

Antiretroviral & TB drug interactions

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Overview of interactions

- Pharmacodynamic interactions are shared effects (either toxic or therapeutic)
- Pharmacokinetic interactions operate at different levels:
 - Absorption
 - **Distribution**
 - **Metabolism**
 - Excretion

Toxicity of HAART & TB therapy

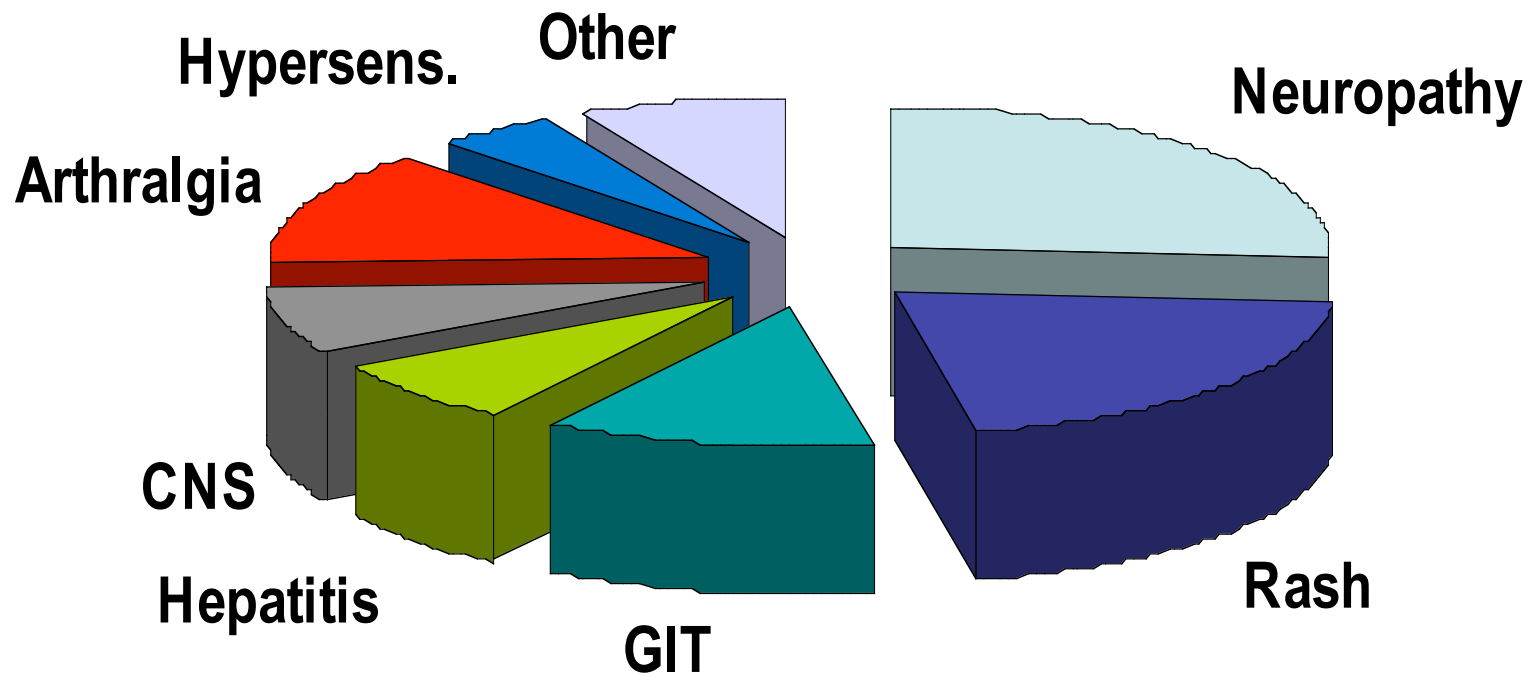
Common shared toxicity:

Toxicity	Anti-tuberculous therapy	Antiretroviral therapy
Peripheral neuropathy	Isoniazid	Stavudine Didanosine
Rash	Rifampicin Isoniazid Pyrazinamide	NNRTI
Nausea	Pyrazinamide	Didanosine Zidovudine Protease inhibitors
Hepatitis	Rifampicin Isoniazid Pyrazinamide	NNRTI Nucleoside RTI Protease inhibitors

Adverse drug reactions

- Retrospective study of 183 adult HIV+ patients on TB therapy (85 started HAART)
- 53% experienced ADR
- 34% had to stop one or more drugs
- Increased ADR risk with HAART (OR 1.88; 95%CI 1.03-3.42)

ADRs contd (Dean 2002)



P-glycoprotein interactions

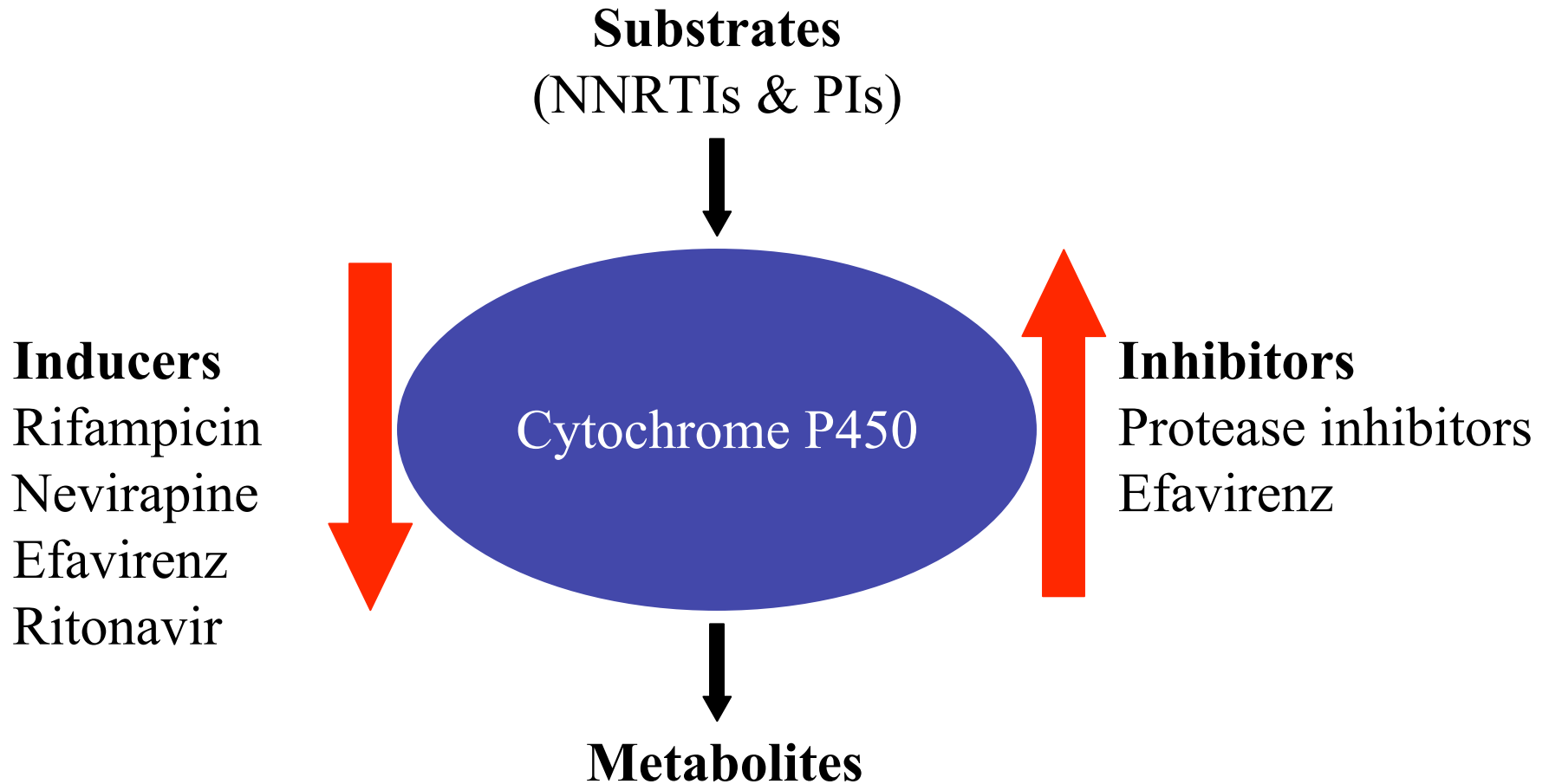
PIs are substrates of P-gp

Ritonavir potent inhibitor

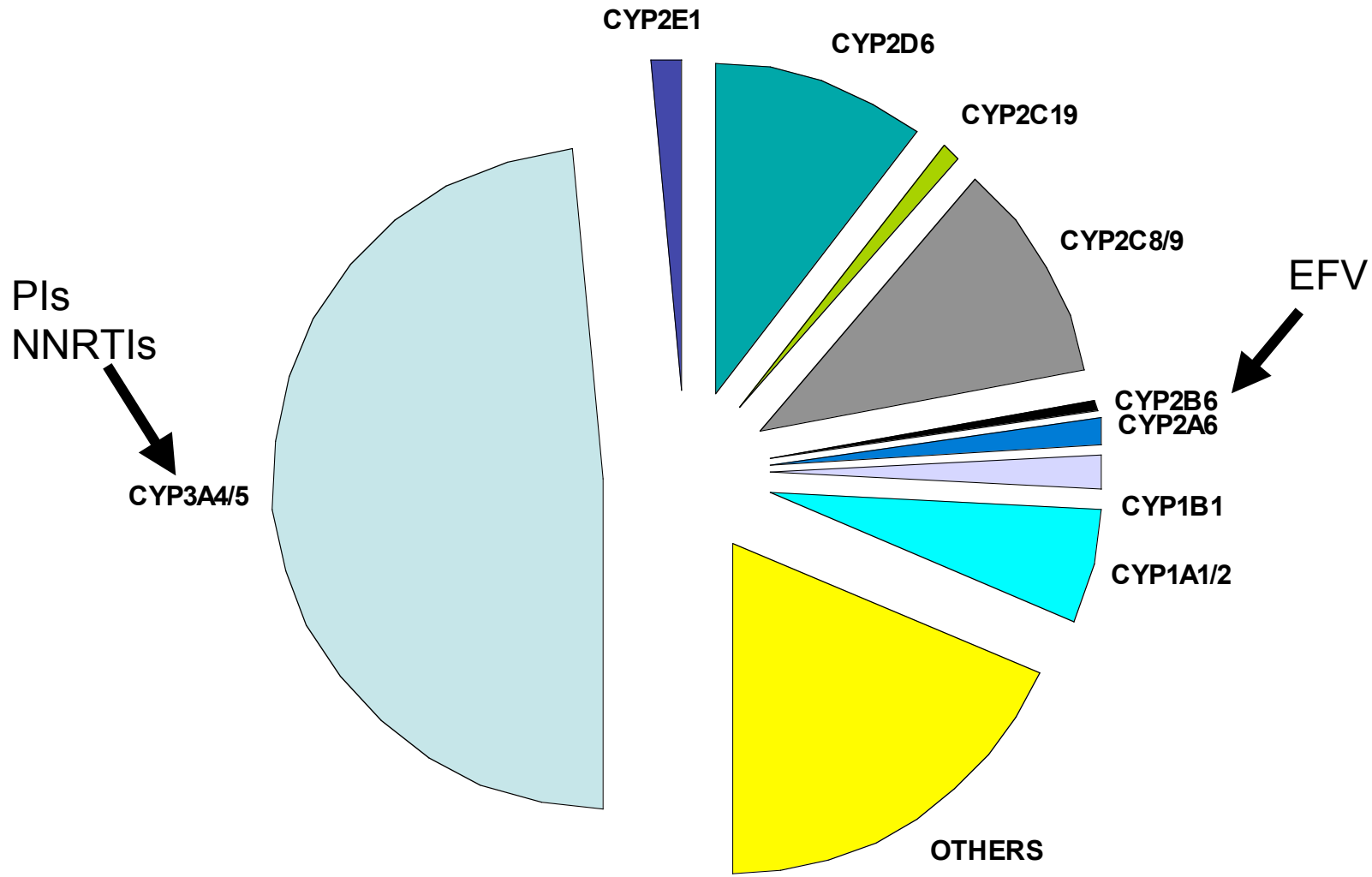
Rifampicin increases P-gp expression

- Decreases PI absorption
- Decreases CSF & testis penetration
- Increases PI elimination

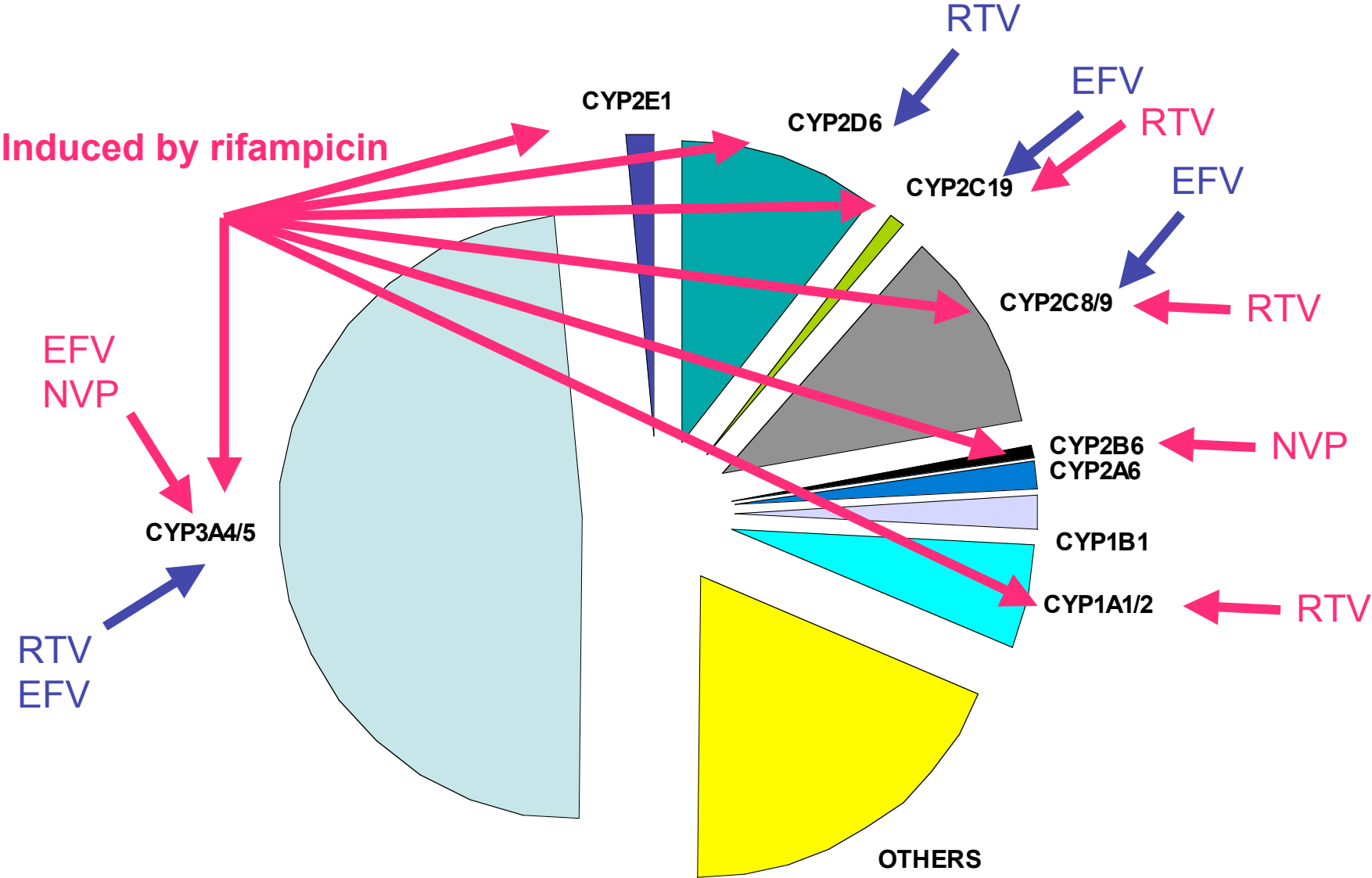
Antiretroviral therapy drug interactions



Proportion of drugs metabolised by phase 1 enzymes



CYP450 enzymes induced or inhibited by ARVs



Kinetics of rifampicin induction

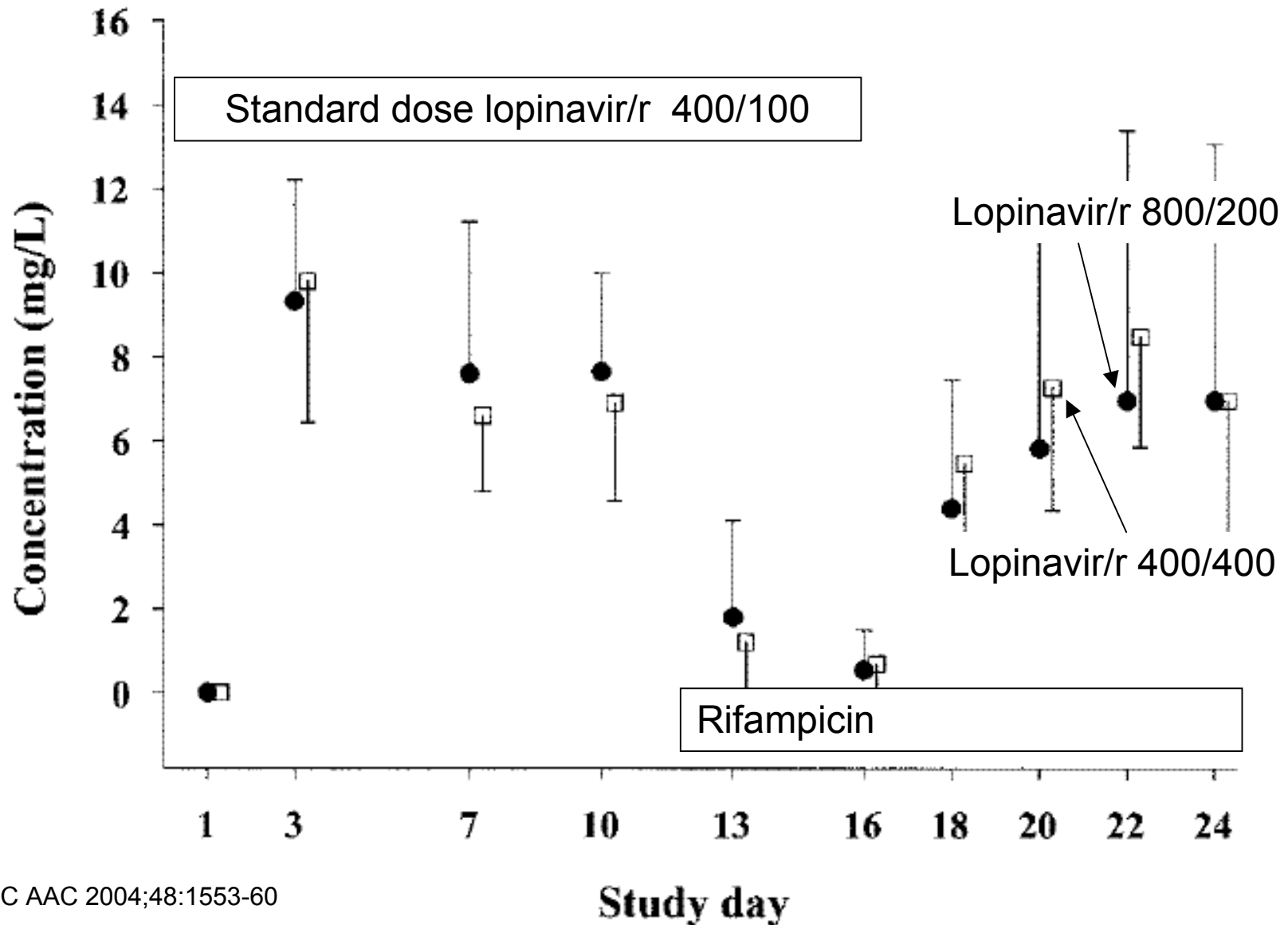
- Maximal in about 1 week
- Resolves after about 2 weeks

Rifampicin & PIs

Rifampicin decreases plasma concentrations of all protease inhibitors

PI		Rifampicin
Saquinavir		↓ 80%
Ritonavir	Levels still therapeutic	↓ 35%
Indinavir		↓ 90%
Nelfinavir		↓ 82%
Amprenavir		↓ 81%
Lopinavir/ritonavir		↓ 75%

Rifampicin & trough lopinavir concentrations: Healthy adult volunteers



Lopinavir/r & rifampicin

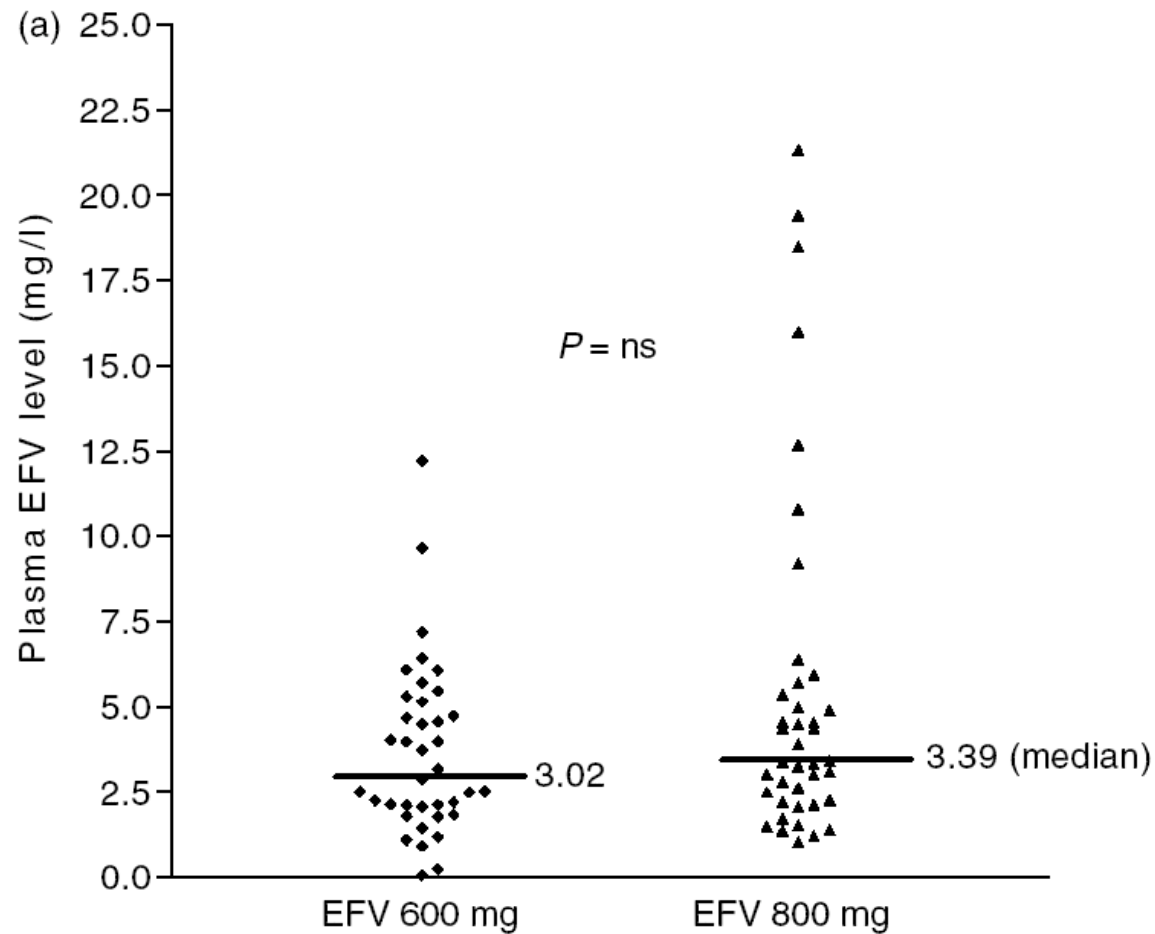
- Double dose LPV/r more practical
 - Ritonavir syrup poorly tolerated
 - Short shelf life
 - Probably more toxic to add ritonavir with LPV/r of 1:1
- Study due to commence this year

Rifampicin & NNRTIs

EFV & rifampicin

- Modest reduction in levels only
- US & European guidelines recommend adult dose increase from 600 to 800 mg

EFV concentrations in adult Thai patients on rifampicin-based TB therapy



Rifampicin & increased NVP dose

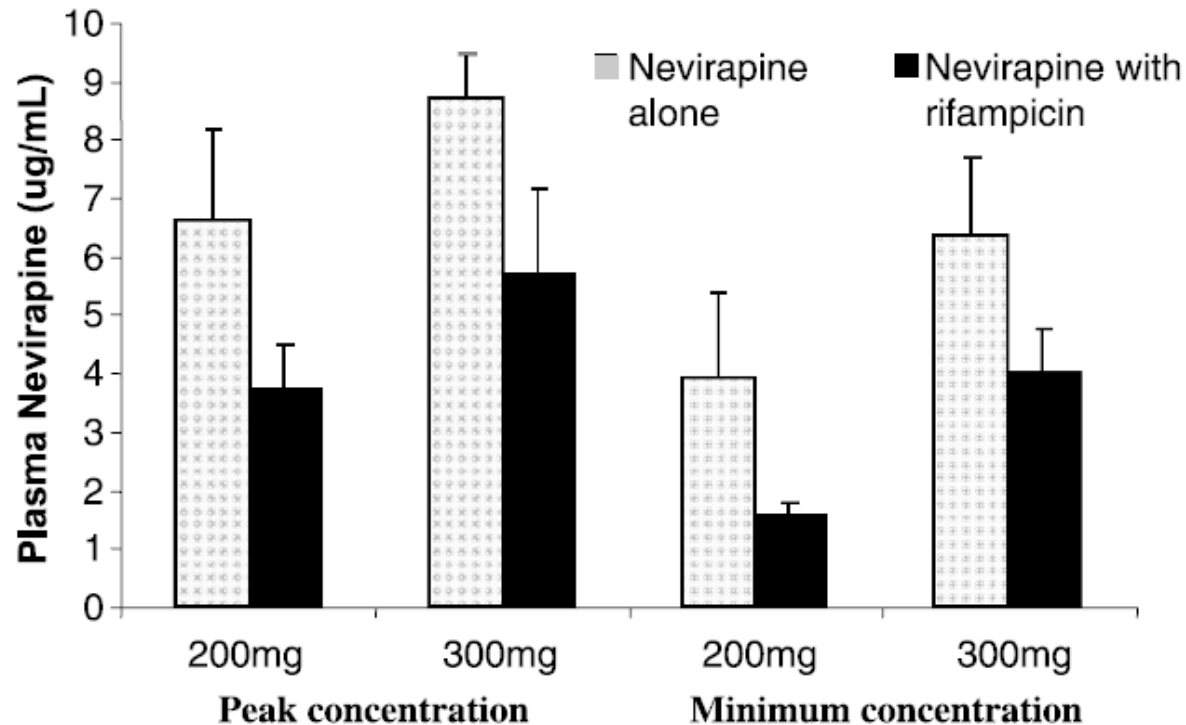


FIGURE 2. Comparison of peak (C_{max}) and minimum (C_{min}) concentrations of nevirapine at 200- and 300-mg doses twice daily. Values are represented as mean \pm SD calculated in 7 patients.

Outcomes with NNRTI & TB therapy

- Cohort studies support EFV – probably no need for dose adjustment (WHO A-II)
- Fewer data on NVP – possibly effective (WHO B-III)

Therapeutic drug monitoring

Ideal to measure trough levels of ARVs if rifampicin co-administered with PIs or NNRTIs

Rifabutin & ARVs

- Increasingly used instead of rifampicin in developed countries
- Unlike rifampicin, rifabutin levels are increased by PIs & decreased by NNRTIs
- Not an option in SA as TB treated with FDCs & no rifabutin in public sector (which is where all TB must be treated)
- No paediatric formulation

Triple NRTIs

- No significant interaction between NRTIs and rifampicin
- Triple NRTI regimens associated with higher failure rates than standard HAART
- Could be considered in selected cases

Conclusions

- Shared toxicity between ARV & TB therapy appears to be common (more data needed)
- Rifampicin dramatically reduces PI concentrations – can be overcome by dose adjustment
- Substituting rifabutin not an option in developing countries
- NNRTIs less affected, but NVP may need dose adjustment (no PK data in children)
- Worryingly low EFV concentrations in children