

14TH ANNUAL CONFERENCE
OF THE BRITISH HIV ASSOCIATION (BHIVA)



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A clinical guide to managing drug-drug interactions in antiretroviral therapy

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Introduction

- PK/PD interactions are common among ARVs and with other prescription drugs, OTC medications, recreational drugs, and herbal products
- Most common/significant interactions are mediated by CYP450 but other mechanisms are involved:
 - P-glycoprotein and other transporters
 - Phase II enzymes (i.e. UDP-glucuronosyltransferase)
 - Renal clearance
 - Oral bioavailability
 - pH dependent absorption
 - Genetic polymorphism

Clinical significance

- When changes in efficacy or toxicity
- Narrow therapeutic window
- Enhance therapeutic outcomes (i.e. role of low dose RTV to boost PIs or counterbalance induction)



Studied interactions

- Phase I interaction studies in healthy volunteers or HIV-infected subjects provide basis for recommendations ^{t6}
- Commonly studied drugs: ARVs combinations, rifampicin, rifabutin, clarithromycin, azoles, methadone, PPIs, H₂ antagonists, estrogens, statins, etc.

Predictable interactions

- Based on known mechanism of potential interactions (i.e. itraconazole and maraviroc)
- Some interaction studies are not performed because of harmful risks (i.e. QT prolongation)

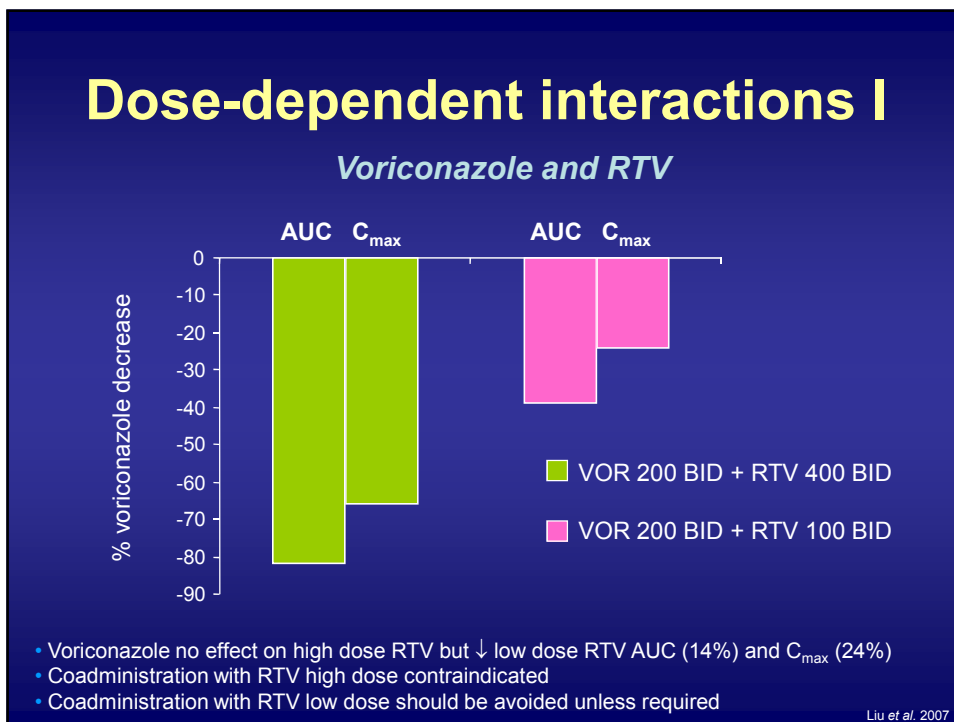
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t6 such as weather certain combinations should be avoided or if dosage adjustments are necessary
temp, 04/03/2008

Antiarrhythmics	Ritonavir
Amiodarone	⊘
Bepidil	⊘
Disopyramide	⊠
Flecainide	⊘
Lidocaine (Lignocaine)	⊠
Mexiletine	⊠
Propafenone	⊘
Quinidine	⊘
Antimigraine Agents	Ritonavir
Dihydroergotamine	⊘
Ergometrine (Ergonovine)	⊘
Ergotamine	⊘
Sumatriptan	◇

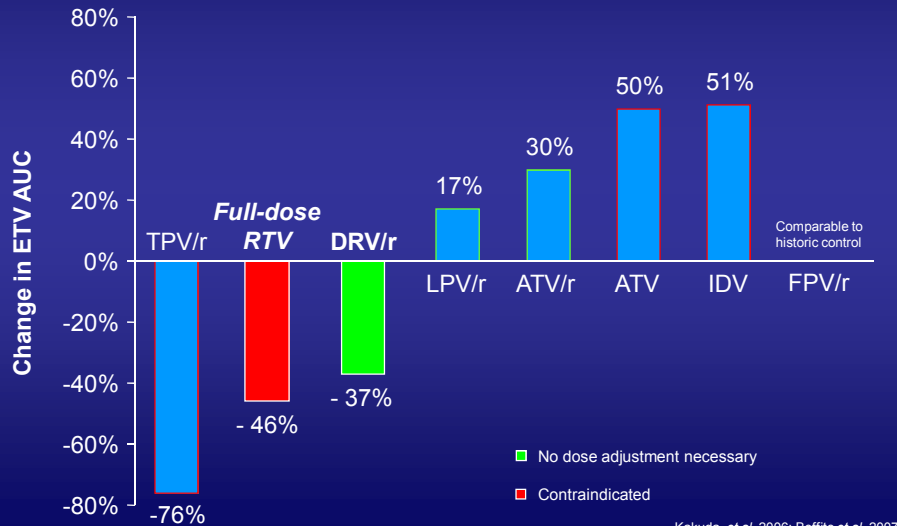
⊘ These drugs should not be co-administered
 ⊠ Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration
 ◇ No clinically significant interaction expected

www.hiv-druginteractions.org



Dose-dependent interactions II

Effect of PIs on ETV

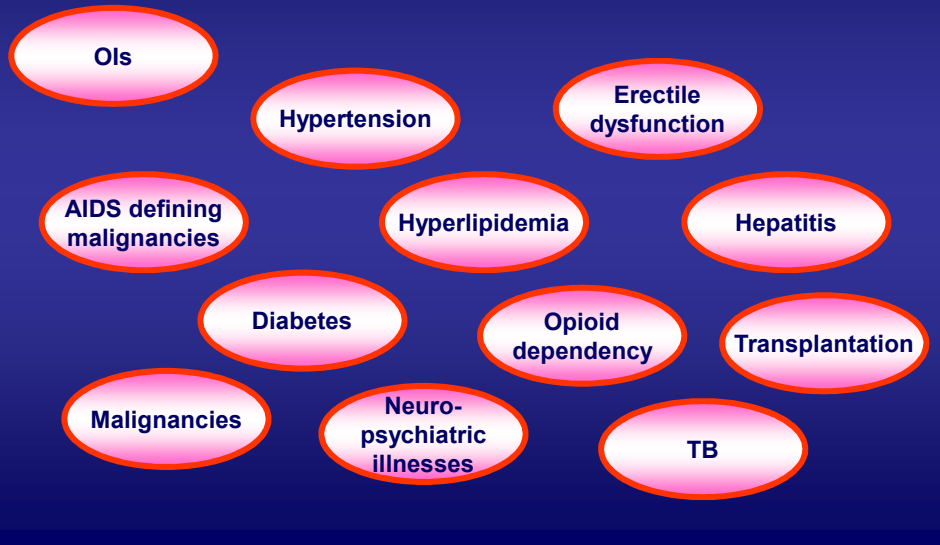


Unpredictable interactions

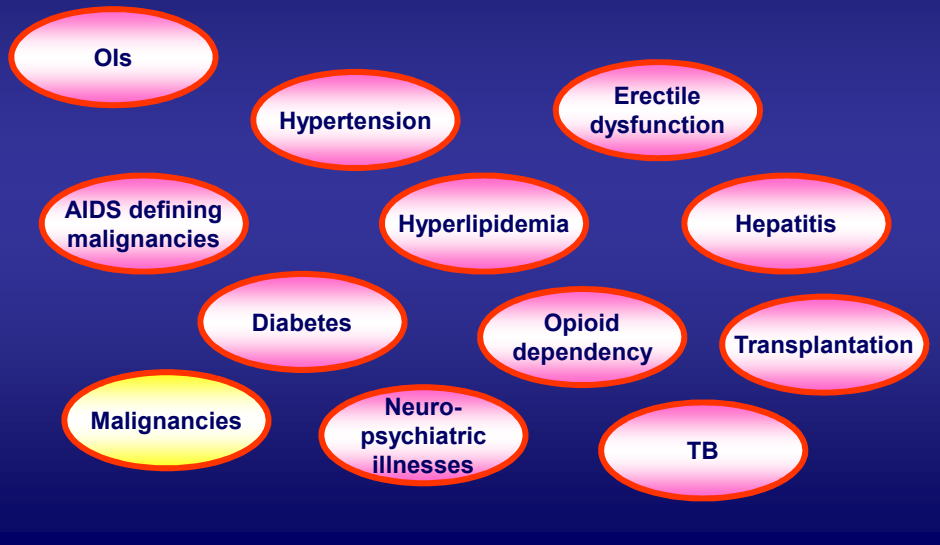
- Fluticasone (nasal/oral inhalation) and RTV: corticosteroid-associated toxicity¹⁻⁴
- ddI and TDF: pancreatitis due to increased didanosine concentrations and impaired immunologic and virologic responses^{5,6}

¹St. Germain et al. 2007; ²Bhumbra et al. 2007; ³Passanha et al. 2007; ⁴Arrington-Sanders et al. 2006; ⁵Barreiro et al. 2006; ⁶Ray et al. 2004

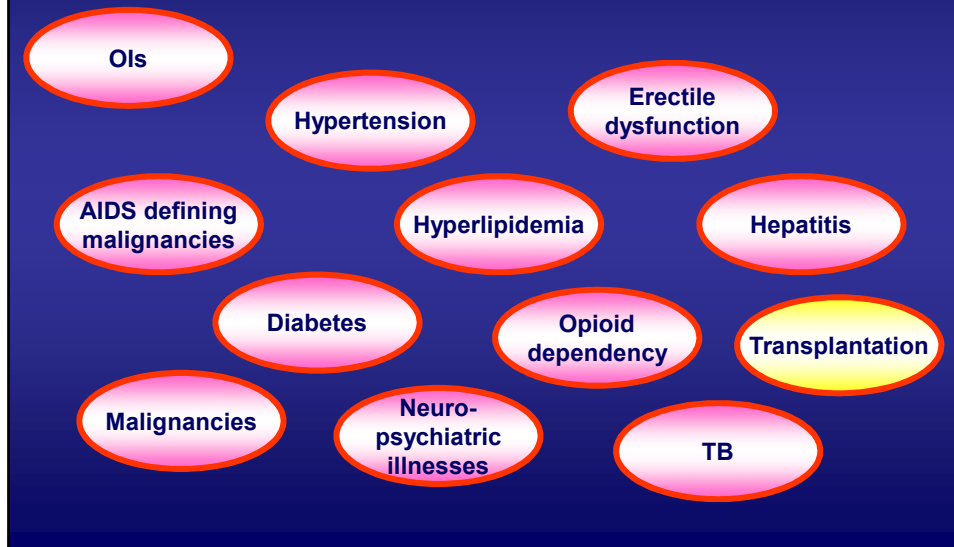
Pharmacologic management of co-morbidities and potential for significant interactions



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Pharmacologic management of co-morbidities and potential for significant interactions



Clinical management

- Primary goal when prescribing ARVs: to provide safest and most efficacious therapy
- Case reports:
 - Neurologic toxicity from tacrolimus + PIs*
 - Hematological and GI effect from vinblastine + LPV/r*
 - Methadone withdrawal with NVP and EFV*
 - Carbamazepine toxicity with RTV*

Consider reviewing therapy for an HIV-infected patient when...

- When prescribing new drug therapy
- Switching drugs / drug classes
- Discontinuing drugs with interactive potential
- Prescribing more than 2 interactive drugs
- Caring for patients with multiple providers
- Caring for patients with organ dysfunction

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E. C.

- Male, HIV+ since 2004
- CD4 211 (17%) cells/mm³
- VL 29,000 copies/mL
- History of epilepsy
- Stable on carbamazepine (Ca) and phenytoin (Ph)

E. C.

- Ca and Ph are inducers of different CYP450 enzymes (CYP3A4)
- Metabolized by CYP3A4
- Interaction between Ca and EFV documented

EFV and carbamazepine

Arm	Drug	PK parameter	GMR and 90% CI	
			EFV + CBZ vs. EFV	CBZ + EFV vs. CBZ
A*	EFV	C _{max}	0.792 (0.740-0.848)	
		AUC	0.637 (0.601-0.676)	
		C _{min}	0.526 (0.470-0.490)	
B**	CBZ	C _{max}		0.804 (0.761-0.849)
		AUC		0.729 (0.668-0.796)
		C _{min}		0.652 (0.560-0.760)
	CBZE [^]	C _{max}		01.050 (0.905-1.219)
		AUC		0.989 (0.854-1.145)
		C _{min}		0.866 (0.703-1.066)

[^]CBZE = carbamazepine epoxide

*n=18, EFV 600 mg OD days 1-14, EFV 600 mg OD days 15-35 plus carb 200 first then 400 mg OD up to day 35

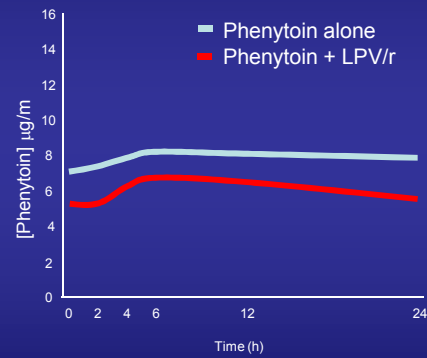
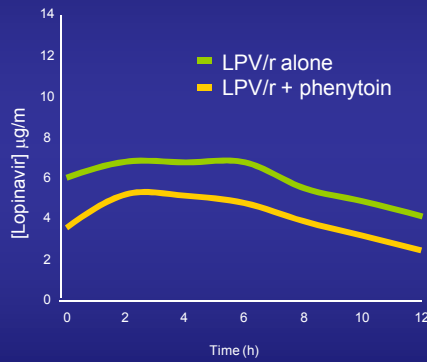
**n=18, carb 200 first then 400 mg OD up to day 21, carb 400 mg OD plus EFV 600 mg days 22-35

Kaul et al. 2006

E. C.

- Ca and Ph are inducers of different CYP450 enzymes (CYP3A4)
- Metabolized by CYP3A4
- Interaction between Ca and EFV documented
- Interaction between Ph and LPV/r documented

Phenytoin and LPV/r



Phenytoin was also found to reduce the concentration of RTV

Lim et al. 2004

E. C. - Options

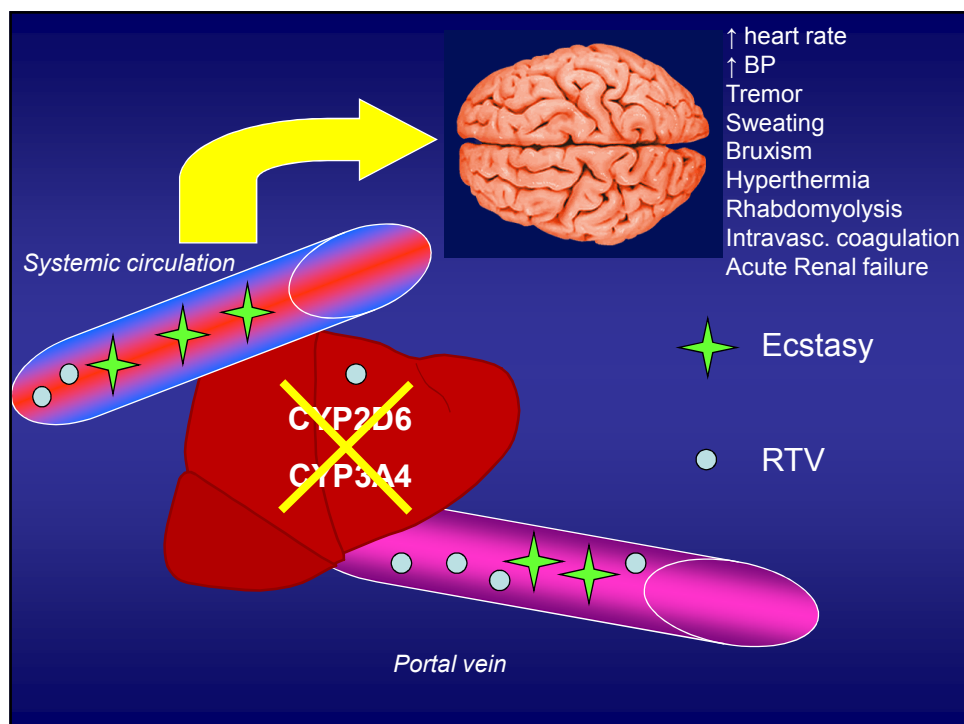
- 1) Stop Ca and Ph and prescribe alternative antiepileptic (i.e. levetiracetam)
- 2) Valproate and lamotrigine might be safe with NNRTI (more data needed)
- 3) Initiate a 4 NRTI regimen for HIV (i.e. AZT/3TC/ABC/TDF)
- 4) Other?

R. E.

- Male, HIV+ 1 month ago
- CD4 101 (15%) cells/mm³
- VL 89,000 copies/mL
- Primary transmitted resistance (103N)
- Recreational drugs: ecstasy (MDMA)

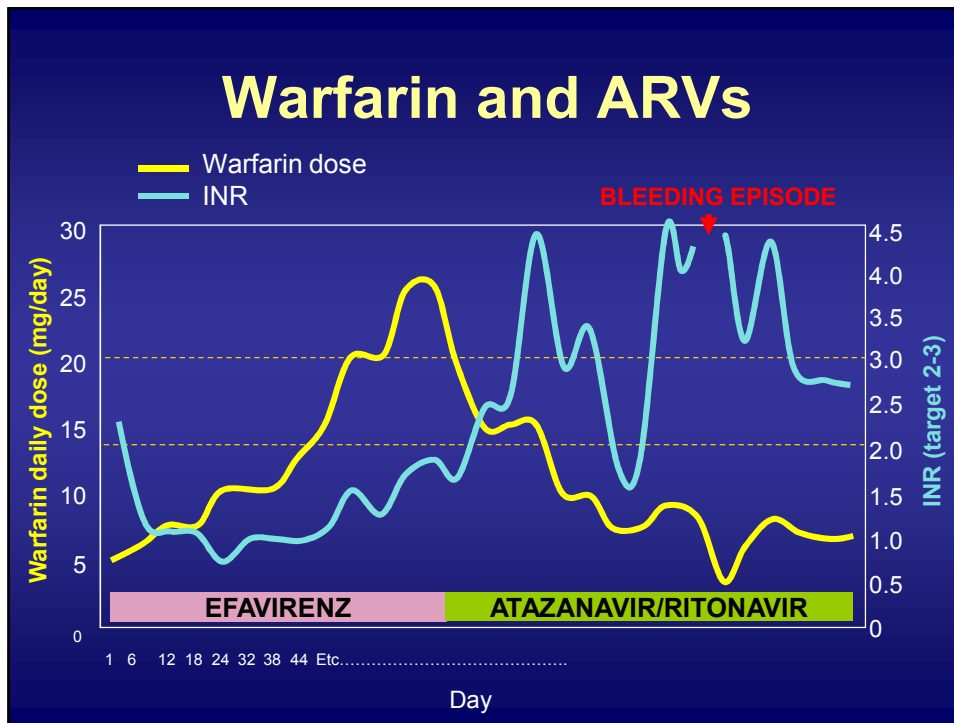
R. E.

- MDMA metabolized CYP2D6, CYP1A2, CYP2B6, CYP3A4
- RTV inhibits CYP3A4 & CYP2D6
- Caution when prescribing PI/r



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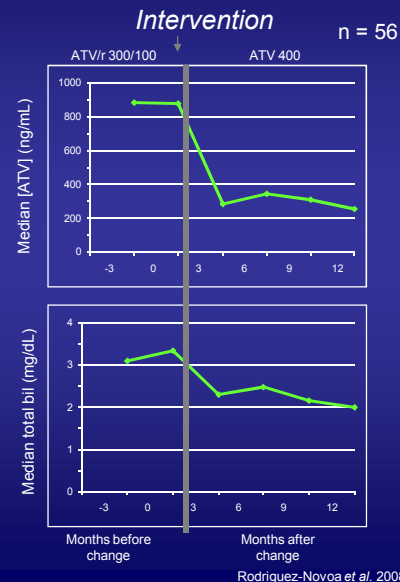


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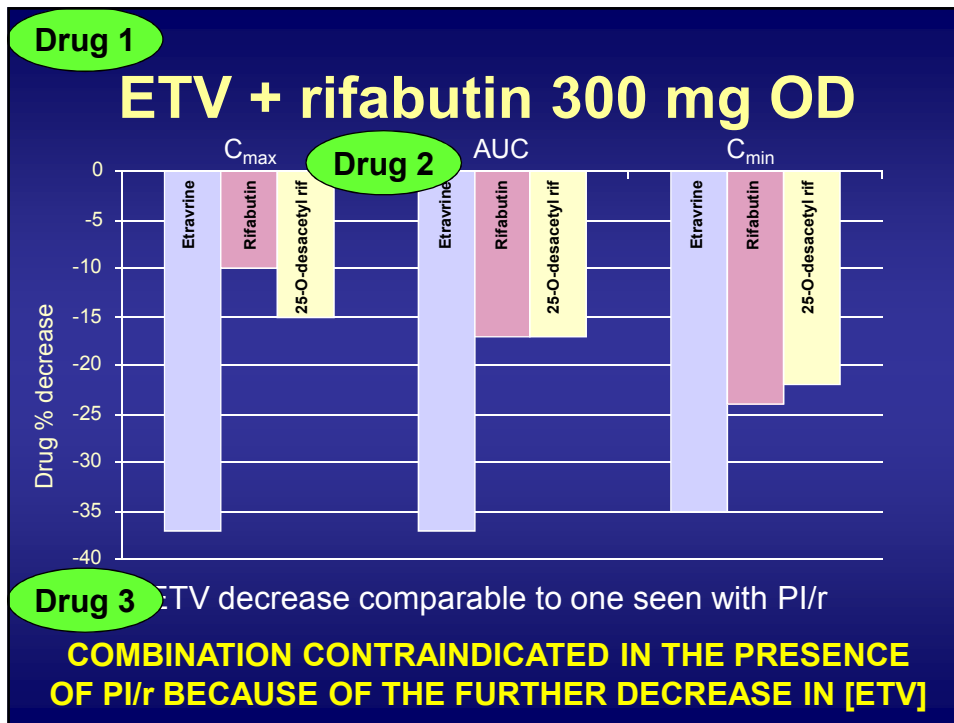
Switch from RTV-boosted to unboosted ATV guided by monitoring [ATV] in a clinical setting

- Retrospective analysis
- TDM useful to minimize ATV/r - AEs, to ensure efficacy if simplification to unboosted ATV
- Strategy seems to maintain HIV-RNA suppression in most cases, although [ATV] should be monitored



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PI/r and statins

- We reported a series of patients on PI/r who were prescribed simvastatin¹
- Simvastatin increased 3000% with PI/r²
- Co-administration contraindicated
- GPs (and all physicians) under pressure to prescribe cheaper medications and this is driving the switch to simvastatin

¹Fichtenbaum *et al.*, 2002; ²Coyne *et al.*, 2007

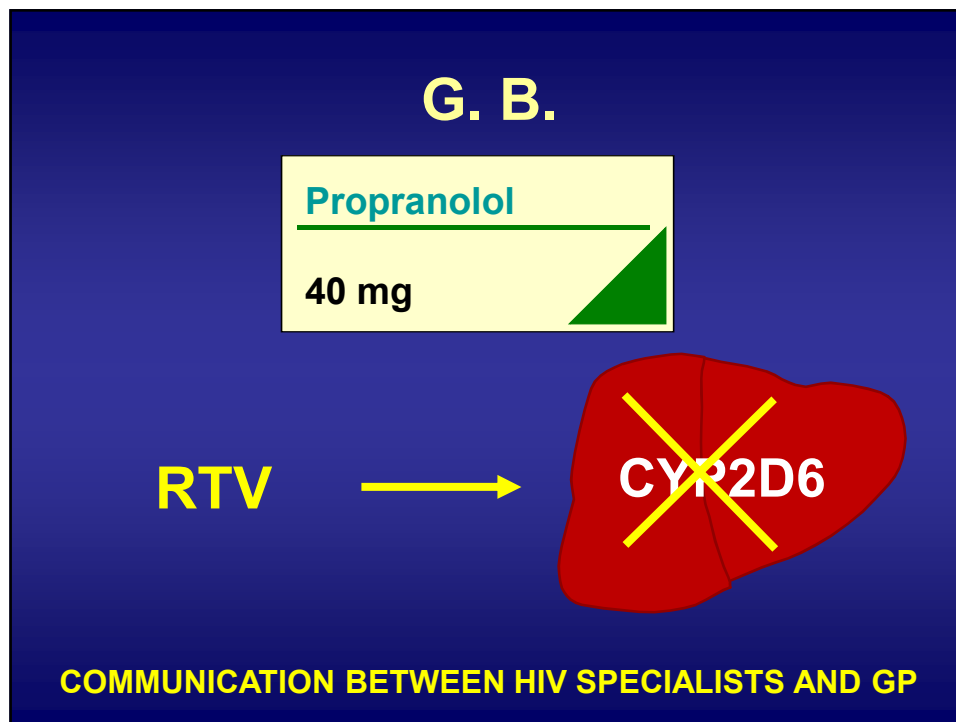
G. B.

- 55 year old HIV+ (since 1998) male
- On TDF/FTC/LPV/r
- CD4 210 cells/mm³; VL < 50 copies/mL
- History of depression currently untreated
- Admitted to A&E complaining of vomiting, extreme weakness, palpitations, confusion
- Few days later comes to HIV clinic for regular follow up and reports recent anxiety attacks...

“My GP gave me this...”

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t7 either as the first statin or as a switch from another more expensive statin such as atorvasatin
temp, 10/04/2008



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Organ dysfunction

- DDI studies generally in patients with normal hepatic and renal f(x)
- HIV+ individuals may have some degree of organ dysfunction
- DDI in pts with organ dysfunction is not defined
- Caution and close monitoring

Resources for assessing drug interactions

- www.HIV-druginteractions.org
- Prescribing information
- Think about metabolic pathways and try to predict the interaction....



Thank you

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t8 either due to drug toxicity or co-infection with hep b or c viruses for examples or caused by hiv itself
temp, 17/04/2008



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