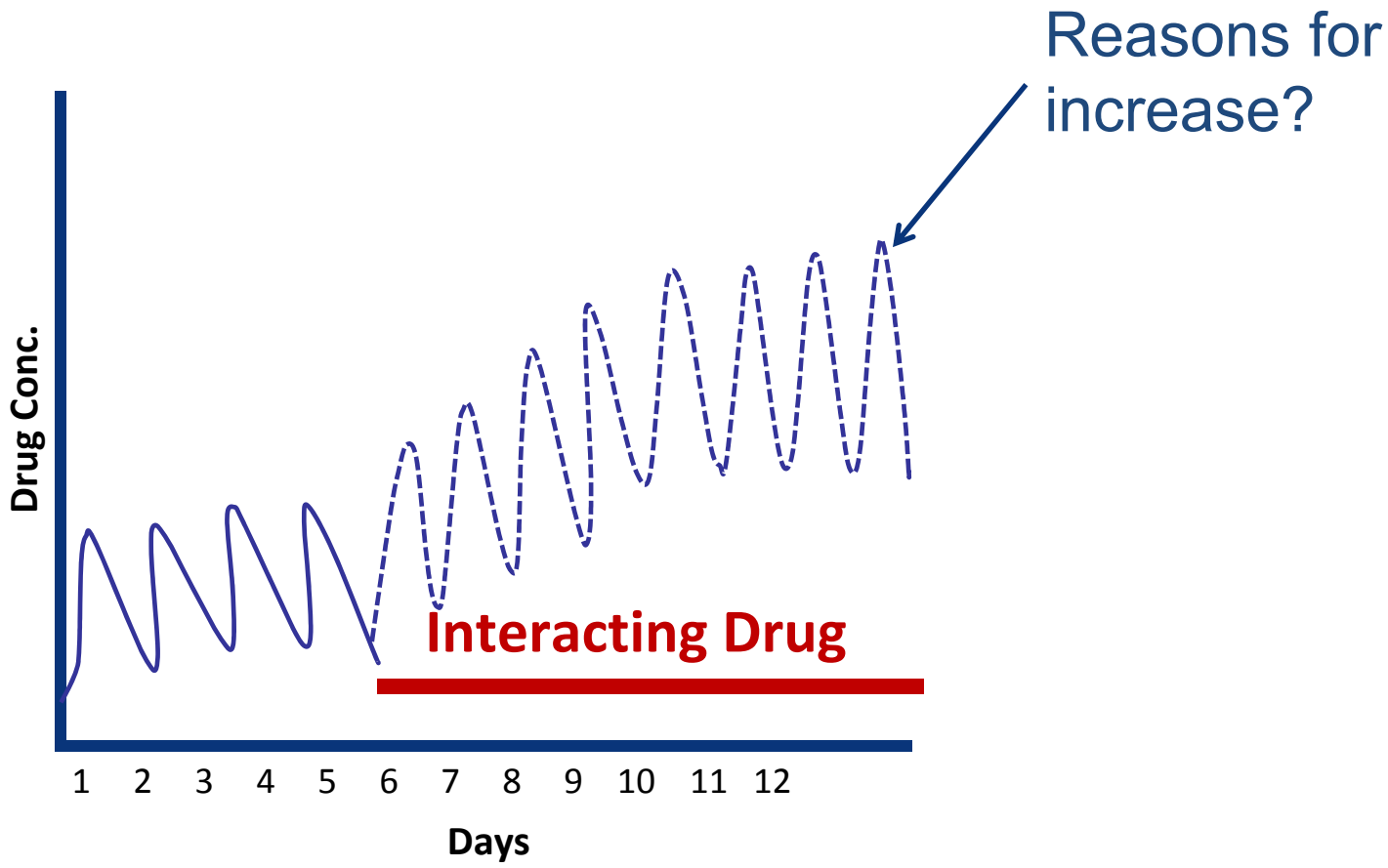
Albumin

Total drug concentration: 2
Free concentration: 1
Free fraction: 50%

Displacement trend:
↓ Total concentration
Free concentration unchanged
↑Free fraction
LIMITED CLINICAL IMPACT

Bertilsen K – personal communication

Key mechanisms of drug interactions: alteration of steady state of a crug



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Effects of Omeprazole on Plasma Levels of Raltegravir

Marian Iwamoto,[1] Larissa A. Wenning,[1] Bach-Yen Nguyen,[1]

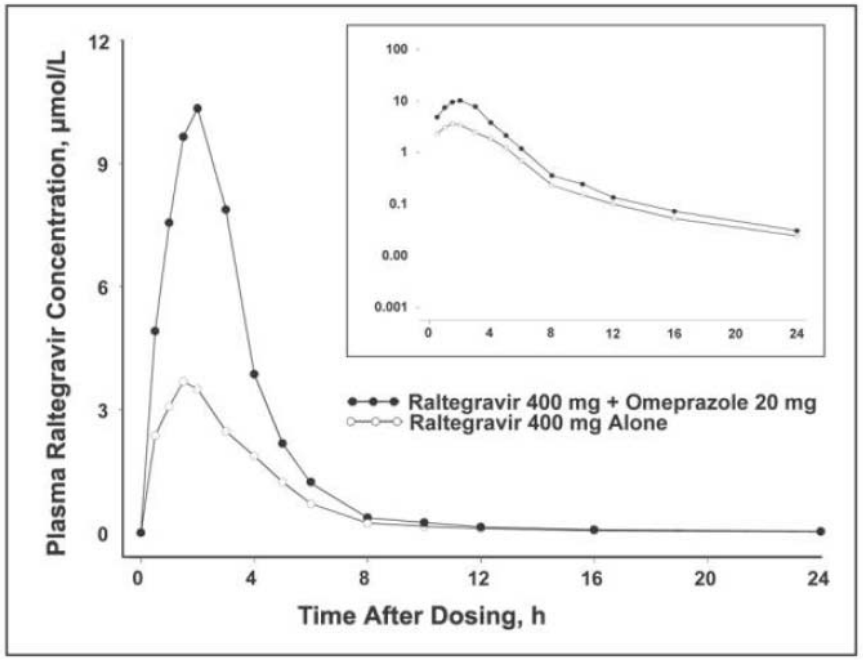
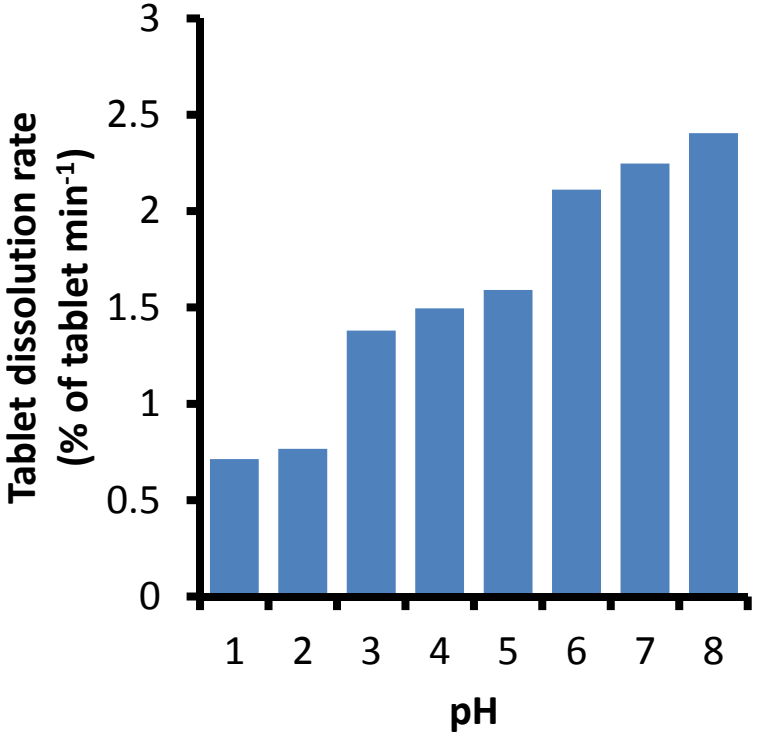
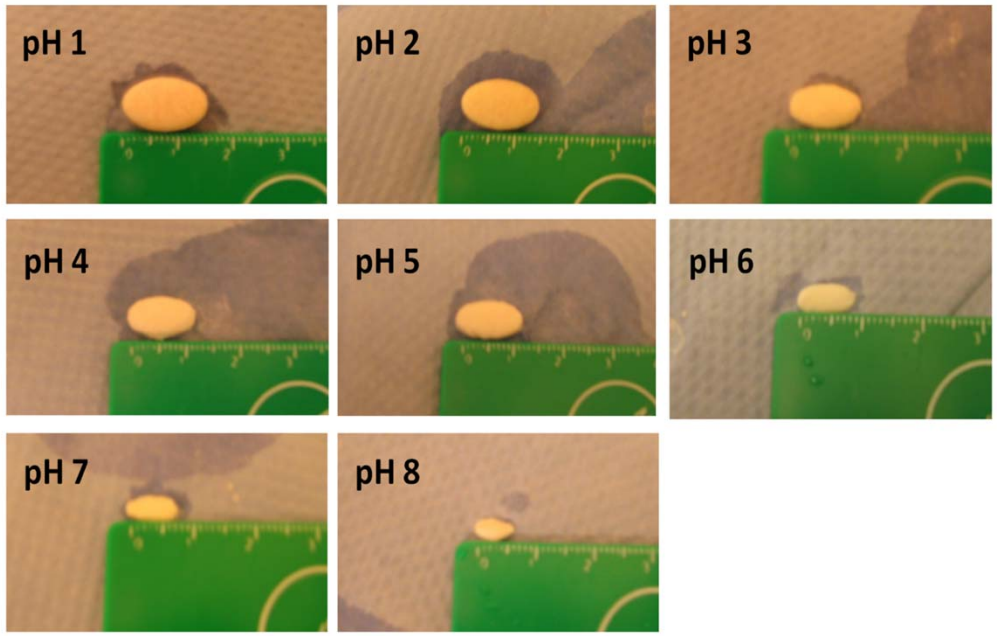


Figure 1. Arithmetic mean raltegravir plasma concentration-time profiles in healthy men and women after the single-dose administration of 400-mg raltegravir with or without the administration of 20-mg omeprazole once-daily (Inset: semilog scale).

Raltegravir tablet dissolution rate

The breakdown rate of standard raltegravir 400 mg tablets determined in buffered aqueous solutions (pH 1 to 8)

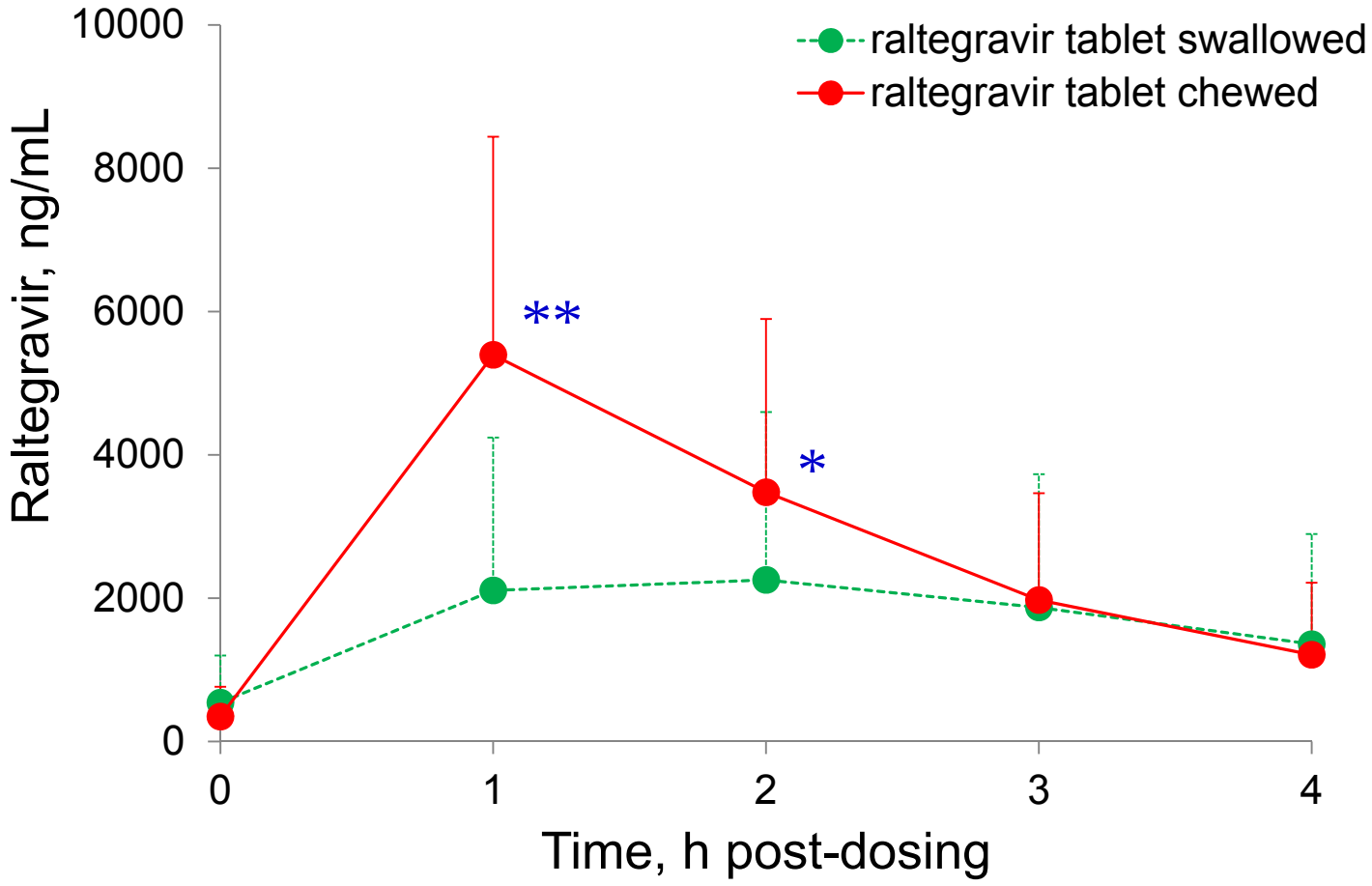




Tablet breakdown rate increased at higher pH

Moss D & Back DJ – Unpublished observation

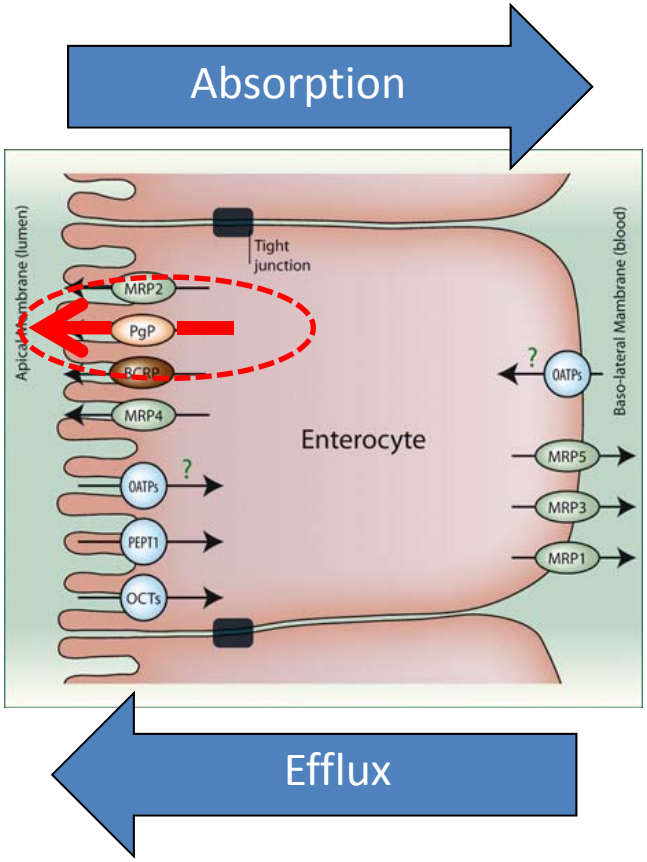
Raltegravir time-concentration profiles in 60 HIV-patients given the drug by swallowing the whole tablet (n=50) or by chewing the tablet before swallowing (n=10)

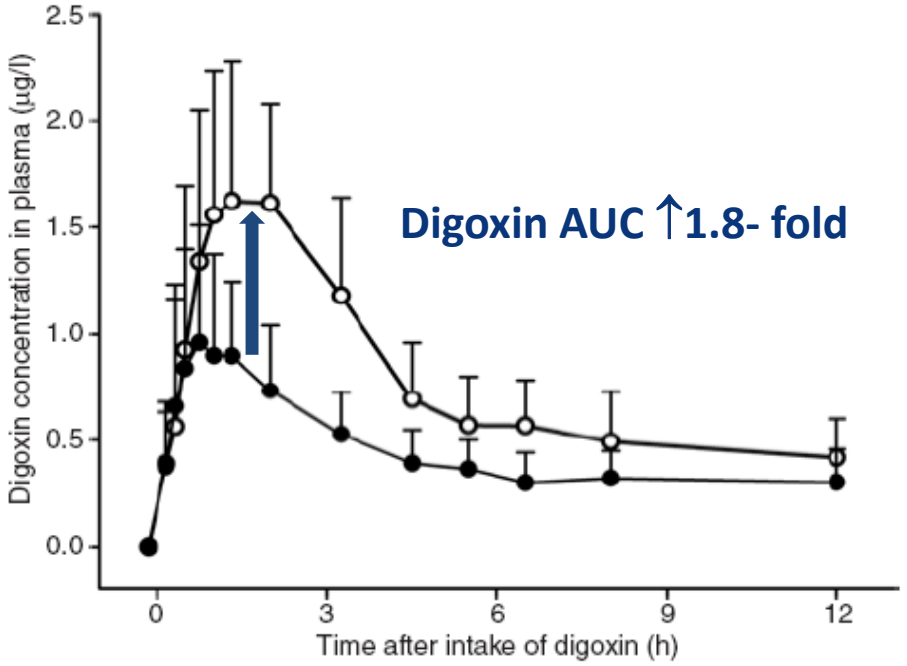


Gervasoni C et al; International AIDS Conference, Washington, July 2012

DDI via P-glycoprotein

Effect of LPV/r on digoxin in HIV+ patients



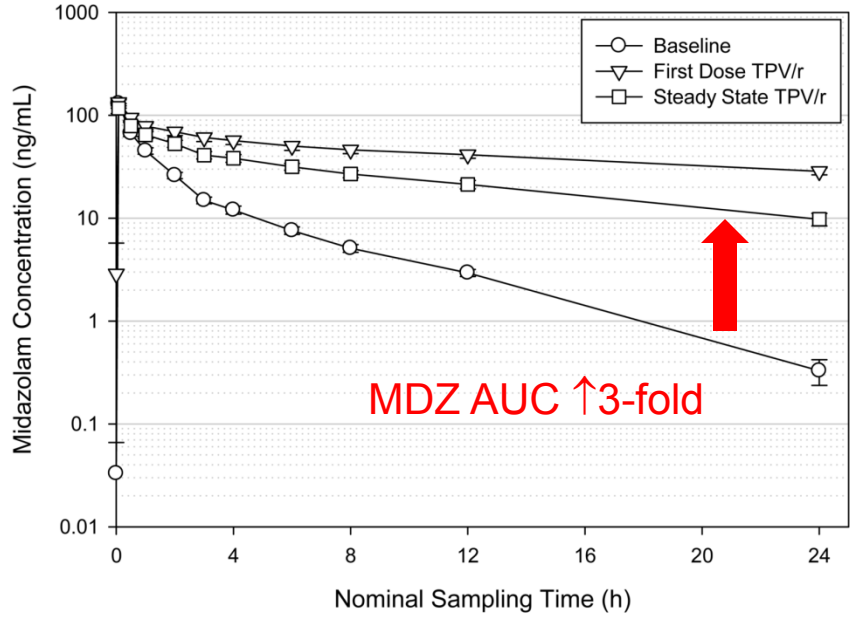


Wyen C et al Clin Pharm Ther; 2008; 84: 75-82

Effect of tipranavir/r on intestinal and hepatic CYP3A4

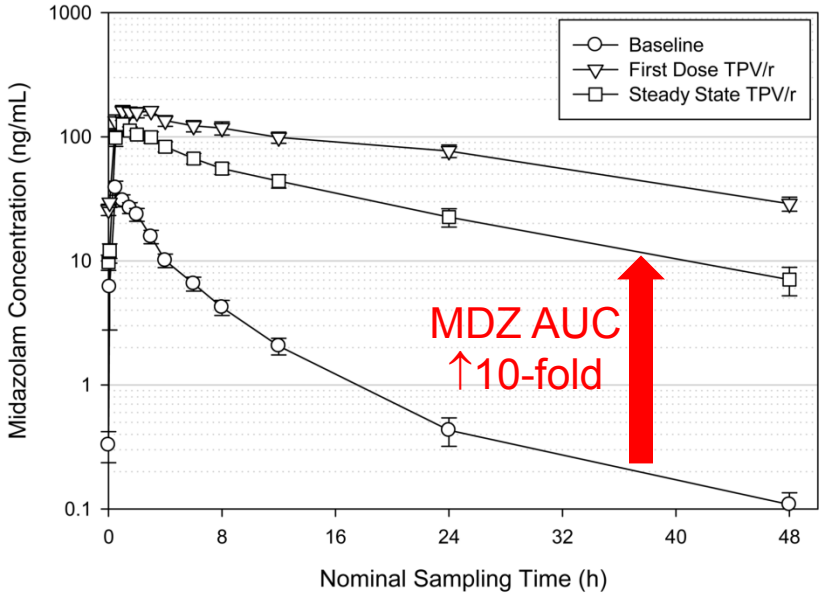
I.V. Midazolam

Figure 1e.



Oral Midazolam

Figure 1f.



Dumond JB et al., Clin Pharmacol Ther. 2010; 87: 735–742.

Drug/Drug Interaction Between Lopinavir/Ritonavir and Rosuvastatin in Healthy Volunteers

Jennifer J. Kiser, PharmD, John G. Gerber, MD,† Julie A. Predhomme, RN, MS, C-ANP,* Pamela Wolfe, MS,‡ Devon M. Flynn, PharmD,§ and Dorie W. Hoody, PharmD§*

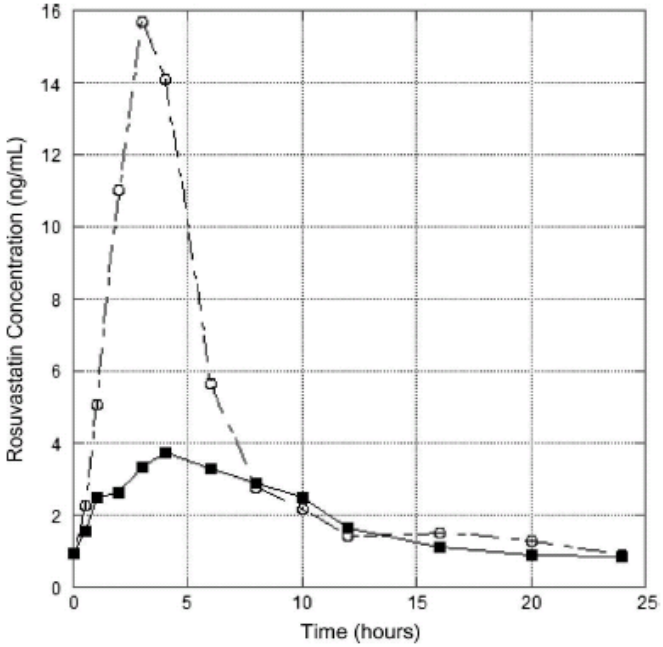
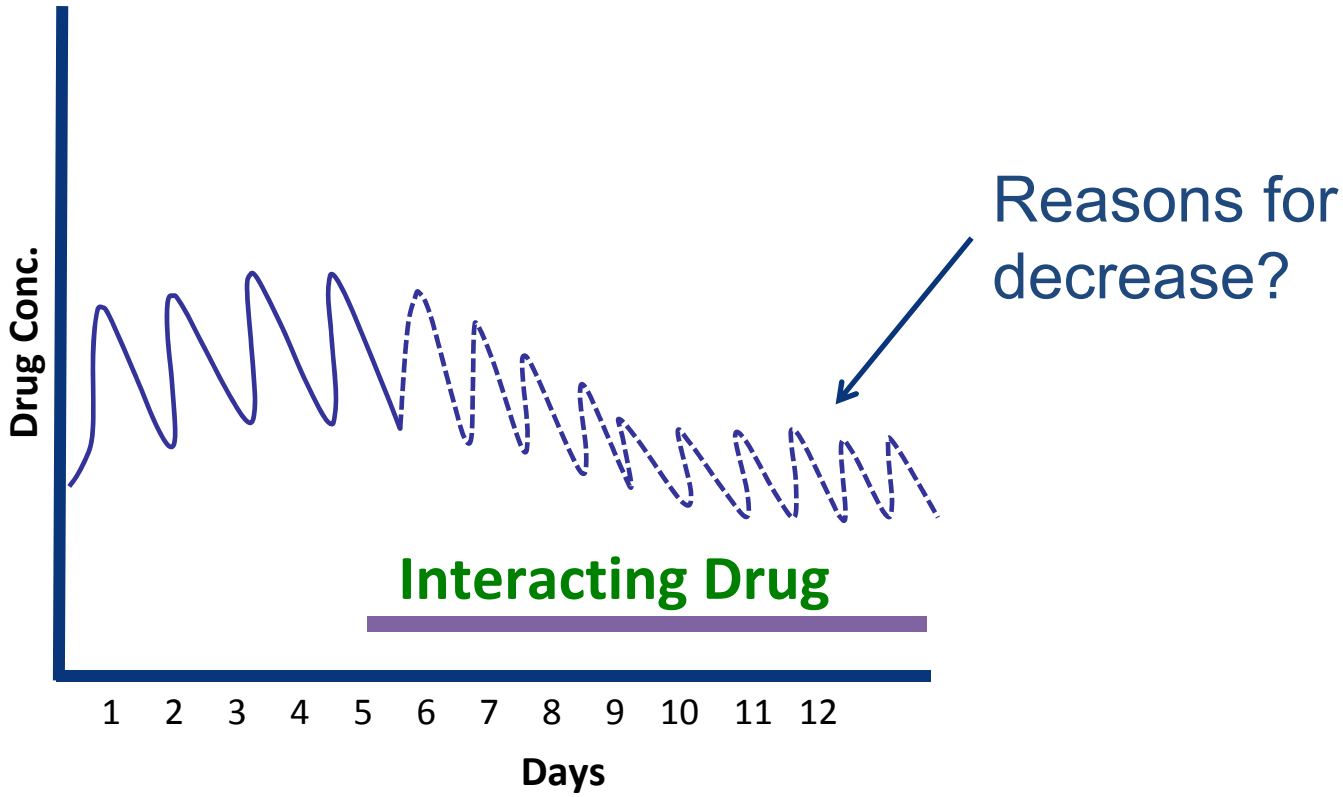


FIGURE 1. Rosuvastatin AUCs for subjects on rosuvastatin alone (black squares, solid line) and subjects on rosuvastatin plus lopinavir/ritonavir (open circles, dashed line).

Kiser JJ et al., JAIDS 2008; 15: 570-578

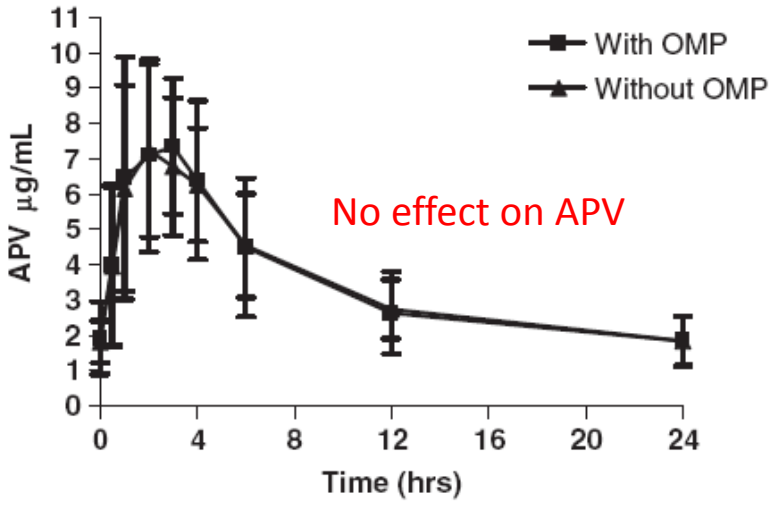
Key mechanisms of drug interactions: alteration of steady state of a drug

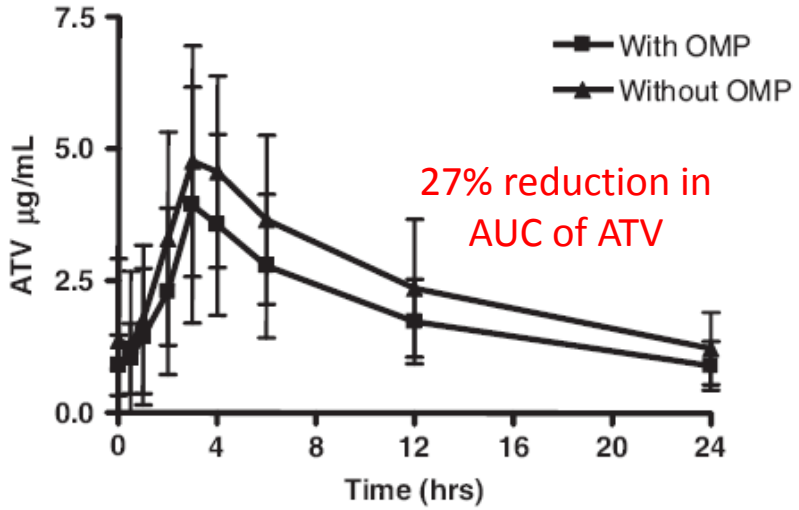


Back D Unpublished

Effect of omeprazole on APV or ATV

Healthy volunteers received omeprazole 20 mg qd in the evening, and APV/r or ATV/r qd in the morning.



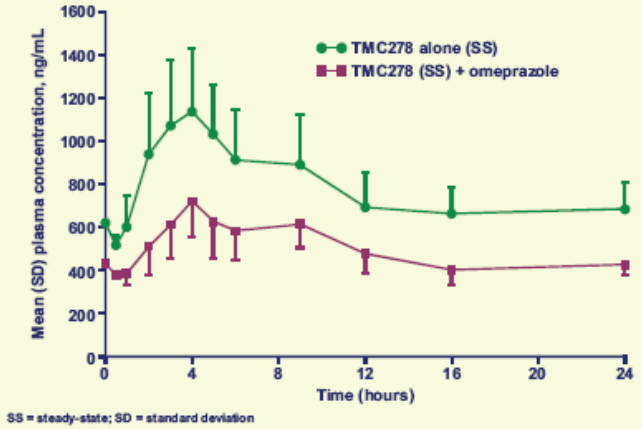


ATV/rtv 300/100 mg qd + OMP <u>40 mg</u> reduced ATV AUC by 76% (CROI 2005, #658)

Luber A et al. HIV Medicine (2007) 8, 457–464

Rilpivirine + pH modifiers

Omeprazole decreased TMC278 plasma concentrations



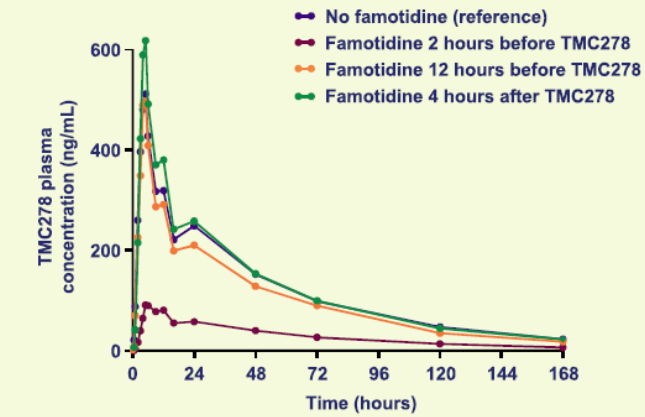
SS = steady-state; SD = standard deviation

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

Combination of rilpivirine with PPIs is <u>contraindicated</u>

Crauwels et al. 9th International Congress on Drug Therapy in HIV Infection, Glasgow, UK, 9–13 November 2008.

TMC278 mean PK profiles



Famotidine intake	AUC_{∞}
2 hours before TMC278	0.24 (0.20–0.28)
12 hours before TMC278	0.91 (0.78–1.07)
4 hours after TMC278	1.13 (1.01–1.27)

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

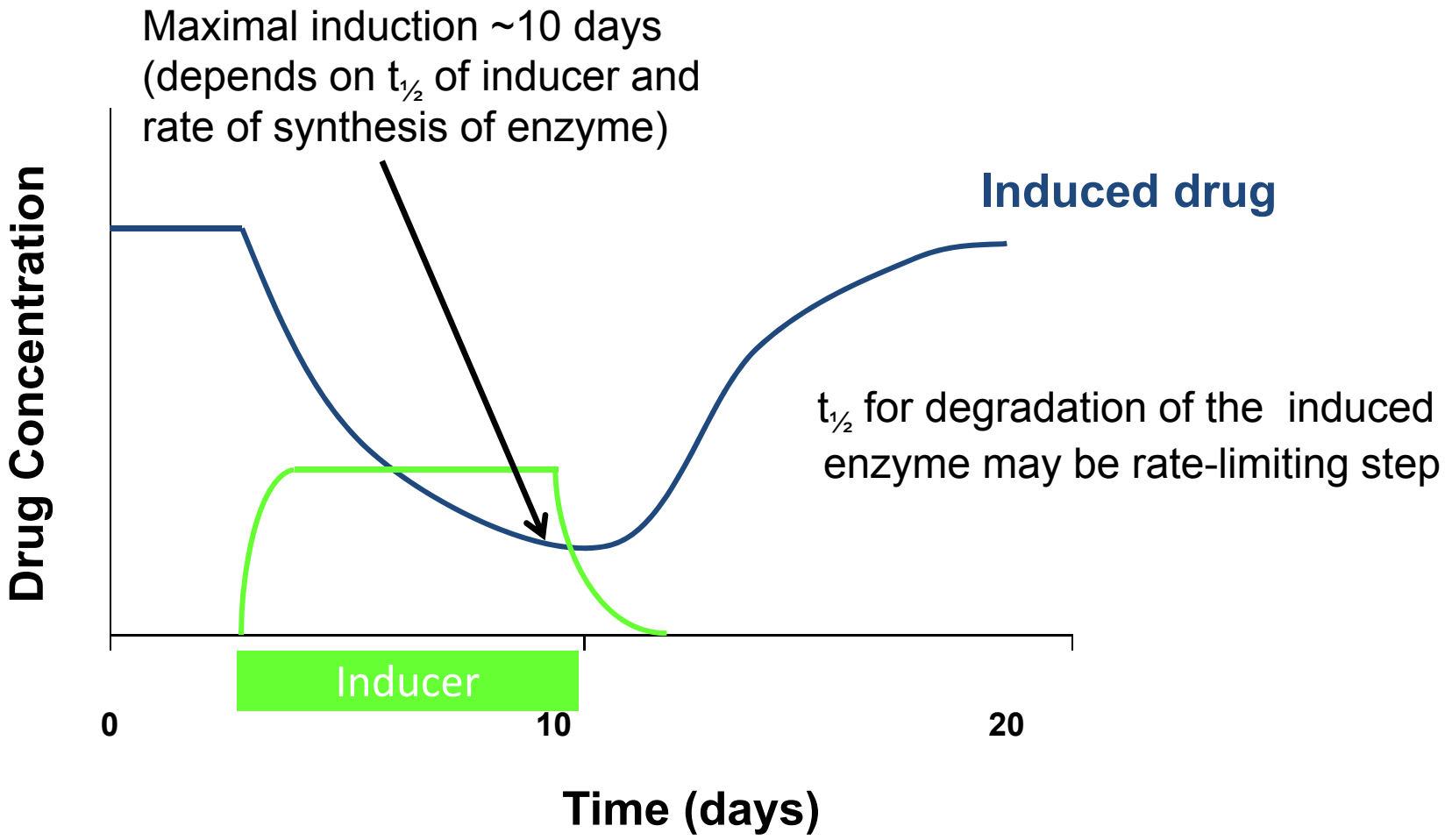
Transporter induction

- A few clinical trials have demonstrated an inductive effect of St John's Wort (SJW) on P-gp.
  Plasma concentrations of P-gp substrates have been reduced by SJW.

- Digoxin[1]
- Fexafenadine[2]
- Talinolol[3]

1, Mueller SC et al., Clin Pharm Ther 2004; 75: 546-557;
2, Wang Z et al., Clin Pharm Ther 2002; 71: 414-420;
3, Schwarz UI et al Clin Pharm Ther 2007; 81: 669-678.

Enzyme induction

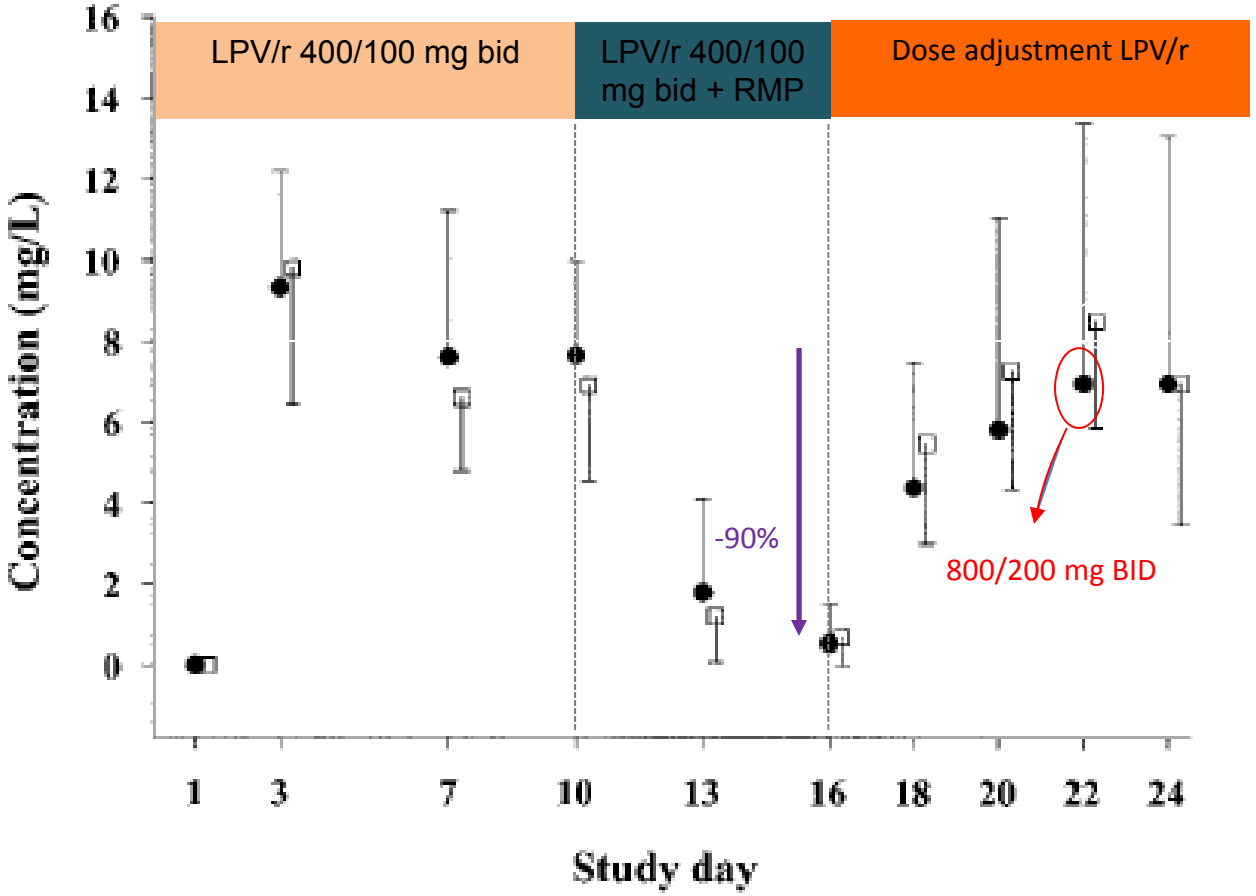


Van Heeswijk R. Personal Communication

Enzyme inducers

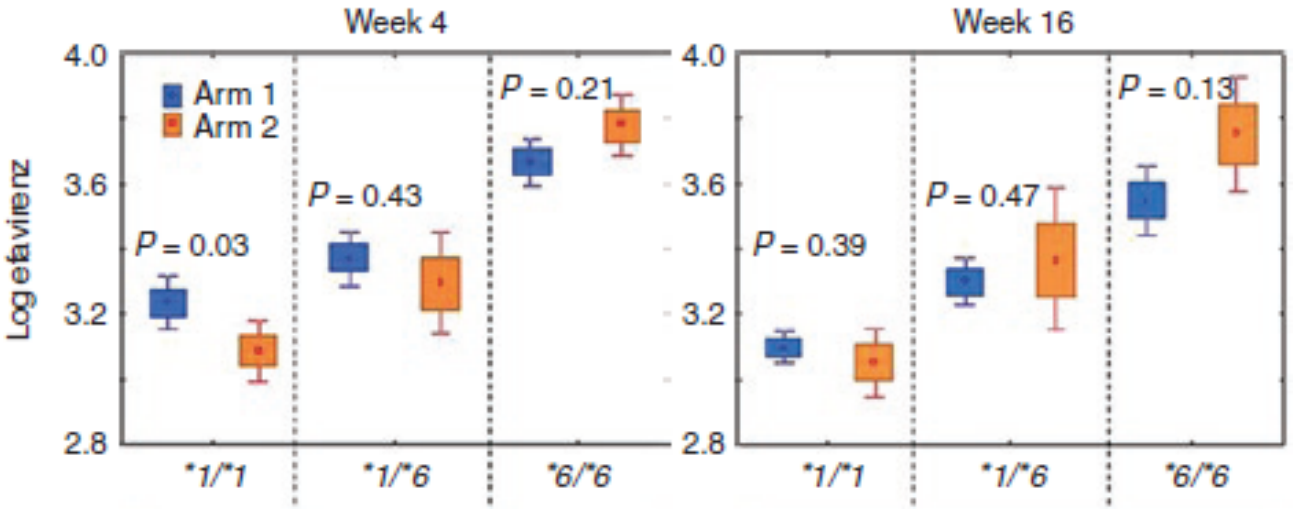
- **Antimycobacterial drugs**
  - Rifampicin (CYP3A, 2C9/19, UGT),
  - Rifabutin (CYP3A)
  - Isoniazid (2E1)
- **Anticonvulsant drugs**
  - Carbamazepine, Phenytoin, Phenobarbital (CYP3A)
- **Herbals**
  - St John’s wort (CYP3A)

Rifampicin induction and LPV/r



La Porte CJ et al., AAC 2004; 48: 1553-1560.

EFV exposure and CYP2B6 genotype: differential effect of rifampicin



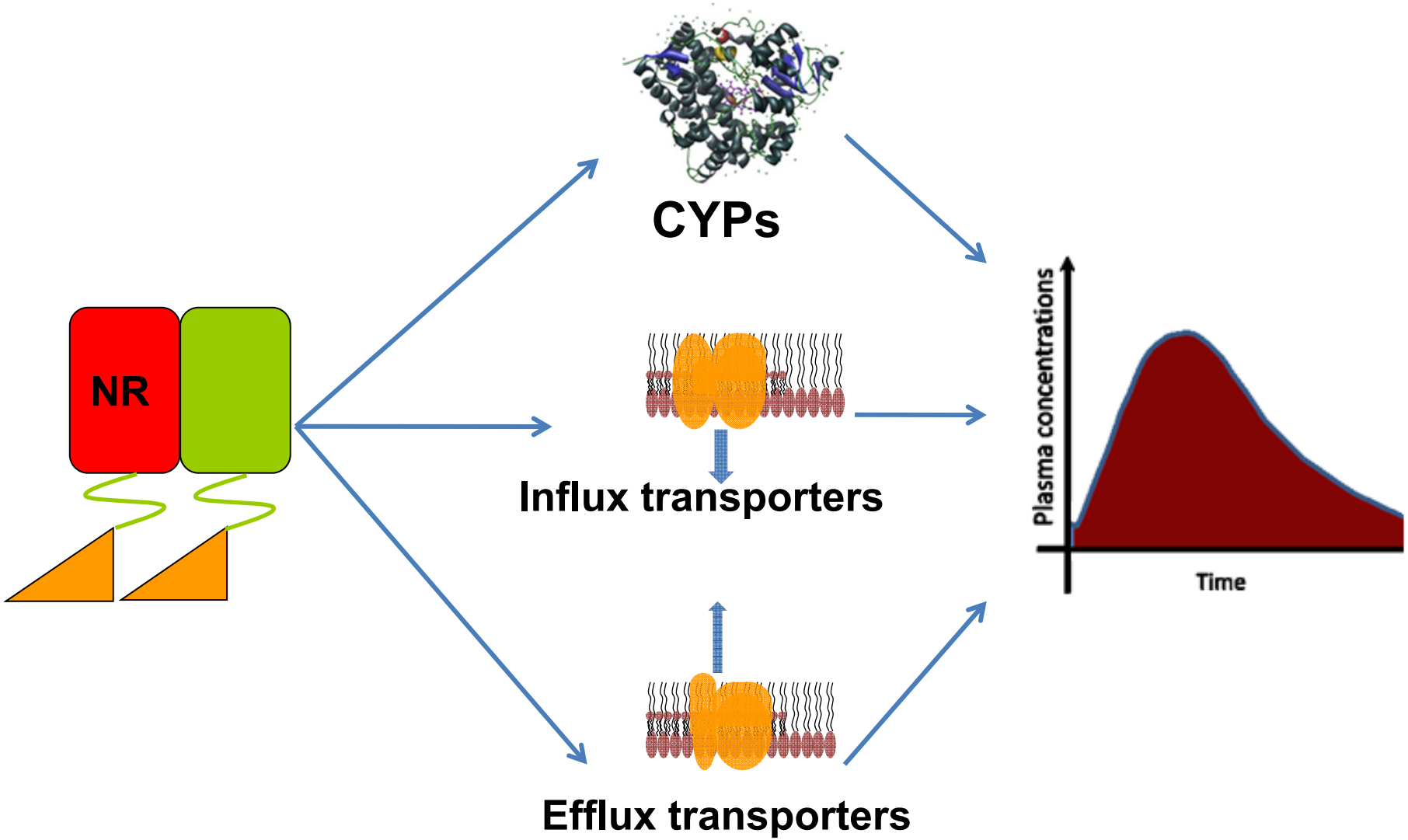
Mean log EFV with RIF

Mean log EFV alone

Note: Rifampicin induces and inhibits depending on genotype

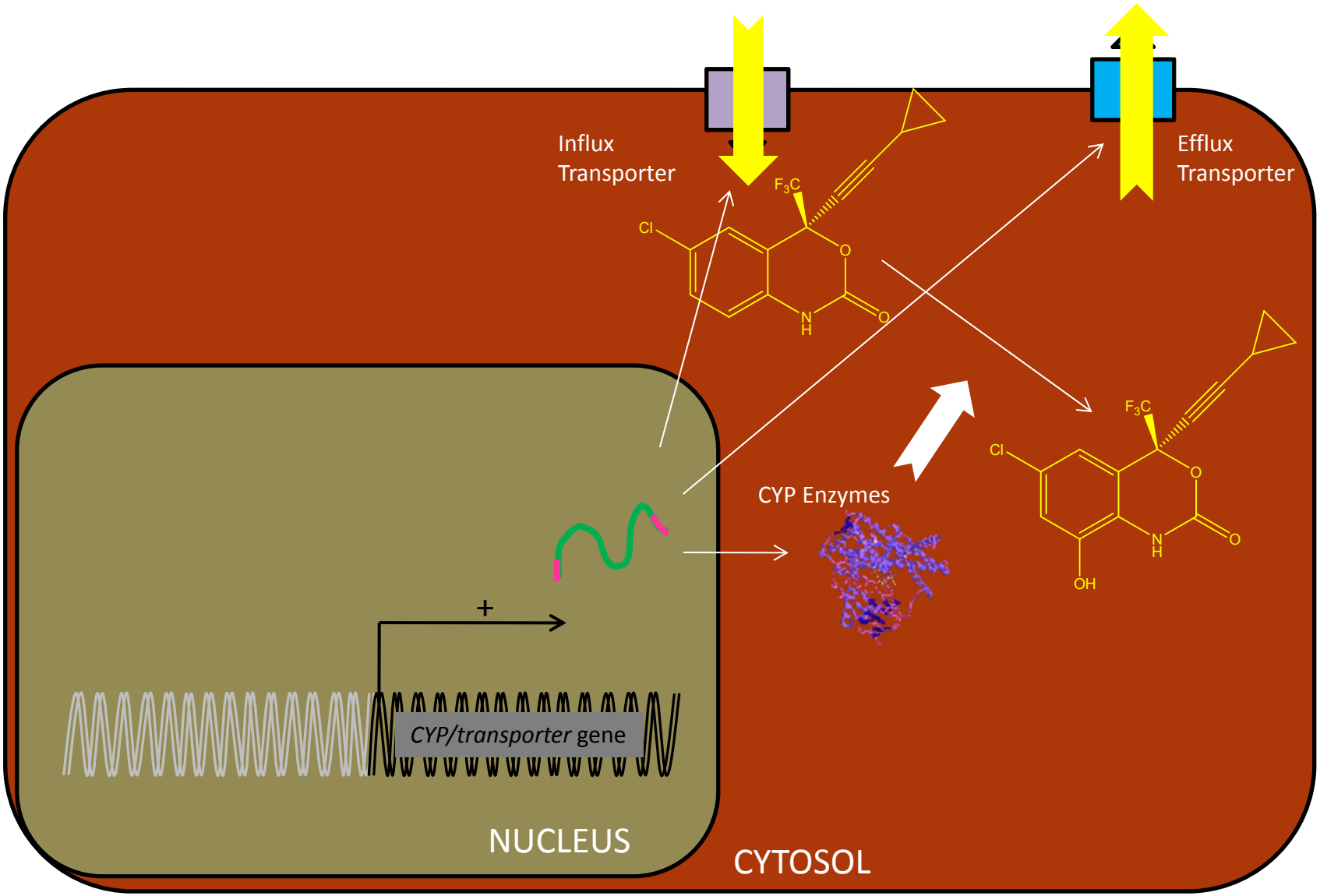
Ngaimisi et al. Clin Pharm Ther 2011; 90: 406-413

Role of nuclear receptors



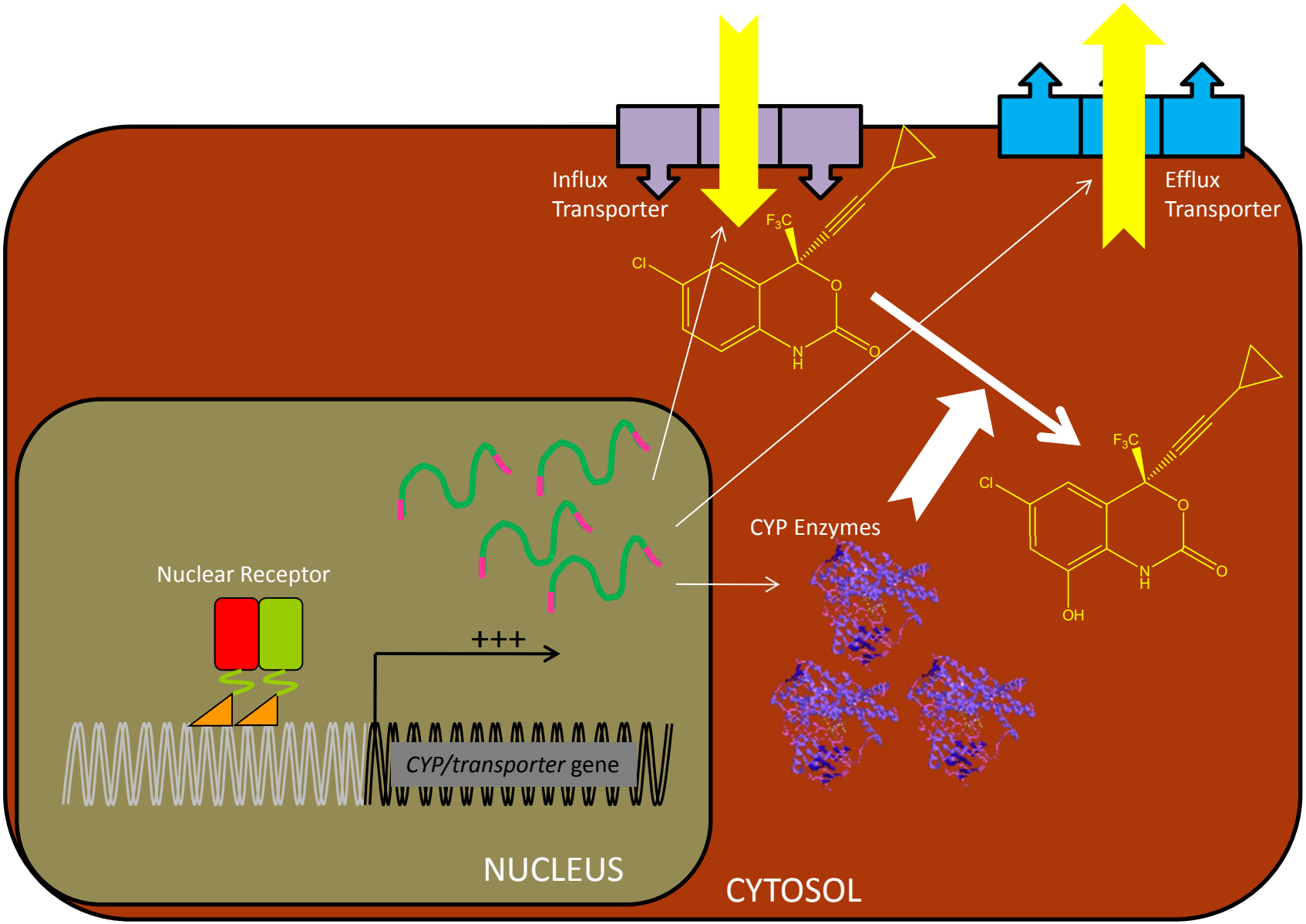
Owen A, Personal Communication

Nuclear receptor regulation of induction



Owen A Personal Communication

Nuclear receptor regulation of induction



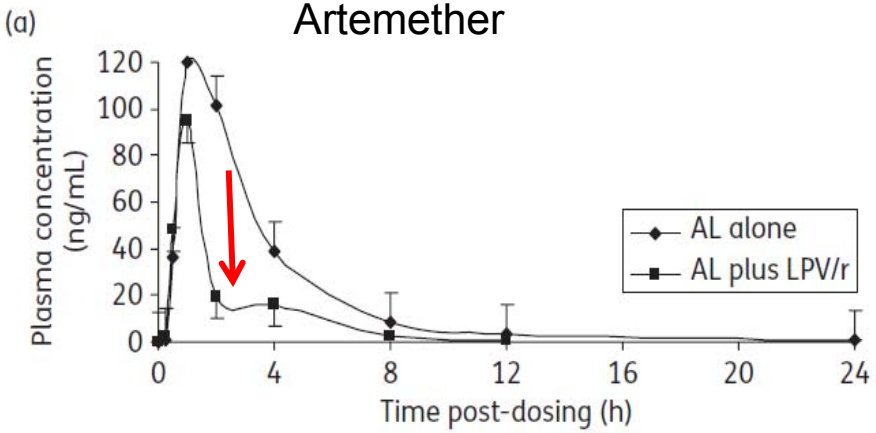
Owen A Personal Communication

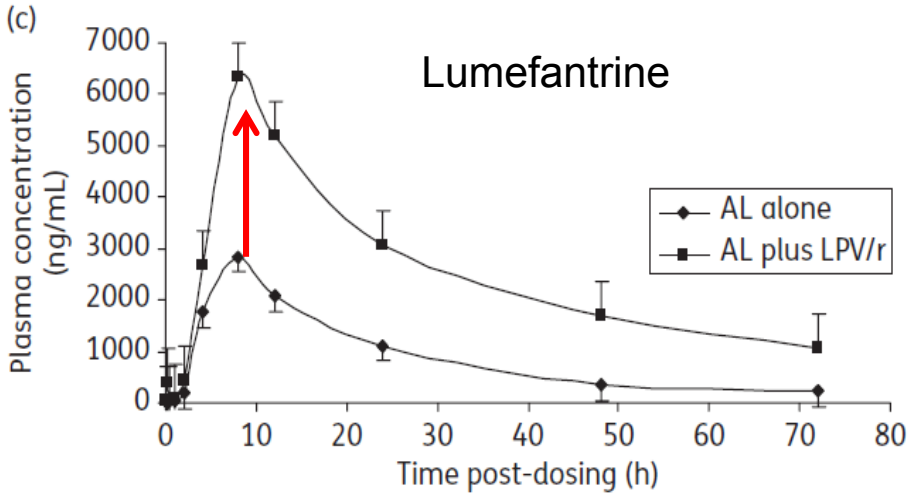
Inhibition versus induction of CYP450

- Inhibition usually occurs rapidly (immediate or within 48 hours).
- Induction occurs after repeated exposure and may take up to 14 days to reach a maximum.
- Enzyme activity slowly returns to baseline when modulating drug is discontinued (up to 14 days).

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

Pauline Byakika-Kibwika[1–3]*, Mohammed Lamorde[1,2], Violet Okaba-Kayom[1], Harriet Mayanja-Kizza[1,3], Elly Katabira[1,3], Warunee Hanpithakpong[4], Nadine Pakker[3], Thomas P. C. Dorlo[5,6], Joel Tarning[4,7], Niklas Lindegardh[4,7], Peter J. de Vries[6], David Back[8], Saye Khoo[8] and Concepta Merry[1–3]





J Antimicrob Chemother 2012; 67: 1217-1223

Some Key Questions

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!

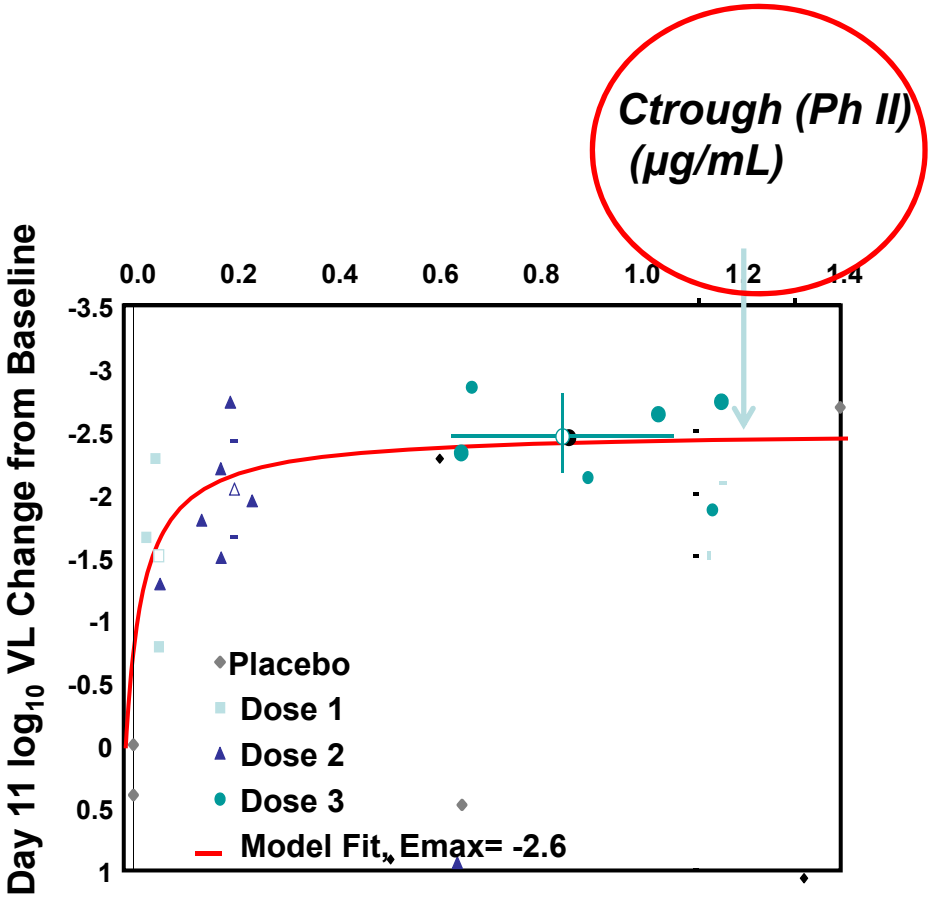
Interaction of efavirenz with other antivirals

Antiviral	% Decrease in exposure of antiviral with efavirenz	Recommendation
Atazanavir/r	AUC 0% ; C_{min} 42%	Not recommended but increase to 400/200 mg possibly considered (European SPC)
Maraviroc	AUC 45%; Cmin 45%	Increase MVC to 600 mg bid
Dolutegravir[1]	AUC 75%; Cmin 70%	No dose adjustment likely
Telaprevir	AUC 26%; C_{min} 47%	Dose increase from 750 mg tid to 1125 mg tid
Boceprevir	AUC 19%; C_{min} 44%	Clinical outcome not assessed

[1]Dolutegravir is not licensed.
From Song I et al. 12th IWCPHT, 2011, Miami.

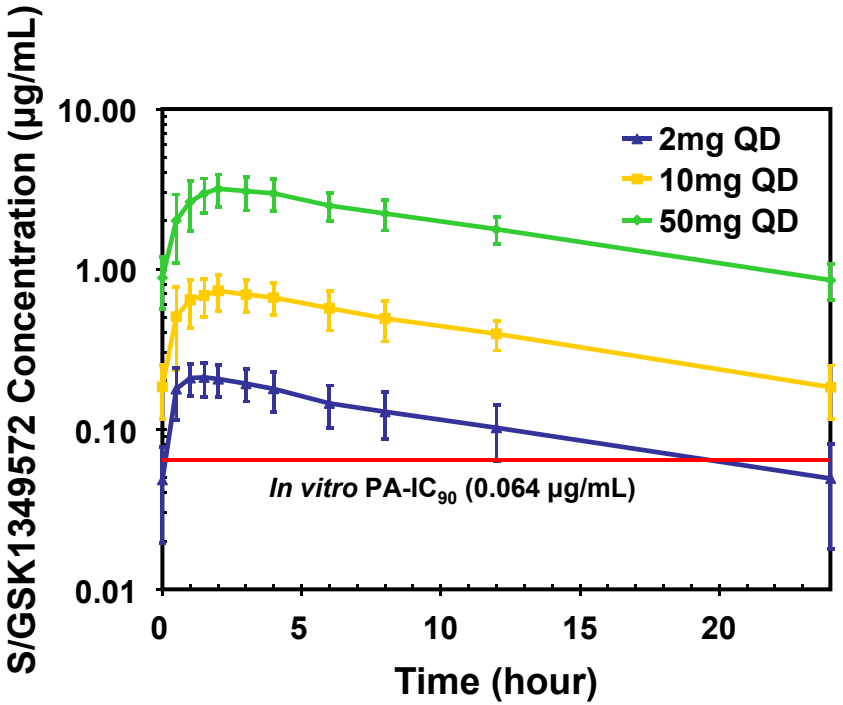
Data taken from relevant SmPCs – accessed October 2012

Exposure-response relationship (HIV)

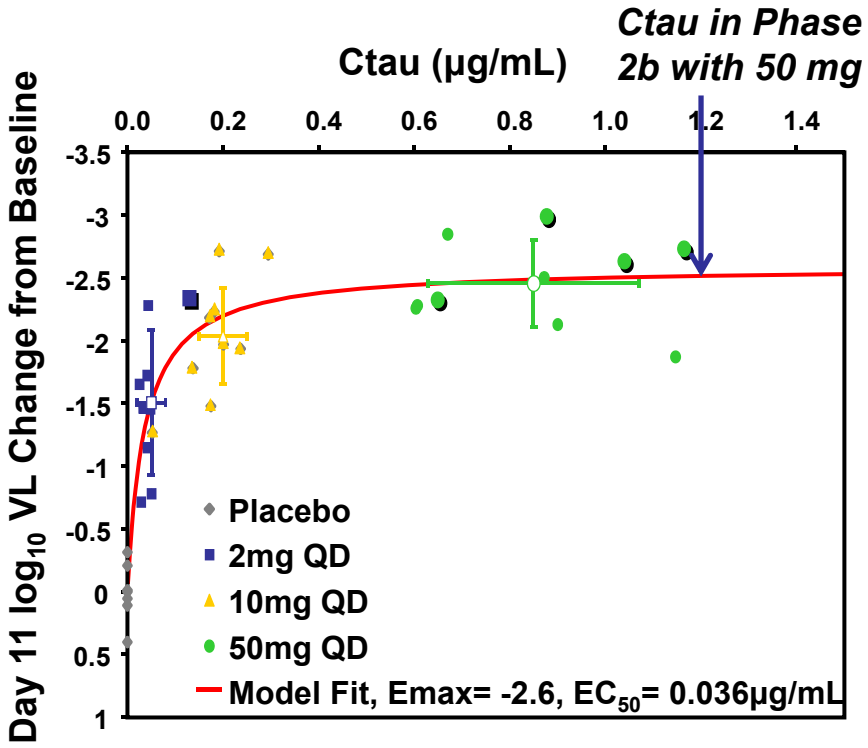


Exposure-response relationship of dolutegravir from phase IIa[1]

Dolutegravir Plasma Concentrations on Day 10

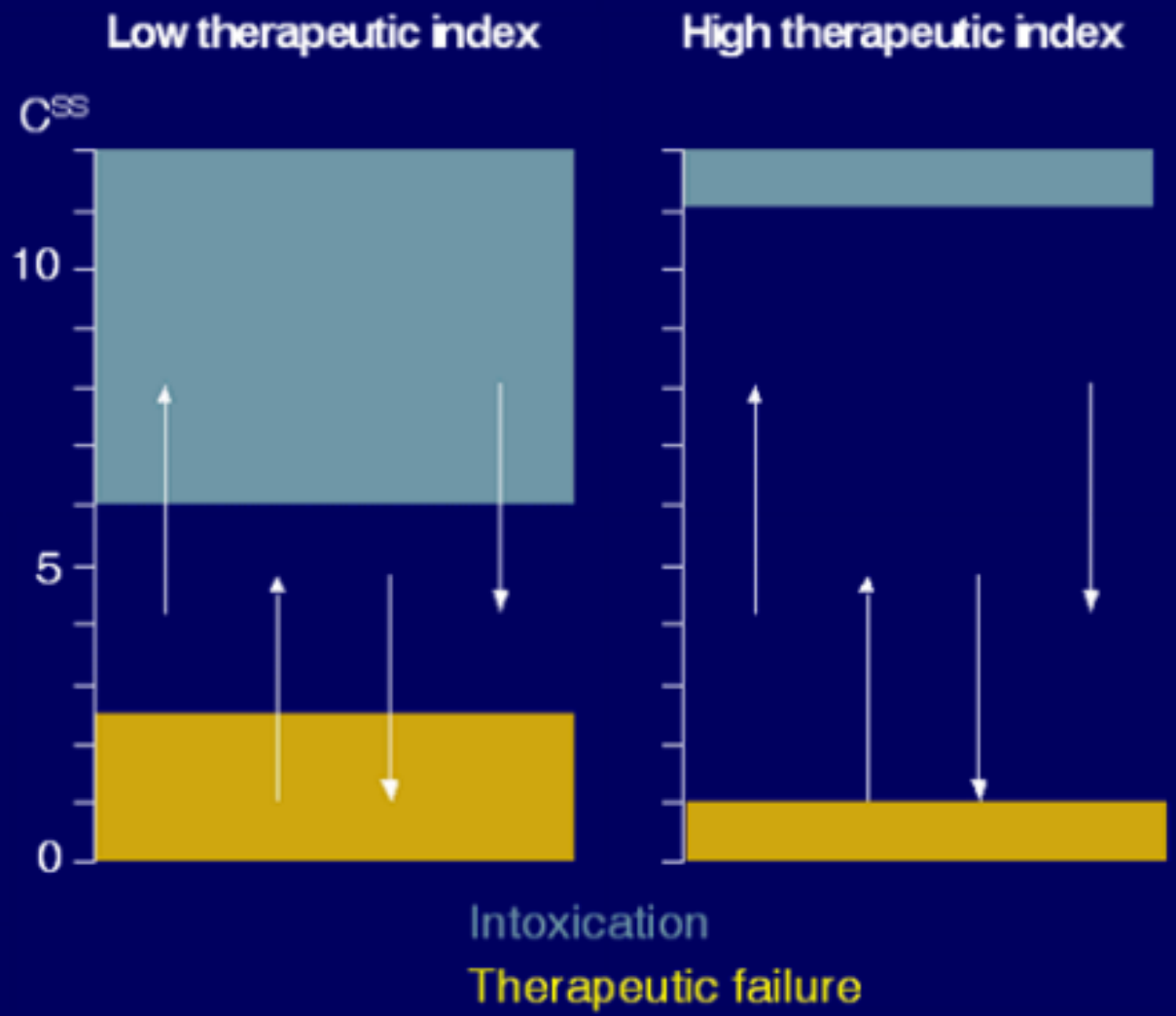


Emax model of Dolutegravir Exposure vs. Response



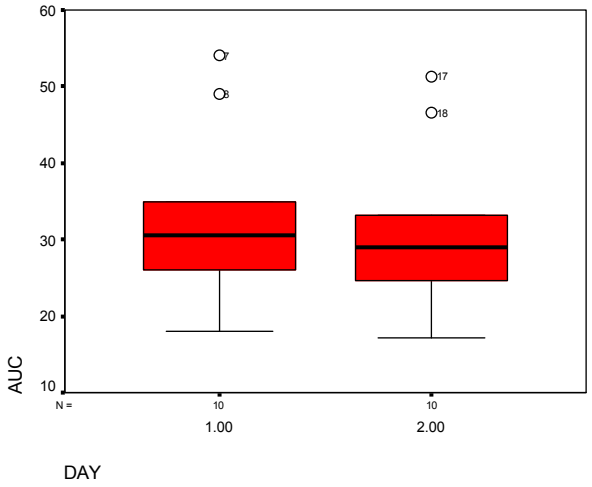
Song I, et al. IAS 2009, Cape Town, Wednesday poster #WEPEB250

Lalezari, et. al. – IAS 2009 – 5th Conference on HIV Pathogenesis, Treatment and Prevention 19-22 July 2009, Cape Town South Africa – Abstract TUAB105


Low therapeutic index
High therapeutic index
C^{ss}
10
5
0
Intoxication
Therapeutic failure

Statistical versus clinical significance

- A clinically relevant PK interaction would require a dose modification/warning/contra-indication
- A statistically significant effect may not be clinically relevant



A consistent 10% decrease in AUC in 10 subjects is statistically significant ($p<0.01$), but not clinically relevant.

Van Heeswijk R Personal Communication

Will DDI data from healthy volunteer studies reflect what will happen in patients?

Physiological changes (versus healthy volunteers)

Parameter	HIV-infected	HCV-infected	HIV/HCV co-infected
Albumin	↓[1,2]	↓*[3]	↓†[4]
α1-acid glycoprotein	↑[5]	↑[6]	↑
Gastric pH	↑[7]	↑[8]	↑
Cytochrome P450	↓	↓	↓
Cytokines	↑	↑	↑

* Decreased albumin associated more with cirrhosis and significant liver damage
† Significantly lower than HIV or HCV mono-infected patients

[1]Mehta SH, et al. AIDS Res Human Retrovir 2006;22:14–21; [2]Graham SM, et al. AIDS Res Human Retrovir 2007;23:1197–1200
[3]Nagao Y & Sata M. Virology Journal 2010;7:375; [4]Monga HK, et al. Clin Infect Dis 2001;33:240–7
; [5]Boffito M, et al. Drug Metab Dispos 2002;30:859–60; [6]Ozeki T, et al. Br J Exp Path 1988;69:589–95
[7]Welage LS, et al. Clin Infect Dis 1995;21:1431–38; [8]Nam YJ, et al. Korean J Hepatol 2004;10:216–22

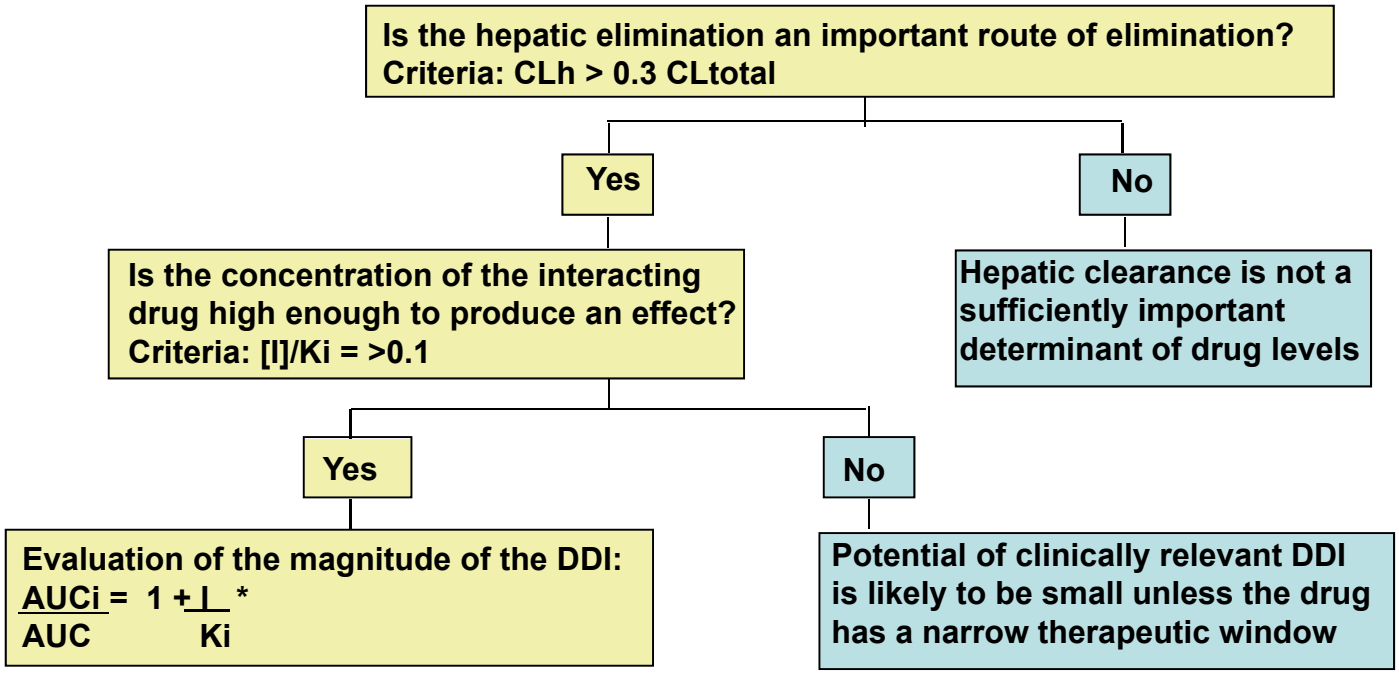
PK Differences (*vs.* healthy volunteers)

Drug	HIV-infected	HIV/HCV co-infected*
ATV	↓ (Reyataz SPC)	↑ (Regazzi et al. Ther Drug Monit 2011)
ATV/RTV	↓ (Reyataz SPC)	↔ (Di Biagio et al. J Infect Chemother 2012) ↔ (Regazzi et al. Ther Drug Monit 2011)
DRV/RTV	↑ (Prezista SPC)	↔† (Sekar et al. Clin Pharmacokinet 2010) ↑ RTV † (Sekar et al. Clin Pharmacokinet 2010) ↔ (Sekar et al. 11th EACS 2011) ↔ cirrhosis *vs.* historical controls (Curran et al. 13th WCPHT 2012)
LPV/RTV	↔ (Kaletra SPC)	↔ (Barreiro et al. J Infect Dis 2007) ↑ (Peng et al. J Clin Pharmacol 2006) ↑ RTV (Peng et al. J Clin Pharmacol 2006) ↔ (Canta et al. JAC 2005) ↔ but ↑ V/F (Molto et al. Clin Pharmacokinet 2007) ↑ RTV, ↓ CL/F V/F (Molto et al. Clin Pharmacokinet 2007) ↔ (Seminari et al. JAC 2005) ↓ (Dominguez et al. JAC 2010)
EFV	↓ (Mukonzo et al. Clin Pharmcokinet 2011) (Ugandan study) ↓ (Dupont review report1998) (↔ Caucasian; ↓ Black)	↔ (Katsounas et al. Eur J Med Res 2007) ↔ (Pereira et al. BJCP 2008) ↑ cirrhosis *vs.* no cirrhosis (Barreiro et al. J Infect Dis 2007) ↑ (Dominguez et al. JAC 2010)
RAL	↓ (Arab-Alameddine et al. AAC 2012) ↔ (composite analysis, Merck)	↑ cirrhosis *vs.* no cirrhosis (Hemandez-Novoa et al. 19th CROI 2012) ↔ ¥ (Iwamoto et al. AAC 2009)

* Compared to HIV mono-infected
† Healthy individuals with & without mild/moderate hepatic impairment
¥ Healthy individuals with & without moderate hepatic impairment

How do you predict interactions where there are no study data?

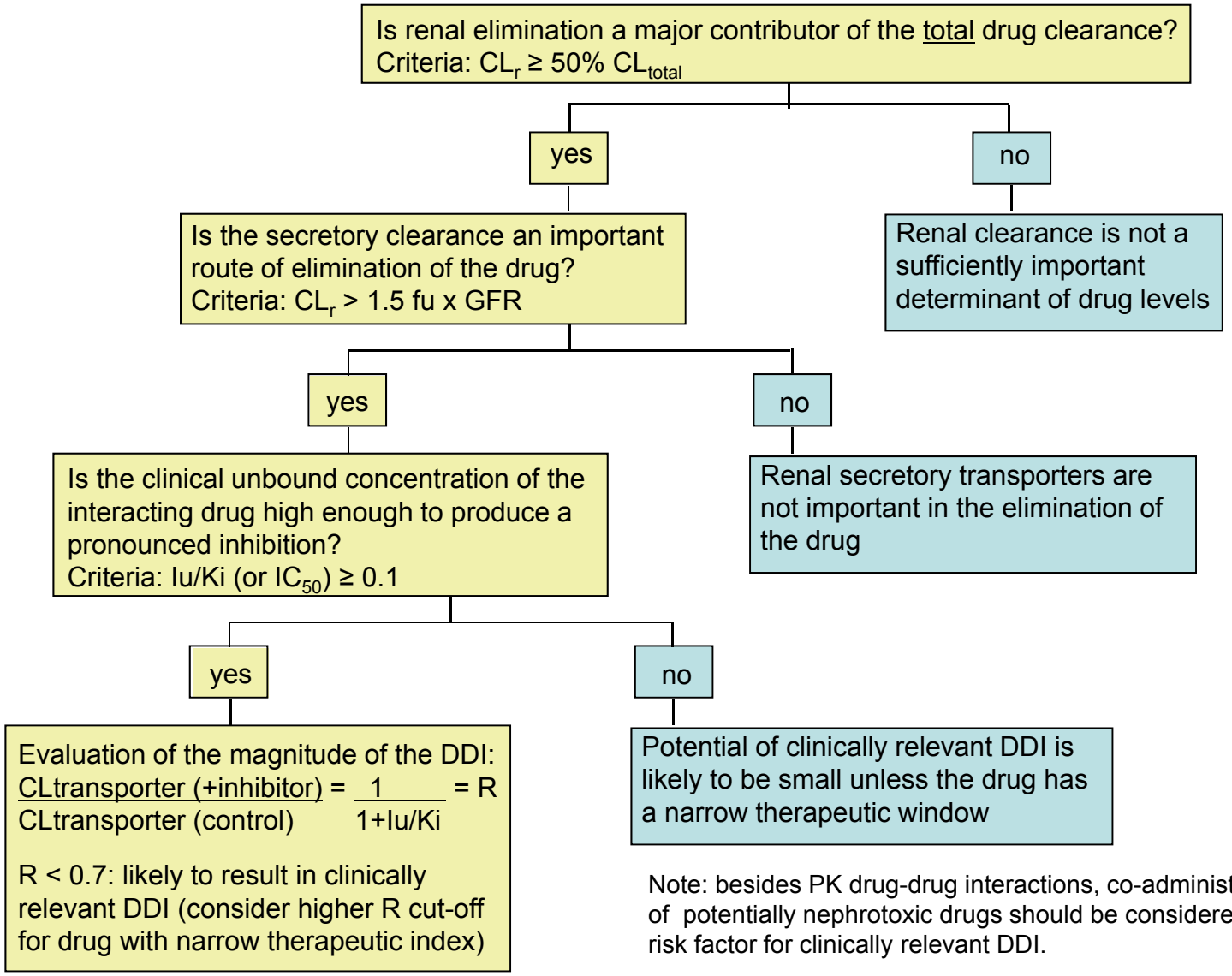
Decision tree for clinically relevant DDI of CYP substrates



Note: According to the FDA, if the inhibitor produces a change in AUC of a probe drug of 5-fold or higher (ie >80% decrease in clearance the inhibitor is considered **strong**; if the change in AUC is >2 to <5-fold, the inhibitor is considered as **moderate**; if the change in AUC is >1.25 to < 2-fold, the inihibitor is considered **weak**.

FDA guidance for DDI studies 2006
Ito K et al. Pharmacol Rev 1998

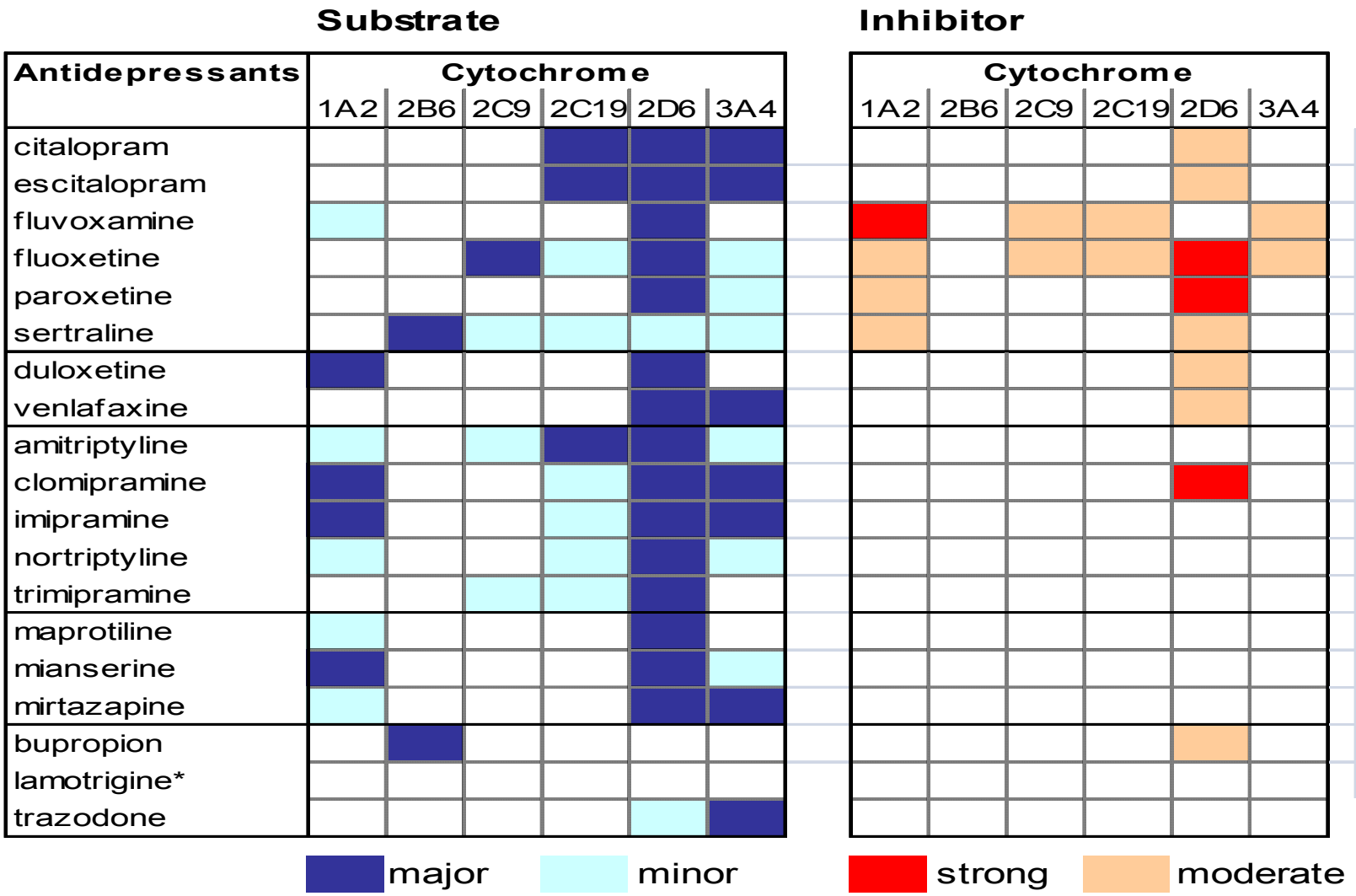
Decision tree for clinically relevant DDI at the renal level



Note: besides PK drug-drug interactions, co-administration of potentially nephrotoxic drugs should be considered as risk factor for clinically relevant DDI.

International Transporter Consortium. Nat Reviews 2010
Shitara et al. Ann Rev Pharmacol Toxicol 2005

Interactions with antidepressants



* lamotrigine is glucuronidated

http://pharmacoclin.hug-ge.ch/actualites.html
Spina E et al. Clinical Therapeutics 2008

Are we only concerned about interactions with oral drugs?

Corticosteroid metabolism and formulations

Drug	Oral	Inhaled	Topical	Eye/ear drops	Injection	Rectal
Budesonide *CYP3A4*	✓	✓				✓
Dexamethasone *CYP3A4*	✓		✓	✓	✓	
Fludrocortisone *CYP3A4*	✓					
Fluticasone *CYP3A4*		✓	✓			
Hydrocortisone *CYP3A4*			✓	✓	✓	✓
Prednisolone *CYP3A4*	✓		✓	✓	✓	✓
Beclomethasone *Esterase to active met*		✓				
Triamcinolone *CYP3A4*	✓	✓	✓		✓	
Mometasone *CYP3A4*		✓	✓			

Created from SmPCs for all included drugs. Available at: http://www.medicines.org.uk/emc/.

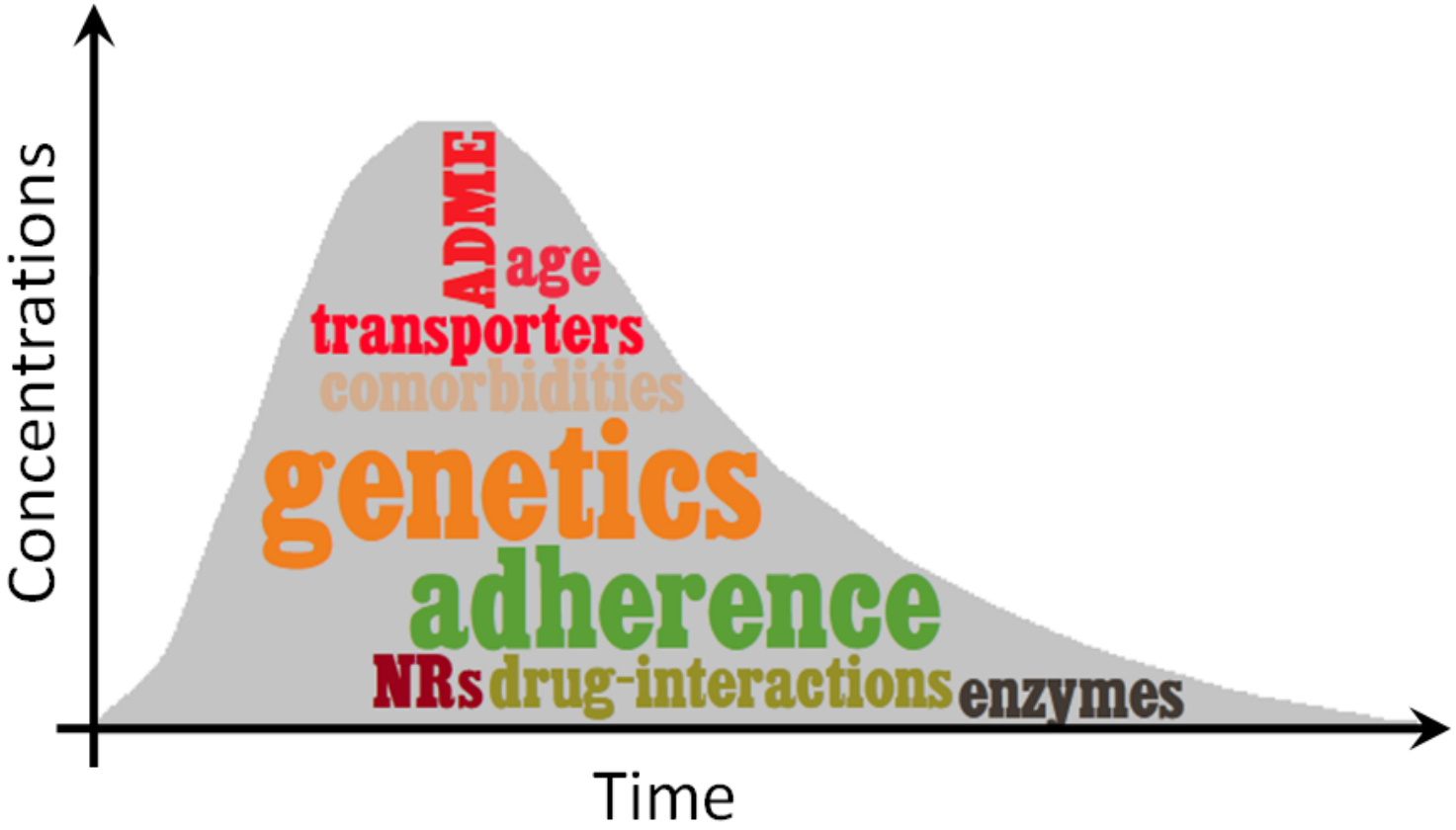
Are there ‘less risky’ ARVs?

Drug-drug interactions between HIV drugs and non-HIV drugs [i]

EACS Guidelines 2012

	Non-HIV drugs	ATV	DRV	LPV	RTV [ii]	EFV	ETV	NVP	MVC	RAL
CARDIOVASCULAR DRUGS	atorvastatin	↑	↑	↑	↑	↓	↓	↓*	↔	↔
	fluvastatin	↔*	↔*	↔*	↔*		↑*		↔*	↔*
	pravastatin	↔*	↑	↔	↔	↓	↓*	↔*	↔	↔
	rosuvastatin	↑	↑*	↑	↑	↔	↑*	↔	↔	↔
	simvastatin	↑	↑	↑	↑	↓	↓*	↓*	↔	↔
	amlodipine	↑*[iii]	↑*	↑*	↑*	↓*	↓*	↓*	↔*	↔
	diltiazem	↑[iii]	↑*	↑	↑	↓	↓*	↓	E*	↔
	metoprolol	↑*	↑*	↑*	↑*	↔*	↔*	↔*	↔*	↔*
	verapamil	↑*[iii]	↑*	↑*	↑*	↓*	↓*	↓*	E*	↔*
	warfarin	↑ or ↓*	↓	↓	↓	↑ or ↓*	↑*	↑ or ↓*	↔*	↔*
CNS DRUGS	diazepam	↑*	↑*	↑*	↑*	↓*	↑*	↓*	↔*	↔*
	midazolam	↑	↑	↑	↑	↑			↔	↔
	triazolam	↑	↑	↑	↑	↑			↔*	↔*
	citalopram	↑*	↑*	↑*	↑*	↓*	↑*	↓*	↔*	↔*
	mirtazapine	↑*	↑*	↑*	↑*	↓*	↓*	↓*	↔*	↔*
	paroxetine	↑*	↓	↑*	↑	↔	↔	↔*	↔*	↔*
	sertraline	↑*	↓	↑*	↑	↓	↓*	↓*	↔*	↔*
	pimozide	↑	↑	↑	↑	↑			↔*	↔*
	carbamazepine	↑D	↑	↑D	↑	↓D	D	↓D	D	D
	lamotrigine	↔**	↔*	↓	↓	↔*	↔*	↔*	↔*	↔*
	phenytoin	D	D	D	↓	↓D	D	↓D	D	D

Numerous factors determine the pharmacokinetic phenotype



Personal communication: D Back