

## Drug Interactions

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## Drug Interactions

With anti-microbial agents, several types of interactions can occur. These can be positive or negative.

Patient – Drug : tolerability, adverse reactions  
Bug – Drug : binding, inhibition, efficacy  
Drug – Drug : PK: altered clearance  
PD: synergy, antagonism

## Bug – Drug Interactions: How Do Antibiotics Work ?

The drug enters the organism,  
binds to a target,  
and produces an inhibitory or lethal effect.

## How Do Antibiotics Work ?

For drugs given orally or parenterally,  
the drug must reach the organism  
through the blood stream.

## How Do Antibiotics Work ?

If the drug is not in the blood,  
the drug is not in the bug.  
  
Poor pharmacokinetics leads to poor effect  
for ALL classes of systemic antimicrobials

## Drug – Drug Interactions

Early *in vitro* data on hepatic microsomal  
enzyme clearance ( Phase I reactions ),  
  
conjugation ( Phase II reactions ),  
  
and transporters ( P-gp, SLC01B1 )  
  
allow one to qualitatively anticipate  
drug – drug interactions.

### Drug – Drug Interactions

Early phase human studies allow one to quantitate these reactions.

However, increasingly there are situations where healthy volunteers have quantitatively different PK and interactions from TB / HIV infected patients.

### Drug – Drug Interactions

Examples:

etravirine - plasma concentrations 35 – 50 % lower in HIV + patients vs. healthy volunteers

adding ritonavir to rifabutin

healthy volunteers: 3 x parent and 48 x desacetyl  
TB / HIV patients: 2 x parent and 2 to 8 x desacetyl  
Therefore, concentrations much lower in patients, with implications for toxicity and efficacy.

### Drug – Drug Interactions

Ultimately, drug – drug interaction studies need to be done in the intended patient population.

Sound study designs can incorporate women and children, allowing for sex and age effects to be quantified within the parent trial.

Resist the urge to over – simplify dosing

### Drug – Drug Interactions

Example:

Maraviroc : 300 mg twice daily

With any CYP 3A4 inducer : 600 mg twice daily

With any CYP 3A4 inhibitor : 150 mg twice daily

With any inducer + inhibitor : 150 mg twice daily

This approach assumes that each and every patient will have the median interaction response

### Antiviral Pharmacokinetics

- Given the variability in expression of CYP 3A4 and other CYP isoenzymes across the HIV + patient population, it is highly unlikely that 1 dose will be the effective dose for all patients.

Updated guideline to perform therapeutic drug monitoring for antiretroviral agents

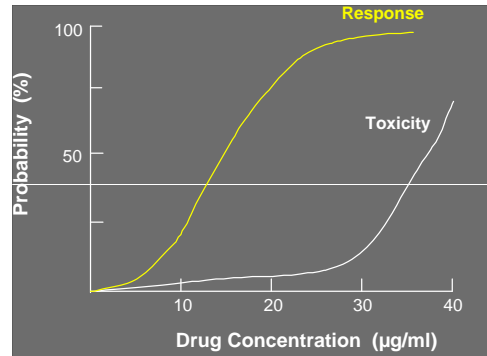
C.J.L. la Porte, D.J. Back,  
T. Blaschke, C.A.B. Boucher,  
C.V. Fletcher, C. Flexner,  
J.G. Gerber, A.D.M. Kashuba,  
J. Schapiro, D.M. Burger

Reviews in Antiviral Therapy - volume 3; 2006

Table 2. Concentration based cutoff values for performing TDM of antiretroviral agents in naive patients

	Efficacy (C <sub>trough</sub> )	Toxicity
Atazanavir	0.15 <sup>1</sup>	
Fosamprenavir	0.40 <sup>2</sup>	
Indinavir	0.10 <sup>3</sup>	C <sub>max</sub> 10.0 <sup>4,2</sup>
Lopinavir/r	1.0 <sup>4</sup>	
Nelfinavir	0.80 <sup>3</sup>	
Ritonavir <sup>5</sup>	2.1 <sup>4,4</sup>	
Saquinavir	0.10 <sup>23,26</sup>	
Tipranavir <sup>*</sup>	20.5 <sup>28</sup>	
Efavirenz	1.0 <sup>45</sup>	C <sub>trough</sub> 4.0 <sup>45</sup>
Nevirapine	3.0 <sup>28</sup>	

All values are in mg/L.



Evans, 1986

### Antiviral Drug and Assay Costs

- Typically, an NNRTI, PI, or newer class drug costs \$ 8,000 to \$11,000 per year.
- Therapeutic drug monitoring (TDM) costs \$ 80 for a trough value (in our lab).
- TDM may extend the duration of effectiveness of a given drug in a given patient.
- This can “buy time” for newer drugs to enter the market by the time a patient’s regimen no longer is active.

### Drug – Drug Interactions

- Therapeutic drug monitoring can confirm whether or not PK – PD targets have been achieved in individual patients.
- Therapeutic drug monitoring can de – convolute multi – drug interactions.

### Rifamycins : The Key TB Drugs

Ideally, we would like to use rifamycins to treat TB, regardless of HIV status.

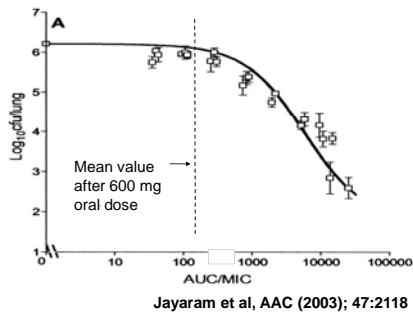
Ideally, we would give **LARGE DOSES** of rifamycins to maximize response, since as a class rifamycins have profound concentration – dependent activity.

### Rifampin has profound concentration – dependent killing

Week		5 mg/kg	10 mg/kg	20 mg/kg	40 mg/kg
Lung week 1	CFU	100,000,000	100,000,000	100,000,000	100,000,000
Lung week 10	CFU	10,000	100	10	0
% reduction		99.99000%	99.99990%	99.99999%	100.00000%

Verbist L. Acta Tuberculosa et Phneumolgia Belgica 1969; number 3 - 4: 397 - 412.;

## Rifampin has profound concentration – dependent killing



## Rifamycins : The Key TB Drugs

In HIV patients with TB, we choose rifabutin (RBN) to minimize drug – drug interactions.

But... RBN appears to have concentration – related toxicity, unlike rifampin, capping how large a dose can be used.

RBN, unlike rifampin, has 2 - way interactions with macrolides, azoles, HIV PI and NNRTI

## Rifabutin for treating pulmonary tuberculosis (Review)

Davies GR, Cerri S, Richeldi L

### Authors' conclusions

The replacement of rifampicin by rifabutin for first-line treatment of tuberculosis is not supported by the current evidence. HIV positive people with tuberculosis, the group most likely to benefit from the rifabutin use, are under-represented in trials to date, and further trials in this group would be useful.

*Cochrane Database of Systematic Reviews*  
17 October 2007 in Issue 4, 2007

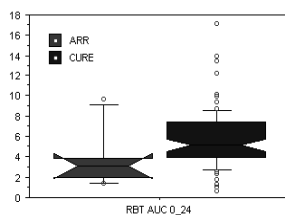
## PD: Response Data

### Association between Acquired Rifamycin Resistance and the Pharmacokinetics of Rifabutin and Isoniazid among Patients with HIV and TB [ Study 23A ].

Weiner M, Benator D, Burman W, Peloquin CA, Khan A, Vernon A, Jones B S, Silva-Trigo C, Zhao Z, Hodge T and the Tuberculosis Trials Consortium

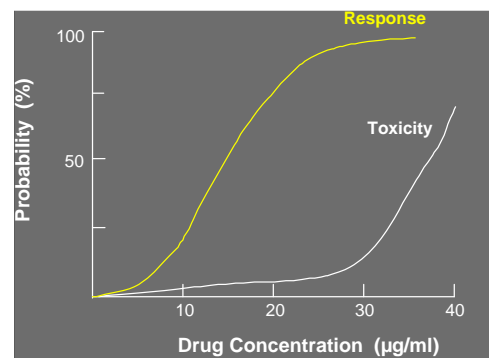
*Clinical Infectious Diseases* 2005; 40: 1481 - 1491.

## Lower rifabutin AUC linked with ARR versus cure



Group	No.	Dose mg/kg Med (IQC)	AUC <sub>0-24</sub> Med (IQC)	P-Value*
ARR	6	4.6 (3.5 - 5.7)	3.1 (2.0 - 3.8)	
CURE	82	4.8 (4.2 - 6.2)	5.1 (4.0 - 7.4)	0.04

\* P for RBT AUC ARR vs. cure, Mann-Whitney



Evans, 1986

**Pharmacokinetic Evaluation of Rifabutin in Combination with Lopinavir-Ritonavir in Patients with HIV Infection and Active Tuberculosis**

Catherine Boulanger, Elena Hollender, Karen Farrell, Jerry Jean Stambaugh, Diane Maasen, David Ashkin, Stephen Symes, Luis A. Espinoza, Rafael O. Rivero, Jenny J. Graham, and Charles A. Peloquin

Clinical Infectious Diseases 2009; 49:1305-11

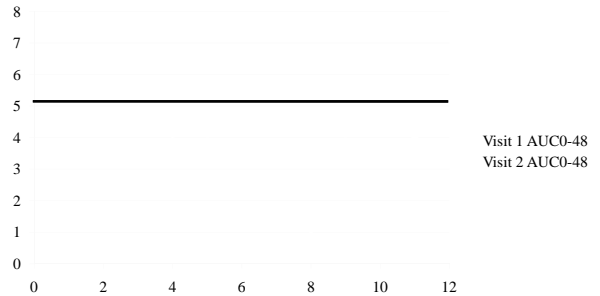
**Rifabutin and LPV / r in HIV+ TB Patients**

- 10 patients included in a PK study of RBN, desacetyl – RBN, and lopinavir
- PK after 2 weeks of 300 mg RBN given 3 times weekly without LPV / r
- PK after 2 weeks of 150 mg RBN given 3 times weekly with twice daily LPV / r

**Rifabutin and LPV / r in HIV+ TB Patients**

- Low RBN concentrations were common
- 1 patient developed ARR during the course of the PK study (very small study, 10 % ARR )
- desacetyl – RBN activity against TB is questionable

**RBN AUC 0-24 before and after LPV / r**  
(data oriented vertically by subject)

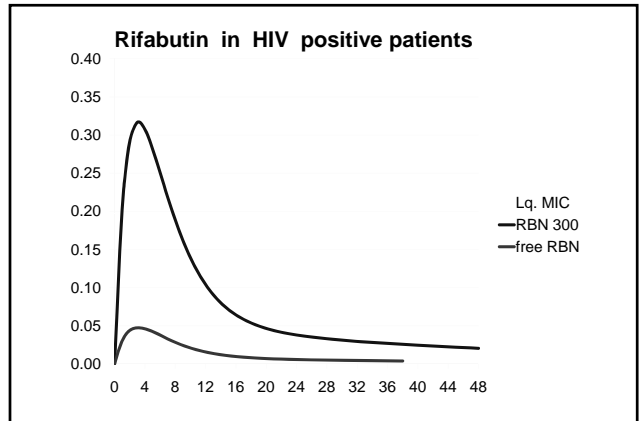
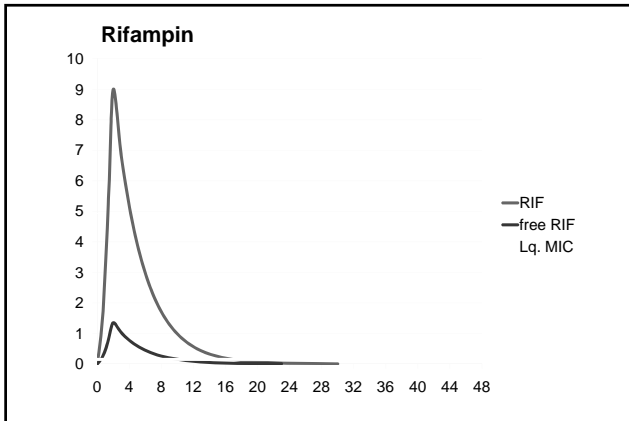


RBN and desacetyl-RBN MIC values for RBN susceptible isolate

RBN	desacetyl-RBN	fold difference
≤ 0.03	= 0.06	≥ 2
= 0.12	> 0.50	> 4
= 0.25	> 0.50	> 2
= 0.06	= 0.06	= 0
= 0.06	= 0.12	= 2
= 0.06	= 0.06	= 0

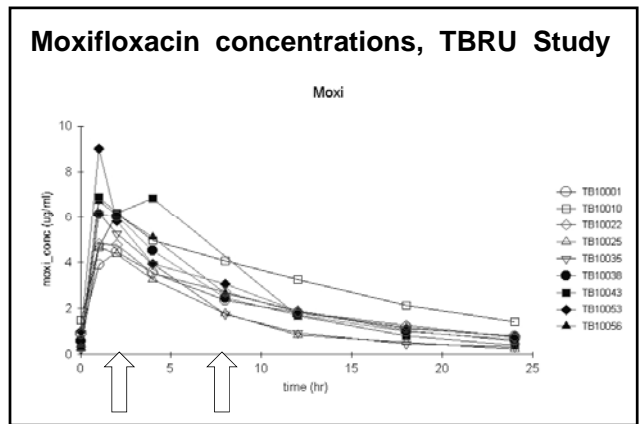
**Interactions: Rifabutin**

- Many dosage recommendations are based on healthy volunteer data only.
- Dosing recommendations assume that all patients are the median healthy volunteer.
- MIC data are not routinely collected in clinical practice to identify patients who might need more RBN for a more resistant TB isolate.
- Unlike RIF regimens, RBN failures have acquired rifamycin resistance (ARR)



### Rifamycin Pharmacokinetics

- RIF, INH, PZA, and EMB are reasonably well matched for PK, especially when given daily.
- Intermittent RBN regimens using INH, PZA, and EMB leave sub-MIC RBN serum concentrations as monotherapy for about 3 days every week.
- Intermittent RPNT regimens using INH, PZA, and EMB leave supra-MIC RPNT serum concentrations as monotherapy for about 3 days every week.

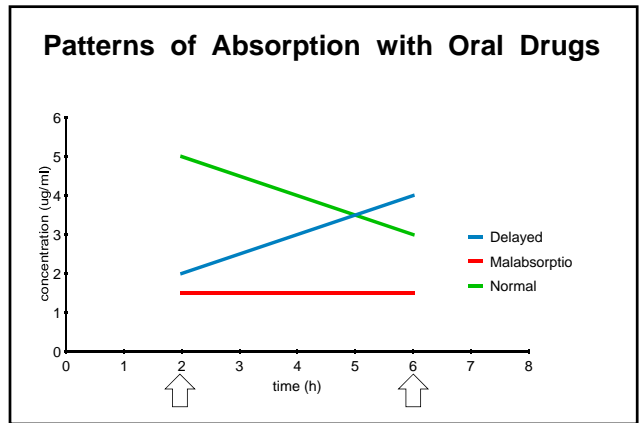


### TDM with Oral TB Drugs

Two hour post dose blood draws generally capture the “peak” concentration.

Six hour post dose blood draws generally separate delayed absorption from malabsorption.

Peloquin CA. Therapeutic Drug Monitoring in the Treatment of Tuberculosis. *Drugs* 2002; 62: 2169 - 2183.



### Conclusions

- PK – PD mismatch appears to have a role in the significant rate of ARR seen with RBN in HIV + TB patients.
- Early phase PK – PD data need to be confirmed in TB and TB / HIV infected patients.

### Conclusions

- Therapeutic drug monitoring can confirm whether or not PK – PD targets have been achieved in individual patients.
- Therapeutic drug monitoring can de – convolute multi – drug interactions.

#### Useful links

<http://idpl.cop.ufl.edu/>

<http://www.hivinsite.org/>

<http://aidsinfo.nih.gov/>

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

<http://www.cdc.gov/tb/>

