Strategies for co-treatment:

1st and 2nd line ART and TB treatment

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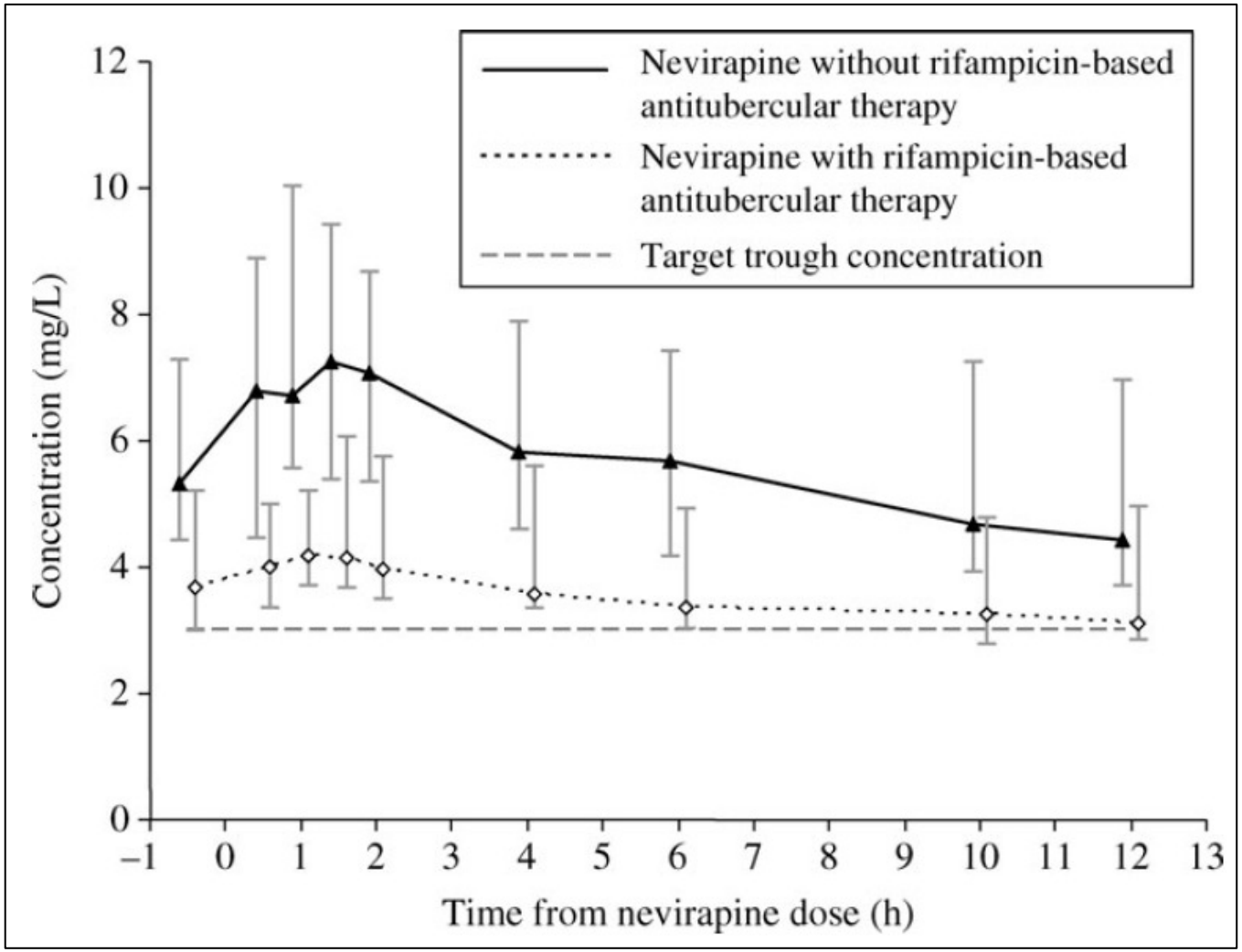
Rifampicin induction

Enzyme/transporter	**ARV substrate**
CYP3A4 CYP2B6	PIs, NVP EFV
P glycoprotein	PIs

1st line regimen:

Rifampicin & NNRTIs

Impact of rifampicin on nevirapine PK



Cohen K JAC 2008;61:389

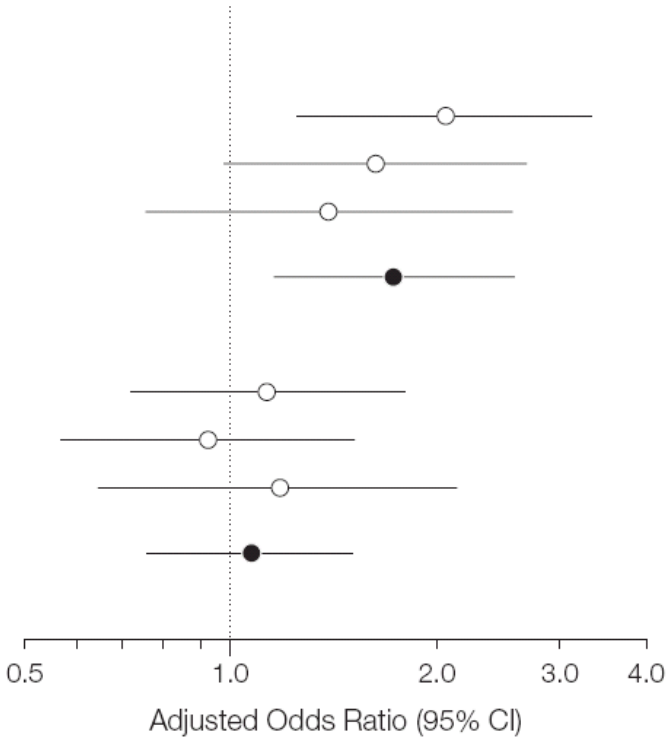
Rifampicin effect on EFV PK

- PK studies in patients with TB show no significant effect:
  - Spain
  - South African adults (2 studies) & children
  - India
- Package insert says AUC reduced 26% (n=12, no P value given)
- Retrospective TDM database found significant reduction in EFV concentrations

Clin Pharmacokinet 2002;41:681
JAC 2006;58:1299
Cohen K Antivir Ther in press
JAIDS 2009;50:439
AAC 2009;53:863
Antivir Ther 2008;13:675

MSF Khayelitsha cohort: Risk of virologic failure when ART commenced on TB R_x

	Viral Load ≥400 Copies/mL		Adjusted Odds Ratio[a] (95% CI)
Nevirapine	No. (%[95% CI]) Without TB	No. (%[95 CI]) With TB	
6 mo	93 (8.3 [6.7-10.0])	23 (16.3 [10.6-23.5])	2.1 (1.2-3.4)
12 mo	96 (12.2 [10.0-14.7])	23 (20.0 [13.1-28.5])	1.6 (1.0-2.7)
18 mo	73 (14.0 [11.2-17.3])	16 (20.0 [11.9-30.4])	1.4 (0.7-2.6)
Combined[b]			1.7 (1.2-2.6)
Efavirenz			
6 mo	35 (5.7 [4.0-7.9])	45 (6.4 [4.7-8.4])	1.1 (0.7-1.8)
12 mo	35 (8.1 [5.7-11.0])	34 (8.0 [5.6-11.0])	0.9 (0.6-1.5)
18 mo	24 (10.4 [6.8-15.1])	25 (11.5 [7.6-16.5])	1.2 (0.6-2.2)
Combined[b]			1.1 (0.8-1.5)



EFV n=2035 (1074 with TB) & NVP n=1935 (209 with TB)
EFV used at standard doses
84% on NVP with TB VL<400 at 6 months

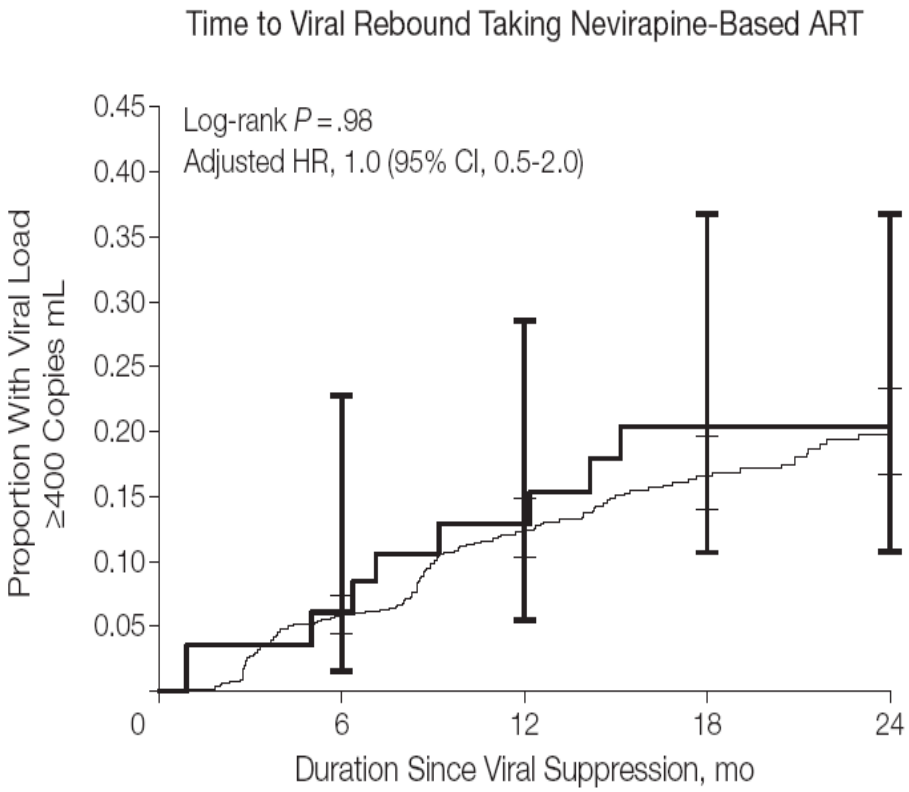
Boulle JAMA 2008;300:530

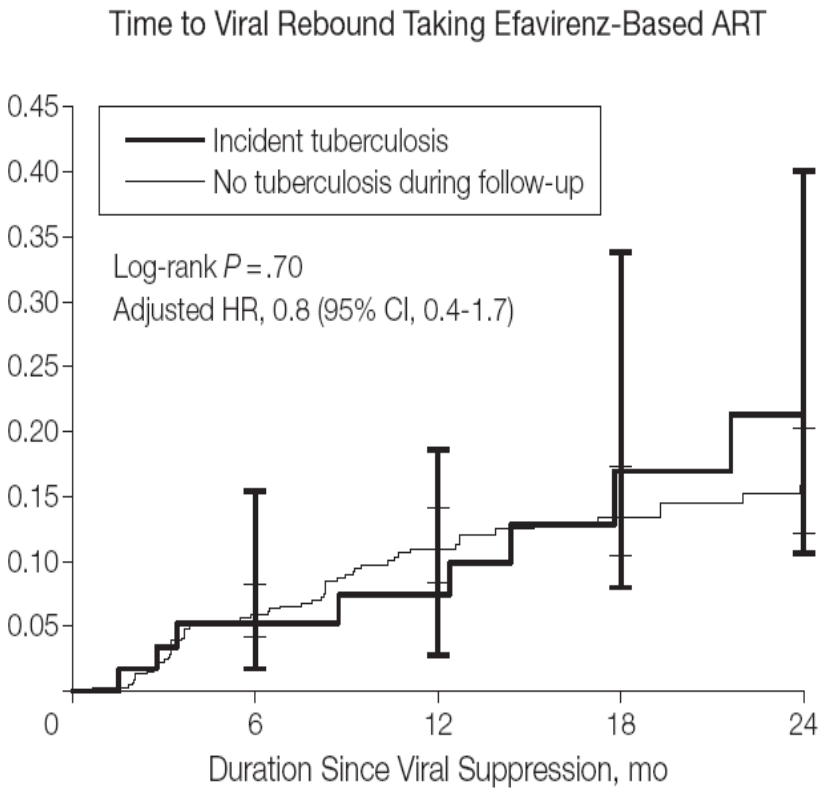
Other effectiveness studies: NVP vs EFV

- No difference noted 2 other studies:
  - Retrospective cohort Botswana n=310 (NVP+TB = 55; EFV+TB=100)
  - RCT Thailand n=142
- Large RCT started Mozambique (ANRS due to end 2011)

Int J Tuberc Lung Dis 2009;13:360
Manosuthi CID 2009

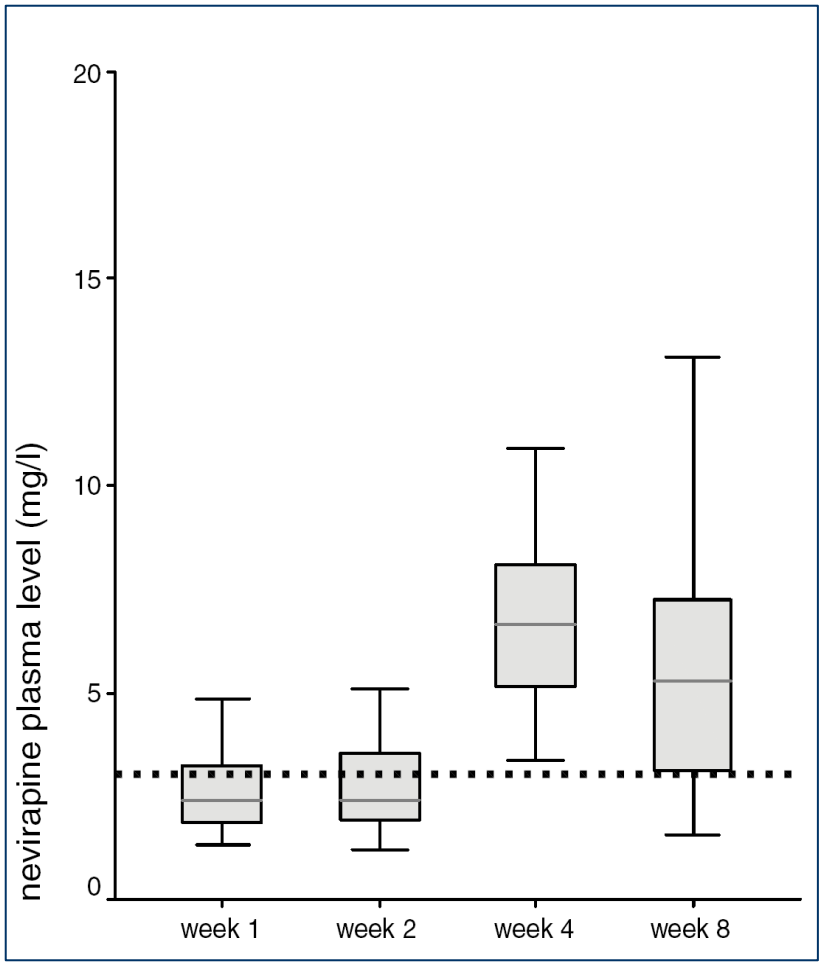
MSF Khayelitsha cohort: ART commenced before TB treatment





Boulle JAMA 2008;300:530

Low NVP concentrations in Malawians on TB treatment during NVP lead-in dose phase



Thai study

High-dose (NVP 200 mg 12 hourly lead-in then 300 mg 12 hourly) vs standard doses with rifampicin.

Hypersensitivity reactions:

4/16 high vs 1/16 standard-dose

P=0.33

Antivir Ther 2007;12:515-21
Antivir Ther 2008;13:529-36

NNRTI tolerability withTB Rx

- Drug substitution for toxicity
  - EFV HR 0.99 (95%CI 0.4-2.0) **no lab monitoring**
  - NVP HR 1.50 (95%CI 0.8-2.8)
- Grade 3 or 4 LFT lab abnormality
  - EFV HR 8.5 (95%CI 2.7-27)

AIDS 2007;21;1301
JAMA 2008;300:530

Research priorities: 1st line regimen

- Adequately powered RCT EFV vs NVP
- Effectiveness & PK studies in children
- Safety of omitting NVP lead-in dose, as when switching from EFV to NVP

HIV Med 2008;9:514

2nd line regimen:

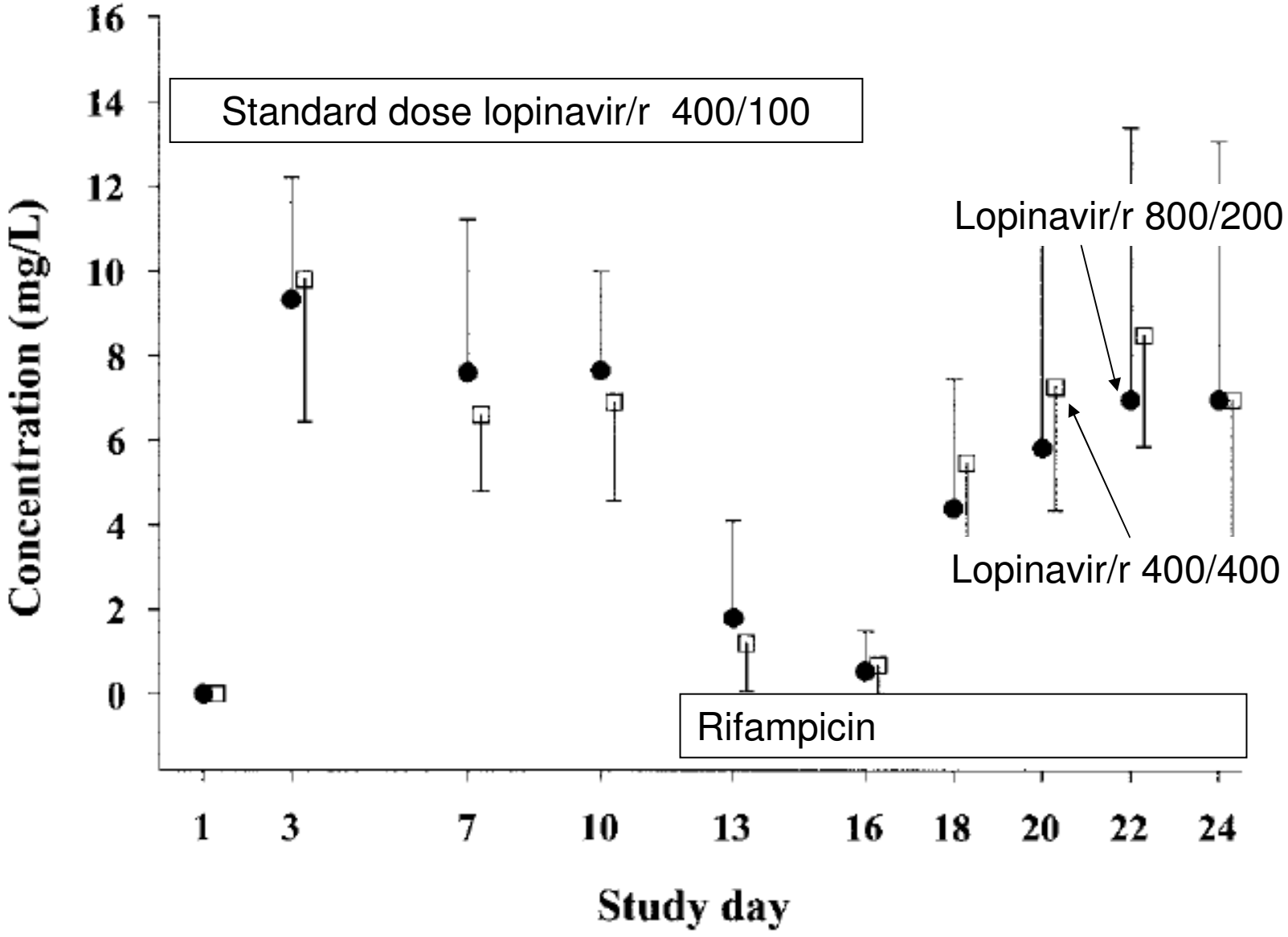
Rifampicin & boosted PIs

Rifampicin decreases AUC of all protease inhibitors

PI	Rifampicin
Saquinavir	**↓ 84%**
Atazanavir	**↓ 95%**
Indinavir	**↓ 89%**
Nelfinavir	**↓ 82%**
Amprenavir	**↓ 81%**
Lopinavir/ritonavir	**↓ 75%**

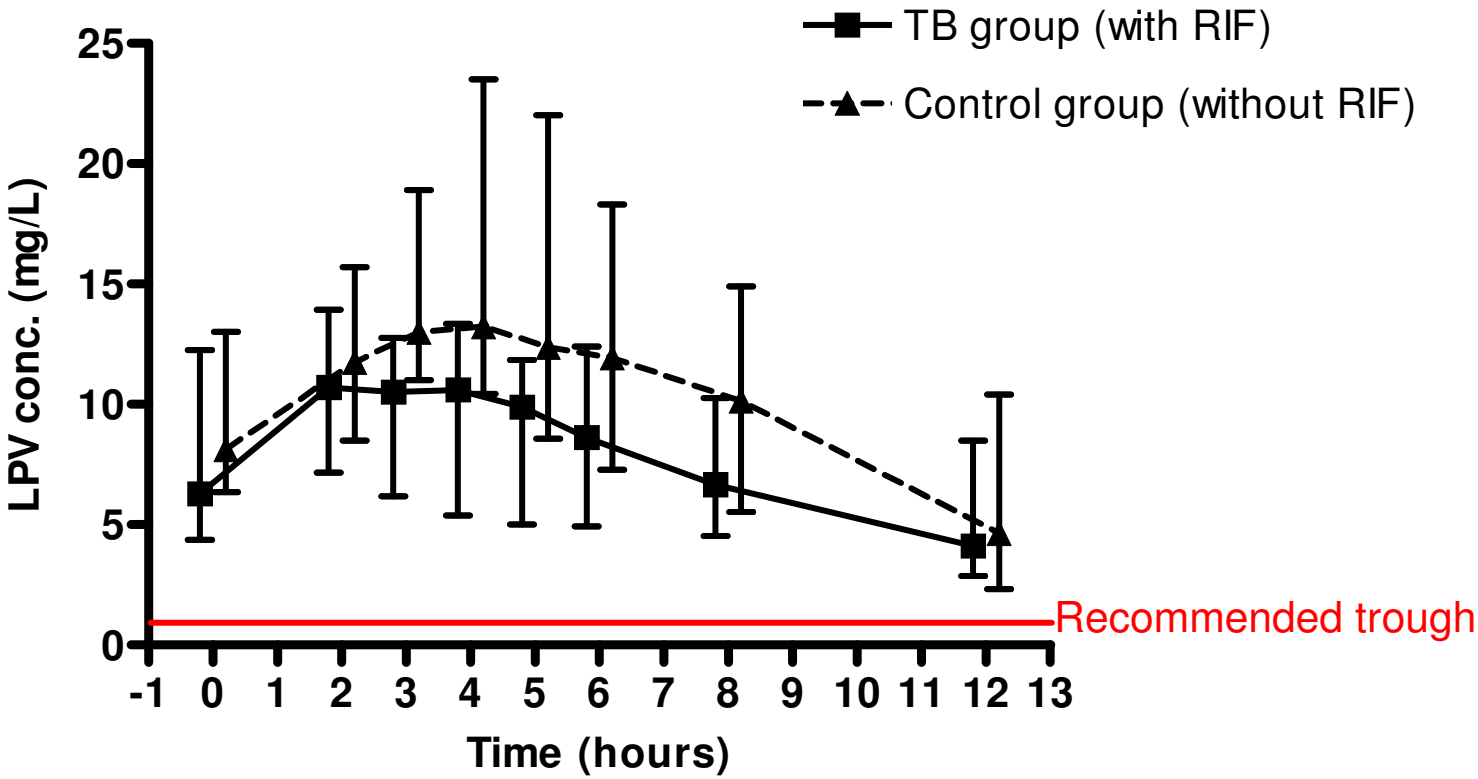
CDC 2008

“Super boosted” lopinavir/r & rifampicin



La Porte C AAC 2004;48:1553

Lopinavir/r + RTV in SA children with TB



PK measures Median (IQR)	**TB Group LPV:RTV=1:1**	**Control Group LPV:RTV=4:1**	***P***
T_{max} (hr)	3.0 (2.0, 4.07)	3.92 (2.78, 4.0)	0.660
C_{max} (mg/L)	11.9 (7.24, 14.3)	14.2 (11.9, 23.5)	0.038
C_{min} (mg/L)	**4.12 (2.89, 7.66)**	**4.64 (2.32, 10.4)**	**0.872**
AUC_{0-12}	84.29 (53.51, 113.37)	113.70 (78.81, 168.61)	0.056
Half life (hr)	10.98 (5.44, 16.61)	4.86 (3.82, 8.29)	0.062

JAIDS 2008;47:566

Double dose lopinavir/r in kids

- Median trough LPV concentrations:
  - TB 0.63 (IQR 0.11-1.62)
  - Controls 4.25 (IQR 3.42-8.1)
  - 60% of children with TB were sub-therapeutic
- Study stopped early by DSMB

Hepatitis with adjusted dose PIs & rifampicin in healthy volunteers

- Very high rates of hepatitis reported in 3 studies (Saquinavir, Atazanavir, Lopinavir)
- All 3 studies stopped early due to toxicity
- Saquinavir study - hepatitis much more common if rifampicin started first
- Limited data on super boosted LPV/r safety in patients with TB: safe in children, but hepatitis not uncommon in adults

Grange 6th Int Workshop Clin Pharm HIV Ther, Montreal 2005
AIDS 2008;22:931-5
JAIDS 2009;50:290-3
Moultrie 16th IAC Toronto 2006
JAIDS 2008;47:566-9

“Super-boosted” PI & rifampicin safety

- Can’t extrapolate from healthy volunteers e.g. Rif & PZA safe for LTBI in HIV+, hepatotoxic in HIV-
- With 2nd line ART patients will be on PI before rifampicin started
- CDC 2008 recommends SQV:RTV 400:400 BD or double dose LPV/r or LPV/r + RTV: “Use with caution”

http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm

Rifabutin & PIs

- Preferentially used instead of rifampicin in developed countries for patients on PIs
- Unlike rifampicin, rifabutin needs dose adjustment as concentrations are increased by PIs & decreased by NNRTIs
- WHO added rifabutin to essential medicines list
- Even if rifabutin were less expensive, would be difficult to implement in TB clinics, especially with FDCs

Rifabutin for TB: Cochrane review

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.

Research Priorities: 2nd line regimen

- Urgent need for data as more will inevitably move to 2nd line
- Hepatotoxicity & PK of “super-boosted” PIs needs to be defined in adults with HIV-TB coinfection
- Effectiveness studies in adults & children
- Rifabutin not currently an option – need for more evidence of efficacy vs rifampicin in HIV-TB coinfection
- Alternative regimens (triple NRTI, double dose raltegravir)