



**TB – ARV  
interactions**

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# Antituberculosis DRUGS

## std. short course chemother.

rifampicin  
isoniazid  
pyrazinamide  
ethambutol

## other rifamycins

rifabutin  
rifapentine

## 'new' fluoroquinolones

moxifloxacin  
gatifloxacin

## novel agents

TMC-207, PA-824,  
OPC-67683, SQ-109,  
PNU-100480

## 2<sup>nd</sup>- line drugs

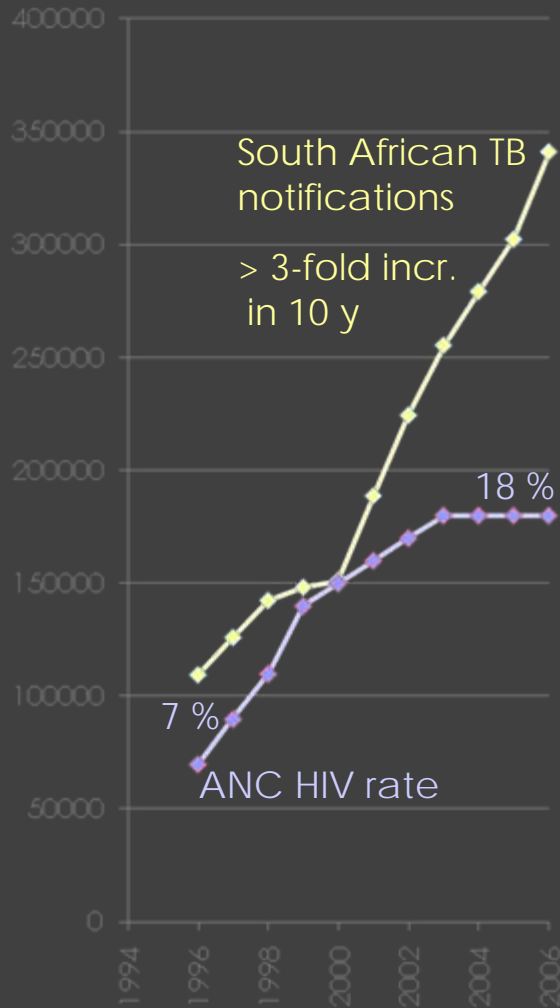
ofloxacin/levofloxacin  
aminoglycosides  
capreomycin  
ethionamide/  
prothionamide  
terizidone/cycloserine  
PAS

## 'role unclear'/efficacy not established

linezolid  
clofazimine  
co-amoxiclav.  
thioacetazone  
clarithromycin  
imipenem

## treatment of LTBI

# TB/HIV: duo of anarchy



9.4 million incident cases of TB in 2008

1.4 million (15%) with HIV infection

➤ 78 % of TB/HIV is in Africa

➤ 24% in South Africa

(71 % of TB cases have HIV)

15-20% of TB patients in hyper-endemic areas are children

*WHO/HTM/TB/2009.426: Global tuberculosis control: a short update to the 2009 report WHO-Nov. 2009. Int J Tuberc Lung Dis 2006, 10:259-63. Semin Pediatr Infect Dis 2004, 15:150-4.*

number of people receiving ART  
in low- and middle- income  
countries 2002–2008

“Start ART in all HIV-infected individuals with active tuberculosis (TB) irrespective of CD4 cell count.  
*(Strong recommendation, low quality of evidence)*”

WHO 2009 - rapid advice: antiretroviral therapy for HIV infection in adults and adolescents  
[[http://www.who.int/hiv/pub/arv/rapid\\_advice\\_art.pdf](http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf); accessed 22.03.2010].

Yves Souteyrand, HIV/AIDS Department, WHO, Geneva.  
Scaling up access to antiretroviral therapy in low- and middle-income countries: global and regional progress in 2008. Accessed 7.1.2010 at [http://www.ias2009.org/PAGMaterial/WELBD105\\_Souteyrand\\_1.ppt](http://www.ias2009.org/PAGMaterial/WELBD105_Souteyrand_1.ppt)

WHO/HTM/STB/2007.40. Accessed 28.3.2010 at  
<http://www.stophiv.org/resources/publications/>  
Journal of Clinical Pharmacology of HIV Therapy - 2010

# Antituberculosis DRUGS

std. short course chemother.

rifampicin

isoniazid

pyrazinamide

ethambutol

2<sup>nd</sup>- line drugs

ofloxacin/levofloxacin

aminoglycosides

capreomycin

ethionamide/

std. short course  
chemotherapy  
(SCC)

rifamycins are a key component of  
TB treatment regimens

Rifampicin

(rifampicin-based SCC in 146  
countries)

Rifapentine

Rifabutin

other rifamycins

rifabutin

rifapentine

'new' fluoroquinolones

moxifloxacin

gatifloxacin

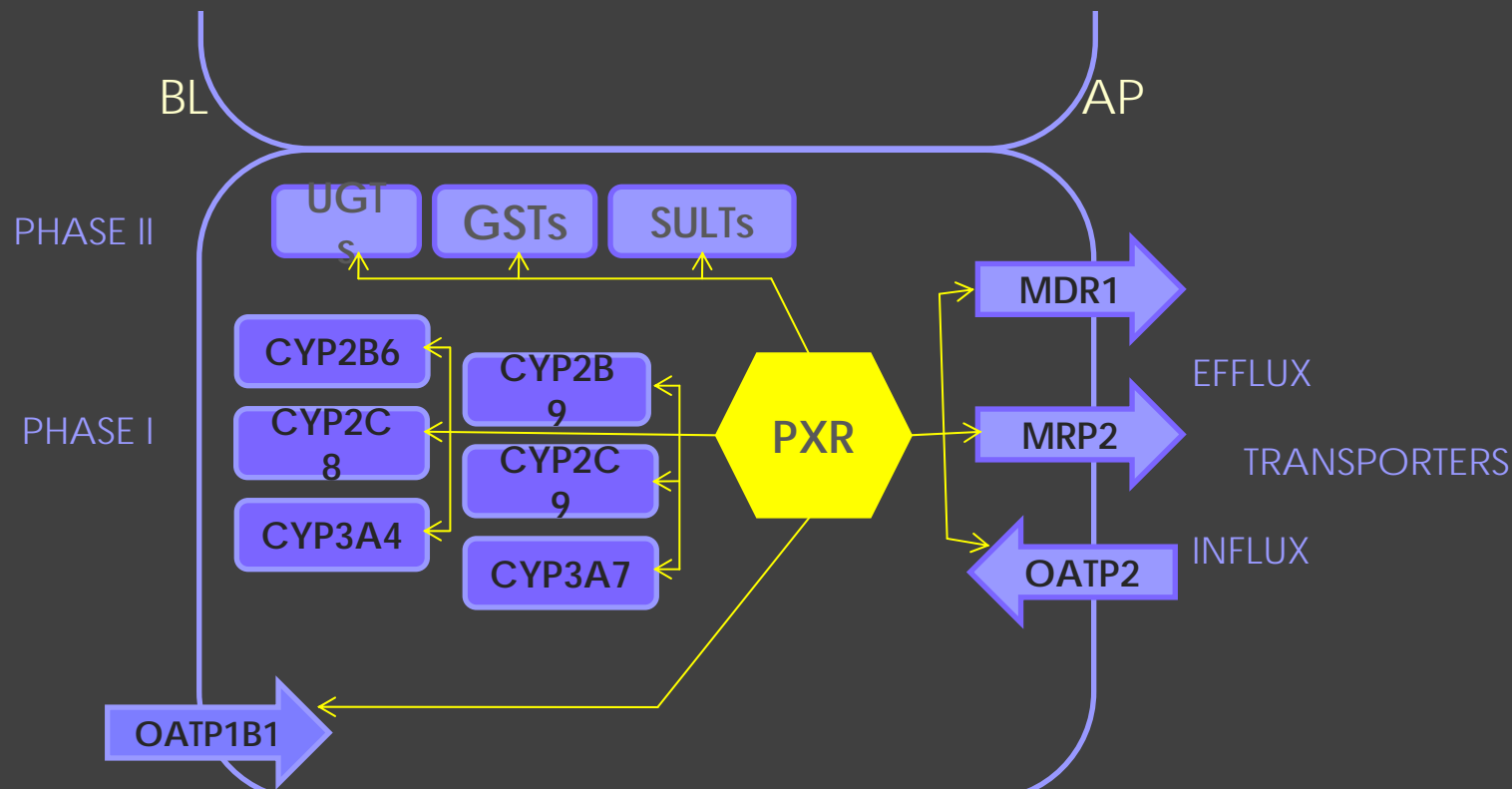
novel agents

diarylquinolines (TMC)

nitroimidazoles (PA-823)

OPC-67683), others

# PXR – powerful regulator of xenobiotic and endobiotic disposition



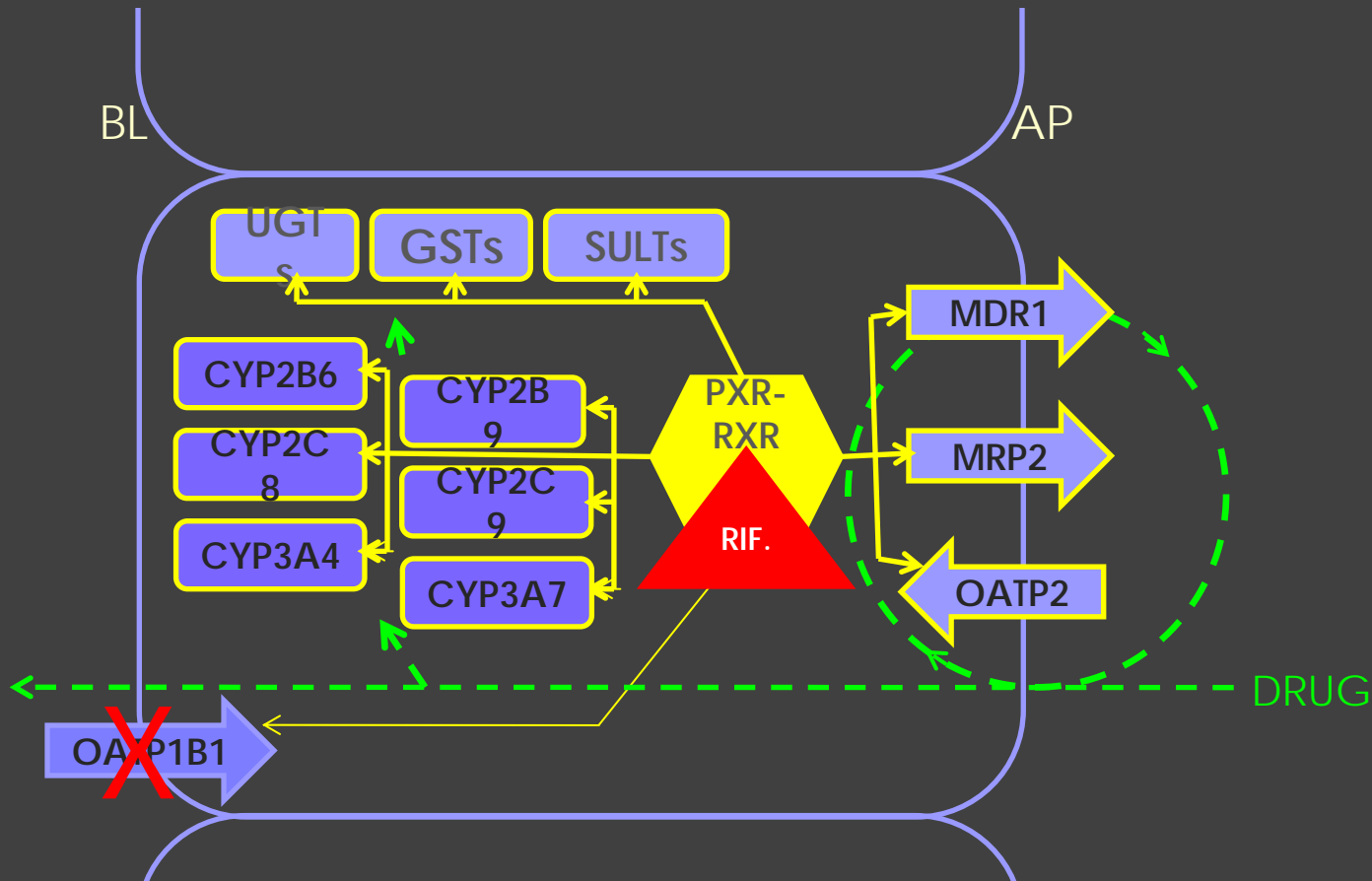
## BASELINE ACTIVITY:

- PXR
- enzymes & transporters

expression activity

*Pharmacogenomics 2008, 9: 1695–1709.  
Drug Metab Dispos 2006, 10:1756-63  
& 2007, 35:1400-7.*

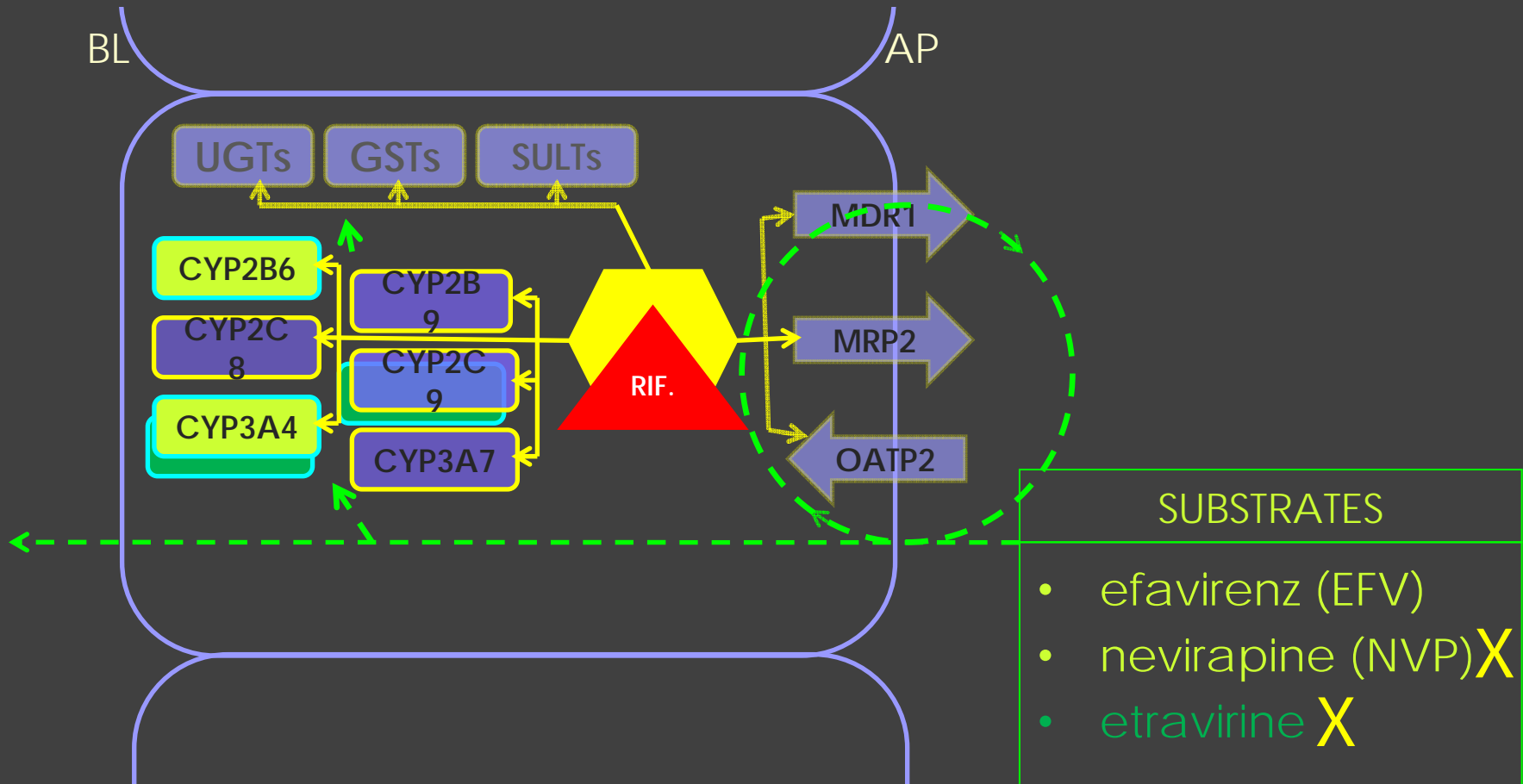
# the consequences of rifampicin



Activating ligands trigger altered expression of multiple of enzymes and transporters, with compound effects on substrate concentrations.

*J Pharmacol Exp Ther* 2003, 304: 223-28

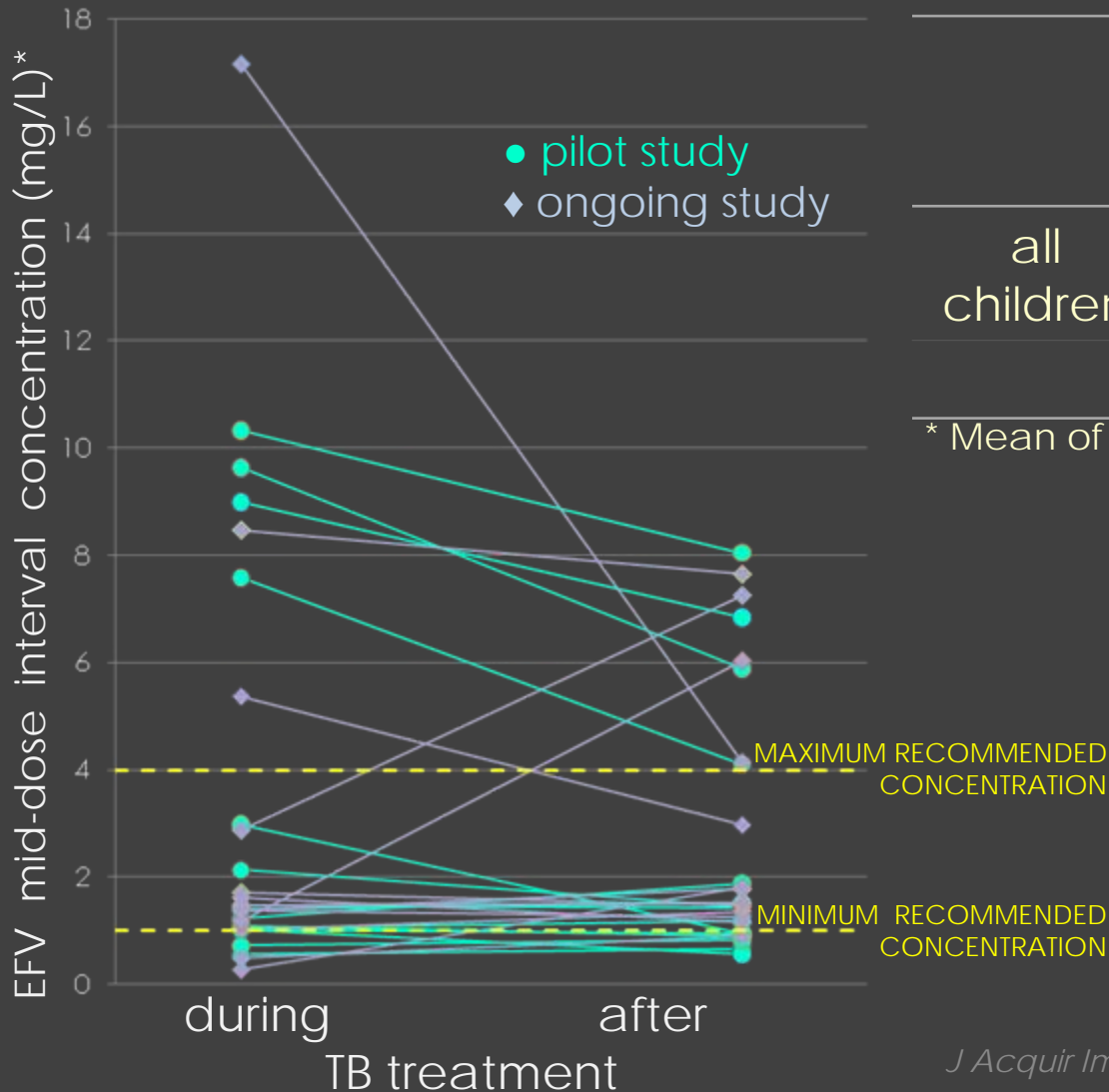
# PK interactions – NNRTIs + rifampicin



Centers for Disease Control and Prevention. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. MMWR 2009;58(#RR-4).

CDC guidelines:  
'Do not coadminister'

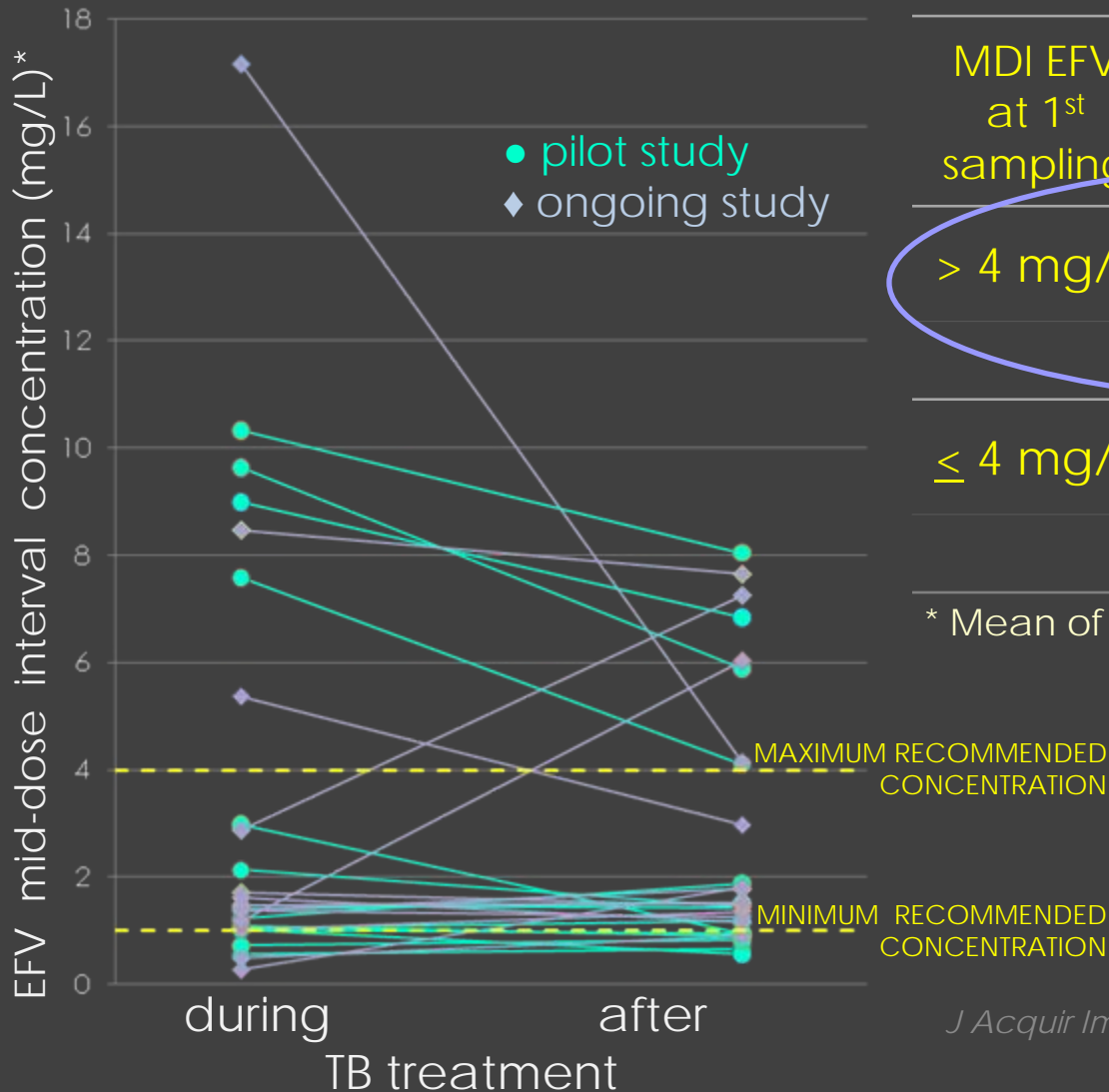
# the effect of rifampicin-based TB treatment on EFV concentrations in children



|              | n  | Med. (IQR) EFV            |                           |
|--------------|----|---------------------------|---------------------------|
|              |    | during TB                 | after TB                  |
| all children | 28 | 1.43 mg/L<br>(1.03, 4.17) | 1.49 mg/L<br>(1.05, 4.12) |
| NS           |    |                           |                           |

\* Mean of 3 concentrations, 12-24 h after the dose

# the effect of rifampicin-based TB treatment on EFV concentrations in children



| MDI EFV at 1 <sup>st</sup> sampling | n | Med. (IQR) EFV             |                           |
|-------------------------------------|---|----------------------------|---------------------------|
|                                     |   | during TB                  | after TB                  |
| > 4 mg/L                            | 7 | 8.99 mg/L<br>(7.58, 10.33) | 5.89 mg/L<br>(4.11, 7.65) |
| <i>p</i> =0.018                     |   |                            |                           |

|           |    |                           |                           |
|-----------|----|---------------------------|---------------------------|
| ≤ 4 mg/L  | 21 | 1.22 mg/L<br>(1.03, 1.47) | 1.36 mg/L<br>(0.94, 1.52) |
| <i>NS</i> |    |                           |                           |

\* Mean of 3 concentrations, 12-24 h after the dose

*J Acquir Immune Defic Syndr* 2009, 50:439-43; *AIDS* 2005, 19:1541-6; *AIDS* 2009, 23:742-4.

## Prospective studies do not show significant reductions in EFV concentrations during TB treatment:

Spain, South Africa (2 studies in adults), India, Thailand

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*Clin Pharmacokinet* 2002,41:681. *JAC* 2006,58:1299-1302. *Antivir Ther* 2009, 14:687-95. *JAIDS* 2009;50:439. *AAC* 2009;53:863. *AIDS Res Ther.* 2010, 7:8 [doi:10.1186/1742-6405-7-8]

## Determinants of EFV concentrations in TDM samples; retrospective multivariate analysis; n=339

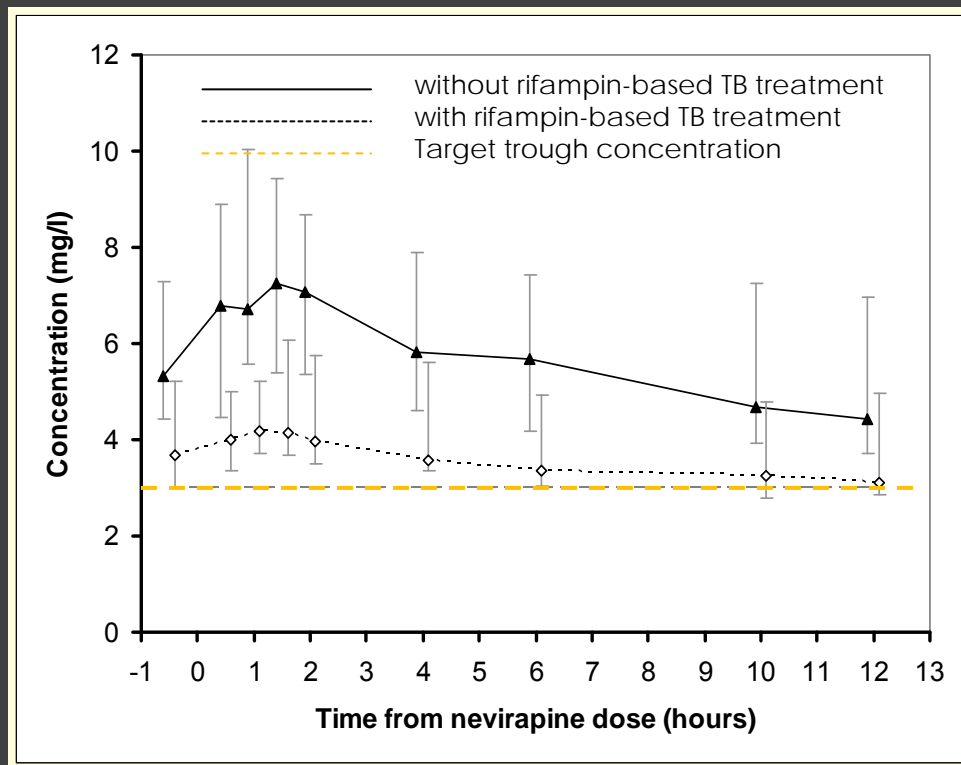
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|                      |                 |
|----------------------|-----------------|
| Black ethnicity      | +59% (+27, +98) |
| body weight (/10 kg) | -10% (-15, -4)  |
| EFV dose 800 mg/d    | +52% (+5, +119) |
| rifampicin           | -35% (-56, -2)  |
| zidovudine           | -25% (-39,-7)   |

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*Antiviral Ther* 2008, 13: 675-85

# NVP concentrations in adults with rifampicin-based TB treatment



$C_{\min} < 3 \text{ mg/L}$

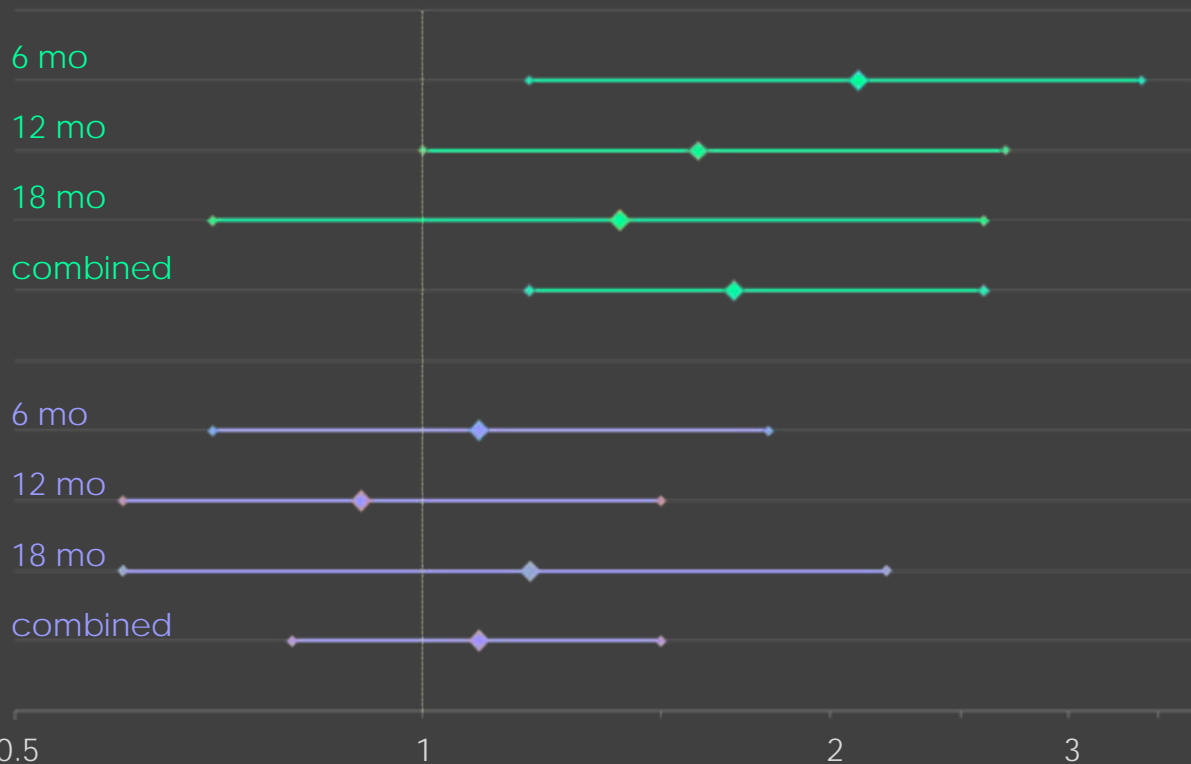
|                  | LEAD IN<br>(200 mg 1x/d) | FULL DOSE<br>(200 mg 2x/d) |
|------------------|--------------------------|----------------------------|
| Malawi [1]       | 59%                      | 14%                        |
| Mozambique [2]   | N/A                      | 13%                        |
| Thailand [5,6,7] | 79%                      | 12-23%                     |
| South Africa [3] | -                        | 38%                        |
| Burkina Faso [4] | -                        | 31-40%                     |
| Uganda [8]       | 86%                      | 64%                        |

[1] *Antiviral Ther* 2007, 12: 515-21. [2] *AIS Conference 2009, Abstract #WEPEB253*. [3] *J Antimicrob Chemother* 2008, 61: 389-93. [4] *J Acquir Immune Defic Syndr* 2009,52:64-9. [5] *Antivir Ther* 2005, 10:937-43. [6] *Clin Infect Dis* 2007, 44:141-4. [7] *Antivir Ther* 2008, 13: 529-36. [8] *CROI 2010, #602*.

# risk of virologic failure when EFV- or NVP-based ART started in South African patients on TB treatment vs. patients without TB treatment

**NVP: n=1935 (209 with TB)**

84% on NVP with TB had VL<400 at 6 months

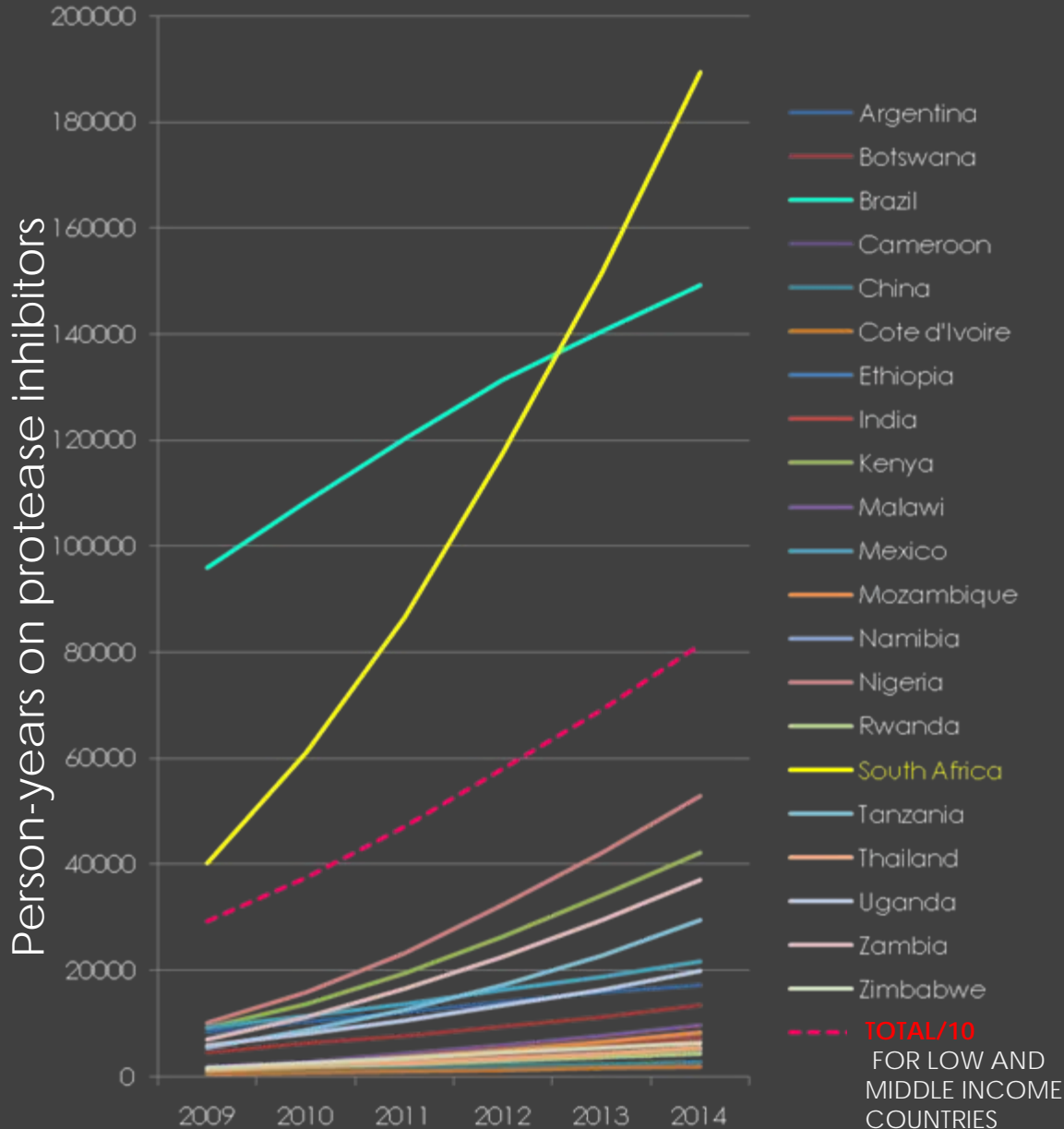


**EFV: n=2035 (1074 with TB)**

EFV used at standard doses

ODDS RATIO OF VL > 400  
(adjusted for age, sex, and baseline CD4+ cell count)

# projected use of PI-based ART



ADULTS  
- failed 1<sup>st</sup> line ART

Infants and young children  
- 1<sup>st</sup> line

Data courtesy of Drs D Ripin and M O'Brien (CSHOR), Clinton Health Access Initiative [05.01.2010].

- rifampicin reduces AUC of protease inhibitors

DO NOT CO-ADMINISTER

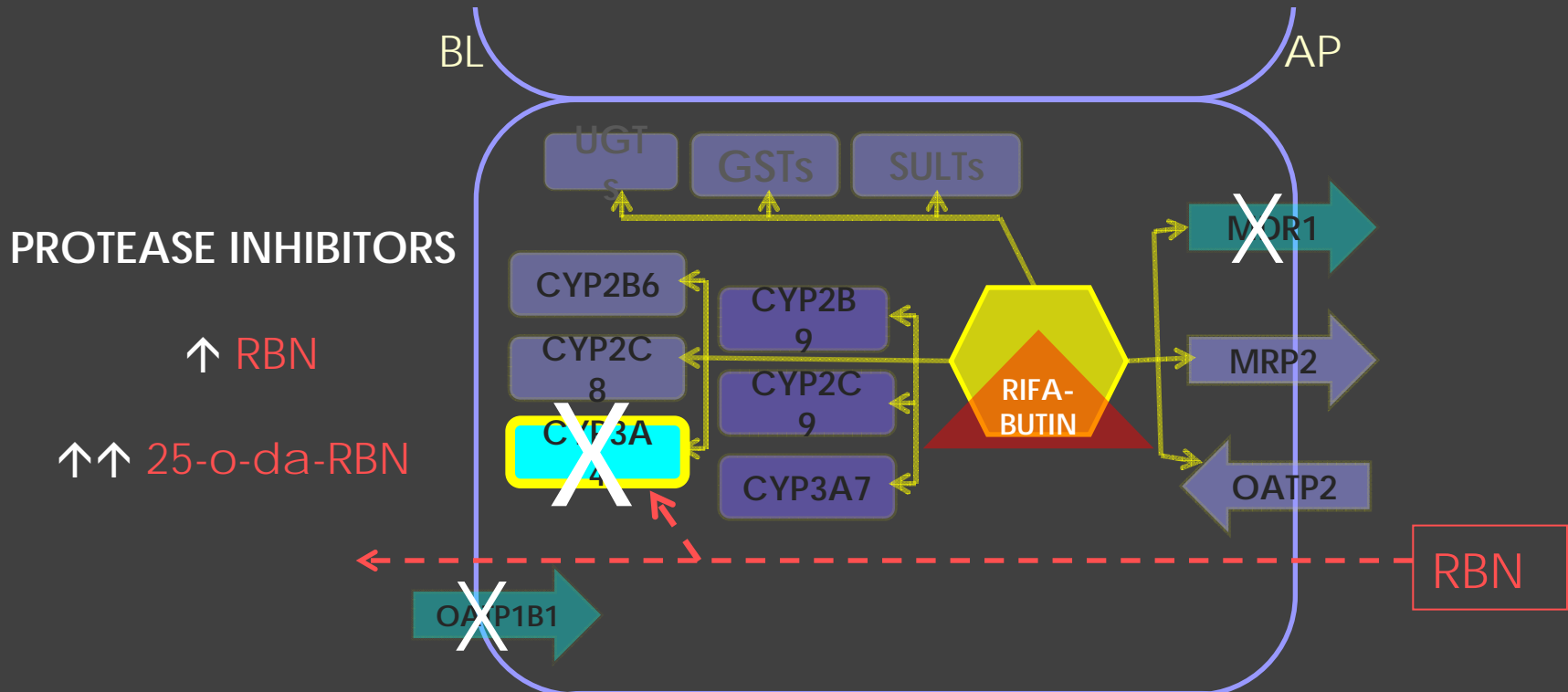
*Centers for Disease Control and Prevention. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. MMWR 2009; 58(No. RR-4)*

- **hepatotoxicity in HNVs on rifampicin + adjusted PI doses**

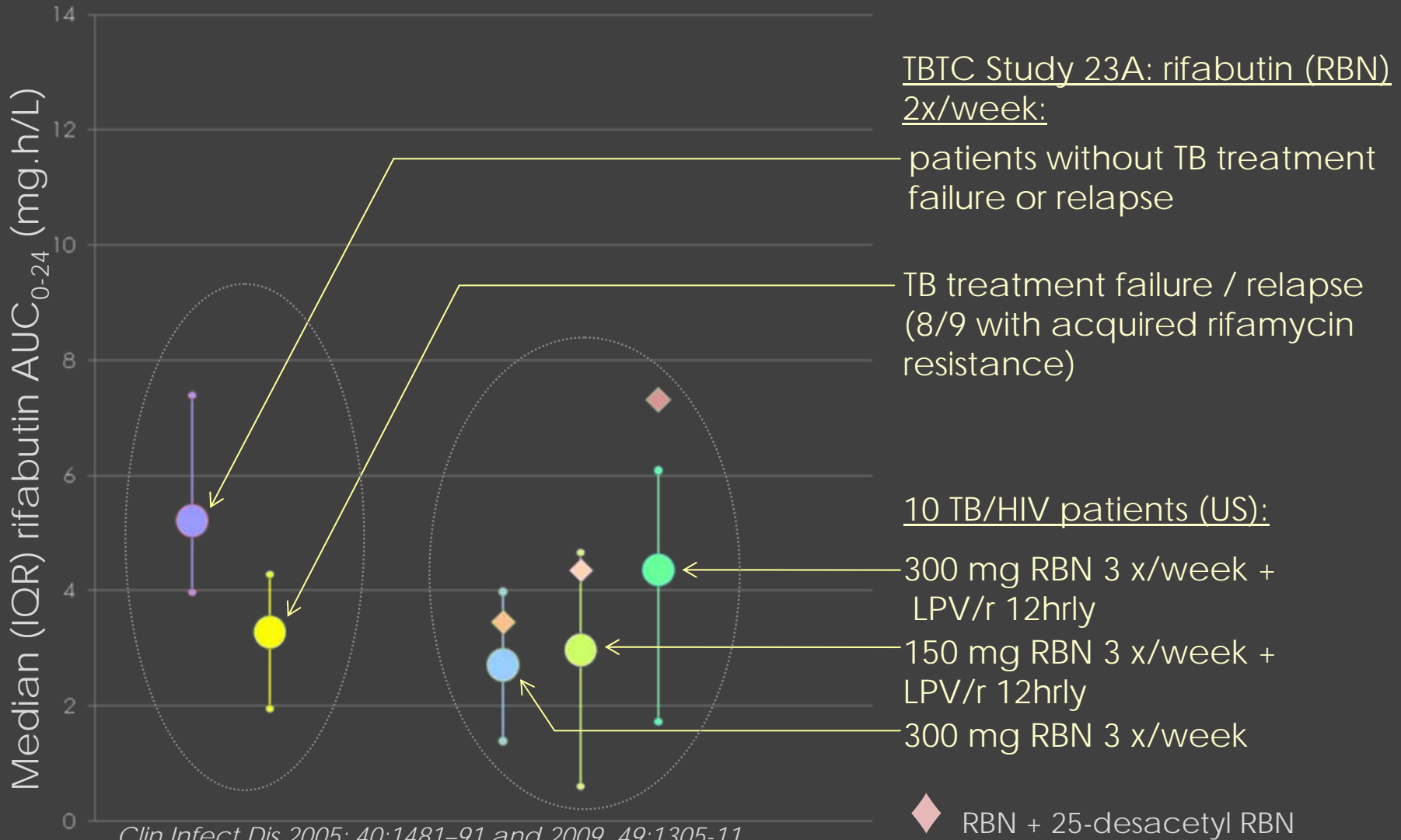
*CDC 2007. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis [http://www.cdc.gov/tb/TB\_HIV\_Drugs/PDF/tbhiv.pdf].*

*Antimicrob Agents Chemother 2004; 48:1553–60. AIDS 2008, 22:931–935*

# PK interactions – PIs + rifabutin (RBN)



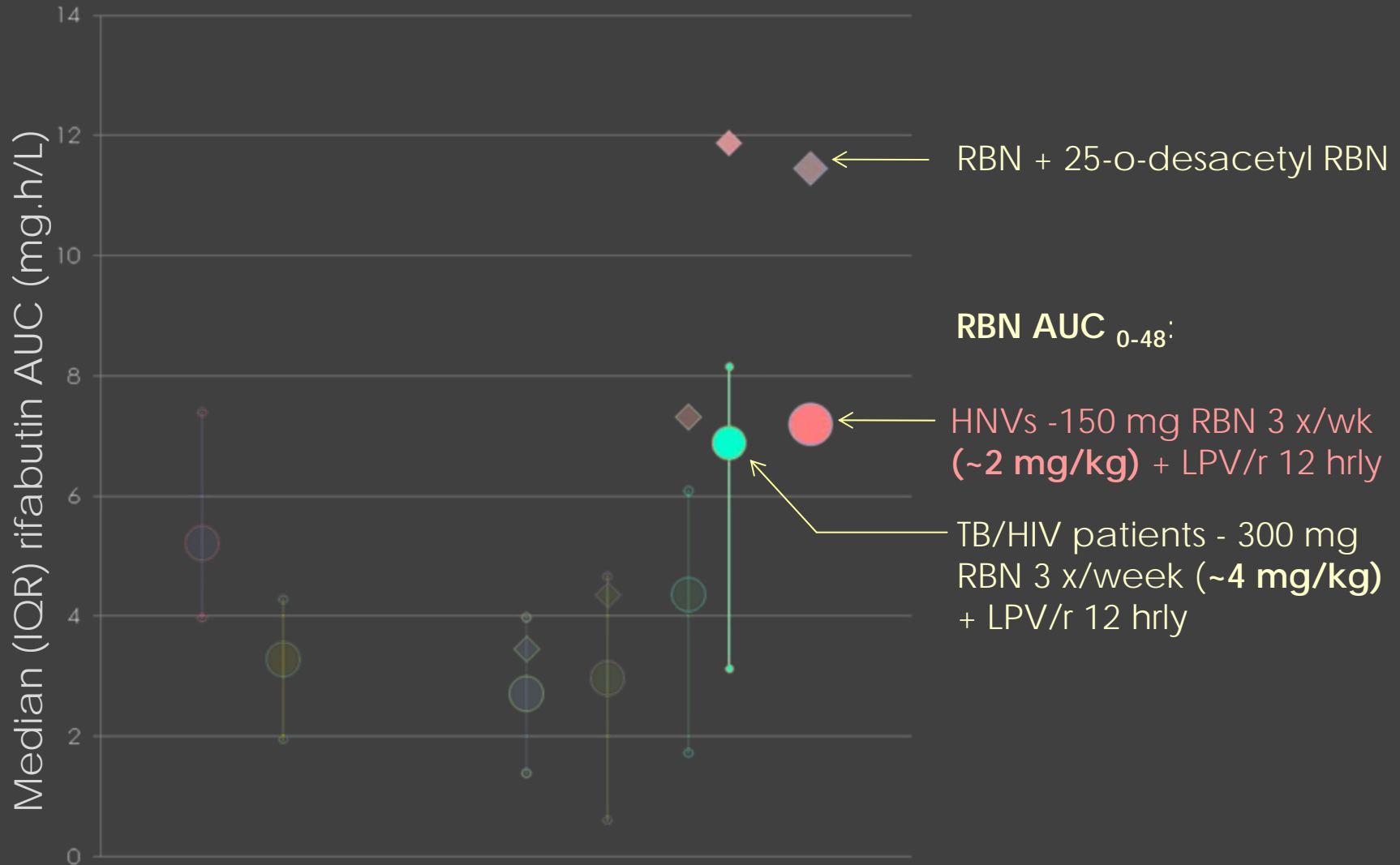
# rifabutin in HIV infected patients



*Clin Infect Dis* 2005; 40:1481-91 and 2009, 49:1305-11

Presented at the 11<sup>th</sup> International Workshop on Clinical Pharmacology of HIV Therapy - 2010

# rifabutin – safety concerns



*Clin Infect Dis* 2009, 49:1305-11; 10<sup>th</sup> Int WS Clin Pharm HIV Ther 2009, # O\_21

# lopinavir (LPV)/ritonavir(RTV) with rifampicin-based TB treatment

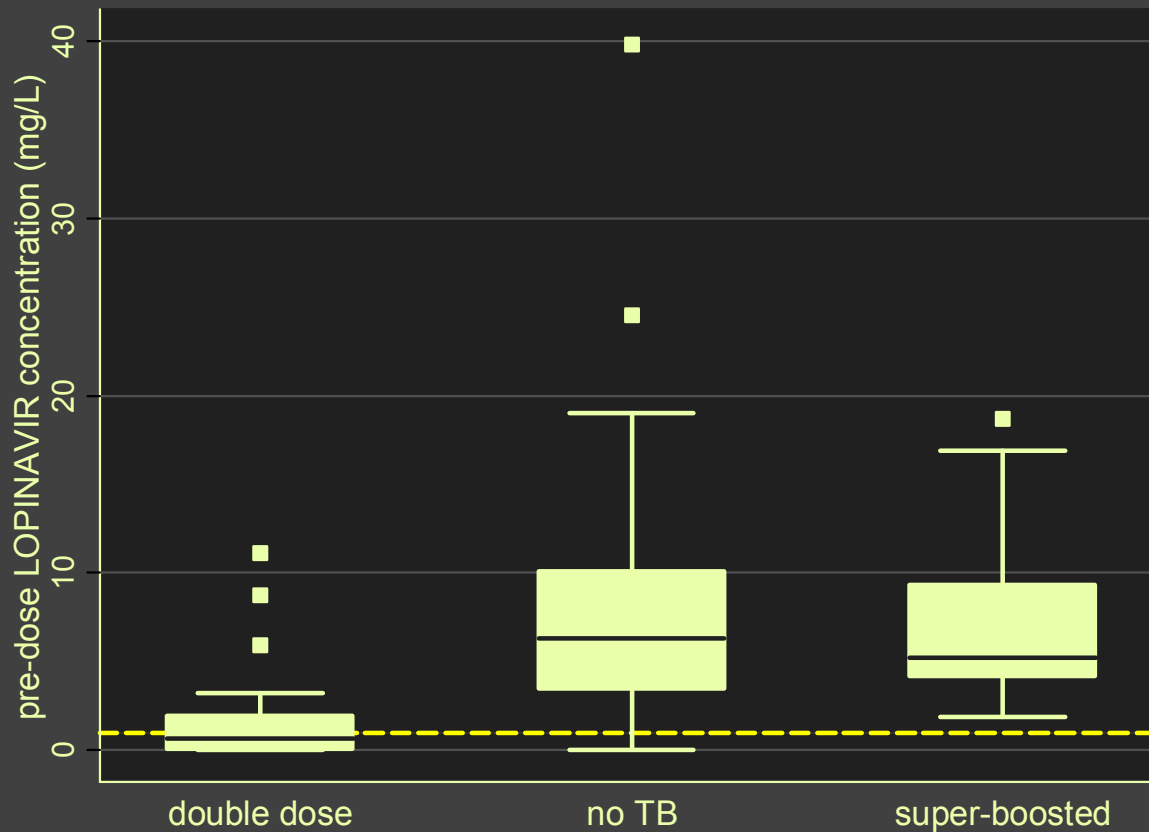
- rifabutin access is limited (although improving)
- rifampicin is established in programmes and in FDCs

LPV/RTV=400/400 mg  
"super-boosted LPV"

LPV/RTV=800/200 mg  
"double dose LPV/RTV"

} adequate LPV  
concentrations in  
adult HNVs

# LPV concentrations in children with and without TB



|             |             |            |           |
|-------------|-------------|------------|-----------|
| median:     | 0.69 mg/L   | 6.34 mg/L  | 5.20 mg/L |
| <1 mg/L:    | 12/20 (60%) | 5/51 (10%) | 0/15      |
| median age: | 1.3 y       | 1.9 y      | 1.3 y     |

*J Acquir Immune Defic Syndr.* 2008; 47:566-9; 16<sup>th</sup> CROI 2009, abstract # 98

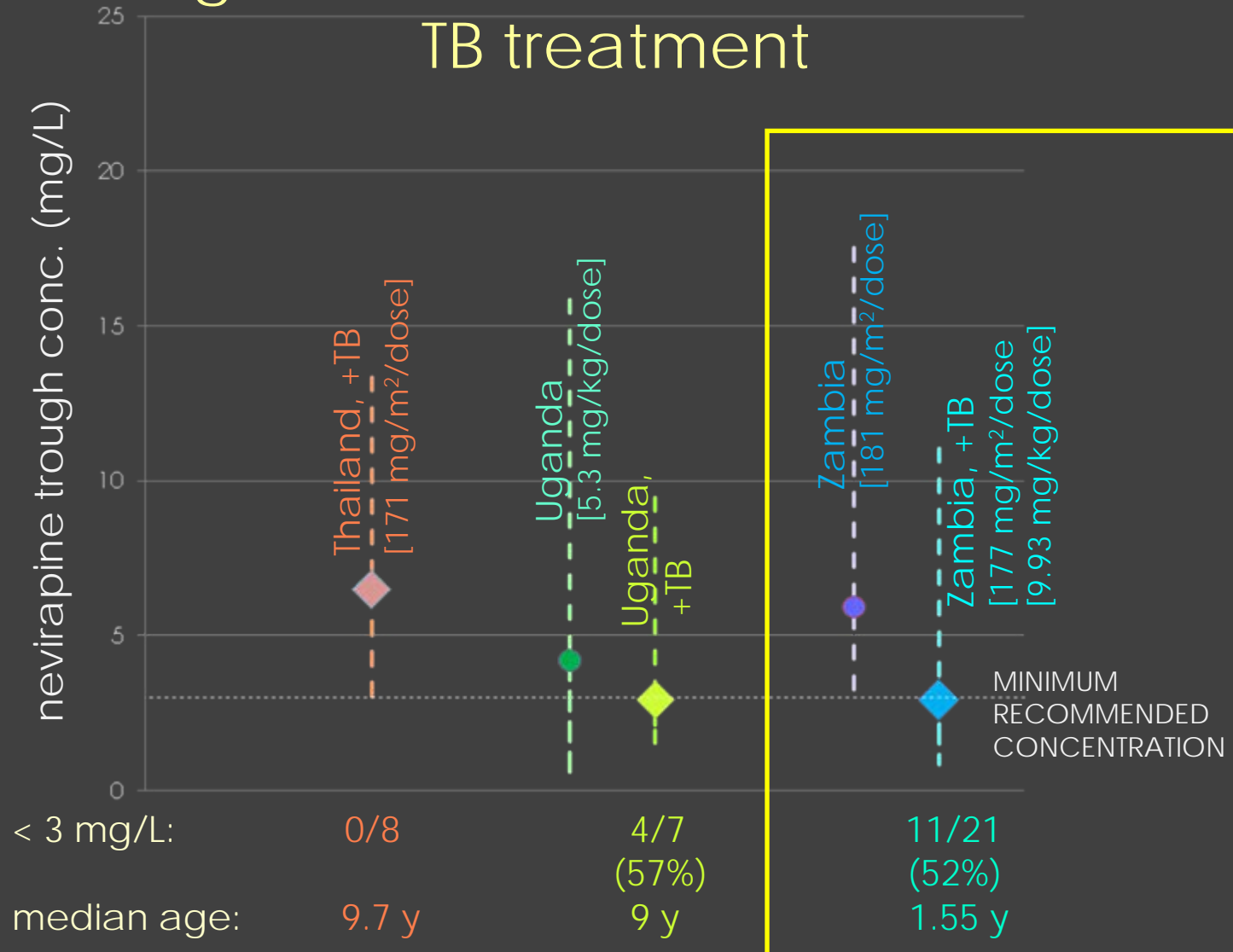
8 hourly dose of LPV in LPV/r oral solution required to maintain LPV concentration > 1 mg/L in  $\geq 95\%$  of children

| weight     | actual median dose/12 h | predicted 8 hourly dose required to maintain LPV concentration > 1 mg/L in $\geq 95\%$ of children |            |
|------------|-------------------------|--|------------|
| 4-5.9 kg   | 26 mg/kg                | 65 mg/kg   | (RD X 5.4) |
| 6-7.9 kg   | 26 mg/kg                | 50 mg/kg   | (RD X 4.2) |
| 8-11.9 kg  | 23 mg/kg                | 37 mg/kg   | (RD X 3.1) |
| 12-17.9 kg | ----                    | 30 mg/kg   | (RD X 2.5) |

RD: 12 mg/kg 12 hrly (std. recommended dose for children > 6 months and < 15 kg)

*Modeling and Simulation: Chao Zhang and Paolo Denti, Div. Clin. Pharm. Univ. Cape Town*

# NVP trough concentrations in children during TB treatment



*AIDS 2005, 19:1495-9. CROI 2009, abstract #909. CROI 2009 abstract #908. 5<sup>th</sup> IAS Conference, abstract # LBPEB10, Dr L Barlow-Mosha, Personal communication, 01.2010.*

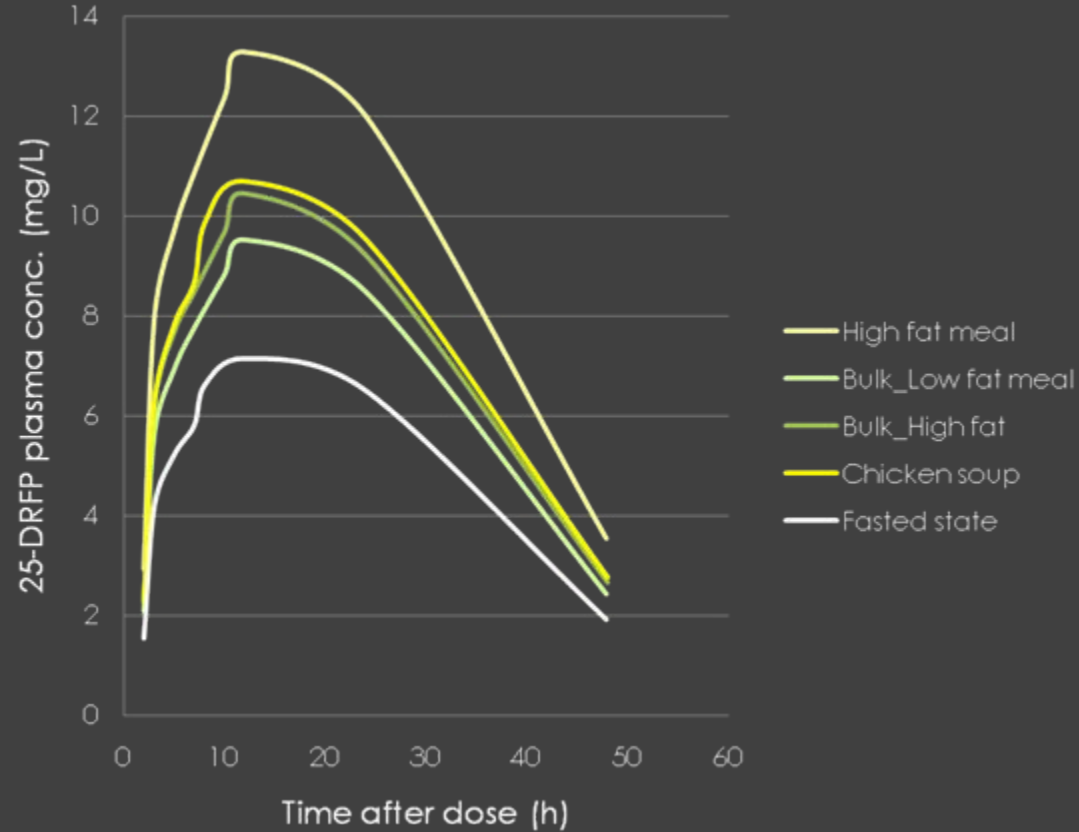
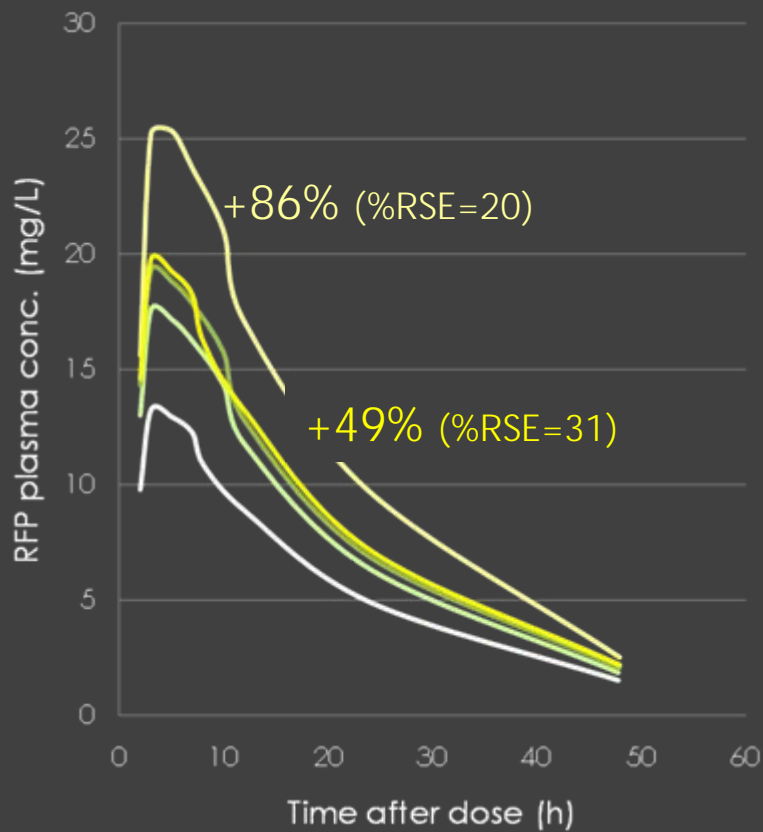
# Urgent need for safe, effective and feasible co-treatment regimens in young children

- EFV is not used in children <3 years-old
- low NVP concentrations during TB treatment in > 50%
- PI-based ART is recommended if exposed to NVP or EFV
  - No rifabutin pediatric formulation
  - Super-boosting of LPV with extra RTV is not feasible in many settings
- triple NRTI regimens are associated with high rates of NRTI mutations and virologic failure in children without TB. The consequences of reductions in ABC or ZDV concentrations due to rifampicin is not known

*WHO Antiretroviral Therapy for Infants and Children 2008; CROI 2010, #879; 4<sup>th</sup> IAS Conf. 2007, # TUBE053*

Presented at the 11<sup>th</sup> International Workshop on Clinical Pharmacology of HIV Therapy - 2010

rifapentine – emerging regimens should be evaluated under food conditions that can realistically be expected under program conditions



*PK modeling and graphics: Simbarashe Zvada*

# FQs in emerging TB regimens

- anti-TB activity: **moxifloxacin & gatifloxacin** (> ofloxacin)
- generally well tolerated
- potential safety interactions with ARVs:
  - **QT prolongation**, hepatotoxicity, dysglycaemia
- potential PK interactions with ARVs
  - chelation by multivalent anions (buffered ddl)
  - moxifloxacin UGT, SGT substrate

## ***WITHIN TB REGIMEN INTERACTIONS:***

moxifloxacin + rifampicin

moxi.  $AUC_{0-24}$  GMR 0.73 (90% CI 0.64, 0.84)  
0.69 (90% CI 0.65, 0.74)

moxifloxacin + rifapentine

moxi.  $AUC_{0-24}$  GMR 0.83 (0.77–0.89)

gatifloxacin + R/H/Z

gati.  $AUC_{0-\infty}$  GMR 1.14 (1.10, 1.18);  
rif.  $AUC_{0-\infty}$  GMR 0.88 (0.81, 0.96)

*Antimicrob Agents Chemother* 2007, 51:2861–6 and 2008, 52:4037-42; *J Antimicrob Chemother.* 2007; 60:1398-401; *Clin Infect Dis* 2007, 45:1001–7. *J Int. AIDS Soc.* 2008, 11: S95 (abstr); *J Infect* 2008; 57, 78-81

# Antituberculosis DRUGS

- novel mechanisms: DS - and DR – TB
- promising sterilizing activity

no important PK interactions  
with isoniazid/pyrazinamide

results awaited: PK interaction  
studies with EFV, NVP, LPV/r

long half-life

CYP 3A4  
substrate

no hepatic  
metabolism

CYP 2D6  
CYP 2C19  
substrate

## novel agents

diarylquinolines (TMC207)

nitroimidazoles (PA-824,  
OPC-67683)

ethylenediamines (SQ-109)

oxalidinones (PNU-100480)

# Antituberculosis DRUGS

std. short course chemother.

rifampicin

isoniazid

pyrazinamide

ethambutol

M/XDR-TB

• 0.5 million cases

• drugs more toxic and less

effective; treatment lengthy

other drugs

rifabutin

rifapentine

• 2 % getting appropriate treatment

'new' fluoroquinolones

• in the therapeutically destitute,

ART may be the most effective

intervention available

moxifloxacin

gatifloxacin

novel agents

• limited information about

interactions

diarylquinolines (OPC-67683),

nitroimidazoles (PA-827),

OPC-67683), others

2<sup>nd</sup>- line drugs

ofloxacin/levofloxacin

aminoglycosides

capreomycin

ethionamide/

protionamide

terizidone/cycloserine

PAS

'role unclear'

linezolid

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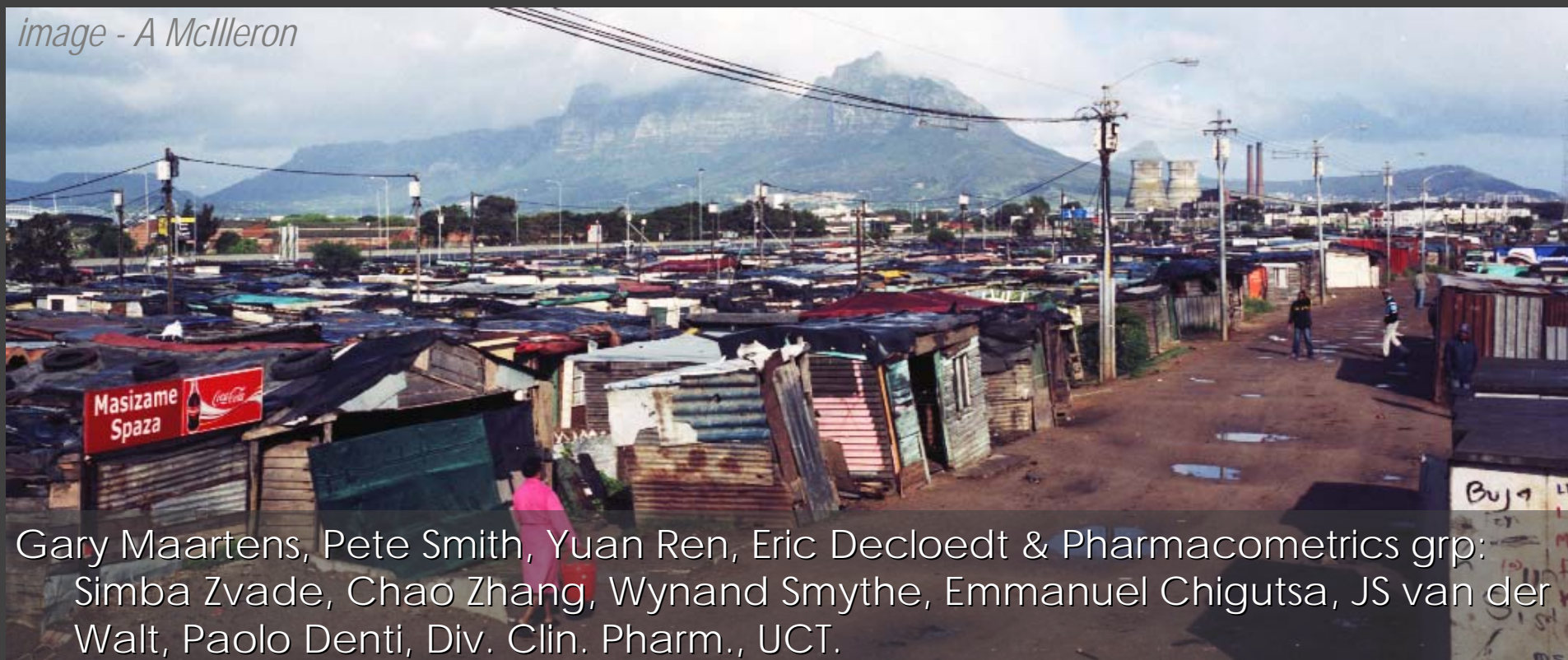
thioacetazone

clarithromycin

imipenem

treatment of LTBI





Gary Maartens, Pete Smith, Yuan Ren, Eric Decloedt & Pharmacometrics grp:  
Simba Zvade, Chao Zhang, Wynand Smythe, Emmanuel Chigutsa, JS van der  
Walt, Paolo Denti, Div. Clin. Pharm., UCT.

James Nuttal, Harry Moultrie, Brian Eley, Tammy Meyers, Mark Cotton, Helena  
Rabie, Mackie Prins, Cynthia Dalamo, Hermien Gous, Shenaaz Raiman, and  
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VIROLOGY EDUCATION, Organizing Com. 11<sup>th</sup> Int. WS Clin. Pharm. HIV