Managing Drug Interactions Between Rifamycin Antibiotics and ART

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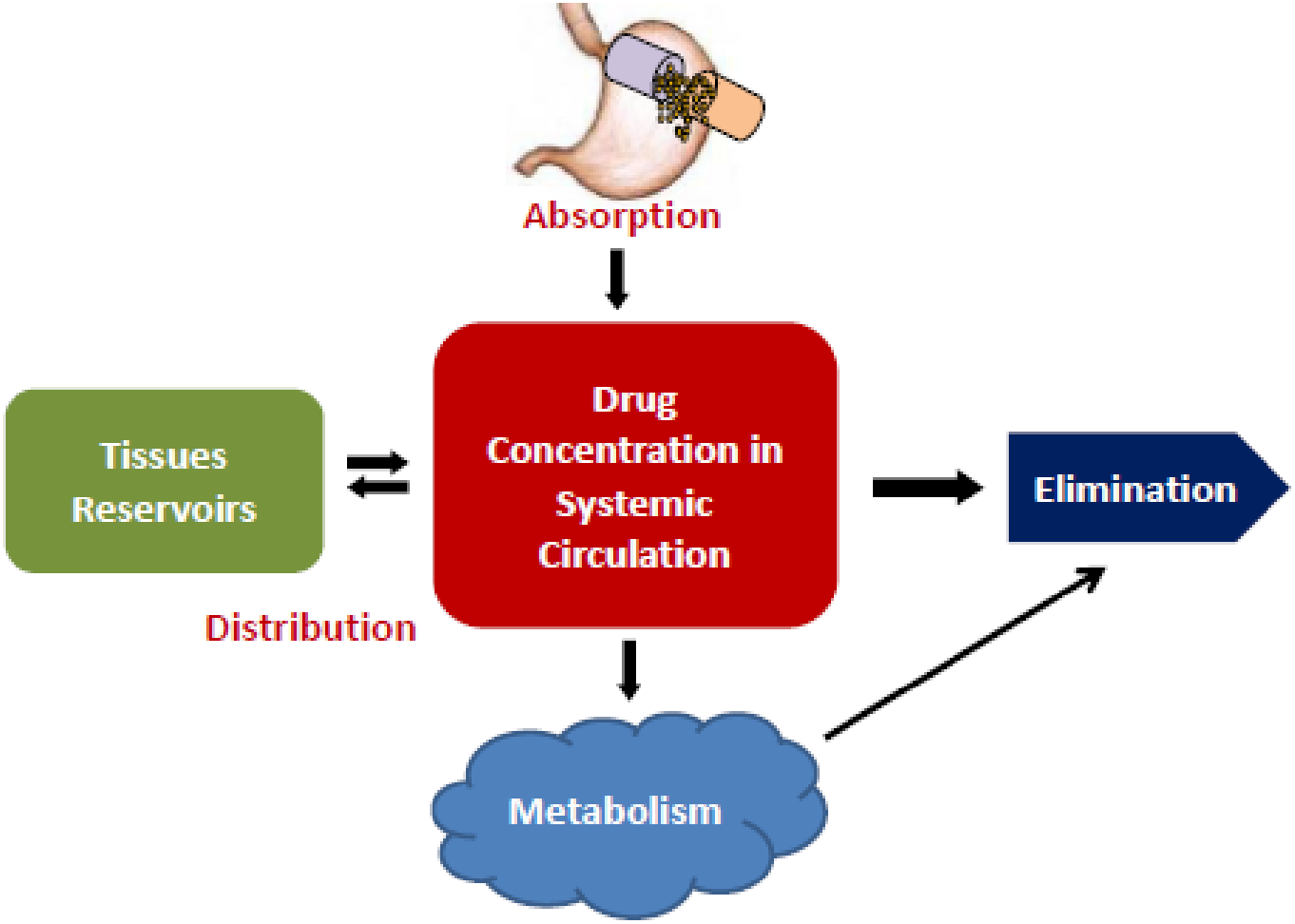
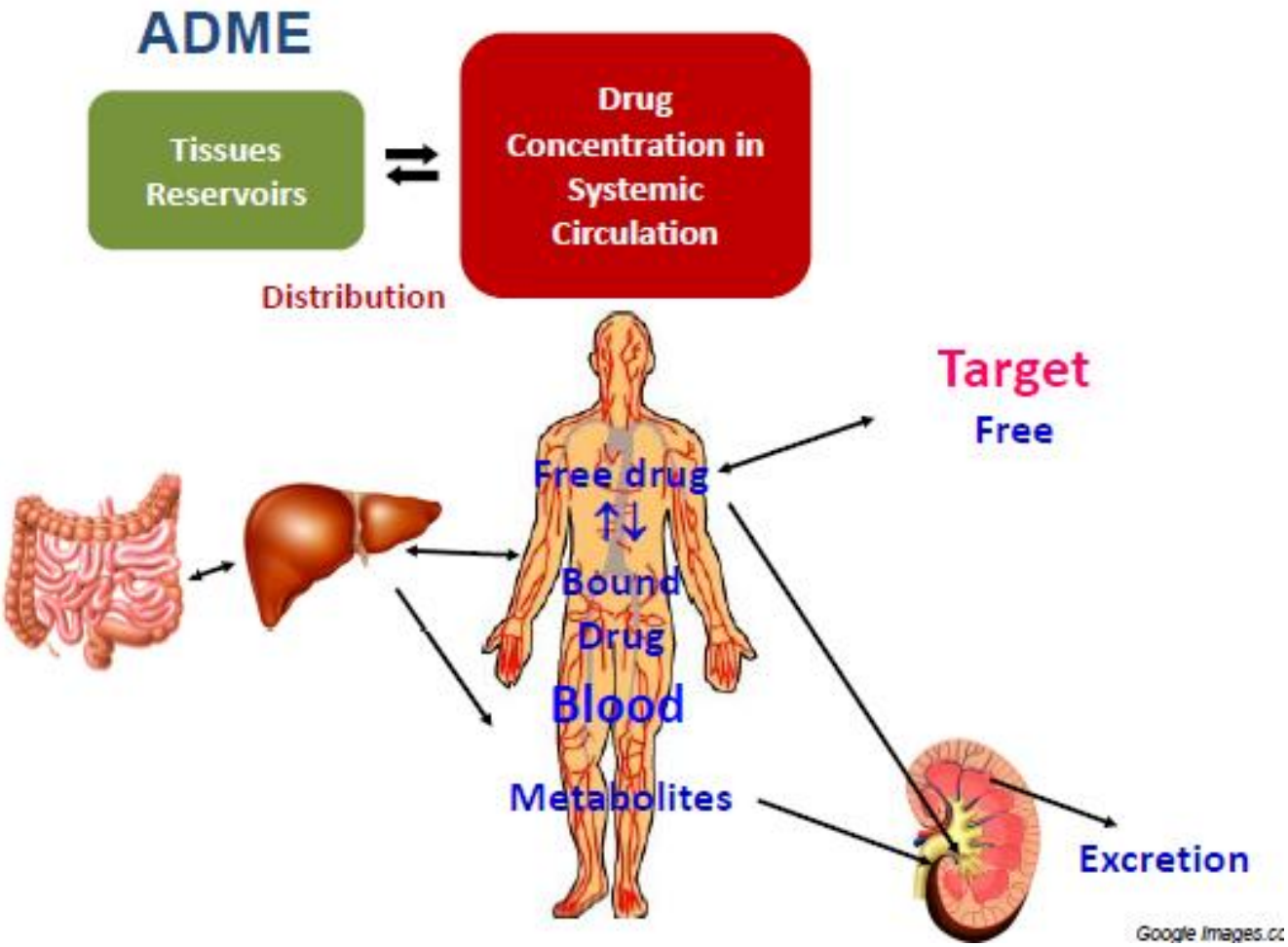
MDR TB TA

Right to Care


Absorption
Drug Concentration in Systemic Circulation
Tissues Reservoirs
Distribution
Elimination
Metabolism


ADME
Tissues Reservoirs
Drug Concentration in Systemic Circulation
Distribution
Target
Free
Free drug
Bound Drug
Blood
Metabolites
Excretion
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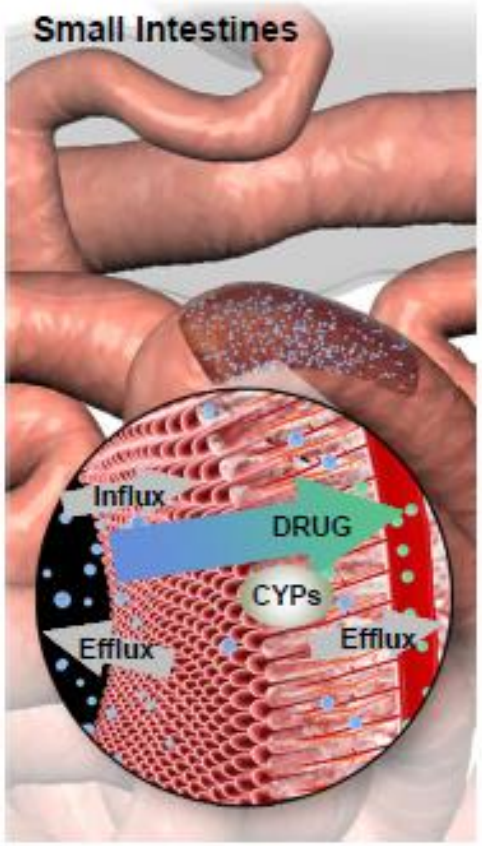
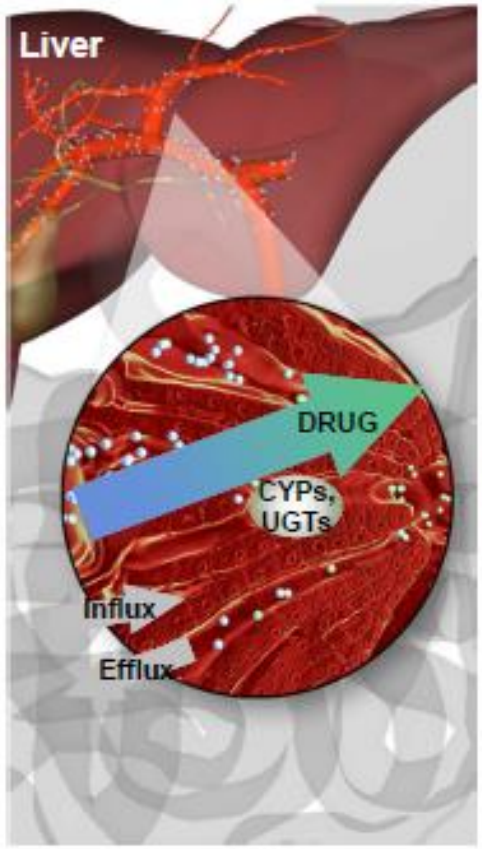
Importance of transport and metabolism in relation to systemic drug levels

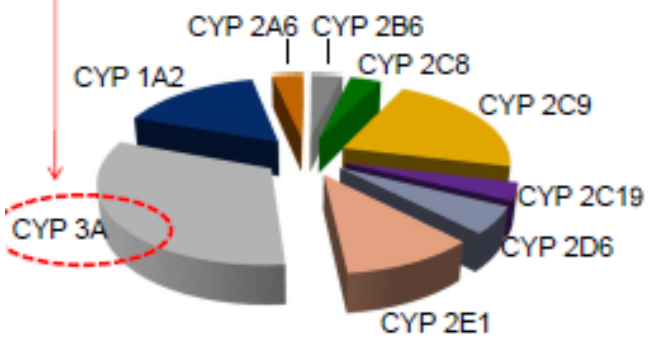




Adapted from Bailey DG, et al. Br J Clin Pharmacol. 1998;46:101–10

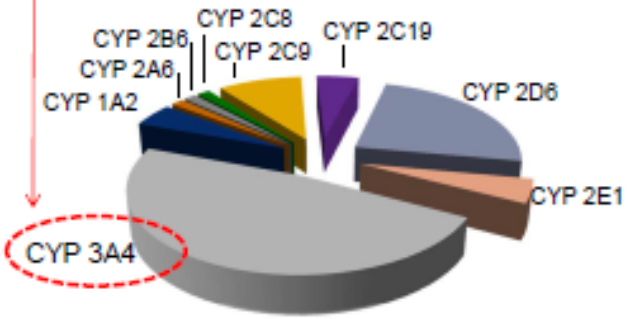
CYP Enzymes

CYP 3A is the most abundant CYP isozyme



Proportion of total CYP enzymes present in human liver

CYP 3A 4 involved in the metabolism of majority of drugs



Proportion of drugs that are substrates for major CYP enzymes

CYP: cytochrome P450
All percentages are approximate. For illustrative purposes, hepatic CYP enzymes present at <5% are all represented as 3.3%

Hacker MP, et al. Pharmacology: Principles and Practice. Academic Press 2009

Rifamycins

- Rifampicin
- Rifapentine
- Rifabutin

Rifampicin

- Undergoes rapid oral administration
- Wide distribution into most body tissues and fluids, including CSF
- 80% protein bound.
- Undergoes extensive hepatic metabolism to less active metabolites, with a half-life of three hours.
- Renal elimination of unchanged drug is minimal (<30 percent).

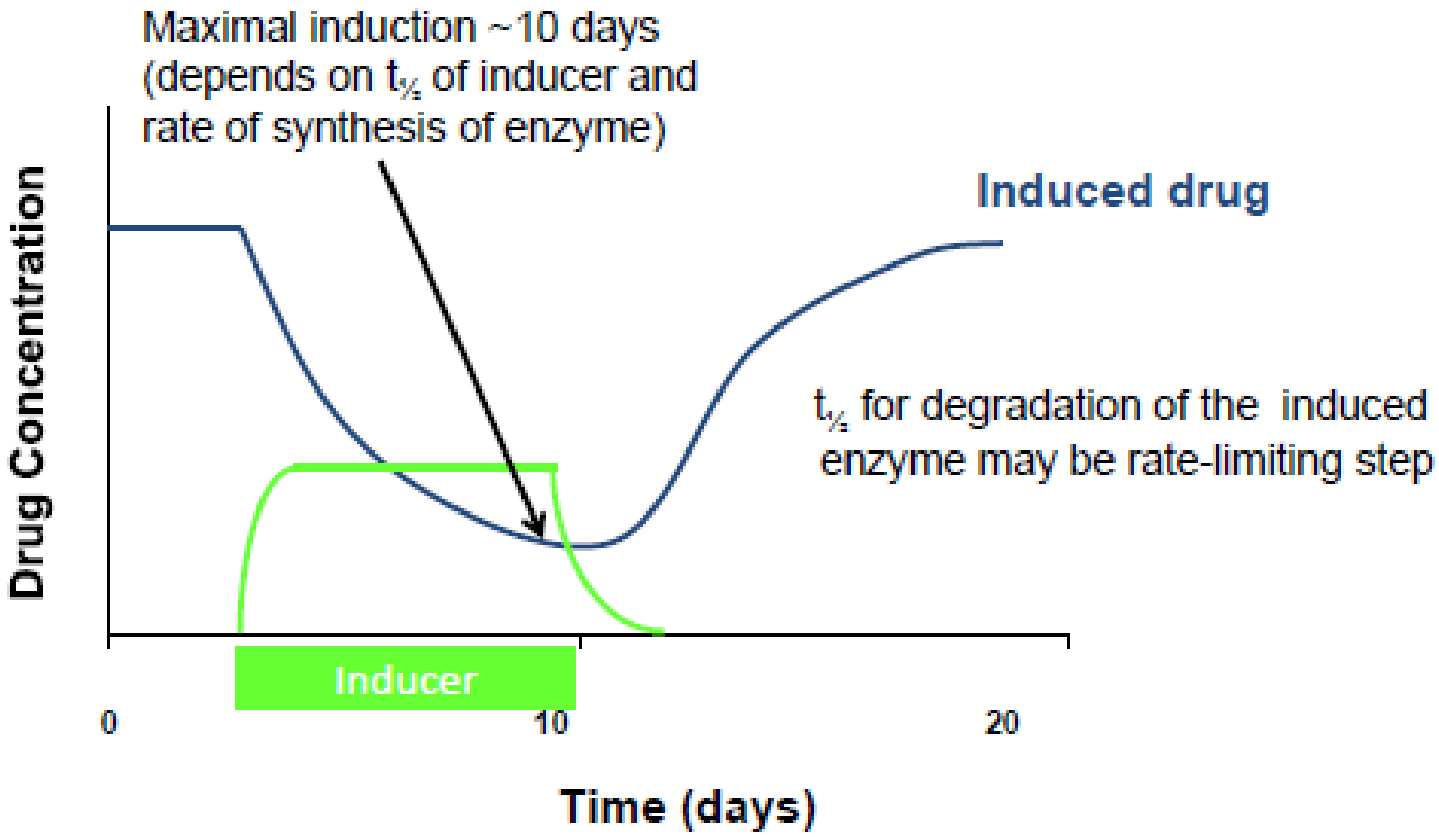
Rifapentine

- Longer half-life rifampicin
- Absorption is increased in the presence of food High protein binding (97 percent)
- Most of the drug is eliminated in the faeces

Inhibition versus induction of CYP 450

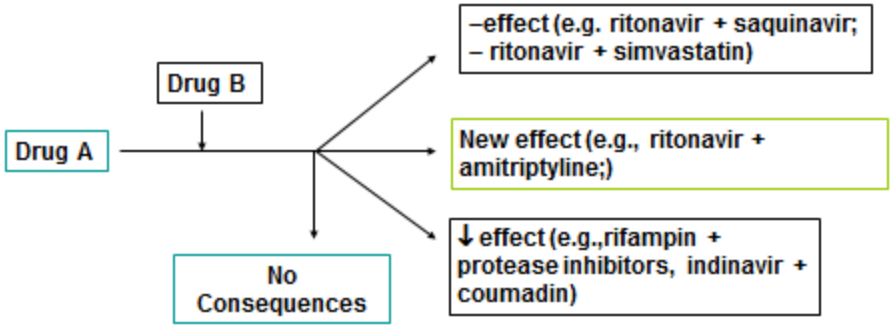
- Inhibition usually occurs rapidly (immediate or within 48 hours)
- Induction occurs after repeated exposure and may take up to 14 days to reach the maximum
- Enzyme activity returns slowly to baseline when modulating drug is discontinued

Enzyme induction



CYP P450 Drug-Drug Interactions

- Pharmacologic action of drug is altered by coadministration of second drug
- Co-administration may:



Inducers

- Both are strong inducers of CYP P450 system
- CYP P450 3A4
- (CYP2C8 and CYP2C9)
- Decreasing serum concentrations of co-administered drugs

Four classes of ART

- NRTI
- NNRTI
- PI
- Intergrase inhibitors

		Predicted Enzyme Effect						
	Antiretroviral	3A4	2B6	2C9	2C19	2D6	1A2	UGT
PIs	Atazanavir		–		–[a]	–		
	Darunavir/r					–[a]		
	Fosamprenavir			–	–[a]	–	–	–
	Indinavir		–	–	–	–[a]	–	
	Lopinavir/r					–[a]		
	Nelfinavir		–			–		
	Ritonavir	[b]						
	Saquinavir		–	–[a]	–	–	–	–
	Tipranavir/r							
NNRTIs	Delavirdine		–			–[a]	–	–
	Efavirenz							
	Etravirine					–	–	
	Nevirapine				–	–	–	
	Rilpivirine			*		*		*
INSTI	Raltegravir	–	–	–	–	–	–	
	Elvitegravir/r		*	*	*	*	*	
	Dolutegravir		*	*	*	*	*	
CRA	Maraviroc		–	–	–	–	–	–

The predicted metabolic effects of antiretroviral agents on various cytochrome (CYP) P450 isoenzymes and uridine diphosphate glucuronosyltransferase (UGT) are illustrated according to the following: ■ inhibition, ■ induction, ■ mixed induction/inhibition, ■ substrate, [□] no significant effect, [*] not determined. The clinical significance of

Now down to practicalities

- NRTI
- NNRTI
- PI

Now down to the practicalities

- NRTI 
- NNRTI 
- PI
- Intergrase inhibitors 

● / ●	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

Antibacterials	Atazanavir	Darunavir	Lopinavir	Efavirenz	Etravirine	Nevirapine	Rilpivirine	Dolutegravir	Raltegravir
Rifabutin	■	■	■	■	■	■	●	◆	◆
Rifampicin	●	●	●	■	●	●	●	■	■
Rifapentine	■	■	■	■	●	■	●	■	◆

NNRTI and Rifampicin

- EFV: give at standard dose of 600mg, data on lower dose of 400mg pending
- RPV: significant decreases in RPV plasma concentrations may occur which may result in loss of therapeutic effect of RPV
- ETV: significant decreases in ETV plasma concentrations may occur which may result in loss of therapeutic effect of ETV

PI and Rifampicin

- ATZ/r :decrease in atazanavir AUC which can result in virological failure and resistance development. If ATZ dose increased, increase in liver dysfunction
- DRV/r: decreases in concentrations of other protease inhibitors, which can result in virological failure and resistance development If ATZ dose increased, increase in liver dysfunction
- .

PI and Rifampicin

- LPV/r : decreases in LPV/r concentrations which may in turn significantly decrease LPV/r therapeutic effect.
- Adequate exposure to LPV/r may be achieved when a higher dose of Kaletra (400/400 mg twice daily)
- Higher risk of liver and gastrointestinal toxicity.
- Therefore, this co-administration should be avoided unless judged strictly necessary.

Rifabutin

- Initial PK studies in healthy volunteers showed that concentrations of rifabutin leading to a reduction of rifabutin dosage to 150 mg three times a week was recommended to reduce the risk of rifabutin related toxicity.
- More recent PK data derived from HIV/TB co-infected patients have shown rifabutin concentrations were too low rifabutin dosage may be inadequate.
- Rif resistant Tb relapses
- The US guidelines for HIV treatment now recommend the administration of rifabutin at a daily dosage of 150 mg with a boosted protease inhibitor.

Intergrase inhibitors

- Dolutegravir: increase to 50 mg twice daily
- Raltegravir: consider increase t0 400mg bid
- In the presence of intergrase class resistance this combination should be avoided.

Case study

- 14 year old boy, diagnosed as HIV infected at 3 years of age
- Took d4T, 3TC and EFV for two months then lost to follow up
- Returned to HIV care at age 12
- Weight 22kg, stunted
- CD4+ 83, VL 50 000
- Started on ABC ,3TC and EFV

Case 1

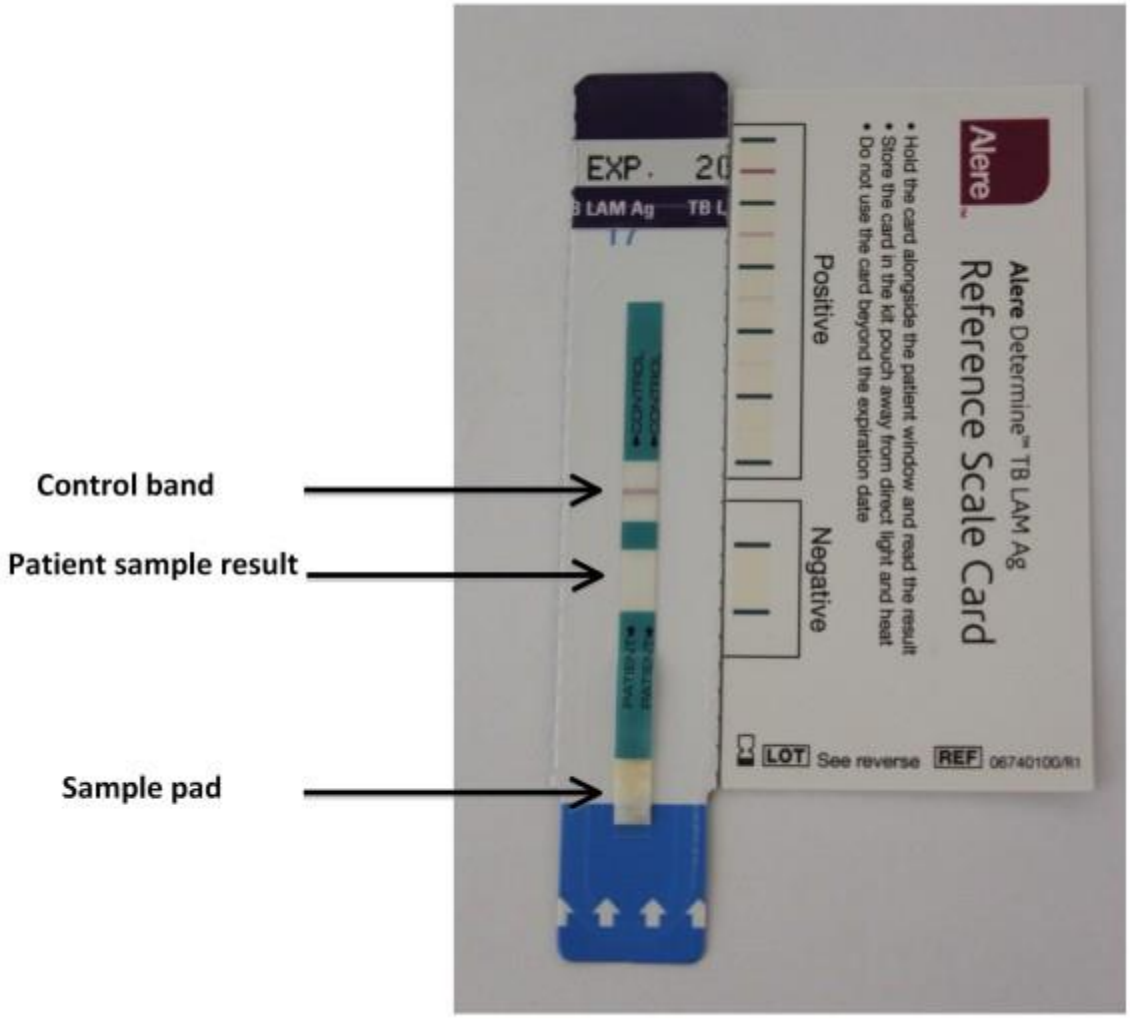
- VL at 3 months 43 000 copies/ml (confirmed in one month)
- Started on AZT, 3TC and Alluvia
- Admitted after 3 months on ART (VL 20 000 copies/ml)
  - Developed diarrhoea on PI and was changed to ATZ/r
  - Weight loss
  - Night sweats
    - CXR normal
    - Sputum for GXP: negative, culture not done

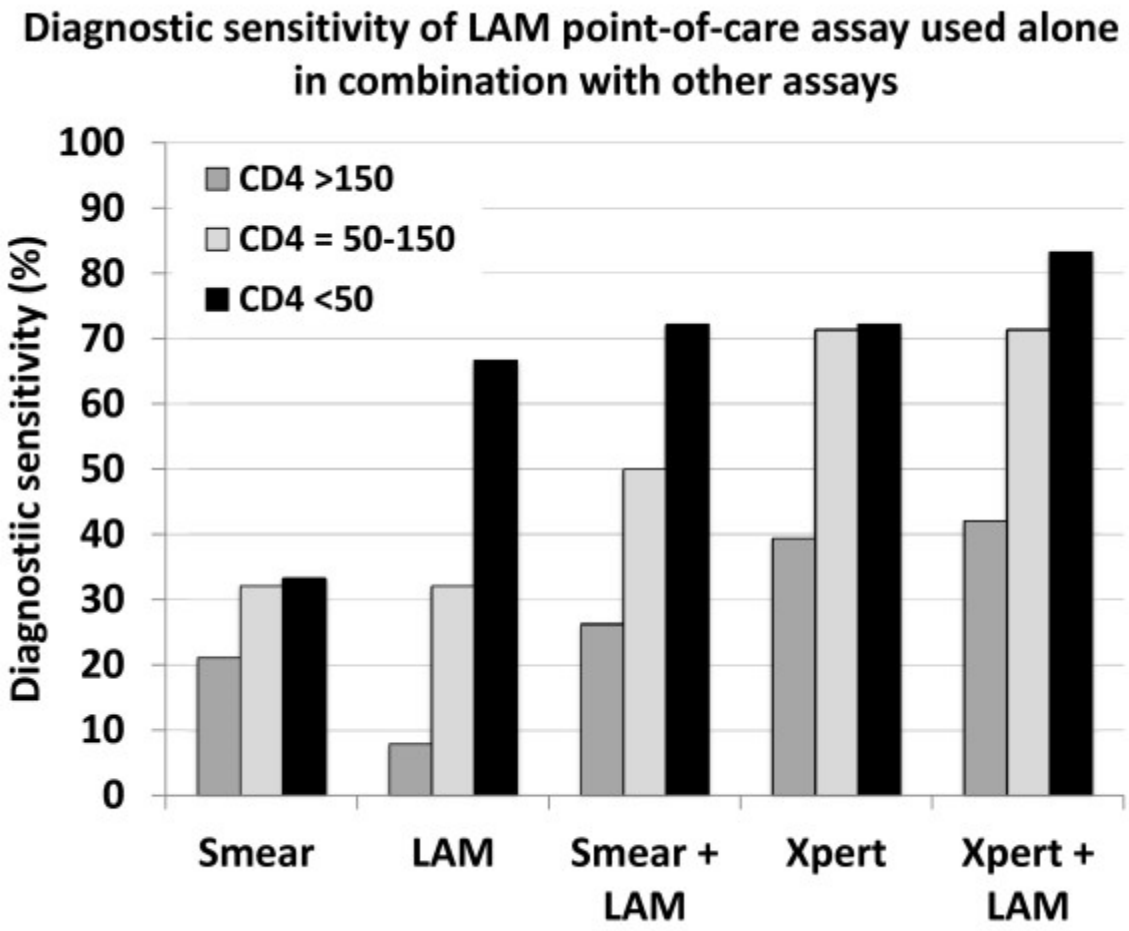
Case 1

- Admitted again after 2 months
  - On-going weight loss
  - CXR ISQ
  - GXP negative
  - CD4+ 46
  - Urinary LAM positive

Urinary lipoarabinomanin

- Lipopolysaccharides within the mycobacterial cell wall
- Systemic antigenaemia in dissemination of *M. tuberculosis* in the blood stream,
- Especially in advanced HIV-associated immunodeficiency


Control band
Patient sample result
Sample pad
Alere
Alere Determine™ TB LAM Ag
Reference Scale Card
• Hold the card alongside the patient window and read the result
• Store the card in the kit pouch away from direct light and heat
• Do not use the card beyond the expiration date
Positive
Negative
LOT See reverse
REF 06740100/R1
EXP.
LAM Ag


Diagnostic sensitivity of LAM point-of-care assay used alone or in combination with other assays
Diagnostiic sensitivity (%)
100
90
80
70
60
50
40
30
20
10
0
CD4 >150
CD4 = 50-150
CD4 <50
Smear
LAM
Smear + LAM
Xpert
Xpert + LAM

Now what?

- ATZ/r
- LPV/r

Introduction

- Untreated TB in pregnancy poses a significant threat to the mother, fetus and family
- The fear of fetal side-effects can sometimes impede proper treatment of the mother
- Early treatment of drug-sensitive TB in pregnancy with standard regimens is safe
- Little evidence to guide clinicians in the treatment of drug-resistant TB in pregnancy

Efavirenz (EFV) concentrations in pregnant women taking EFV-based antiretroviral therapy (ART) with and without rifampin-containing tuberculosis (TB) treatment: the TSHEPISO Study Team

Presented by Kelly E Dooley (United States).

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[1]University of Cape Town, Cape Town, South Africa, [2]Perinatal HIV Research Unit (PHRU), University of the Witwatersrand, Soweto, South Africa, [3]Johns Hopkins University School of Medicine, Baltimore, United States, [4]Chris Hani Baragwanath Hospital and University of the Witwatersrand, Department of Obstetrics, Soweto, South Africa, [5]Vanderbilt University, Nashville, United States

Background: HIV and TB are threats to pregnant women and infants. Treatment with rifampin can reduce ART concentrations and increase risk of treatmen failure and vertical transmission. We describe the pharmacokinetics (PK) and pharmacodynamics of EFV among pregnant HIV-infected women.
Methods: Prospective cohort of HIV-infected pregnant women with and without TB in Soweto. Women taking ART with EFV 600mg had PK sampling at 37 weeks' gestation or at delivery and then six weeks post-partum. EFV concentrations were measured in cord blood at delivery and in infants at 7 days. Post-h Bayesian estimates of PK parameters from nonlinear mixed-effects modeling with allometric scaling are reported.
Results: Among 41 HIV-infected pregnant women taking EFV ART, 19 received rifampin (TB/HIV) and 22 ART alone. Median age and weight were 29 years and 70 kg. For 35 women with pre-/peripartum EFV PK, median (IQR) estimated EFV trough (C_{min}) was 1.31 (0.84, 1.86)mg/L, apparent oral clearance (CL/ 13.62 (10.67, 18.44)L/h, and volume of distribution (V_d/F) 516 (440, 591)L. 31% had C_{min}< 1 mg/L. Predicted median C_{min} by *CYP2B6* 516/983 metabolizer genotype was: 1.04 (extensive), 1.34 (intermediate), and 4.36 mg/L (slow). TB treatment did not significantly affect EFV C_{min} (1.28 v 1.42mg/L). 5/26 wom tested at delivery had viral load >20 copies/mL (one had TB/HIV). Median cord blood EFV concentration was 1.09 (0.46, 2.38)mg/L. EFV concentrations wer BLQ in 6/24 cord blood and 25/30 infant 7-day samples; both correlated with maternal concentrations. 0/35 infants were HIV-infected at 6 weeks. In mothe 6 weeks postpartum, median EFV C_{min} was 1.75mg/L, CL/F 10.79L/h, and V_d/F 433L; 30% had C_{min}< 1mg/L.
Conclusions: TB treatment did not significantly reduce EFV C_{min}, but pregnancy may lower EFV concentrations. Although ~30% of pregnant women had EFV C_{min}< 1mg/L at standard doses, EFV-containing ART suppressed viral load in most and there were no vertical transmissions.

Abstract

MOAB0303 - Oral Abstract Session