International AIDS Society - Industry Liaison Forum Meeting

5 March 2012

Treating HIV in children with tuberculosis

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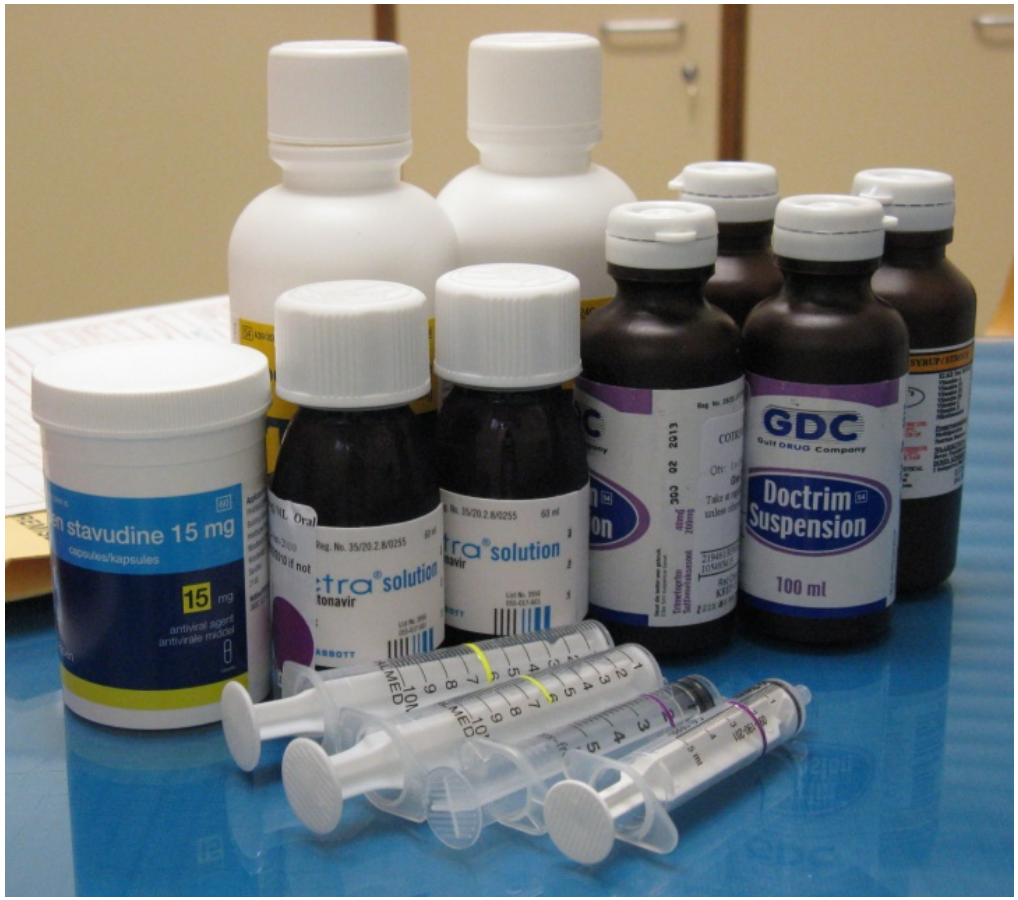
Challenges of combined treatment



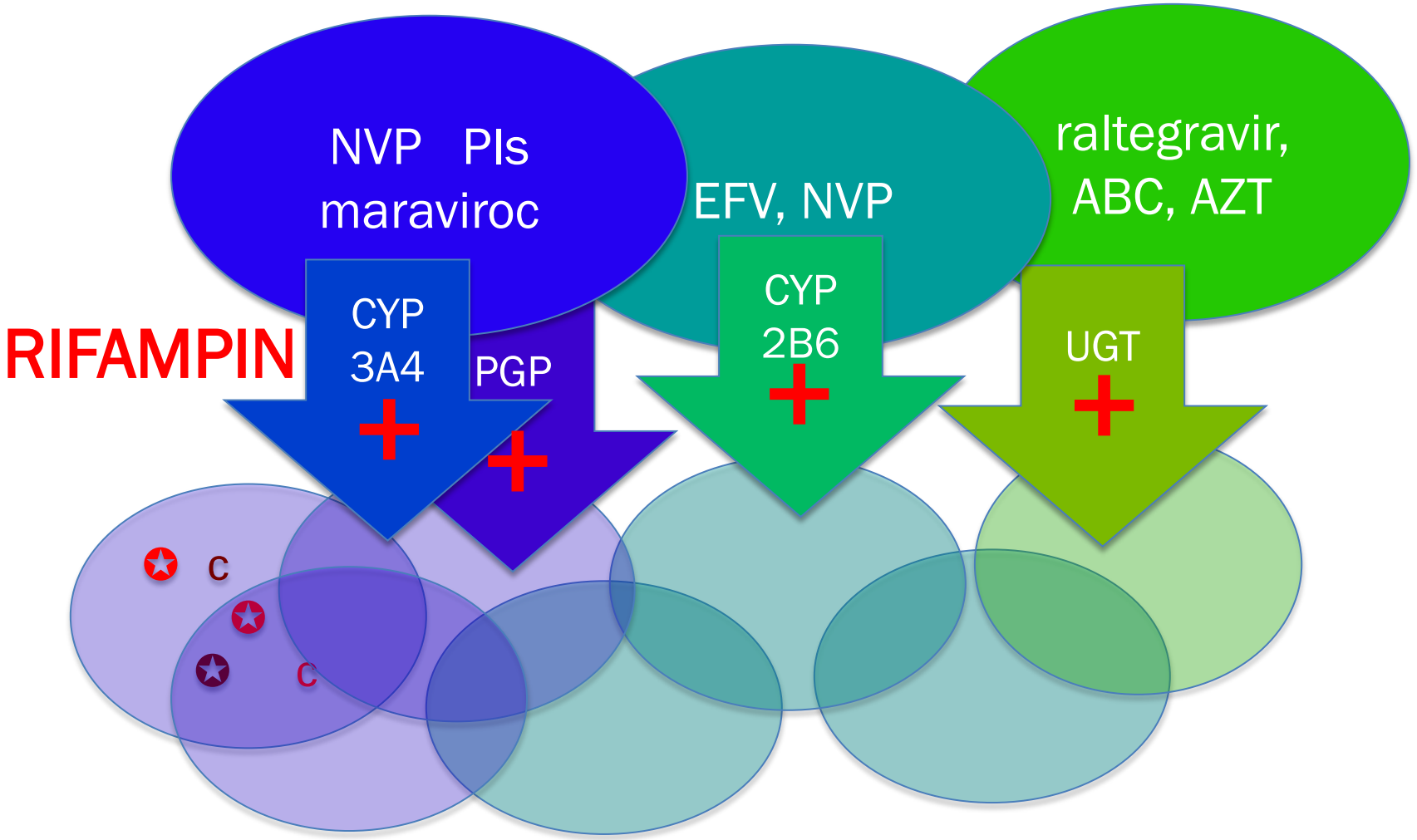
Large pill burdens, complex dosing schedules

Overlapping drug toxicities

Drug-drug interactions

Development of the immune reconstitution syndrome (IRIS)

Drug-drug interactions



NVP, nevirapine; PIs, protease inhibitors; EFV, efavirenz; ABC, abacavir; AZT, zidovudine; CYP, cytochrome P450; PGP, p-glycoprotein; UGT, UDP glucuronosyltransferases

WHO ART guidelines for children with TB

	ART	TB treatment
< 2 years & ARV exposure	3NRTIs[1]	**RIFAMPIN** Isoniazid Pyrazinamide Ethambutol Co-trimoxazole
< 3 years; no ARV exposure (or ARV exposure unknown)	**Nevirapine** +2NRTIs[2] or 3NRTIs	
> 3 years	**Efavirenz** +2NRTIs or 3NRTIs	
On PI-based regimen, or 2nd-line regimen with PI indicated	super-boosted PI (**LPV/RTV=1:1**)+2NRTIs	

[1]ABC+3TC+AZT/d4T; [2]3TC+ABC/AZT/d4T

WHO, 2010

NRTI-only regimens

- Inferior efficacy, especially when viral load is high
  - *Gulick et al. N Engl J Med 2004; 350:1850–61*
  - *Berenguer et al. JAIDS 2006; 41:154-9*
- High rates of NRTI mutations and virological failure in children
  - *Bobat et al., 4th IAS Conf HIV Pathogen Treat Prev, Sydney 2007*
  - *Neely et al., 17th Conf Retroviruses Opportunistic Infect, San Francisco 2010*
- Not evaluated in children with TB
- Rifampin may reduce ABC and AZT concentrations

Nevirapine+2NRTIs in children with TB

21 Zambian children aged 1.6 (0.7-3.2) years on TB treatment and paediatric Triomune®

	Children with TB (n=21)	Controls without TB (n=16)	p-value
$AUC_{0\text{-}12h}$ (mg.h/l)	52.0 (22.6, 159.7)	90.9 (40,4, 232,1)	<0.001
C_0 (mg/l)	2.93 (1.06, 11.40)	5.93 (3.28, 18.13)	0.001
C_{max} (mg/l)	6.33 (2.61, 14.5)	9.59 (5.28, 21.04)	<0.001
Number with C_0 <3.0 mg/l	11	0	0.001

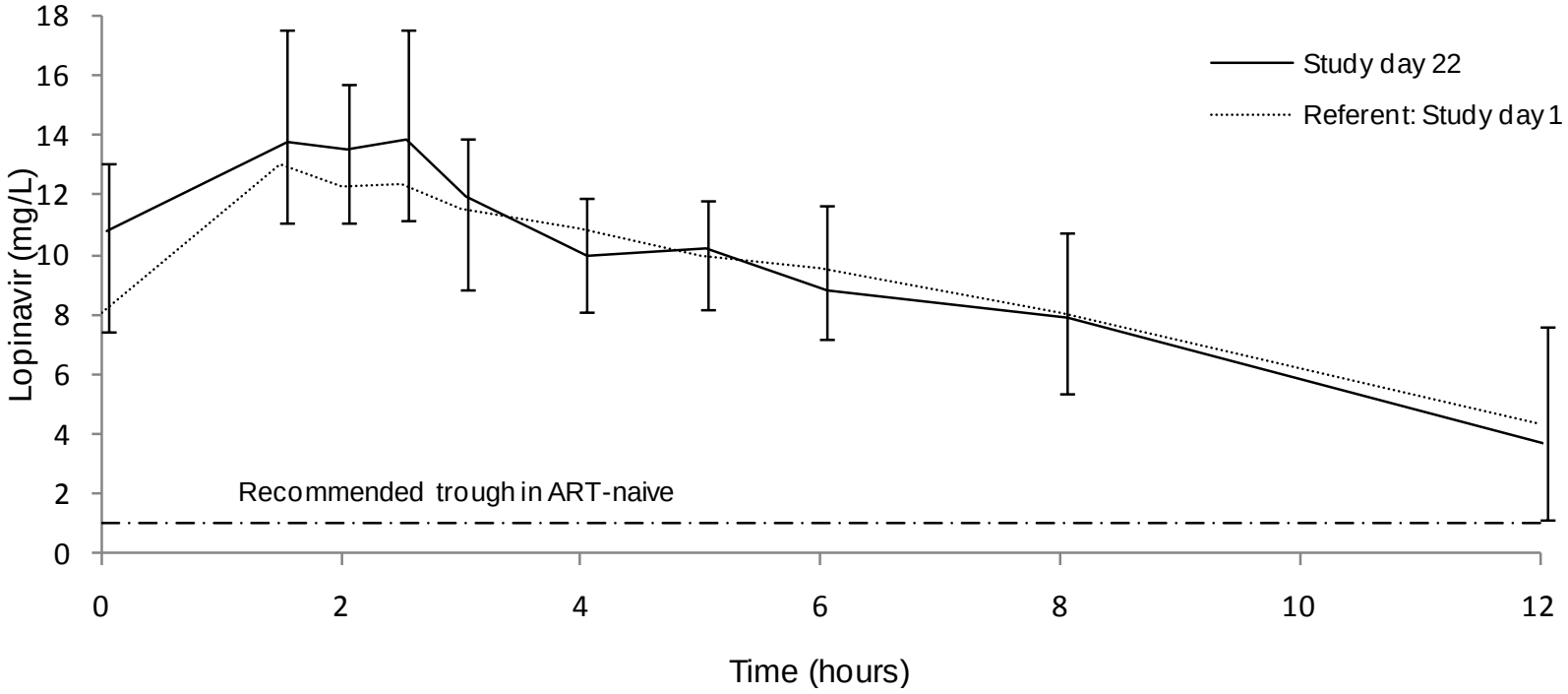
Oudijk et al. 5th IAS Conf Pathogen Treat Prev, Cape Town, July 2009

Adjusted doses of lopinavir(LPV) & ritonavir(RTV)

- double dose LPV/r
  - LPV/RTV = 800/200 mg 12 hly
- super-boosted LPV
  - LPV/RTV = 400/400 mg 12 hrly

adequate LPV concentrations in adults on rifampin; concerns about hepatoxicity

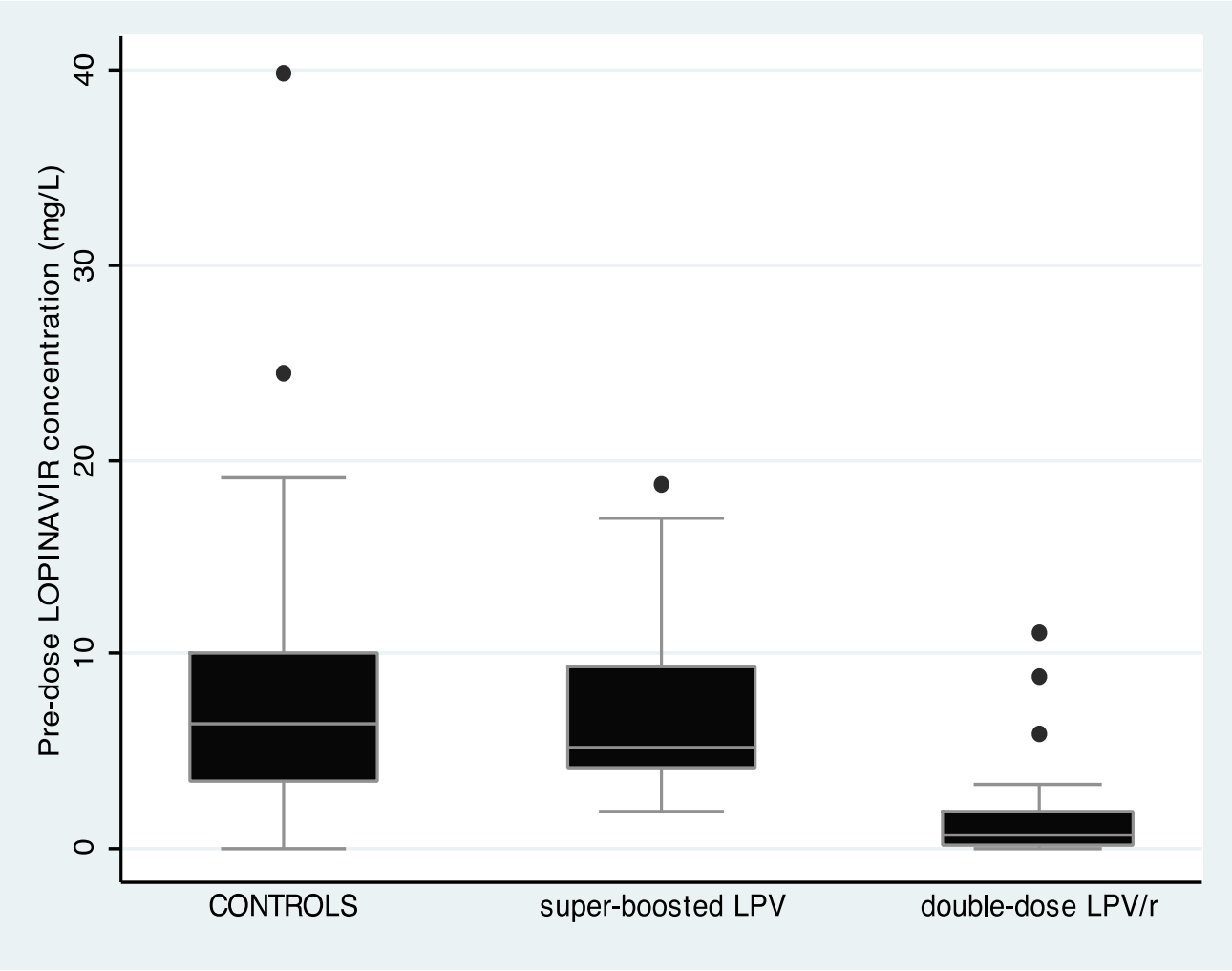
- *La Porte, et al., Antimicrob Agents Chemother 2004;48:1553–60*
- *Nijland et al.,* AIDS 2008;22:931– 935



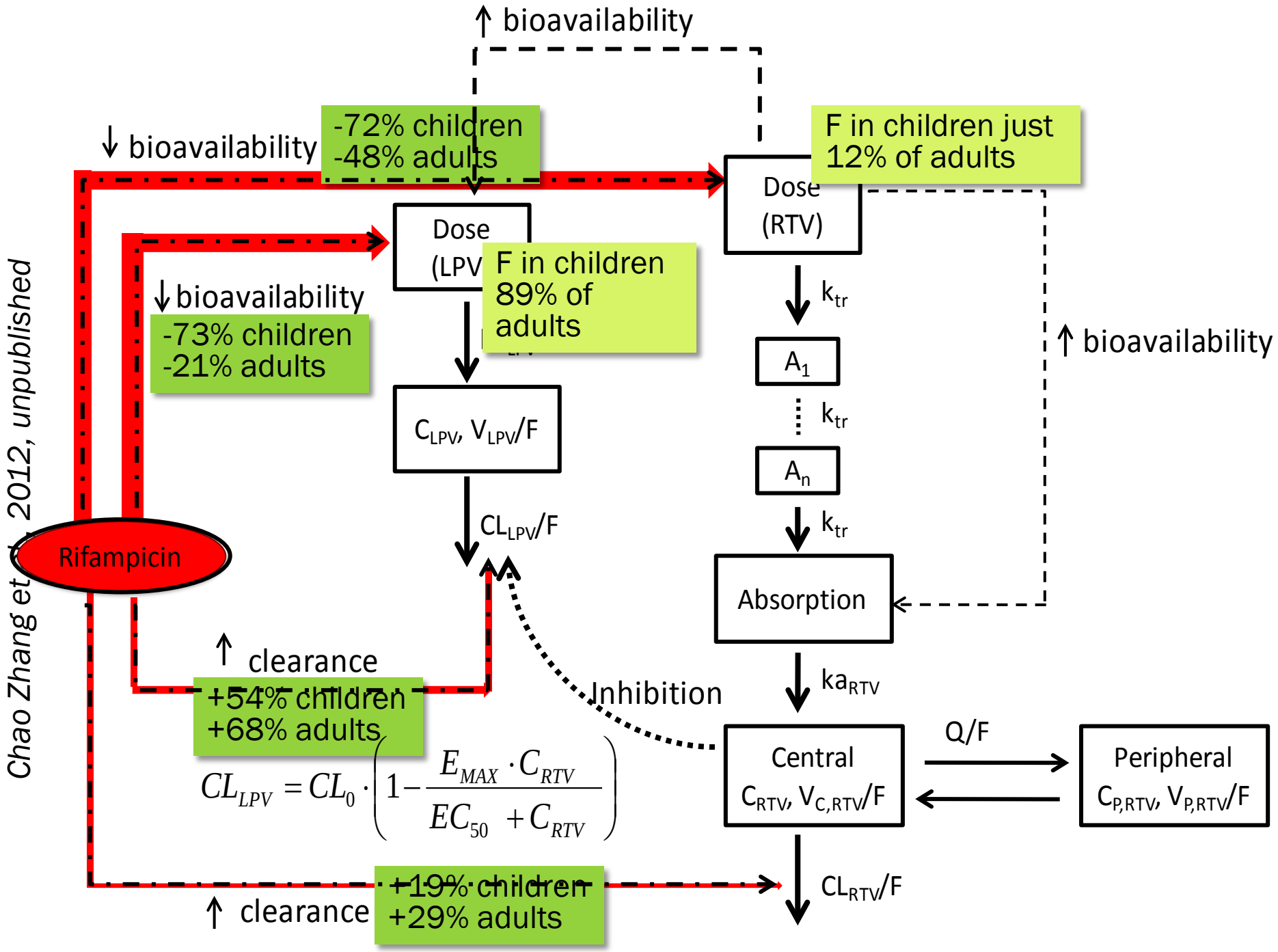
Decloedt, et al., Antimicrob Agents Chemother. 2011;55:3195-200.

Young children are different:

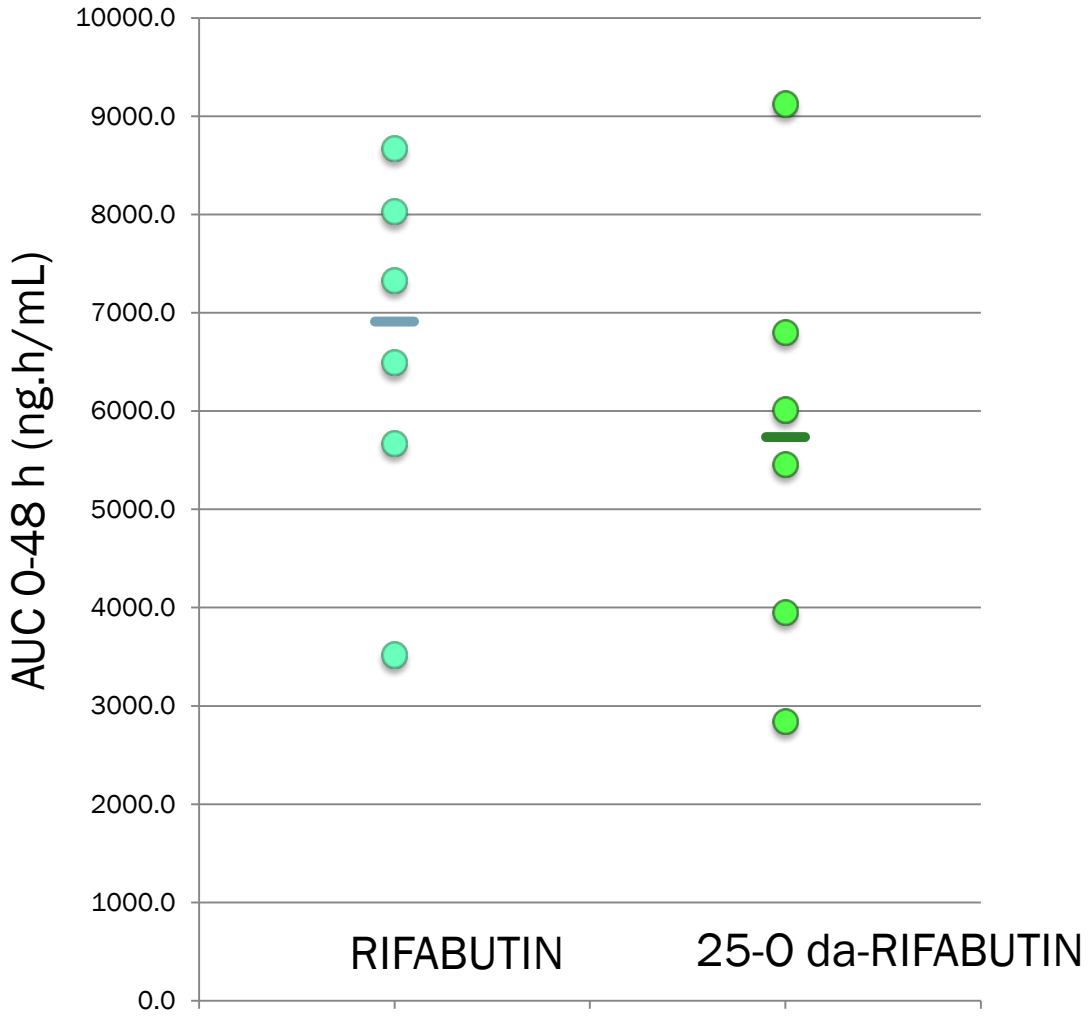
- doubled doses of LPV/r do not overcome the effect of TB treatment;
- super-boosting is not feasible in many settings



Ren et al., J Acquir Immune Defic Syndr. 2008; 47:566-569.
McIlleron et al., Antivir Ther. 2011;16(3):417-21


↑ bioavailability
↓ bioavailability
-72% children
-48% adults
F in children just
12% of adults
Dose
(RTV)
Dose
(LPV
F in children
89% of
adults
↓bioavailability
-73% children
-21% adults
k_{tr}
A_1
k_{tr}
A_n
k_{tr}
↑ bioavailability
C_{LPV}, V_{LPV}/F
CL_{LPV}/F
Rifampicin
Absorption
ka_{RTV}
↑ clearance
+54% children
+68% adults
Inhibition
Q/F
Central
C_{RTV}, $V_{C,RTV}$/F
Peripheral
$C_{P,RTV}$, $V_{P,RTV}$/F
$CL_{LPV} = CL_0 \cdot \left(1 - \frac{E_{MAX} \cdot C_{RTV}}{EC_{50} + C_{RTV}}\right)$
↑ clearance
+19% children
+29% adults
CL_{RTV}/F
Chao Zhang et al., 2012, unpublished

Rifabutin (5 mg/kg, 3 x/week) with LPV/r in young children



Moultrie et al., ABSTRACT S-177; Poster board 993; Sesson 169; Thursday 2-4 PM.

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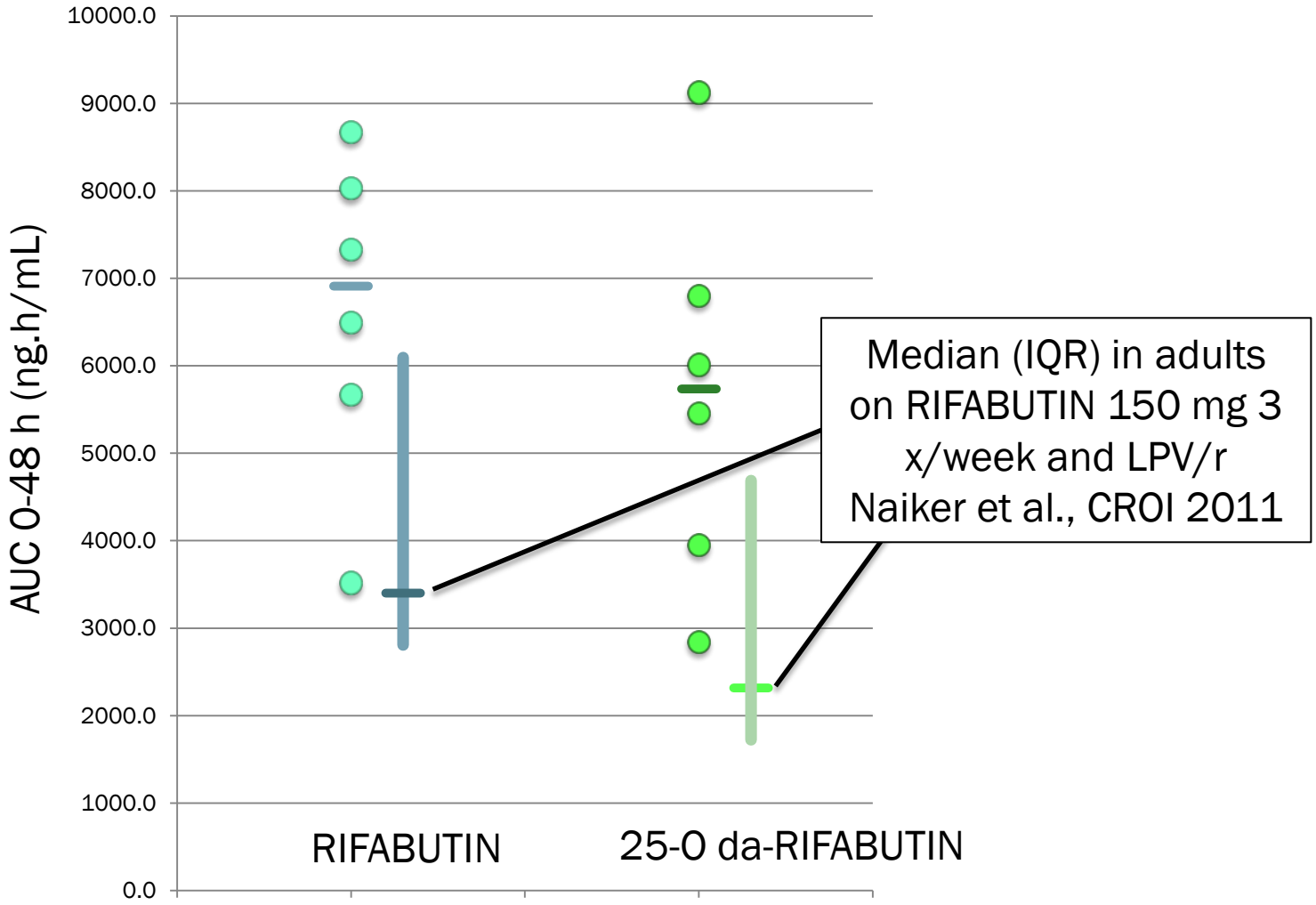

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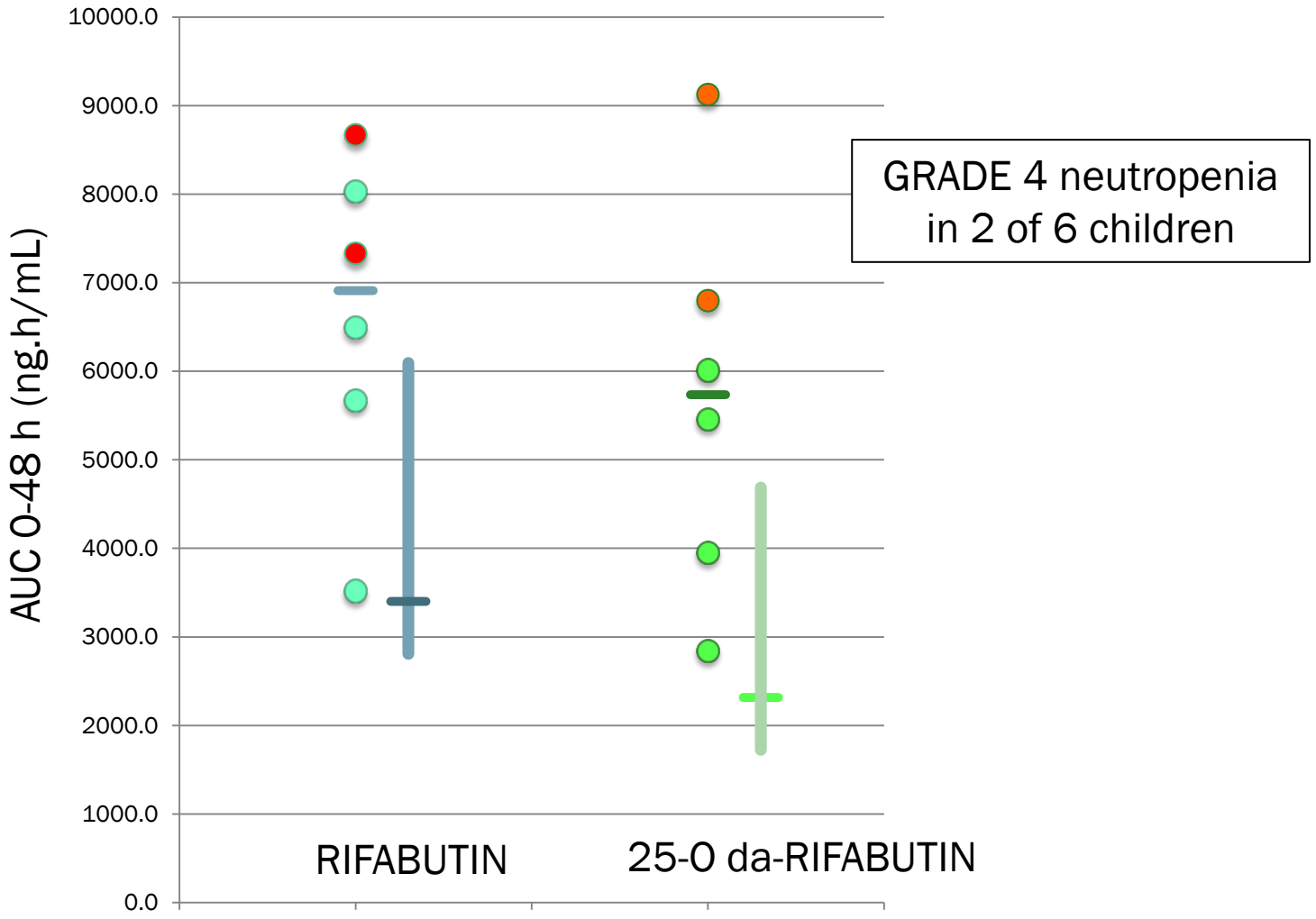

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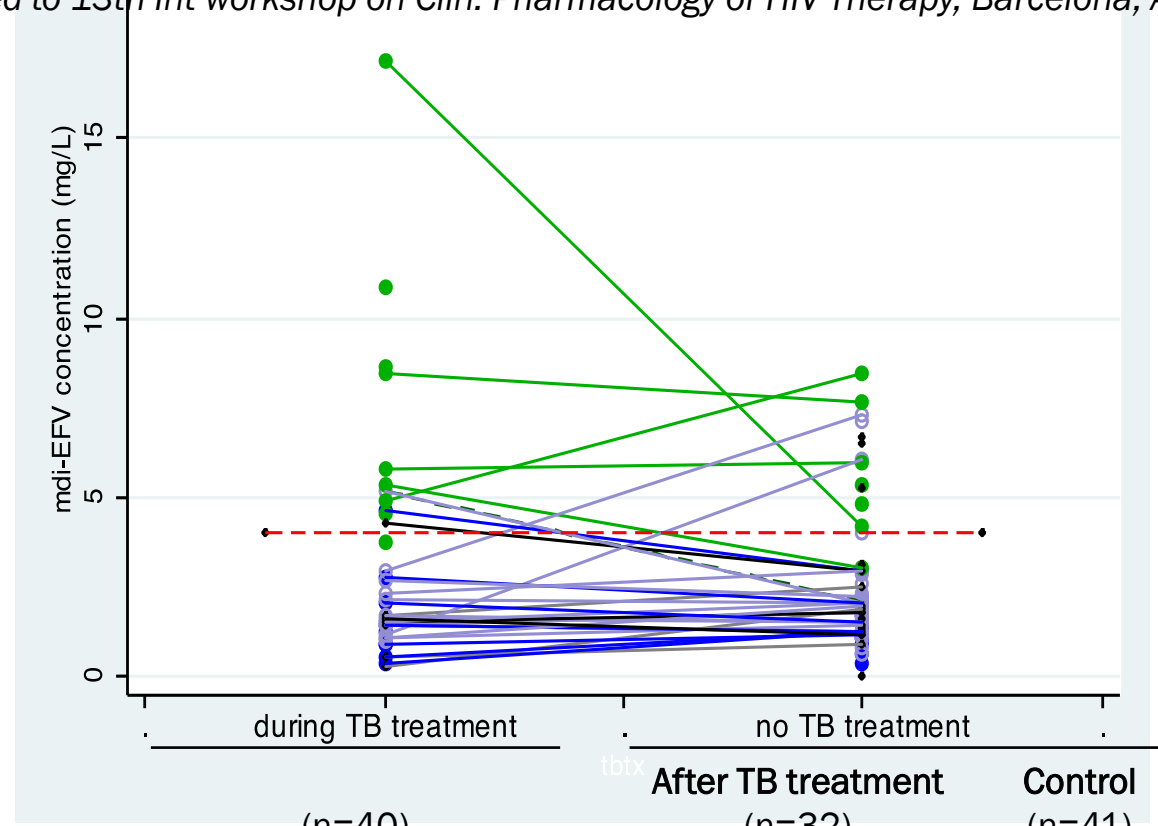
Children ≥3 years-old: mid-dose interval concentrations of EFV (mdi-EFV)

Submitted to 13th Int workshop on Clin. Pharmacology of HIV Therapy, Barcelona, April 2012



	During TB treatment	After TB treatment	Control
	(n=40)	(n=32)	(n=41)
median (IQR)	1.64 (1.21, 4.40)	1.96 (1.32, 2.93)	1.7 (1.14, 2.27)

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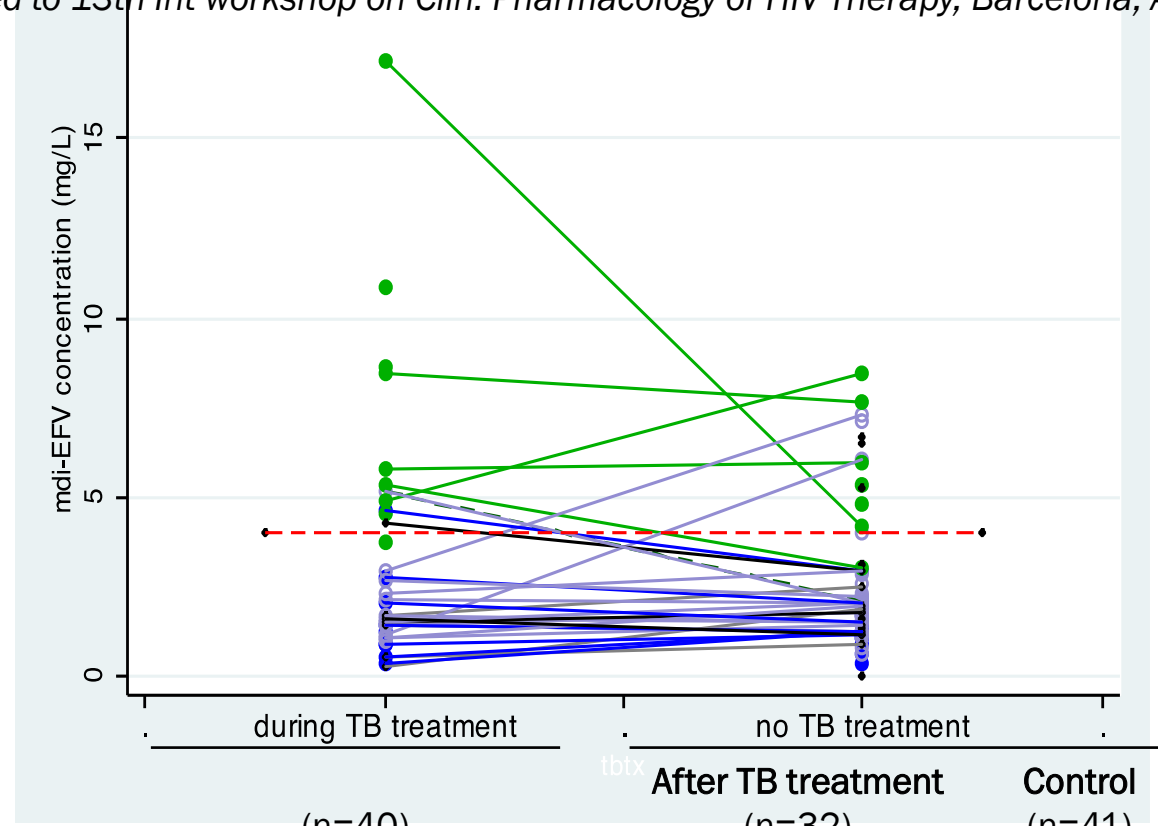

		After TB treatment	Control
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median (IQR)	1.64 (1.21, 4.40)	1.96 (1.32, 2.93)	1.7 (1.14, 2.27)

p=0.640

p=0.626

OVERALL: TB treatment had **NO SIGNIFICANT EFFECT on EFV concentrations**

Conclusions

- There are considerable concerns about the available treatment options for young HIV infected children with TB:
    - inferior efficacy; increased toxicity; complexity of regimens, large pill burden, and a lack of suitable formulations.
- PK, safety and efficacy studies are needed to define the best approaches:-
    - Adjusted doses of LPV (or alternative PI) and RTV
        - Adequately powered studies, across ages
        - Alternative dosing approaches & alternative formulations
    - Optimized NVP dose
    - Efficacy (& Resistance mutations) with triple nucleoside regimen
    - EFV-based regimen in children <3 y
    - RALTEGRAVIR-based ART
    - Optimal RIFABUTIN dose with PI/r (& development of formulation)
- Novel TB regimens
    - RIFAMYCIN-SPARING
- Affordable FORMULATIONS suited to high burden settings are urgently needed

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