



UNIVERSITY OF  
LIVERPOOL

# Clinically Significant Drug Interactions between HIV and CNS drugs

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Diseases



# Points for discussion

- **HIV Pharmacology for non-specialists**
- **Two challenging diseases to treat**
- **Clinically significant drug interactions**
  - *how common are they ?*
  - *what is a 'clinically significant' drug interaction ?*
  - *which antidepressants can I give ?*
  - *which anti-psychotics can I give ?*
  - *which anti-convulsants can I give ?*
- **Strategies for safe prescribing**

# Swiss Cohort

**Patients are getting older ....**

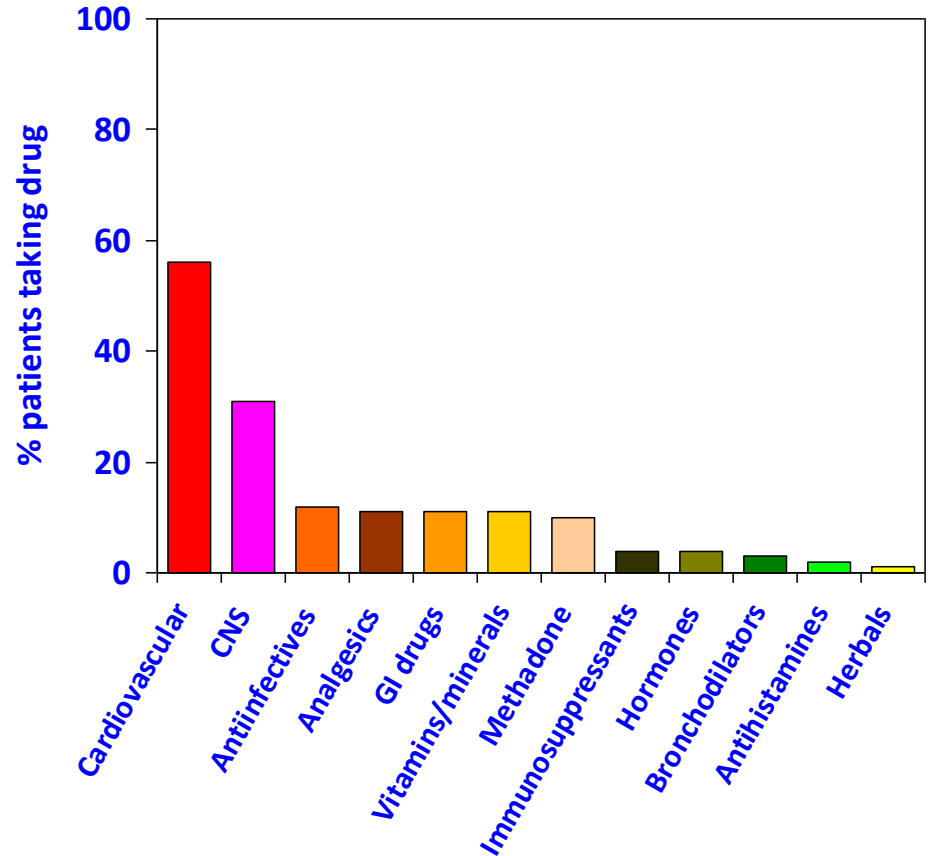
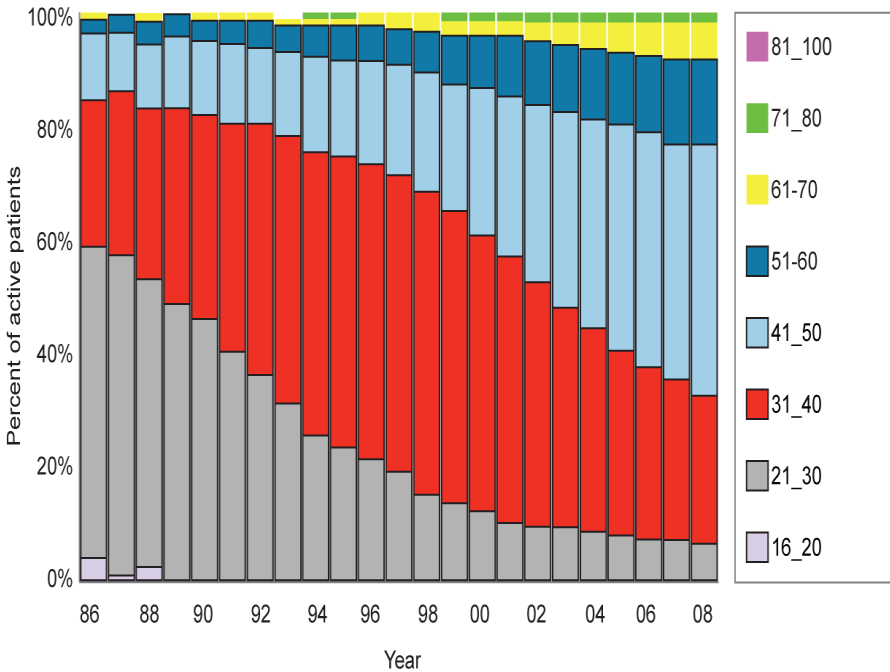
**Proportion aged > 50:**

- 1994 10%
- 2003 20%
- 2006 25%

**.. and take many medications.**

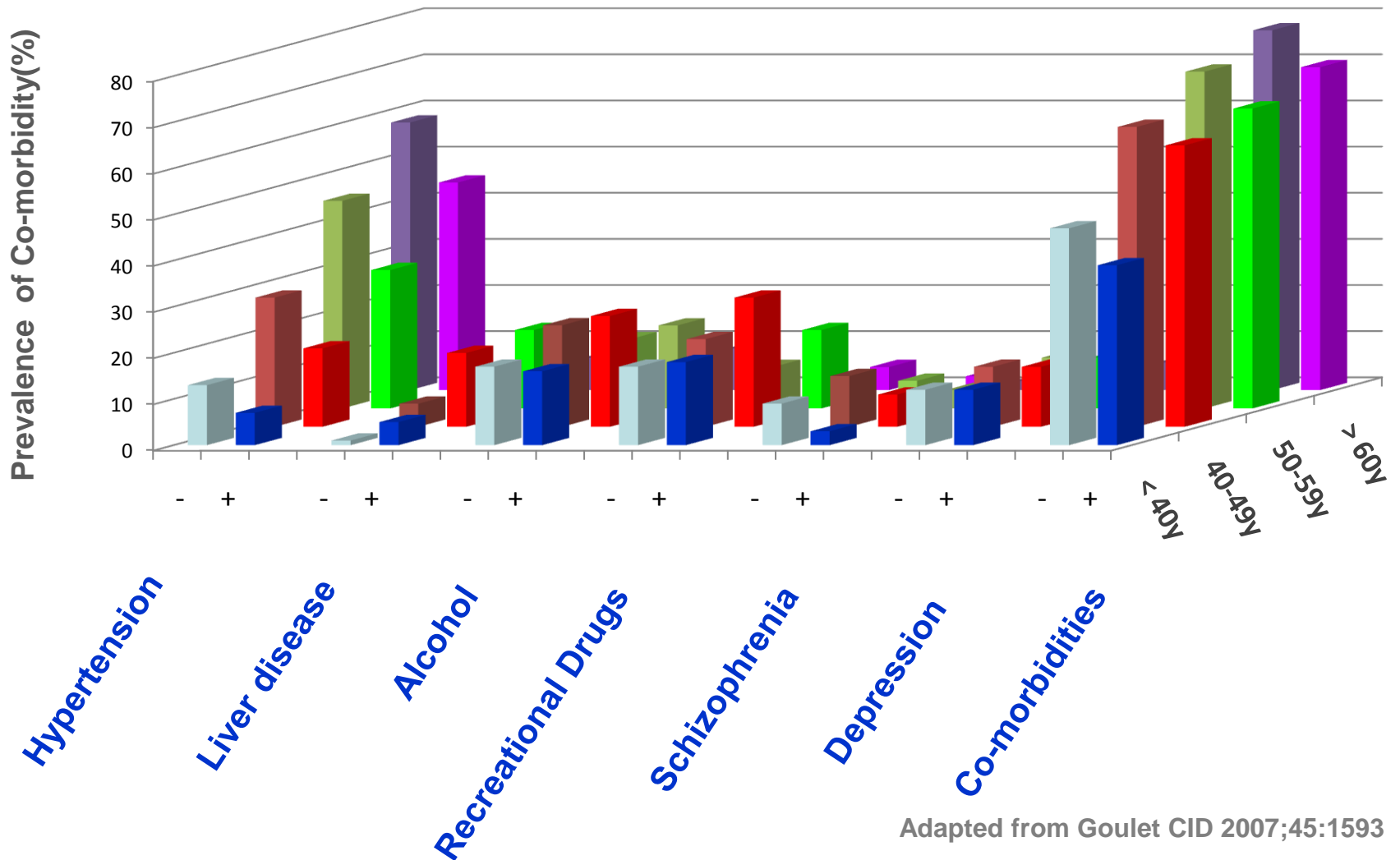
**n = 1471 (2008-2009)**

- 10-15% - lipid lowering, antidepressants, sedatives
- 7-10% - acid-reducing, antithrombotic, ACE inhibitors



# Co-morbidities increase with age

Medical comorbidities amongst 66,840 HIV- and 33,420 HIV+ veterans



# The challenge of treating two diseases

HIV-associated dementia

Depression, anxiety

Psychosis

Seizures

Coping issues

- Denial
- 'self-sabotage'
- Religious beliefs, etc

Lifestyle

- Drug use
- chaotic

## Impacts on HIV treatment:

*Adherence*

*Adherence*

*Drug interactions*

*CNS toxicity of efavirenz*

*Adherence*

*Drug interactions*

*Overlapping toxicity*

*Conflicting treatment priorities*

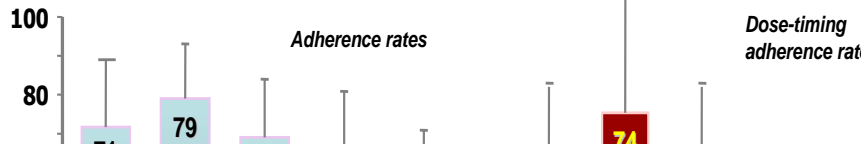
*Drug interactions*

*Adherence*

*Treatment refusal*

*Adherence*

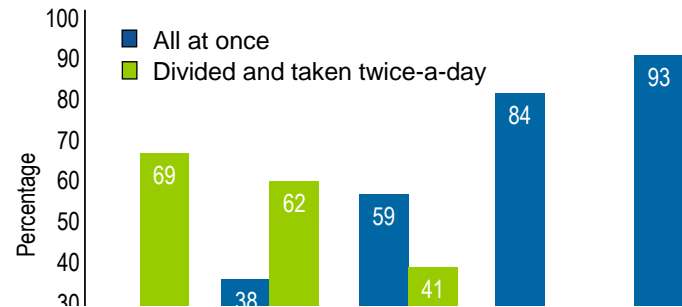
# Simplicity and Pill Burden



**Analysis of 76 studies from a variety of disease areas of electronic monitoring of adherence**

Compliance was higher: OD vs TID:  $p = 0.008$   
 OD vs QID:  $p < 0.001$   
 BID vs QID:  $p = 0.001$

APPT-1 study: % of patients choosing each option



- Once-daily therapy was considered the best lifestyle fit by 81% of participants
- Total number of pills also important factor with participants reporting that even modest reductions in pill burdens would improve adherence

# Adherence-viraemia-resistance relationships

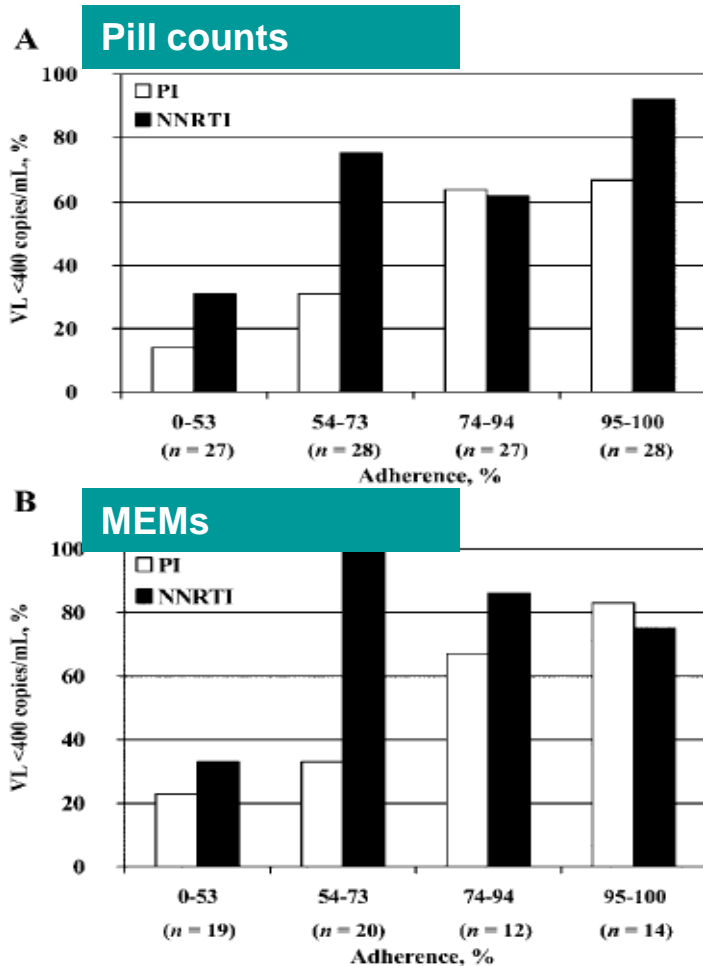
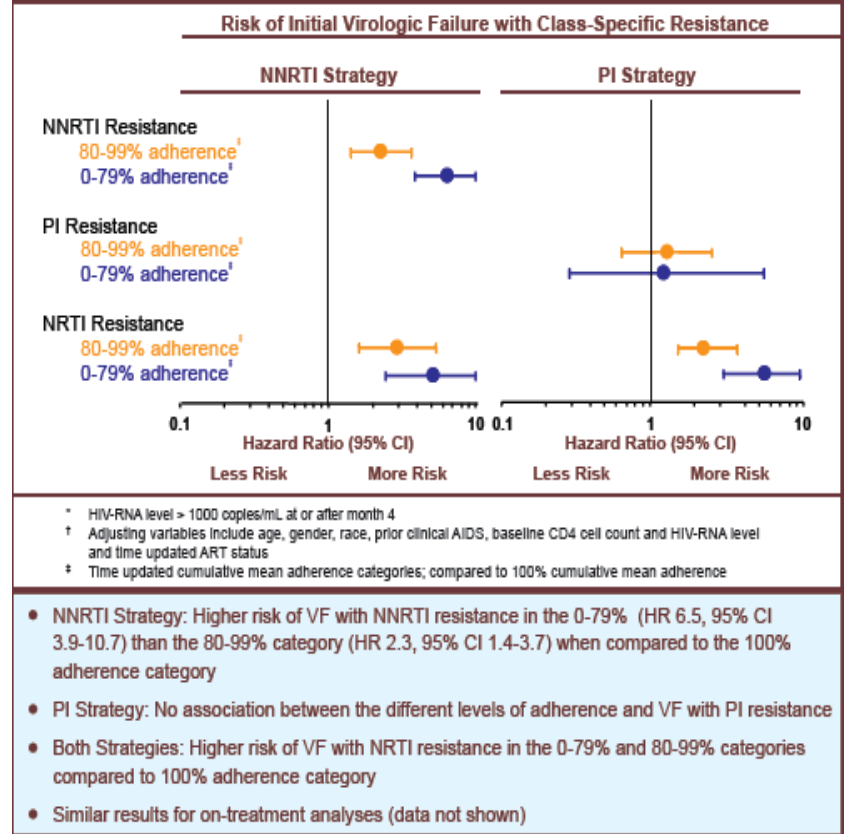


Figure 2: Risk of initial virologic failure\* with resistance by adherence categories: Hazard ratio† (95% confidence interval)

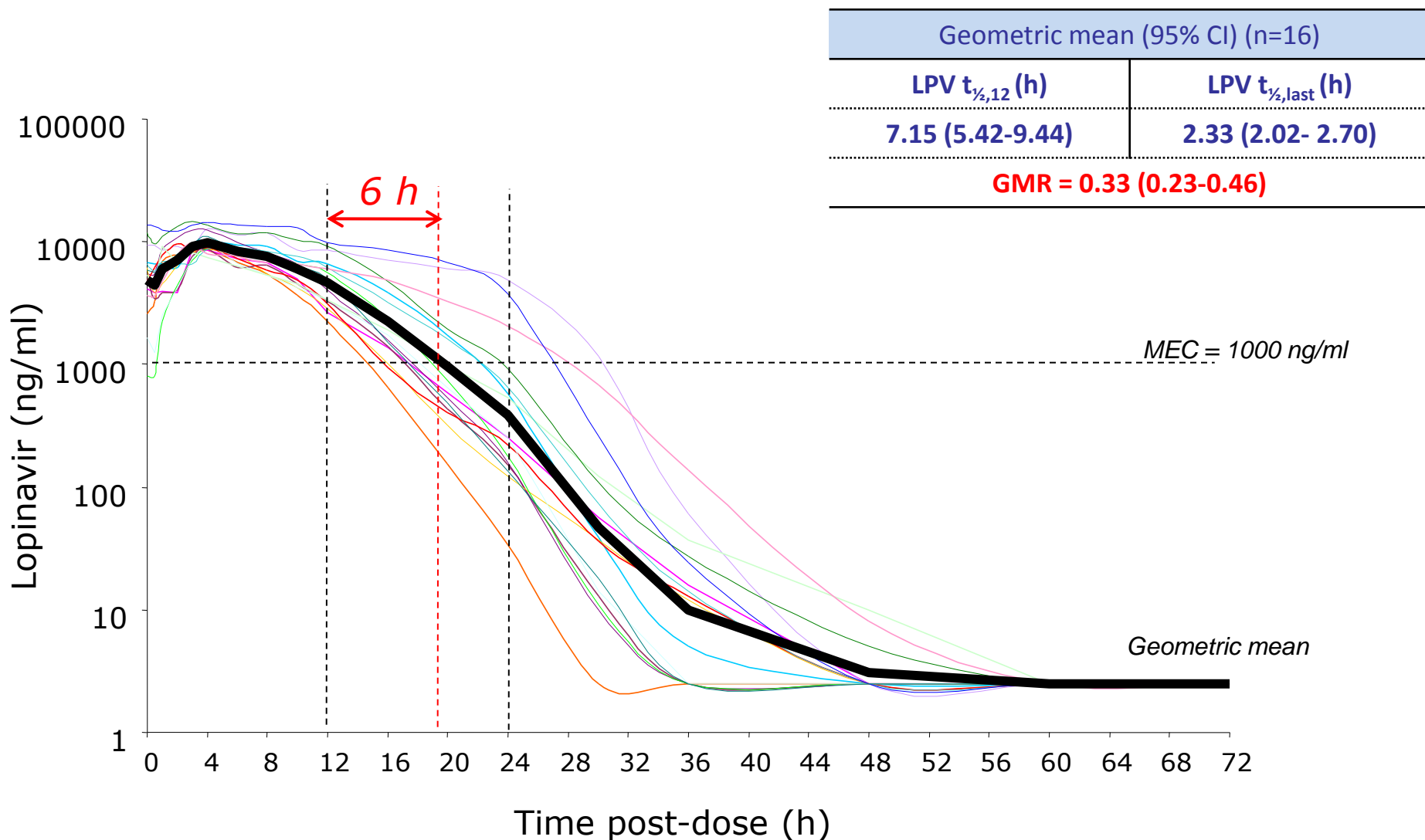


**FIRST Trial: Relationship between Adherence and resistance by drug class:**

Gardner et al CROI 2008 Abs 777  
& AIDS 2010;24:395

# Antiretroviral forgiveness

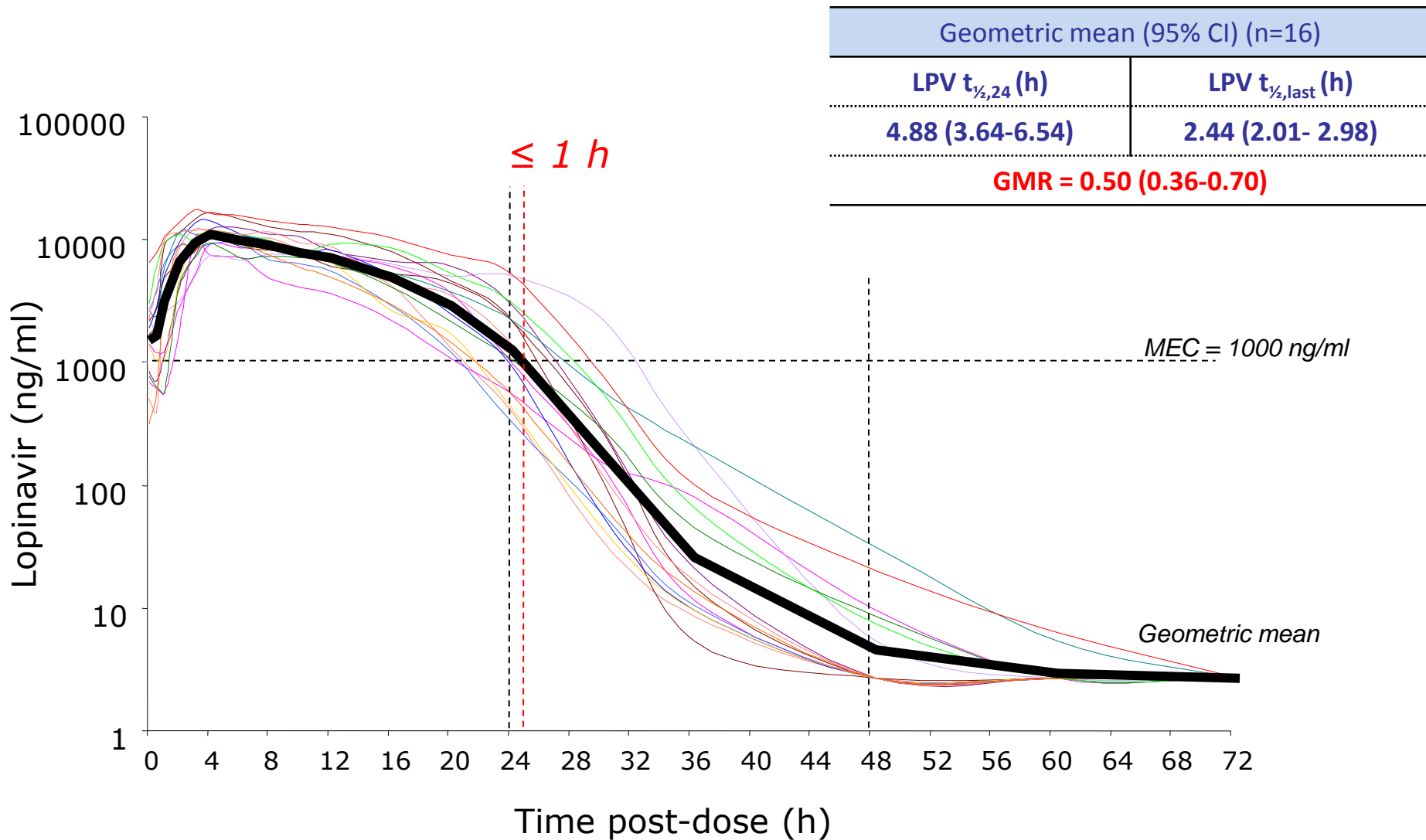
## 72 h LPV (bd) concentrations





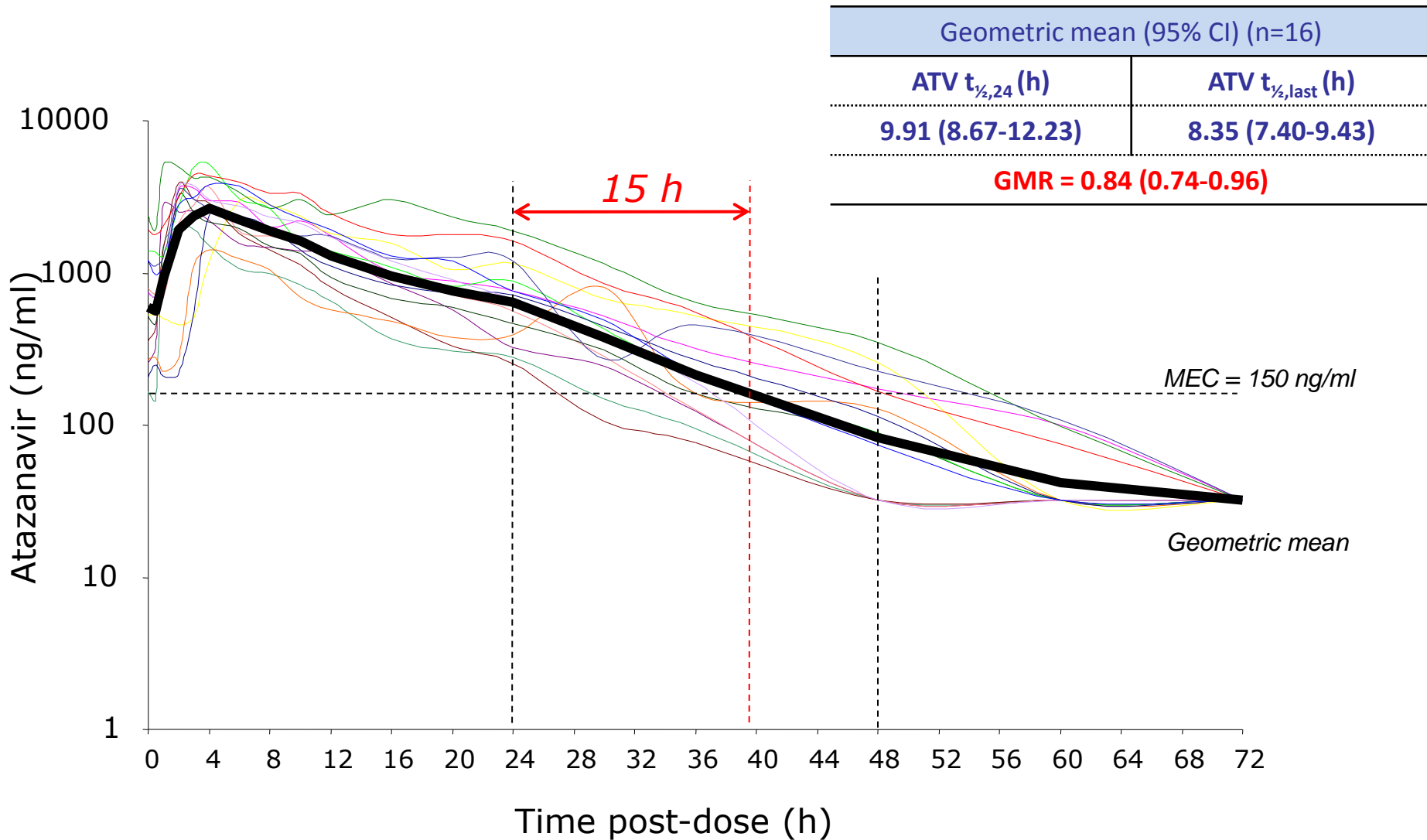
# Antiretroviral forgiveness

## 72 h LPV (qd) concentrations

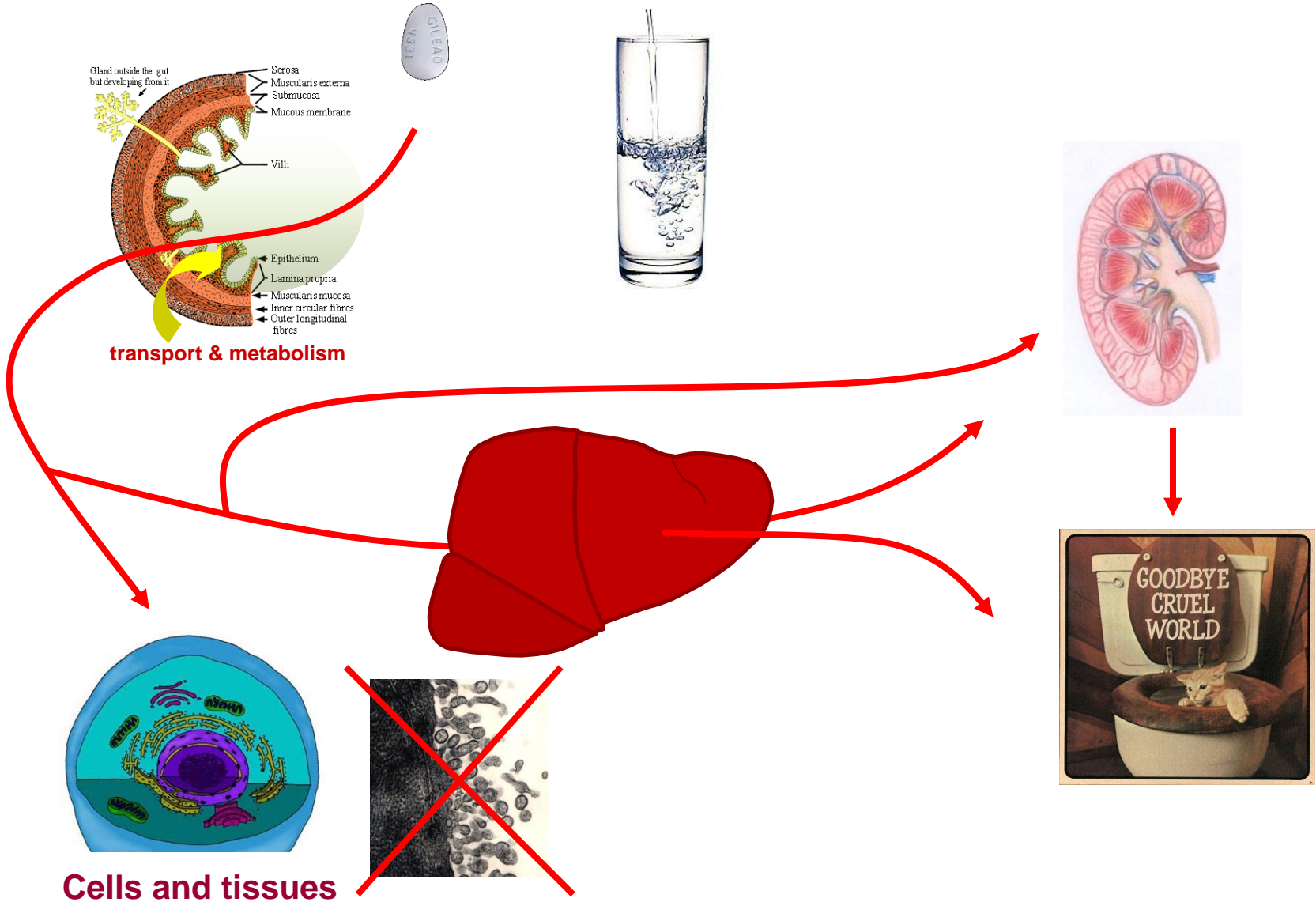


# Antiretroviral forgiveness

## 72 h ATV (qd) concentrations

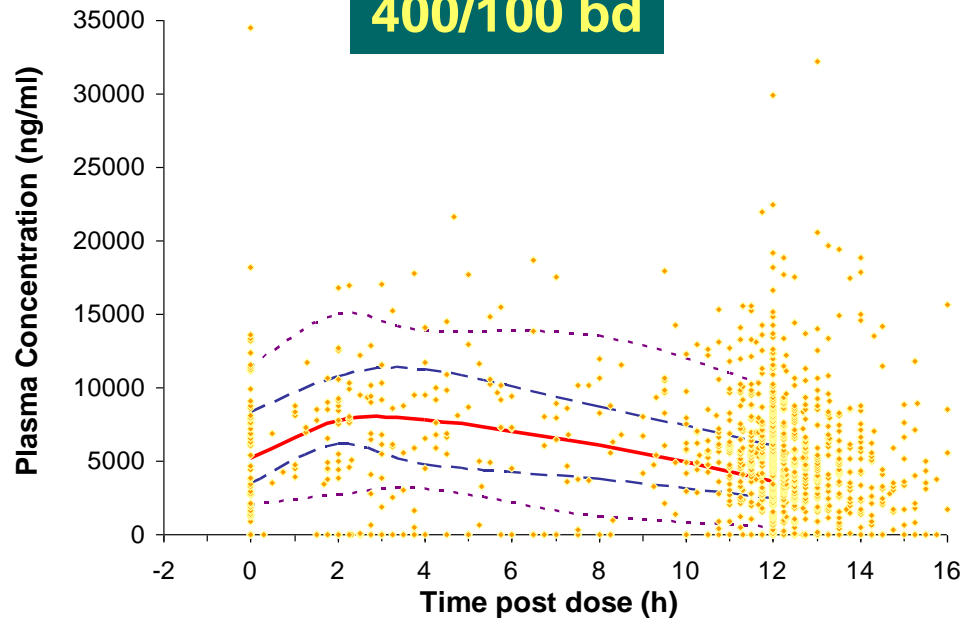


# The life of pills



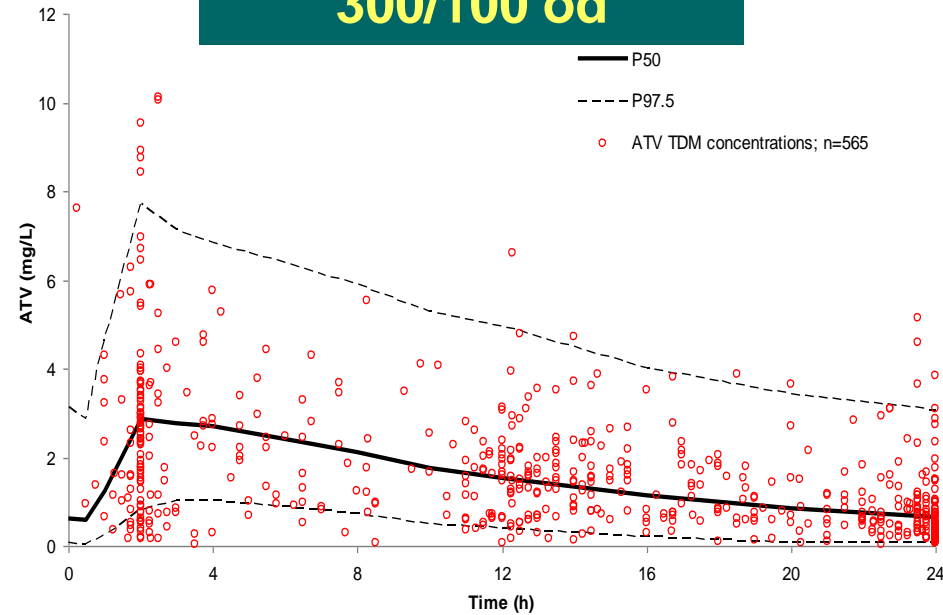
# Inter-individual variability

**Lopinavir/r  
400/100 bd**



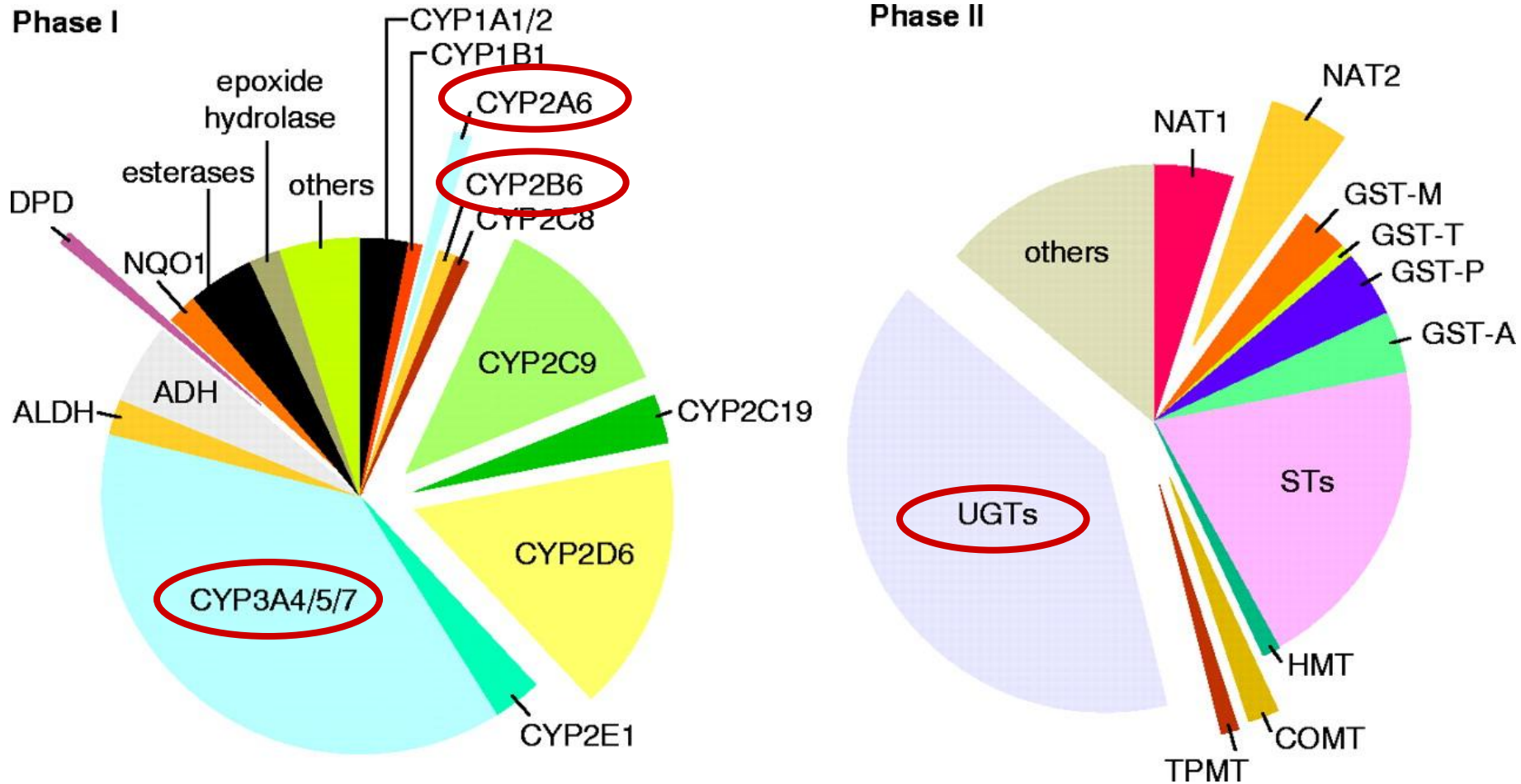
**Clinical Trial (n = 23)  
TDM data ( n = 1122)**

**Atazanavir/r  
300/100 od**



**Pop PK simulated centiles  
TDM data ( n = 565)**

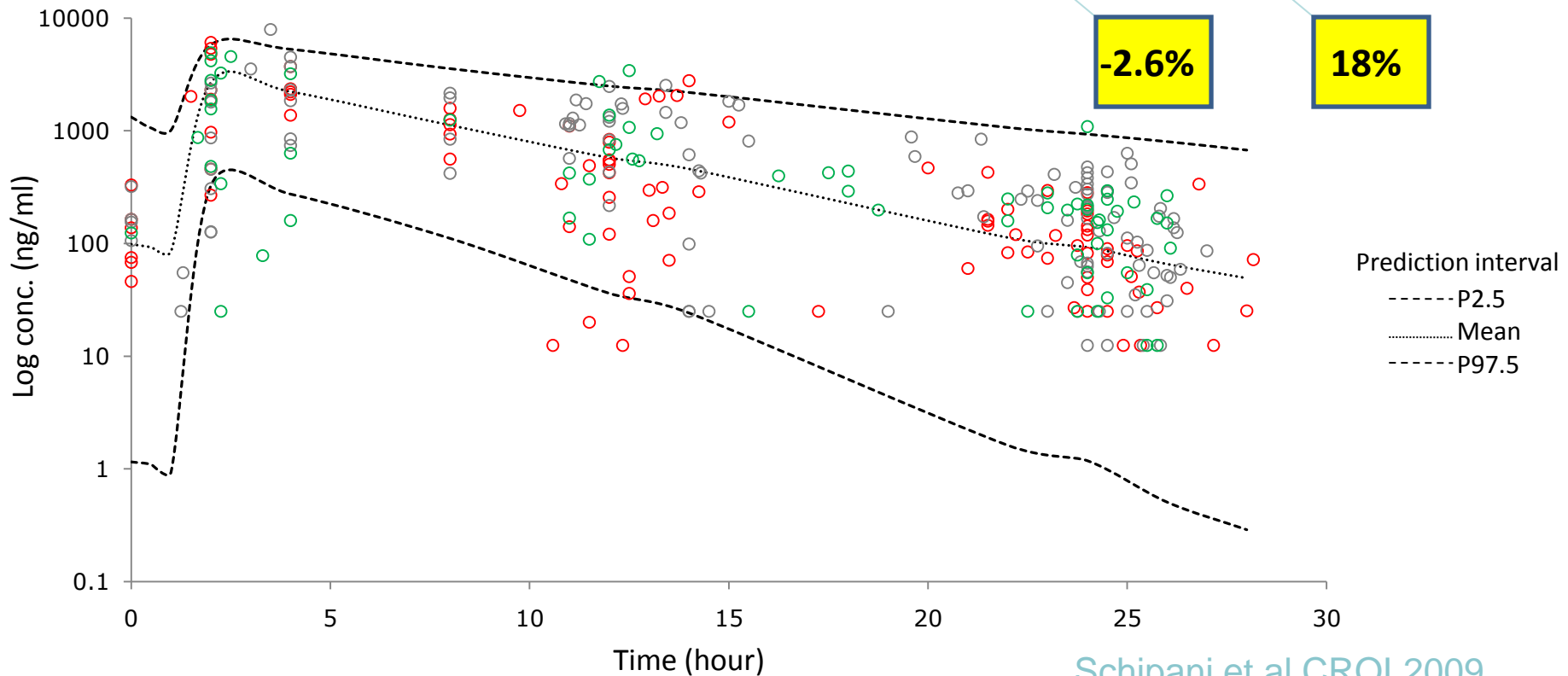
# Drug Metabolizing Enzymes



- Extended = known polymorphisms that affect activity.
- Polymorphisms present in all (?) enzymes.

# Pharmacogenetic influences on ATV PK

$$CL = CL_0 + \theta_1 * PXR_1 + \theta_2 * PXR_2$$



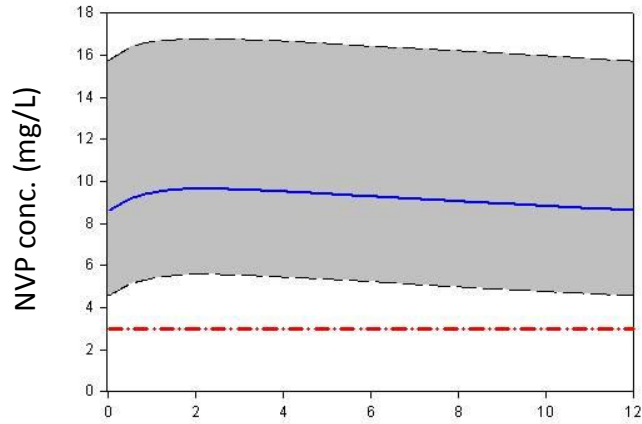
**OATP 1B1**  
**MDR1**  
**PXR**

**SNP 521 T>C**  
**SNP 3435 C>T**  
**SNP 63396 C>T** →

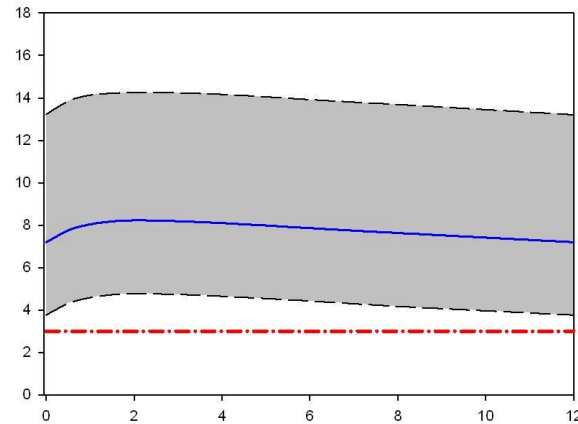
Green = wild type (36 individuals, 69 samples)  
 Grey = heterozygous (59 individuals, 117 samples)  
 Red = mutant (45 individuals, 98 samples)

# Steady-state NVP concentrations predicted at 200mg bid (90% prediction interval)

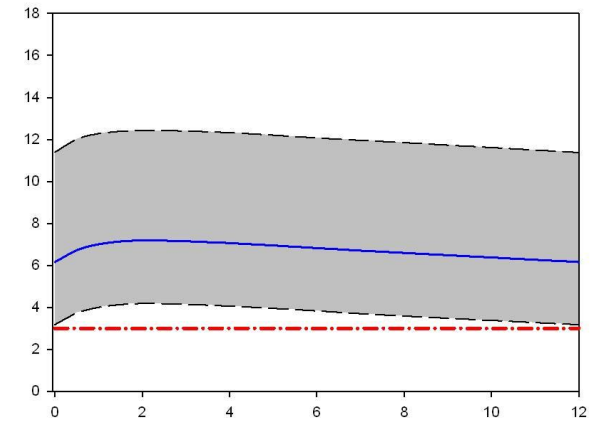
516 TT 50Kg



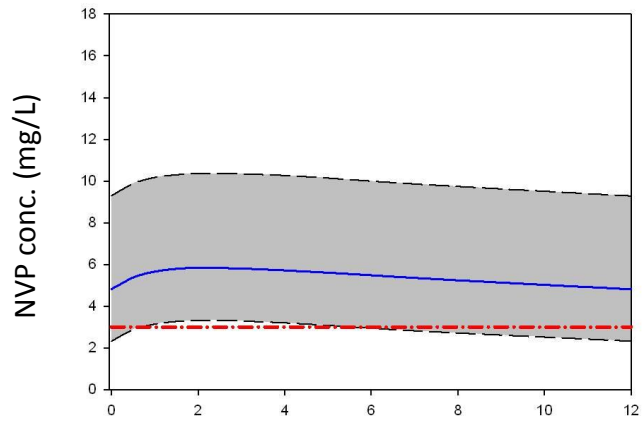
516 TT 70Kg



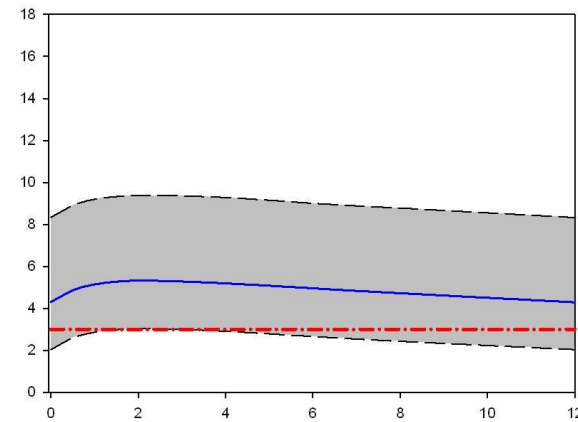
516 TT 90Kg



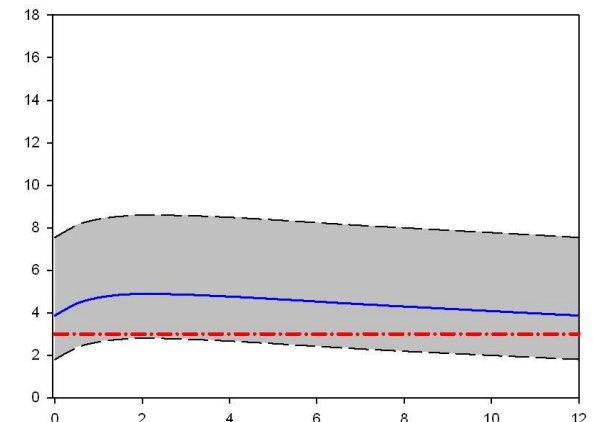
516 GG 50Kg



516 GG 70Kg



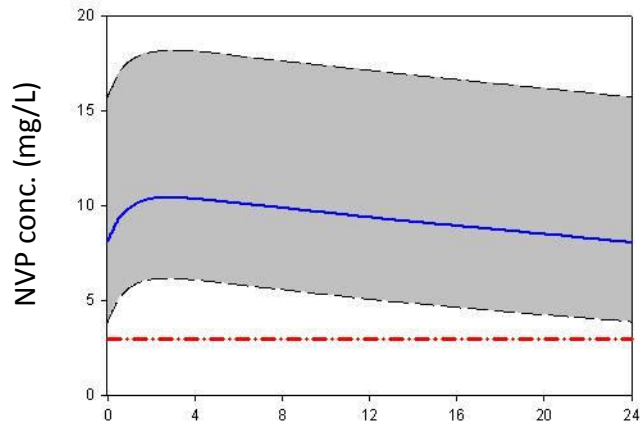
516 GG 90Kg



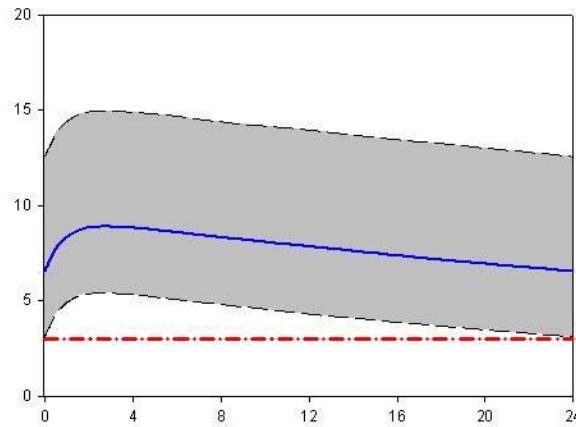


# Steady-state NVP concentrations predicted at 400mg od (90% prediction interval)

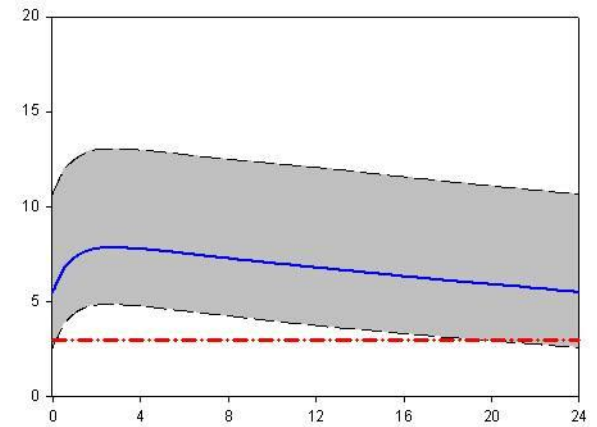
516 TT 50Kg



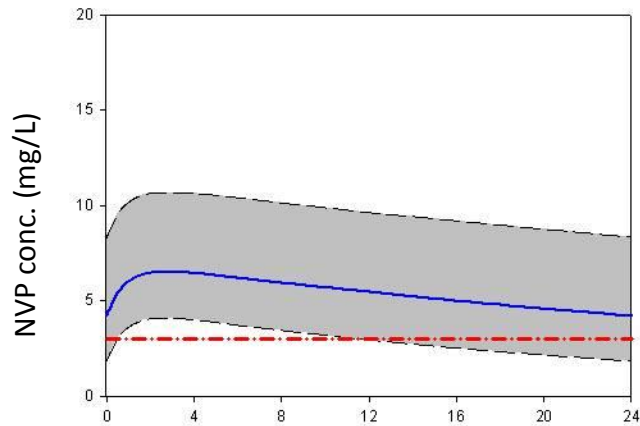
516 TT 70Kg



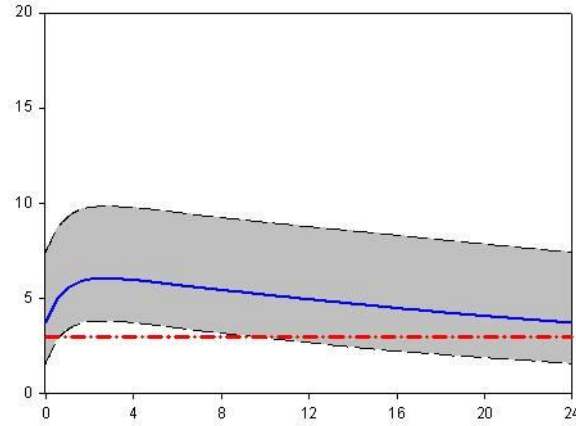
516 TT 90Kg



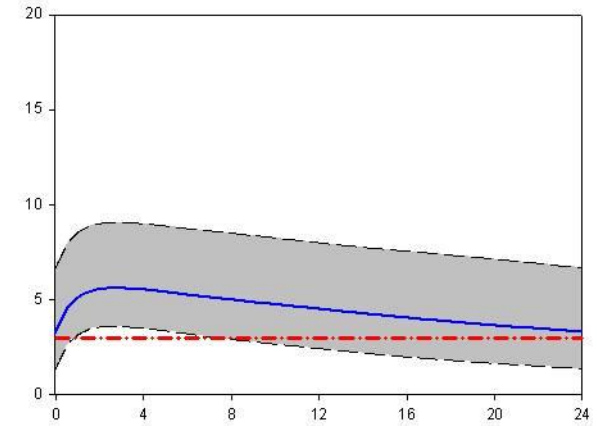
516 GG 50Kg



516 GG 70Kg



516 GG 90Kg



Time (h)

Time (h)

Time (h)



# ***Primum non nocere*** – ***first, do no harm***

- **ARVs have great potential for interactions**  
– *perhaps the greatest for any disease area*
- **PIs > NNRTIs >>> NRTIs** [1]
- **Exacerbated by**  
**polypharmacy** – treatment of multiple conditions  
**multiple prescribers** – 53% drugs dispensed by community pharmacists not recorded in HIV casenotes [2]  
**widespread use of ‘alternative medicines’** – patients on ARVs in Canada (n=628 [3]) and the UK (n=229 [4]) frequently took herbals and supplements (~61%); of these 20% could have compromised HIV management.

1 Miller CD, et al. *Pharmacotherapy*. 2007;27(10):1379-86

2 de Maat Ann *Pharmacother* 2002;36:410-15

3 Dhalla *et al, Compl Therapies in Clin Practice*. 2006 12:242-48.

4 Ladenheim et al. *HIV Med* 2008;9:653

**Potential to affect  
other drugs**

**Potential to be affected  
by other drugs**

**Protease inhibitor**

Cytochrome P450s  
transporters



**NNRTIs**

Cytochrome P450s  
(transporters?)



**Nucleoside analogues**

Intracellular kinases  
UGT (ZDV,ABC)  
transporters



**Integrase inhibitors  
(RAL)**

UGT



**CCR5 anatagonists  
(MVC)**

Cytochrome P450



# How common are HIV Drug Interactions ?

## Antiretroviral Medication Errors among Hospitalized Patients with HIV Infection

**Darius A. Rastegar, Amy M. Knight, and Jim S. Monolakis**

Johns Hopkins Bayview Medical Center, Baltimore, Maryland

**Baltimore** [Rastegar, et al, CID 2006;43:933-8]

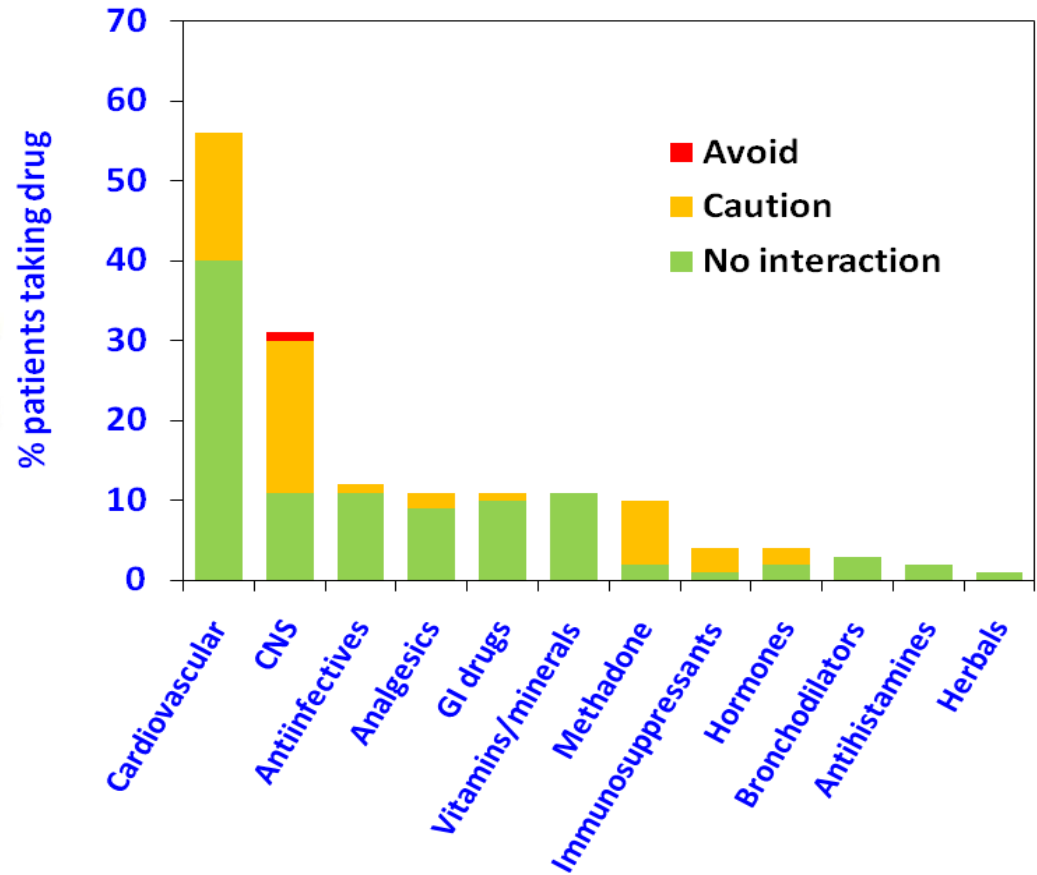
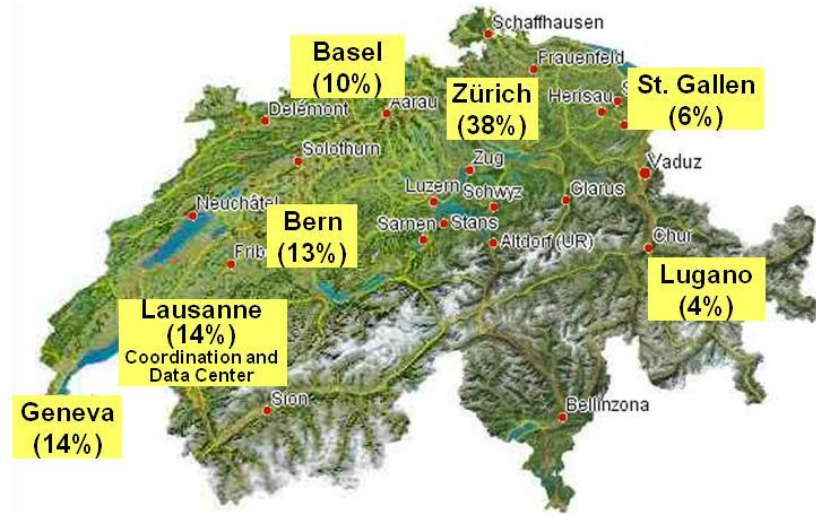
- **209 admissions of patients receiving ARVs over 1 year**
- **Contraindicated medications were prescribed in 5.2%**

# Risk for clinically significant interactions

Study	Year	Setting	N	CSDI	lower	Screening Tool	Adverse	Notes
<i>de Maat et al</i>	2004	Netherlands (hospital)	115	26%	N/A	Liverpool website	N/A	Pharmacy screening effective, further pharmacy input not
			105	23%				
<i>Shah et al</i>	2007	USA (Medicaid)	571	30%	8%	Liverpool website Micromedex	no VL impact	Audit, and re-audit.
			(689)	(15%)	(4%)			
<i>Miller et al</i>	2007	USA (hospital)	153	41%	N/A	DHHS SPC / PI Micromedex	N/A	Age >42y (OR 2.9) >3 conditions (OR 3.0) >3 ARVs (OR 2.4) PI use (OR 11.5)
<i>Kigen et al</i>	2009	Kenya (hospital)	996	34%*	12%	Liverpool website	N/A	
<i>Marzolini et al</i>	2009	Switzerland (hospital)	1497	40%	4%	Liverpool website	no CD4 or VL impact	Antiviral Ther 2010
<i>Evans-Jones et al</i>	2009	UK (hospital)	159	27%	15%	Liverpool website	N/A	CID 2010 Only 36% CSDIs correctly identified

\* excludes ARV-ARV interactions

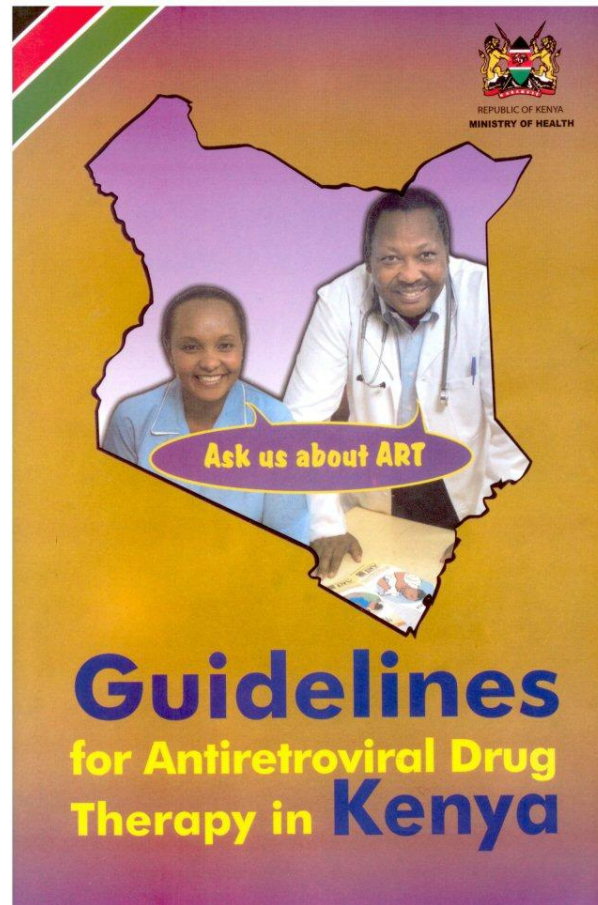
# Swiss Cohort



**68% of 1497 HIV patients were taking co-medications.**

- 31% - CNS drugs (anxiolytics – 13%, antidepressants – 12%, anti-psychotics – 3% anticonvulsants – 3%)
- 4% of interactions could have lowered ARV levels

# How common are HIV Drug Interactions ?



**Kenya** [Kigen et al. HIV8, 2008 Abstract O121]

- 996 consecutive patients receiving ARVs
- Moderate / Major drug interactions identified in 34%
- 12% (1:3 CSDIs) could have lowered ARV concentrations
- Rifampicin > Azoles > Steroids > Antimalarials > PPIs

# HIV Drug Interaction resources

- [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)
- [www.hivinsite.com](http://www.hivinsite.com)
- [www.tthivclinic.com/interact\\_tables.html](http://www.tthivclinic.com/interact_tables.html)
- [www.hopkins-hivguide.org](http://www.hopkins-hivguide.org)
- [www.clinicalcareoptions.com/HIV.aspx](http://www.clinicalcareoptions.com/HIV.aspx)
- [www.medscape.com/druginfo/druginterchecker](http://www.medscape.com/druginfo/druginterchecker)

**RATING QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS**

**GRADE: an emerging consensus on rating quality of evidence and strength of recommendations**

# Traffic light summary of Drug-Drug interactions

## Liverpool Website Definition:

## GRADE Equivalent

*Is it safe to administer both drugs ?*

- 
- |  |  |
|--|--|
| ◆ No clinically significant interaction, or interaction unlikely   | <b>YES</b>   |
| ■ Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration | <b>Probably YES</b> if <ul style="list-style-type: none"><li>▪ Benefit outweighs risk, or</li><li>▪ Interaction safely managed</li></ul> <b>Probably NO</b> if <ul style="list-style-type: none"><li>▪ Risk outweighs benefit</li><li>▪ Interaction not safely managed</li></ul> |
| ● Interaction likely, do not use or use with caution   | <b>NO</b>  |
| ▽ No clear data, actual or theoretical   | <b>DONT KNOW</b>   |



# Assessing Quality of Evidence

GRADE equivalent		Downgrade*	Upgrade*
<b>High</b>	Evidence obtained from at least one properly designed and executed randomized controlled trial.	<u>Study Quality</u> <ul style="list-style-type: none"> <li>serious limitations (-1)</li> <li>very serious limitations (-2)</li> <li>important inconsistency (-1/-2)</li> </ul>	<u>Strong association</u> <ul style="list-style-type: none"> <li>strong, no confounders, consistent &amp; direct evidence (+1)**</li> <li>very strong, no major threats to validity, direct evidence (+2)***</li> <li>evidence of dose response gradient (+1)</li> <li>all plausible confounders would have reduced effect (+1)</li> </ul>
<b>Moderate</b>		<u>Directness</u> <ul style="list-style-type: none"> <li>some uncertainty (-1)</li> <li>major uncertainty (-2)</li> </ul> <p>sparse or imprecise data (-1) probability of publication bias (-1)</p>	
<b>Low</b>	Evidence obtained from observational studies.		
<b>Very Low</b>			


 case reports  
 experience of experts  
 knowledge of mechanisms of drug disposition  
 Manufacturer's Product Information / SPC

# Liverpool HIV Drug Interactions website



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[Case Reports - IV docetaxel and ritonavir.](#)

[Review - Warfarin and antiretrovirals.](#)

[Review - Management of HIV/TB co-infection.](#)

[Drug Interactions - Ritonavir and quinine.](#)

[Drug Interactions - Tenofovir and boosted or unboosted fosamprenavir.](#)

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## SITE UPDATES

### WEBSITE MAINTENANCE

Added: Friday 30th April 2010

The website is having to undergo essential maintenance on its infrastructure which will be completed by August. ...

[>>more](#)

## DRUG INTERACTIONS CHARTS



Access our comprehensive, user-friendly, free, drug interactions charts

[CLICK HERE](#)

Providing clinically useful, reliable, up-to-date evidence-based information

## NEWS ALERT

The recently initiated Editorial Board provides oversight, strategic vision and direction for the site. It also advises on developmental opportunities and the interface with end users.

Editorial Board members are:

David Back (Liverpool – Chair)

Saye Khoo (Liverpool – Website Team)



## EDITORIAL SPONSORSHIP

We are pleased to announce Editorial Sponsorship from BHIVA, EACS and the International Congress on Drug Therapy in HIV (Glasgow).

British HIV Association  
**BHIVA**

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14th International Congress on  
Drug Therapy in HIV Infection  
7-11 NOVEMBER  
**2010**  
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# Liverpool HIV Drug Interactions website



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## Drug Interaction Charts

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 [View all Protease Inhibitors](#) | 
 [View all NNRTIs](#) | 
 [View all NRTIs](#) | 
 [View all Entry/Integrase Inhibitors](#) | 
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<b>Step 1</b>	Choose one or more HIV drugs	<a href="#">Next &gt;&gt;</a>
Step 2	Choose one or more combination classes	
Step 3	Choose one or more combination drugs	
Step 4	View results	

Protease Inhibitors	NNRTIs	NRTIs	Entry & Integrase Inhibitors
<input checked="" type="checkbox"/> Atazanavir	<input type="checkbox"/> Delavirdine	<input checked="" type="checkbox"/> Abacavir	<input checked="" type="checkbox"/> Maraviroc
<input checked="" type="checkbox"/> Darunavir	<input checked="" type="checkbox"/> Efavirenz	<input checked="" type="checkbox"/> Didanosine (ddI)	<input checked="" type="checkbox"/> Raltegravir
<input type="checkbox"/> Fosamprenavir	<input checked="" type="checkbox"/> Etravirine	<input checked="" type="checkbox"/> Emtricitabine (FTC)	
<input type="checkbox"/> Indinavir	<input checked="" type="checkbox"/> Nevirapine	<input checked="" type="checkbox"/> Lamivudine (3TC)	
<input checked="" type="checkbox"/> Lopinavir		<input type="checkbox"/> Stavudine (d4T)	
<input type="checkbox"/> Nelfinavir		<input checked="" type="checkbox"/> Tenofovir	
<input checked="" type="checkbox"/> Ritonavir		<input checked="" type="checkbox"/> Zidovudine (AZT/ZDV)	
<input type="checkbox"/> Saquinavir			
<input type="checkbox"/> Tipranavir			

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Search by alphabetical list of drugs

Search by drug class

Next >>

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Step 1	Searching by: <b>Abacavir, Atazanavir, Darunavir, Didanosine (ddl), Efavirenz, Emtricitabine (FTC), Etravirine, Lamivudine (3TC), Lopinavir, Maraviroc, Nevirapine, Raltegravir, Ritonavir, Tenofovir, Zidovudine (AZT/ZDV)</b>	<a href="#">Amend selection</a>
Step 2	Choose one or more combination classes	<a href="#">Next &gt;&gt;</a>
Step 3	Choose one or more combination drugs	
Step 4	View results	

[Click here to select from an alphabetic list of drugs instead of by class.](#)

Classes		
<input type="checkbox"/> Analgesics	<input type="checkbox"/> Antiarrhythmics	<input type="checkbox"/> Antibacterials
<input type="checkbox"/> Anticonvulsants	<input type="checkbox"/> Antidepressants	<input type="checkbox"/> Anti-diabetics
<input type="checkbox"/> Antifungals	<input type="checkbox"/> Antihistamines	<input type="checkbox"/> Antimigraine Agents
<input type="checkbox"/> Antineoplastics	<input type="checkbox"/> Anti-platelet and Anti-coagulant	<input type="checkbox"/> Antiprotozoals
<input checked="" type="checkbox"/> Antipsychotics/Neuroleptics	<input checked="" type="checkbox"/> Antiretrovirals (Entry Inhibitors)	<input checked="" type="checkbox"/> Antiretrovirals (Integrase Inhibitors)
<input type="checkbox"/> Antiretrovirals (Maturation Inhibitors)	<input checked="" type="checkbox"/> Antiretrovirals (NNRTIs)	<input checked="" type="checkbox"/> Antiretrovirals (Nucleoside/tide Analogues)
<input type="checkbox"/> Antiretrovirals (Nucleotide Analogues)	<input checked="" type="checkbox"/> Antiretrovirals (Protease Inhibitors)	<input type="checkbox"/> Antivirals
<input type="checkbox"/> Anxiolytics/Hypnotics/ Sedatives	<input type="checkbox"/> Beta Blockers	<input type="checkbox"/> Bronchodilator
<input type="checkbox"/> Calcium Channel Antagonists	<input type="checkbox"/> Erectile Dysfunctional Agents	<input type="checkbox"/> Gastrointestinal Agents
<input type="checkbox"/> Gastrointestinal Agents	<input type="checkbox"/> General Anaesthetics	<input type="checkbox"/> Heart Failure Agents

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Drug Interaction Charts

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Step 1	Searching by: <b>Abacavir, Atazanavir, Darunavir, Didanosine (ddl), Efavirenz, Emtricitabine (FTC), Etravirine, Lamivudine (3TC), Lopinavir, Maraviroc, Nevirapine, Raltegravir, Ritonavir, Tenofovir, Zidovudine (AZT/ZDV)</b>	<a href="#">Amend selection</a>
Step 2	Searching by: <b>Antipsychotics/Neuroleptics</b>	<a href="#">Amend selection</a>
Step 3	Choose one or more combination drugs	<a href="#">Next &gt;&gt;</a>
Step 4	View results	

Antipsychotics/Neuroleptics	Antiretrovirals (Entry Inhibitors)	Antiretrovirals (Integrase Inhibitors)
<input type="checkbox"/> Chlorpromazine	<input type="checkbox"/> Enfuvirtide (T20)	<input type="checkbox"/> Elvitegravir
<input checked="" type="checkbox"/> Clozapine	<input checked="" type="checkbox"/> Maraviroc	<input checked="" type="checkbox"/> Raltegravir
<input checked="" type="checkbox"/> Haloperidol		
<input checked="" type="checkbox"/> Olanzapine		
<input type="checkbox"/> Perphenazine		
<input type="checkbox"/> Pimozide		
<input checked="" type="checkbox"/> Quetiapine		
<input checked="" type="checkbox"/> Risperidone		
<input checked="" type="checkbox"/> Sulpiride		
<input type="checkbox"/> Thioridazine		









Antiretrovirals (NNRTIs)	Antiretrovirals (Nucleoside/tide Analogues)	Antiretrovirals (Protease Inhibitors)
<input type="checkbox"/> Delavirdine	<input checked="" type="checkbox"/> Abacavir	<input checked="" type="checkbox"/> Atazanavir


# Liverpool HIV Drug Interactions website













































## Key to symbols:

Clicking on a solid symbol within a table will give further information on the interaction.

Empty symbols indicate that the combination has not been studied and an interaction has been predicted based on the metabolic profiles of the drugs.

 / 	These drugs should not be coadministered
 / 	Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration
 / 	No clinically significant interaction expected
 / 	There are no clear data, actual or theoretical, to indicate whether an interaction will occur
n/a	Data not available

 NEW - [click here to generate a personalised report in PDF format](#)

Antipsychotics/Neuroleptics	Atazanavir	Darunavir	Lopinavir	Ritonavir	Efavirenz	Etravirine	Nevirapine
Clozapine							
Haloperidol							
Olanzapine							
Pimozide							
Quetiapine							
Risperidone							
Sulpiride							
Antiretrovirals	Atazanavir	Darunavir	Lopinavir	Ritonavir	Efavirenz	Etravirine	Nevirapine

# Interaction Report from [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)

Report ID: PYSCH

Date Produced: 05 May 2010

Antiretroviral treatment	Co-medications
Darunavir	Clozapine
Etravirine	Haloperidol
Raltegravir	Olanzapine
Ritonavir	Pimozide
	Quetiapine
	Risperidone
	Sulpiride

This report lists the potentially clinically significant interactions (i.e. "red" and "amber" classifications) for the drugs in the table above. Interactions with a "green" classification (i.e. no clinically significant interaction expected) have been checked but are not shown on this report.

For full details of all interactions, see [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org).

## Description of the interactions

### *Drugs that should not be co-administered (RED)*

- **Darunavir and Pimozide:** Coadministration is contraindicated as it may increase pimozide concentrations which may result in serious and/or life threatening reactions such as cardiac arrhythmias.
- **Ritonavir and Pimozide:** Coadministration is contraindicated as it is likely to increase pimozide concentrations and the potential for serious and/or life threatening reactions such as cardiac arrhythmias.

### *Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration (AMBER)*

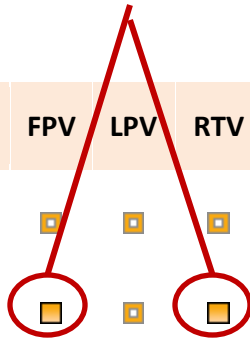
- **Darunavir and Clozapine:** This interaction has not been studied. An interaction has been predicted based on the metabolic profiles of the drugs.
- **Darunavir and Haloperidol:** This interaction has not been studied. An interaction has been predicted based on the metabolic profiles of the drugs.
- **Darunavir and Olanzapine:** This interaction has not been studied. An interaction has been predicted based on the metabolic profiles of the drugs.
- **Darunavir and Quetiapine:** This interaction has not been studied. An interaction has been predicted based on the metabolic profiles of the drugs.



# Drug Interactions – Anti-psychotics

EMEA: hematological toxicity

	ATV	DRV	FPV	LPV	RTV	SQV	TPV	EFV	ETR	NVP	ABC	ddl	FTC	3TC	d4T	TDF	ZDV	MVC	RAL
Chlorpromazine	□	□	□	□	□	□	□	◇	◇	◇	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Clozapine	□	□	◻	□	◻	□	□	◇	◇	◇	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Haloperidol	□	□	□	□	◻	□	□	□	□	□	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Olanzapine	□	□	□	□	◻	□	□	□	□	□	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Pimozide	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	□	□	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Quetiapine	◻	□	□	□	□	□	□	□	□	□	◇	◇	◇	◇	◇	◇	◇	n/a	n/a
Risperidone	◇	◻	◇	◇	◻	◇	◇	◇	◇	◇	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Sulpiride	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	n/a	n/a



# Drug Interactions – Anti-psychotics

	ATV	DRV	FPV	LPV	RTV	SQV	TPV	EFV	ETR	NVP	ABC	ddI	FTC	3TC	d4T	TDF	ZDV	MVC	RAL
Chlorpromazine	■	■	■	■	■	■	■	◆	◆	◆	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Clozapine	■	■	■	■	■	■	■	◆	◆	◆	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Haloperidol	■	■	■	■	■	■	■	■	■	■	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Olanzapine	■	■	■	■	■	■	■	■	■	■	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Pimozide	●	●	●	●	●	●	●	●	■	■	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Quetiapine	■	■	■	■	■	■	■	■	■	■	◆	◆	◆	◆	◆	◆	◆	n/a	n/a
Risperidone	◆	■	◆	◆	■	◆	◆	◆	◆	◆	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Sulpiride	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	n/a	n/a



Olanzapine AUC ↓ 50%

↑ haloperidol.

2 case reports

↑ risperidone

# Drug Interactions – Anti-psychotics

	ATV	DRV	FPV	LPV	RTV	SQV	TPV	EFV	ETR	NVP	ABC	ddl	FTC	3TC	d4T	TDF	ZDV	MVC	RAL
Chlorpromazine	□	□	□	□	□	□	□	◇	◇	◇	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Clozapine	□	□	■	□	■	□	□	◇	◇	◇	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Haloperidol	□	□	□	□	■	□	□	□	□	□	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Olanzapine	□	□	□	□	■	□	□	□	□	□	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Pimozide	●	●	●	●	●	●	●	●	□	□	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Quetiapine	■	□	□	□	□	□	□	□	□	□	◇	◇	◇	◇	◇	◇	◇	n/a	n/a
Risperidone	◇	■	◇	◇	■	◇	◇	◇	◇	◇	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Sulpiride	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	n/a	n/a

↑ risk arrhythmia





# What can be done?

- **In HIV therapy, DDIs are largely unavoidable...**  
..... but the majority are manageable
- **Physician awareness and recognition is poor**  
*unrecognised drug interactions are amongst the commonest causes of serious medication error*
- **Unexpected interactions still catch us out**  
*e.g. SQVr and PPIs, TDF and ddl, LPVr and rosuvastatin*  
*No substitute for doing interaction studies*
- **the problem will not go away with new drugs**  
longer survival – *polypharmacy*  
decentralised care – *to general practitioners (developed countries), or to districts (developing countries)*
- **still ‘black holes’ in our knowledge**  
contraceptives – *oral > injectables > patches*  
herbals, etc

# Interventions which work

- **Prescriber education**

- **Pharmacist input** [1-2]

- **Drug interactions databases**

[www.hiv-druginteractions.org](http://www.hiv-druginteractions.org), [www.clinicalcareoptions.com](http://www.clinicalcareoptions.com), etc

Concordance is variable [3]

Tendency to over-call – ‘Alert fatigue’ !

- **‘Active vs passive’ identification of interactions**

Decision support software for dispensaries / electronic prescribers

Interaction datasheets for patients or prescribers

1 Hanlon Am J Med 1996;100:428.

2 de Maat J Clin Pharm Ther 2004;29:121

3 Pham. CPT 2008;83:396

# Interventions which work

- **Stick to a few known drugs**
- **Keep it simple - Once- or twice- daily dosing**  
given once or twice a day
- **Therapeutic Drug Monitoring**  
to manage interactions, or else to discount them

1 Hanlon Am J Med 1996;100:428.

2 de Maat J Clin Pharm Ther 2004;29:121

3 Pham. CPT 2008;83:396



# Resource-limited settings

- **Training to improve quality of prescribing**
- **Drug Information Centres – e.g. ATIC**
- **Programmatic approach – e.g. national protocols for treatment of TB-HIV co-infection, use of fluconazole prophylaxis**
- **Instituting systems for pharmacovigilance**
- **Incorporate monitoring for serious DDIs within ARV Programmes**

# Acknowledgements

David Back  
Sara Gibbons  
Andrew Owen  
Laura Dickinson  
Laura Else  
Neill Liptrott  
Helen Reynolds  
Wai San Kwan  
Gabriel Kigen  
Kay Seden

Marta Boffito  
Wolfgang Stoehr  
David Dunn  
John Tjia  
Maxine Dunham  
Marco Siccardi  
Gianni diPerri  
Stefano Bonora  
Ceppie Merry

... and many others....

# Declaration of Interests

[www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)

Receives sponsorship from GSK, Abbott, Merck, BMS, Tibotec, Roche, Gilead, Pfizer. Editorial content remains independent.

*Therapeutic Drug Monitoring*

TDM in the UK is sponsored by Roche, Abbott, Merck, GSK, Roche. The University has spun TDM services into Delphic (SK serves as non-exec director)