Overview of pharmacokinetic drug interactions

Gary Maartens

Importance

- Drug interactions increase exponentially with the number of drugs used:
  - 6% with 2 drugs, 50% with 5, 100% with 10
- Some interactions are beneficial
- Other interactions will reduce a drug's action or increase it's toxicity, both of which can be life-threatening
- Importance of drug-herb interactions increasingly recognised (minimal data on SA traditional meds)

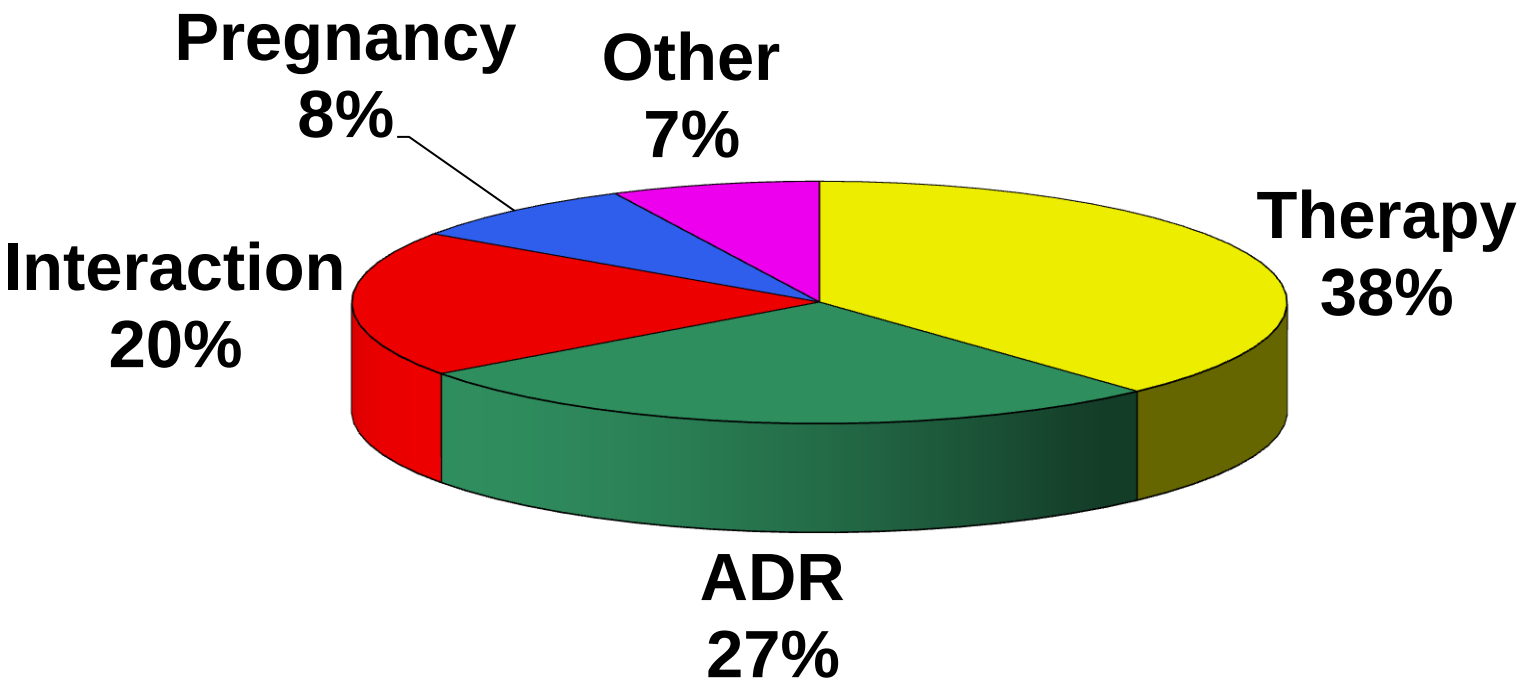
Int J Clin Pharm Ther 1994;32:509

Two mechanisms of interactions

- Pharmacodynamic (what the drug does to the body) interactions are shared effects (either toxic or therapeutic)

- Pharmacokinetic (what the body does to the drug) interactions alter the concentrations & distribution of drugs

Calls to UCT MIC HIV Hotline by Topic



Chisholm, SA AIDS Conf Durban 2005

Patients taking NNRTI & other chronic Rx

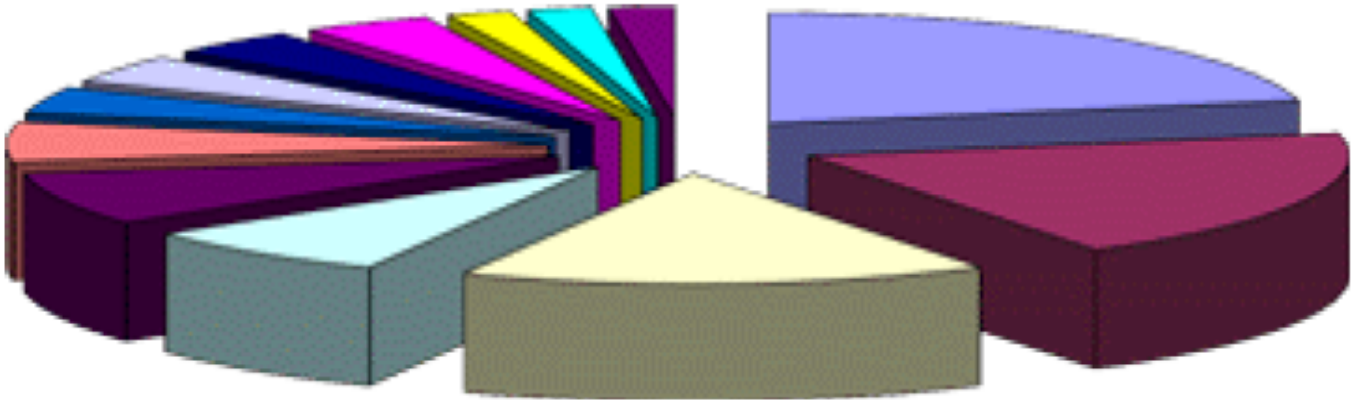
(24% had significant interactions)

- Anticonvulsants 31.8%
- Calcium Channel Blockers 31.8%
- HMGCoA Reductase Inhibitors 7.6%
- Warfarin 6.6%
- Peptic Ulcer Drugs 6.2%
- Antihistamines 4.7%
- Propulsives 3.8%
- Amiodarone 1.4%
- Ergotamine 1.4%
- Azole antimycotics 1.4%
- Corticosteroids 0.9%
- Glipizide 0.9%
- Clarithromycin 0.5%
- Antidepressants 0.5%
- Vincristine 0.5%

Regensberg L. 14th Int AIDS Conf, Barcelona 2002

Patients taking PIs & other chronic Rx

(34% had significant interactions)



- Antidepressants 21.6%
- Calcium Channel Blockers 19.6%
- Anticonvulsants 15.7%
- Antihistamines 7.8%
- Theophylline 7.8%
- Neuroleptics 5.9%
- Azole antimycotics 3.9%
- Benzodiazepines 3.9%
- Beta blockers 3.9%
- HMGCoA Reductase Inhibitors 3.9%
- Warfarin 2.0%
- Clarithromycin 2.0%
- Omeprazole 2.0%

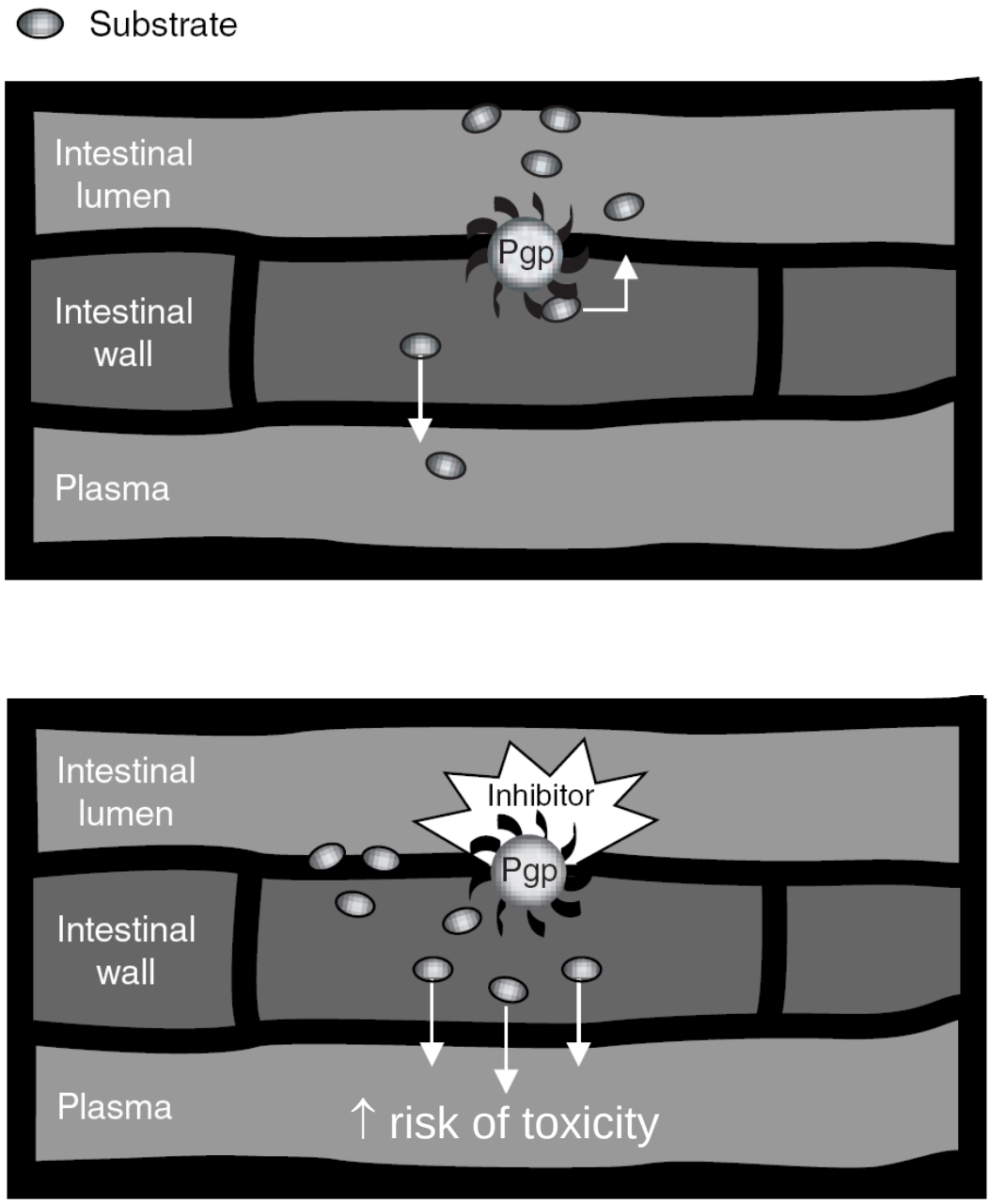
Regensberg L. 14th Int AIDS Conf, Barcelona 2002

Absorption interactions

- Some drugs require low gastric pH, so acid-lowering drugs reduce absorption (eg atazanavir, itraconazole)
- Divalent cations in antacids chelate some drugs (eg dolutegravir, ciprofloxacin, tetracyclines)

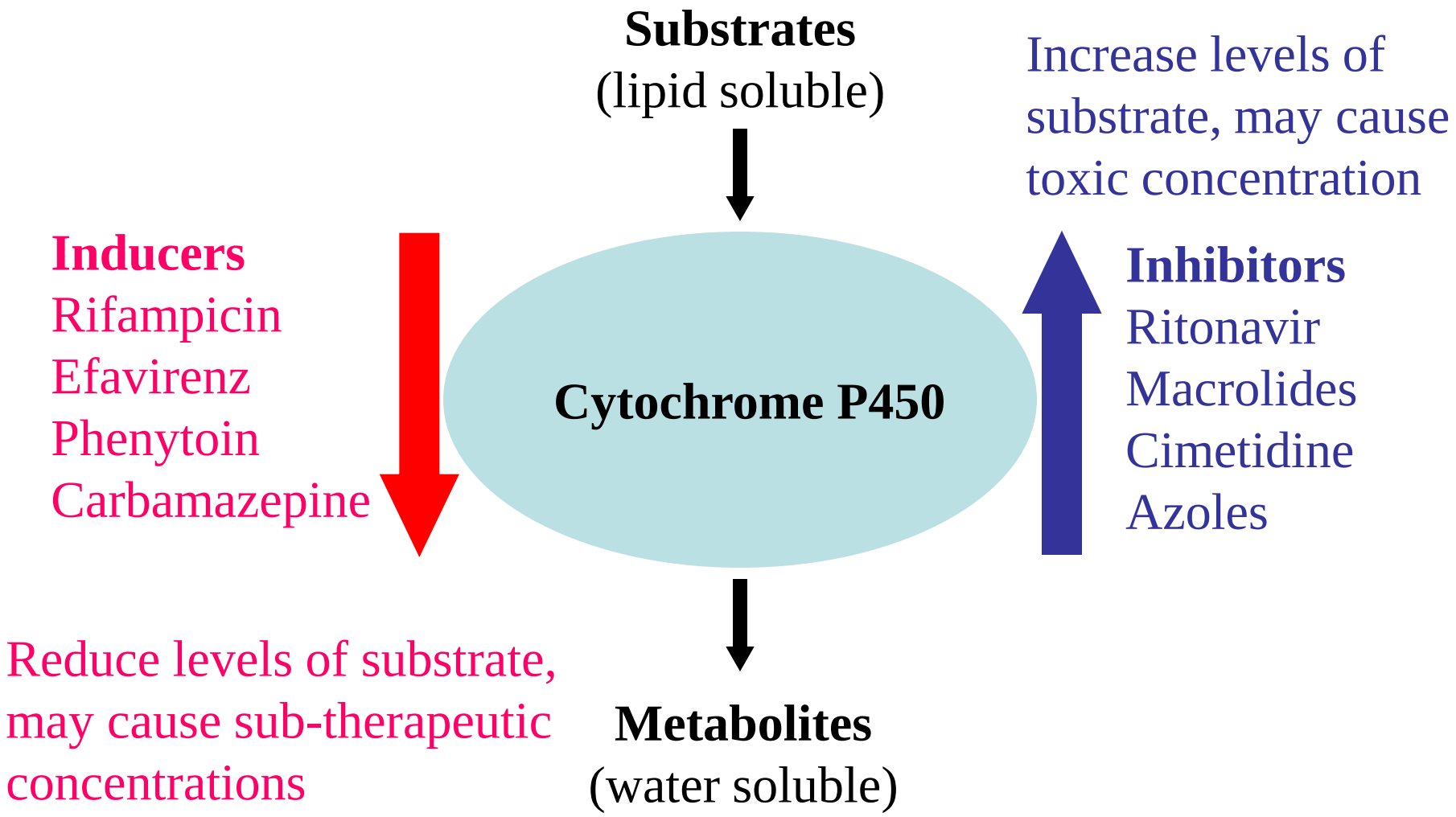
Drug transporters (eg P-glycoprotein)

- P-gp expressed mostly in GIT & blood-tissue barriers (CNS & testis)
- Co-localises with the CYP450 isoenzyme CYP3A4 – most drugs that are substrates of P-gp are also CYP3A4 substrates
- Transporters can be inhibited (eg ritonavir, cobicistat) or induced (eg rifampicin, phenytoin)

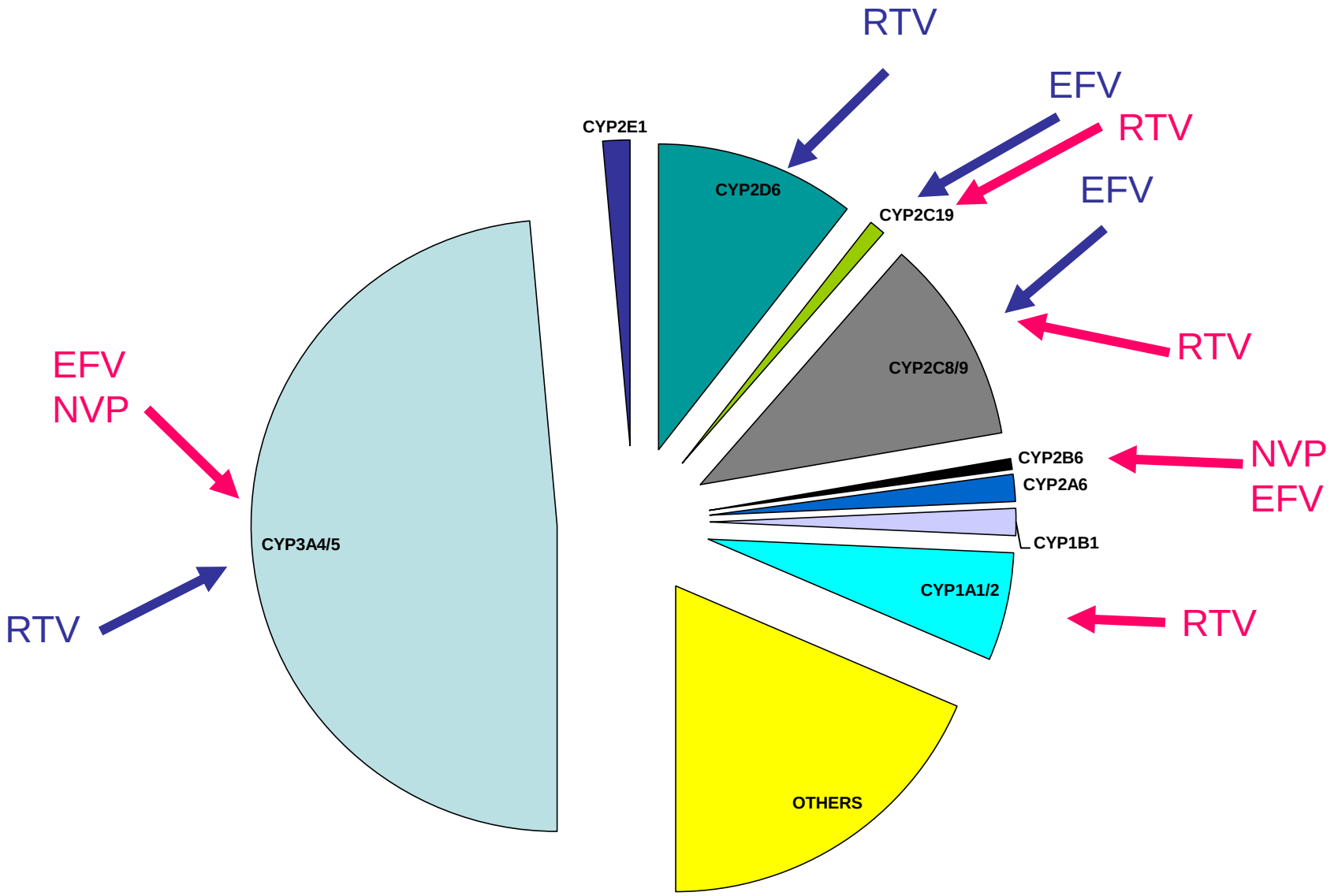


Du Baske 2005

Metabolism:
CYP450 drug interactions



CYP450 enzymes induced or inhibited by ARVs



Inhibition of CYP450

- Inhibition may be reversible or irreversible
- Irreversible inhibitors (e.g. ritonavir):
  - Reactive intermediate metabolite binds irreversibly to enzyme causing inactivation
  - More potent inhibition than reversible
  - Duration of inhibition is longer (5-10 days compared with about 48 hours after stopping) as new enzyme needs to be synthesised
- Severe toxicity may occur if a P450 substrate is co-administered

Effect of boosted PIs on statins

Statin	% change to AUC	Recommendation
Atorvastatin	+390 to +590	Low dose
Pravastatin*	-50 to +180	Same dose
Rosuvastatin*	+148 to +313	↓effect – avoid
Simvastatin	+3159	Avoid

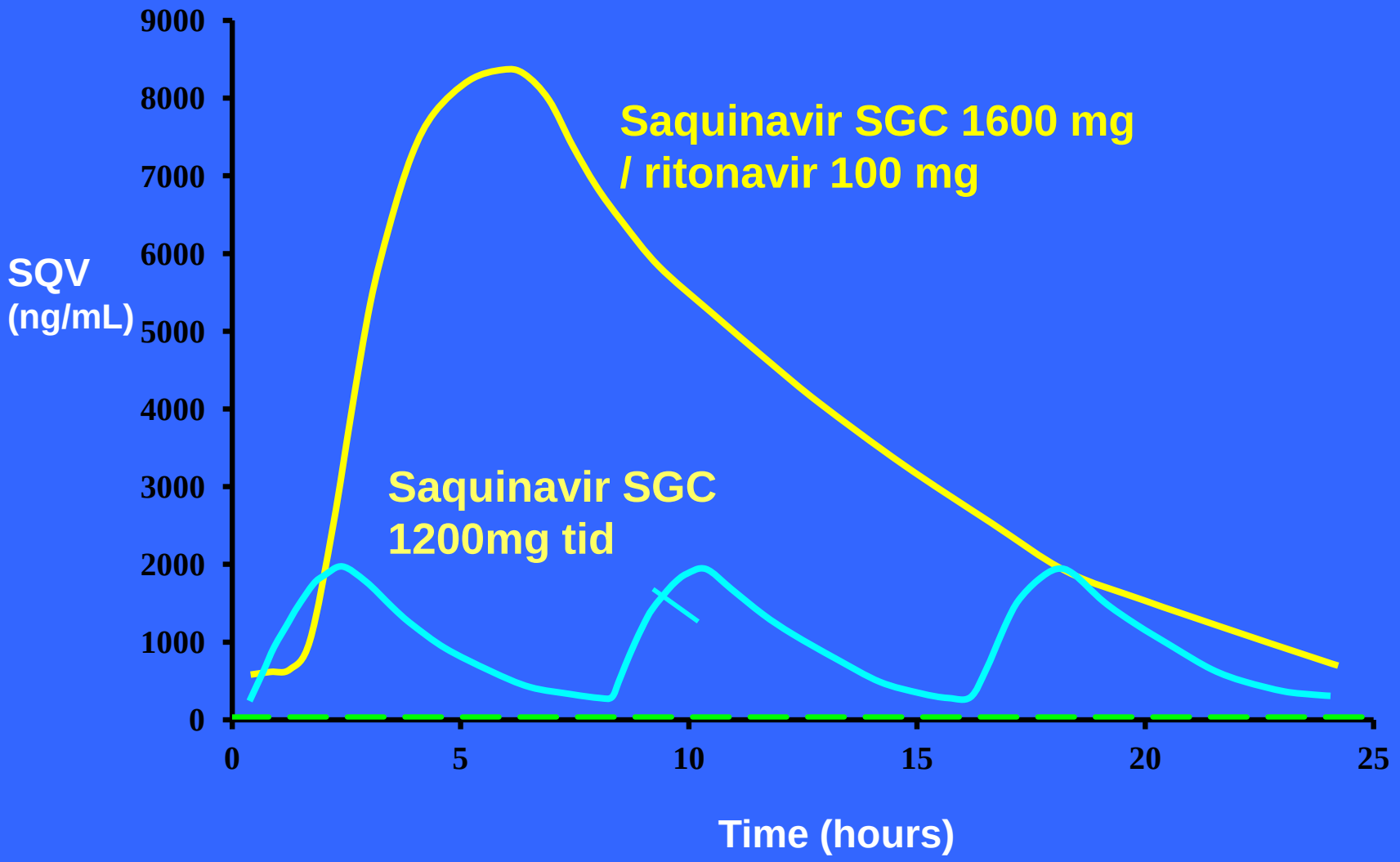
*Not substrates of CYP3A4

http://www.hiv-druginteractions.org/
Clin Pharmacokinet. 2013;52:815

Exploiting PK interactions: PI boosting

- PIs are substrates of CYP3A4 & P-gp
- Ritonavir & cobicistat potently inhibit CYP3A4 & P-glycoprotein
- Co-administered of ritonavir/cobicistat with PIs:
  - PI absorption increased & elimination reduced
  - PI metabolism decreased
- Resulting higher concentrations of PI
  - Dosing less frequent
  - Low-level resistance can be overcome
  - More toxicity

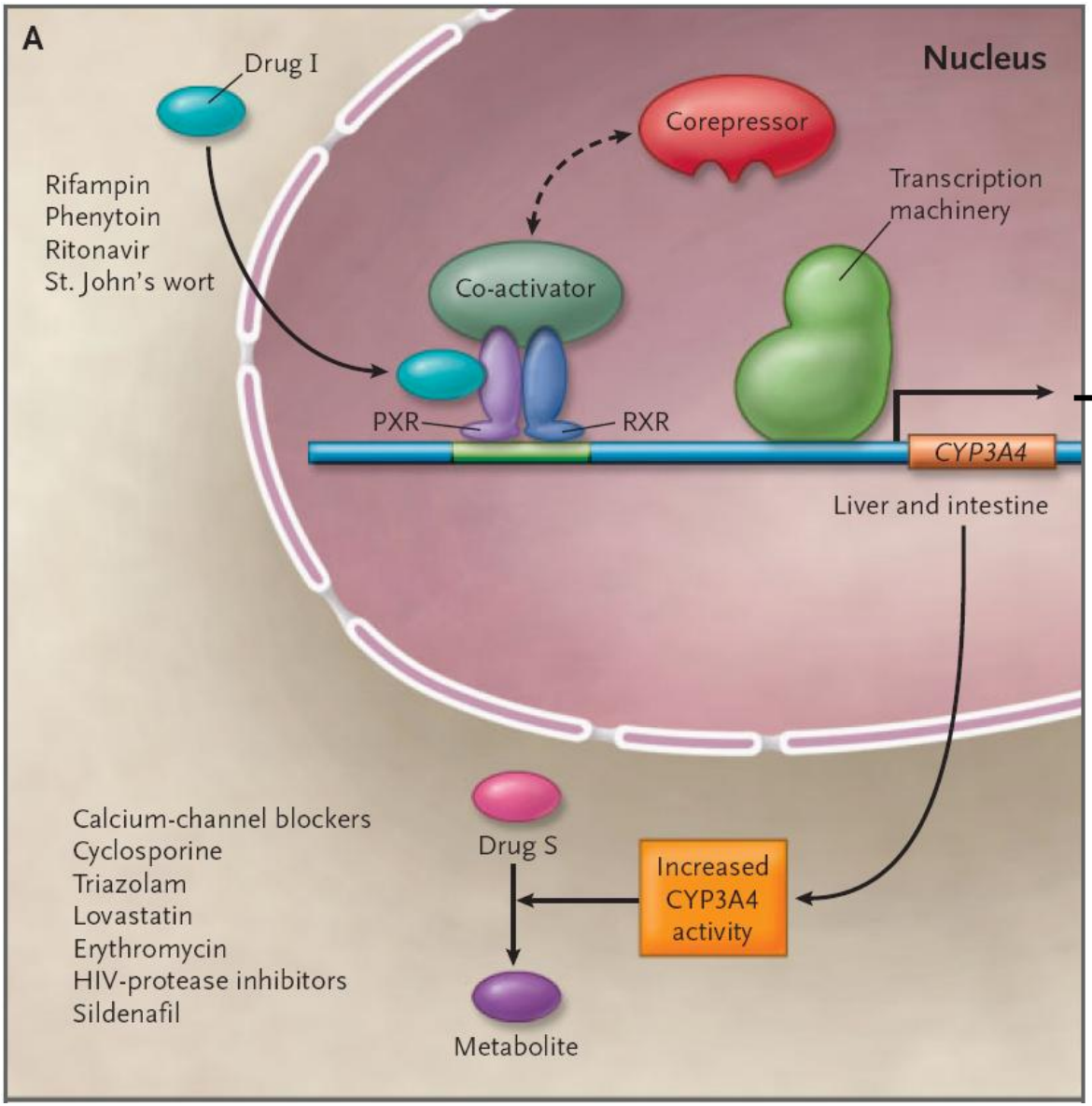
Effect of ritonavir on saquinavir



Induction of metabolism

- Many drugs & exogenous substances (eg smoking, grilled food, garlic) can induce
- Several (2 main) pathways to turn on regulatory gene that affects MANY downstream genes that have the net effect of reducing exposure to a xenobiotic/drug

PXR-RXR mechanism of enzyme induction

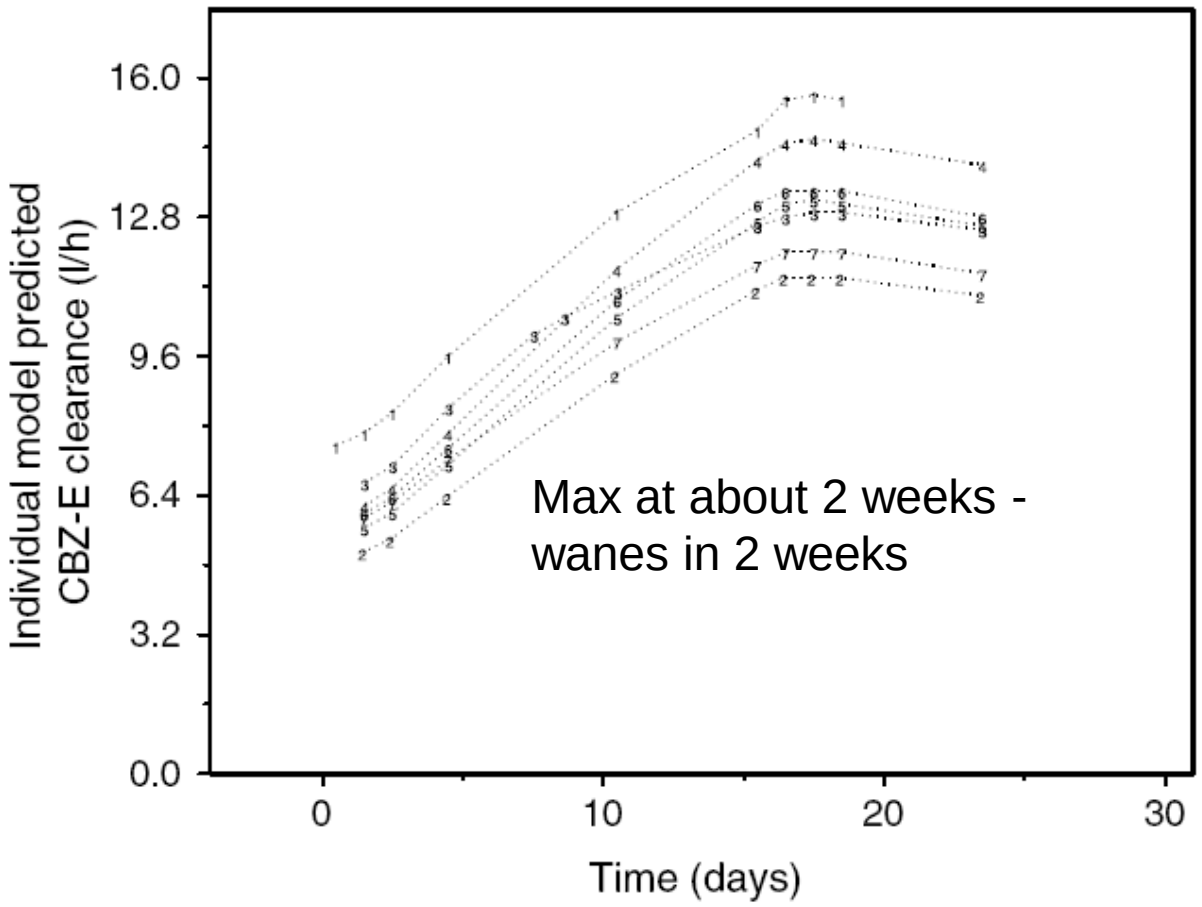


OTHERS ↑

Phase I
CYP2B6
CYP2C8/9
Phase II
UGT
GST
Transporters
P-glycoprotein

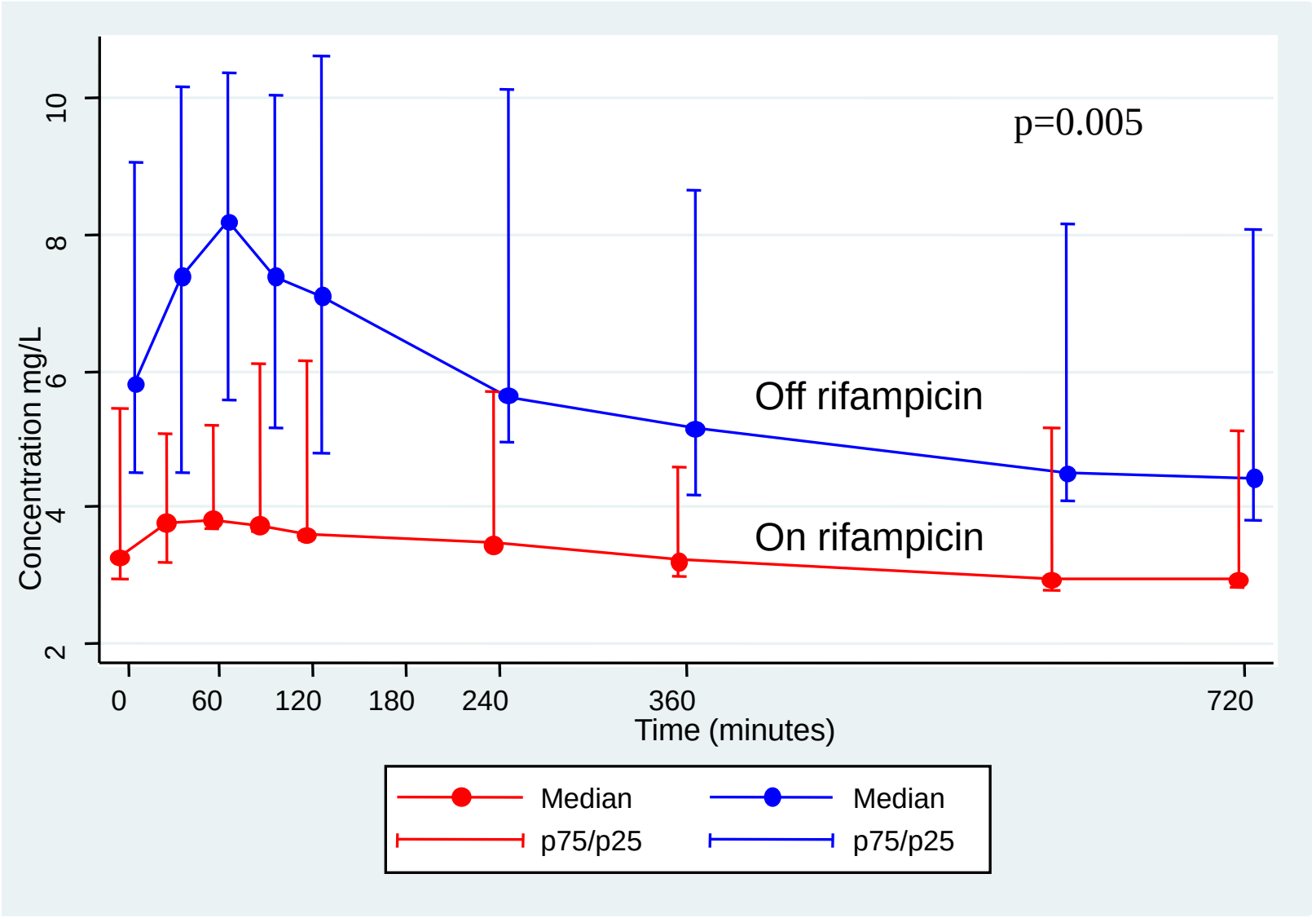
NEJM 2005;352:2211
Chen 2006

Time course of induction



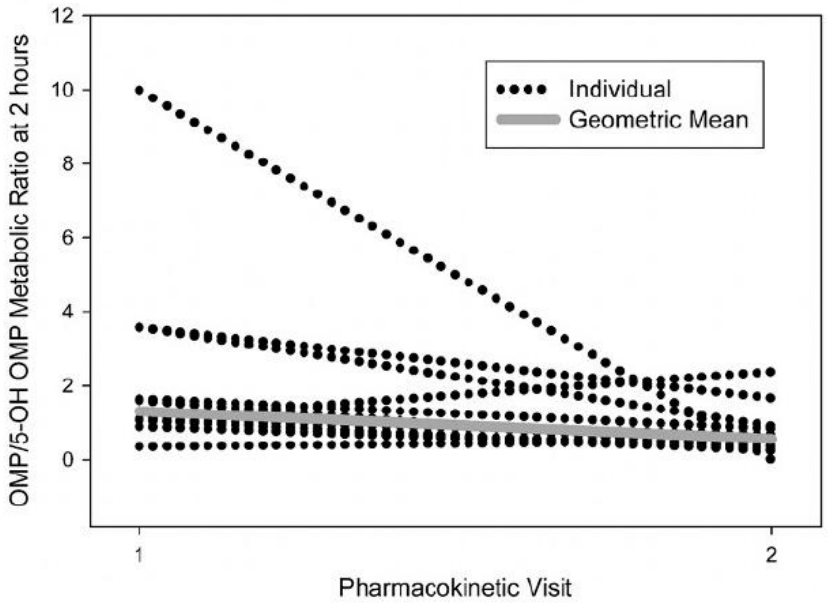
Magnusson Clin Pharm Ther doi:10.1038/sj.clpt.6100431

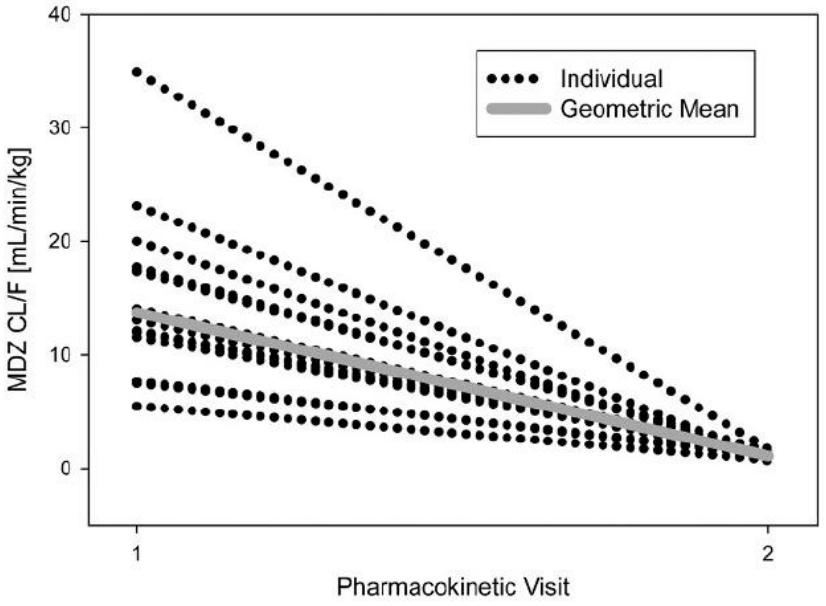
Nevirapine concentrations in adult patients before and after stopping rifampicin-based TB therapy



Cohen, JAC 2008

Individual variability of induction & inhibition





Omeprazole (CYP2C19 induced)

Midazolam clearance (CYP3A4 inhibited)

Lopinavir/r interactions

Yeh R JAIDS 2006

Interaction case

- 32 year old man with background of depression. On fluoxetine 40mg daily long term, with good response. Failed AZT 3TC nevirapine.
- ART switched to AZT ddI indinavir ritonavir
- Within a week, developed severe anxiety, headache and sweating.
  - Serotonin syndrome due to inhibition of CYP3A4 metabolism of fluoxetine by Pis
  - Settled on withdrawal
  - Fluoxetine later reintroduced at 10 mg

Therapeutic drug monitoring

Ideal to measure concentrations of ARVs and the potentially interacting drug, where available

Need to use clinical judgement if no drug assays available

Drug interaction resources

- Package inserts
- SAMF
- UCT Medicines Information Centre
- Software in pharmacies
- Internet & apps

http://www.mic.uct.ac.za/

HIV Drug Interactions

UNIVERSITY OF LIVERPOOL

Interaction Checker →

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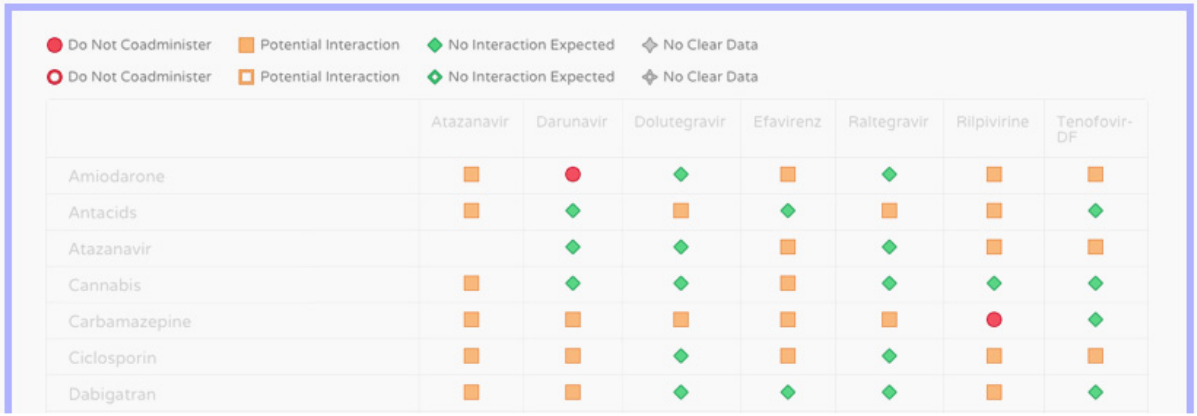

http://www.hiv-druginteractions.org/

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Conclusions

- When using strong inhibitors or inducers ALWAYS check for drug interactions with all drugs you prescribe
- Lots of information resources
- Review all meds when switching to 2nd line