IS IT TIME TO UPDATE DOSING OF ANTITUBERCULOSIS DRUGS IN HIV PATIENTS (AND MAYBE NOT ONLY)?

Andrea Calcagno
University of Turin

DISCLOSURES

I have read and understood ICMJE policy on declaration of interest and I declare that in the past five years

- My institution has received research grants from AbbVie, Gilead Sciences, Bristol Myers Squibb, Janssen-Cilag and ViiV Healthcare

- I received speaker and consultancy honoraria from Gilead Sciences, Insmed, Janssen-Cilag, MSD and ViiV Healthcare

OUTLINE

WHY CONSIDERING HIGHER DOSES IF PATIENTS MAY RECOVER SPONTANEOUSLY AND THE EFFICACY IS APPROXIMATELY 95%?

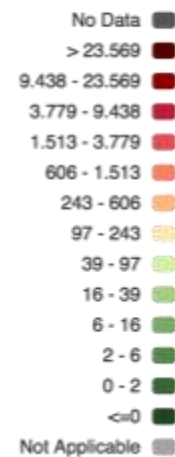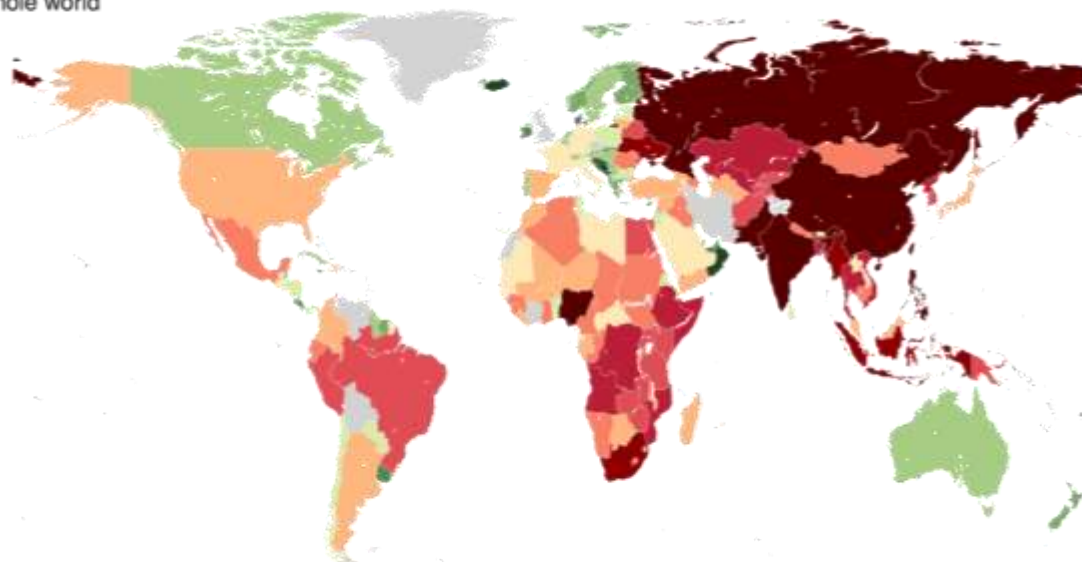Clinical Efficacy is approximately 80% in real-life settings

1.3 M (1.2-1.4) deaths (HIV-negative)
&
214 K (187–242) deaths HIV+

MDR TB AND TT OUTCOMES

Incidence of RR Tuberculosis

2018
501.957 in the whole world

Treatment outcomes for new and relapse TB cases, new and relapse HIV-positive TB cases, and MDR/RR-TB cases, globally,[a] 2012–2019

OUTLINE

1. The origins of current anti-TB dosages

2. PK & PD studies

3. Low exposure of antitubercular drugs
   - in serum
   - in tissues

4. Data on high-dose rifampicin
   - Rifapentine

5. Issues with higher doses
   - DDIs with HD-RIF?

6. Conclusions and Discussion

ANTITUBERCULAR DRUGS

1

4RHZE/2RH

Rifampicin
Isoniazid
Ethambutol
Pyrazinamide

2

Groups and steps	Medicine	Abbreviation
Group A:
Include all three medicines	Levofloxacin *or* moxifloxacin	Lfx
Mfx
	Bedaquiline[b,c]	Bdq
	Linezolid[d]	Lzd
Group B:
Add one or both medicines	Clofazimine	Cfz
	Cycloserine *or* terizidone	Cs
Trd
Group C:
Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[e]	Dlm
	Pyrazinamide[f]	Z
	Imipenem–cilastatin *or* meropenem[g]	Ipm–Cln
Mpm
	Amikacin (*or* streptomycin)[h]	Am
(S)
	Ethionamide *or* prothionamide[i]	Eto
Pto
	P-aminosalicylic acid[i]	PAS

Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946–1986, with relevant subsequent publications

Wallace Fox,* Gordon A. Ellard,† Denis A. Mitchison†

* 28 Mount Ararat Road, Richmond, Surrey, TW10 6PG, UK, † St George's Hospital Medical School, London, SW17 0RE, UK

————————————————— SUMMARY

This review describes the studies on the treatment of tuberculosis carried out by the British Medical Research Council's tuberculosis units and their many collaborators throughout the world during the period from their formation in 1946 to their closure in 1986. References to all publications on studies during the period are listed. The review also includes selected publications by members of their staff who have continued the studies since closure of the units. The review is under four main headings: 1) controlled trials of chemotherapy, 2) bacteriological studies, 3) pharmacological studies, and 4) studies of surveillance and policies relevant to the control of tuberculosis.

Major events in the development of modern chemotherapy and the control of tuberculosis are as follows:

1 1946: The initial trial assessing the value of the addition of streptomycin to bed rest.

2 1948: The demonstration that the emergence of bacterial resistance to either streptomycin or p-aminosalicylic acid (PAS) alone was greatly decreased when combined treatment was given with both drugs.

3 1952–1955: Exploration of treatment with isoniazid alone and in combination with PAS or streptomycin.

4 1958–1967: The search for affordable regimens for developing countries that led to the substitution of thiacetazone for PAS.

5 1959: The demonstration that chemotherapy given at home was as effective as when given in a sanatorium and did not lead to any increase in the rate of infection in family contacts.

6 1958 onwards: Initiation of the policy of full supervision of chemotherapy (directly observed treatment—DOT) and its later implementation in Hong Kong and Madras.

7 1961 onwards: Exploration of intermittent regimens of chemotherapy to assist implementation of full supervision.

8 1970: The first demonstration that inclusion of rifampicin or pyrazinamide in a regimen of streptomycin and isoniazid substantially reduced the subsequent relapse rate.

9 1972–1974: Demonstration that the period of treatment could be shortened to 6 months by the inclusion of rifampicin and pyrazinamide in the regimen.

10 1976: Delineation of modern short-course chemotherapy regimens by showing that the sterilising activity of pyrazinamide was confined to the first 2 months of treatment during the intensive phase, whereas the sterilising activity of rifampicin persisted throughout the continuation phase.

11 1977 onwards: Demonstration of the value of intermittency in short-course regimens, particularly that three times weekly treatment throughout was as effective as, and less toxic and expensive than daily regimens.

When the units were closed in 1986, all of the measures necessary for successful programmes for the control of tuberculosis had been delineated, particularly the regimens of treatment to be used, the need for full supervision of drug-taking (DOT) and the use of surveys to measure the extent to which national programmes were finding and treating infectious disease. These tools were then available to national organisations and to international organisations such as the World Health Organisation (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD), to implement in control programmes.

Table 1.7 Short-course chemotherapy studies in East and Central Africa. Results in patients who had drug-sensitive cultures initially.

Study no.	Date of start	Regimen	Duration (months)	Patients assessed for relapse	Relapse rate in 2-year follow-up (%)	Sputum culture negative at 2 months (%)	Reference
1	1970	a) SHR	6	152	3	69	2
		b) SHZ	6	153	8	66	166
		c) SHT	6	104	22	42	167
		d) SH	6	112	29	49	168
		e) 2STH/TH	18	133	3	56	
2	1972	a) SHR	6	171	2	70	169
		b) HR	6	164	7	64	170
		c) 2SHRZ/TH	6	179	7	83	
		d) 2SHRZ/$S_2H_2Z_2$*	6	159	4	80	
3	1974	a1) 2SHRZ/TH	6	75	13	87	171
		a2) 2SHRZ/TH	8	81	0		172
		b1) 1SHRZ/TH	6	79	18	67	
		b2) 1SHRZ/TH	8	58	7		
		c1) 1SHRZ/$S_2H_2Z_2$	6	75	9	68	
		c2) 1SHRZ/$S_2H_2Z_2$	8	88	2		
		d1) 2SHR/TH	6	82	18	75	
		d2) 2SHR/TH	6	77	6		
4	1976	a) 2SHRZ/HRZ	4	104	16		173
		b) 2SHRZ/HR	4	104	11	85	174
		c) 2SHRZ/HZ	4	98	32		
		d) 2SHRZ/H	4	105	30		
		e) 2HRZ/H	4	100	40	79	
5	1978	a) 2SHRZ/HR	6	166	3		175
		b) 2SHRZ/HZ	6	164	8	84	176
		c) 2SHRZ/H	6	156	10		
		d) 2SHRZ/H	8	123	3		
6	1978	a) 2SHRZ/TH	6	105	3	94	177
		b) 2SHRZ/H	6	100	11		
7	1981	2SHRZ/TH+L†	6	456	7	82	178
8	1982	a) 1.5SHRZ/H	7	113	10		179
		b) 1.5SHRZ/H+(SRZ)	7	114	5	85	

* $S_2H_2Z_2$. See footnote for Table 1.5.
† The results of the three regimens with levamisole added for 4 or 8 weeks or not at all have been amalgamated, as there were no differences between them.

Table 1.9 Short-course chemotherapy studies in Singapore. Results in patients who had drug-sensitive cultures initially.

Study no.	Place (date of start)	Regimen	Duration (months)	Patients assessed for relapse	Relapse rate (%) follow-up for 2 years	Relapse rate (%) follow-up for 5 years	Sputum culture negative at 2 months (%)	Reference
1	Singapore (1973)	a) 2SHRZ/HRZ	4	79	11	13		189–191
		b) 2SHRZ/HRZ	6	78	0	1	98	
		c) 2SHRZ/HR	4	77	8	14		
		d) 2SHRZ/HR	6	80	2	3		
2	Singapore (1978)	a) 2SHRZ/H_3R_3*	6	97	1	2	99	7, 192
		b) 1SHRZ/H_3R_3	6	94	1	2	85	
		c) 2HRZ/H_3R_3	6	109	1	3	90	
3	Singapore (1983)	a) 2SHRZ(C)/H_3R_3†	6	46	7‡	–	98	193
		b) 2SHRZ(S)/H_3R_3	6	47	0‡	–		
		c) 1SHRZ(C)/H_3R_3	6	42	5‡	–	92	
		d) 1SHRZ(S)/H_3R_3	6	46	2‡	–		
		e) 2HRZ(C)/H_3R_3	6	40	8‡	–	97	
		f) 2HRZ(S)/H_3R_3	6	44	2‡	–		

Why Do We Use 600 mg of Rifampicin in Tuberculosis Treatment?

Jakko van Ingen,[1] Rob E. Aarnoutse,[2] Peter R. Donald,[3] Andreas H. Diacon,[4] Rodney Dawson,[5] Georgette Plemper van Balen,[1] Stephen H. Gillespie,[6] and Martin J. Boeree[1]

[1]University Center for Chronic Diseases Dekkerswald and Department of Pulmonary Diseases, [2]Department of Clinical Pharmacy, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; [3]Departments of Pediatrics and Child Health; [4]Internal Medicine, Faculty of Health Sciences, University of Stellenbosch, Cape Town, [5]Centre for Tuberculosis Research Innovation, University of Cape Town Lung Institute, Groote Schuur, South Africa; and [6]Department of Molecular Medicine, School of Medicine, University of St Andrews, St Andrews, Scotland, United Kingdom

The 600-mg once daily dose of rifampicin plays a key role in tuberculosis treatment. The evidence underpinning this dose is scant. A review of the historical literature identified 3 strands of reasoning. The first is the pharmacokinetic argument: The 600-mg dose yields serum drug concentrations well above the minimum inhibitory concentration of rifampicin against *Mycobacterium tuberculosis*. The second is the argument that adverse events may be dose related. The third is the economic argument: Rifampicin was prohibitively expensive at the time of its introduction. Recent in vitro, animal, and early bactericidal activity studies suggest that the 600-mg once daily dose is at the lower end of the dose-response curve, refuting the pharmacokinetic argument. The reduced cost and the lack of evidence of toxicity at higher daily doses remove the other arguments. To optimize tuberculosis treatment, the clinical value of higher doses of rifampicin should be tested in clinical trials.

In 1957, Sensi and coworkers at Lepetit Laboratories discovered a new antibiotic which they named rifamycin. It was obtained from fermentation cultures of *Amycolatopsis rifamycinica* (designated *Streptomyces mediterranei* at the time) and later found to consist of 5 substances, then renamed rifamycin A–E. Absorption of all of these substances from the gastrointestinal tract was minimal; hence, they were first developed as parenteral agents. Rifamycin B proved most stable, least toxic, and active against a broad spectrum of bacteria, mainly gram-positive cocci and *Mycobacterium tuberculosis* [1, 2]. Of note, the name "rifamycin" refers to the popular 1955 French film noir movie *Rififi* [2]. Although rifamycin B was sporadically used clinically in tuberculosis treatment, the search for an oral equivalent with good intestinal absorption continued. In 1965, rifampicin, a hydrazone of a rifamycin B derivate with *N*-amino-*N'*-methylpiperazine, proved to be well absorbed orally and retained its highly bactericidal action (Figure 1) [1–3]. Rifampicin was approved by the Food and Drug Administration (FDA) in 1971 [2]. By this time, a range of trials and case series were finalized or had been published that found efficacy for rifampicin-containing regimens in tuberculosis treatment [4–12]. Virtually all of these studies had used a single daily dose of 600 mg of rifampicin [5–11]. Why was this dose chosen? The reasoning for the 600-mg once daily dosing could not be extracted from any of the published trials. Given the critical role of rifampicin in short-course chemotherapy, we performed a review of the literature to try to understand the reasoning behind the choice of this dose.

SEARCH STRATEGY AND SELECTION CRITERIA

We performed a literature search using PubMed (National Center for Biotechnology Information; http://www.ncbi.nlm.nih.gov), applying the Medical Subject Heading (MeSH) terms "rifampin" with subheading "history" combined with the MeSH term "tuberculosis"; publications in English, German, French, and Italian were considered. The review focused on the first 2 decades after the development of rifampicin (1957–1977) and those

Ermes Pagani in Saint-Raphael

Streptomyces mediterranei
(*Amycolatopsis rifamycinica*)

Piero Sensi in the Lepetit laboratories

Why Do We Use 600 mg of Rifampicin in Tuberculosis Treatment?

Jakko van Ingen,[1] Rob E. Aarnoutse,[2] Peter R. Donald,[3] Andreas H. Diacon,[4] Rodney Dawson,[5] Georgette Plemper van Balen,[1] Stephen H. Gillespie,[6] and Martin J. Boeree[1]

[1]University Center for Chronic Diseases Dekkerswald and Department of Pulmonary Diseases, [2]Department of Clinical Pharmacy, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; [3]Departments of Pediatrics and Child Health; [4]Internal Medicine, Faculty of Health Sciences, University of Stellenbosch, Cape Town, [5]Centre for Tuberculosis Research Innovation, University of Cape Town Lung Institute, Groote Schuur, South Africa; and [6]Department of Molecular Medicine, School of Medicine, University of St Andrews, St Andrews, Scotland, United Kingdom

The 600-mg once daily dose of rifampicin plays a key role in tuberculosis treatment. The evidence underpinning this dose is scant. A review of the historical literature identified 3 strands of reasoning. The first is the pharmacokinetic argument: The 600-mg dose yields serum drug concentrations well above the minimum inhibitory concentration of rifampicin against *Mycobacterium tuberculosis*. The second is the argument that adverse events may be dose related. The third is the economic argument: Rifampicin was prohibitively expensive at the time of its introduction. Recent in vitro, animal, and early bactericidal activity studies suggest that the 600-mg once daily dose is at the lower end of the dose-response curve, refuting the pharmacokinetic argument. The reduced cost and the lack of evidence of toxicity at higher daily doses remove the other arguments. To optimize tuberculosis treatment, the clinical value of higher doses of rifampicin should be tested in clinical trials.

In 1957, Sensi and coworkers at Lepetit Laboratories discovered a new antibiotic which they named rifamycin. It was obtained from fermentation cultures of *Amycolatopsis rifamycinica* (designated *Streptomyces mediterranei* at the time) and later found to consist of 5 substances, then renamed rifamycin A–E. Absorption of all of these substances from the gastrointestinal tract was minimal; hence, they were first developed as parenteral agents. Rifamycin B proved most stable, least toxic, and active against a broad spectrum of bacteria, mainly gram-positive cocci and *Mycobacterium tuberculosis* [1, 2]. Of note, the name "rifamycin" refers to the popular 1955 French film noir movie *Rififi* [2]. Although rifamycin B was sporadically used clinically in tuberculosis treatment, the search for an oral equivalent with good intestinal absorption continued. In 1965, rifampicin, a hydrazone of a rifamycin B derivate with *N*-amino-*N'*-methylpiperazine, proved to be well absorbed orally and retained its highly bactericidal action (Figure 1) [1–3]. Rifampicin was approved by the Food and Drug Administration (FDA) in 1971 [2]. By this time, a range of trials and case series were finalized or had been published that found efficacy for rifampicin-containing regimens in tuberculosis treatment [4–12]. Virtually all of these studies had used a single daily dose of 600 mg of rifampicin [5–11]. Why was this dose chosen? The reasoning for the 600-mg once daily dosing could not be extracted from any of the published trials. Given the critical role of rifampicin in short-course chemotherapy, we performed a review of the literature to try to understand the reasoning behind the choice of this dose.

SEARCH STRATEGY AND SELECTION CRITERIA

We performed a literature search using PubMed (National Center for Biotechnology Information; http://www.ncbi.nlm.nih.gov), applying the Medical Subject Heading (MeSH) terms "rifampin" with subheading "history" combined with the MeSH term "tuberculosis"; publications in English, German, French, and Italian were considered. The review focused on the first 2 decades after the development of rifampicin (1957–1977) and those

1.
Rifampicin PK in patients receiving 600 mg are well above MTB MIC
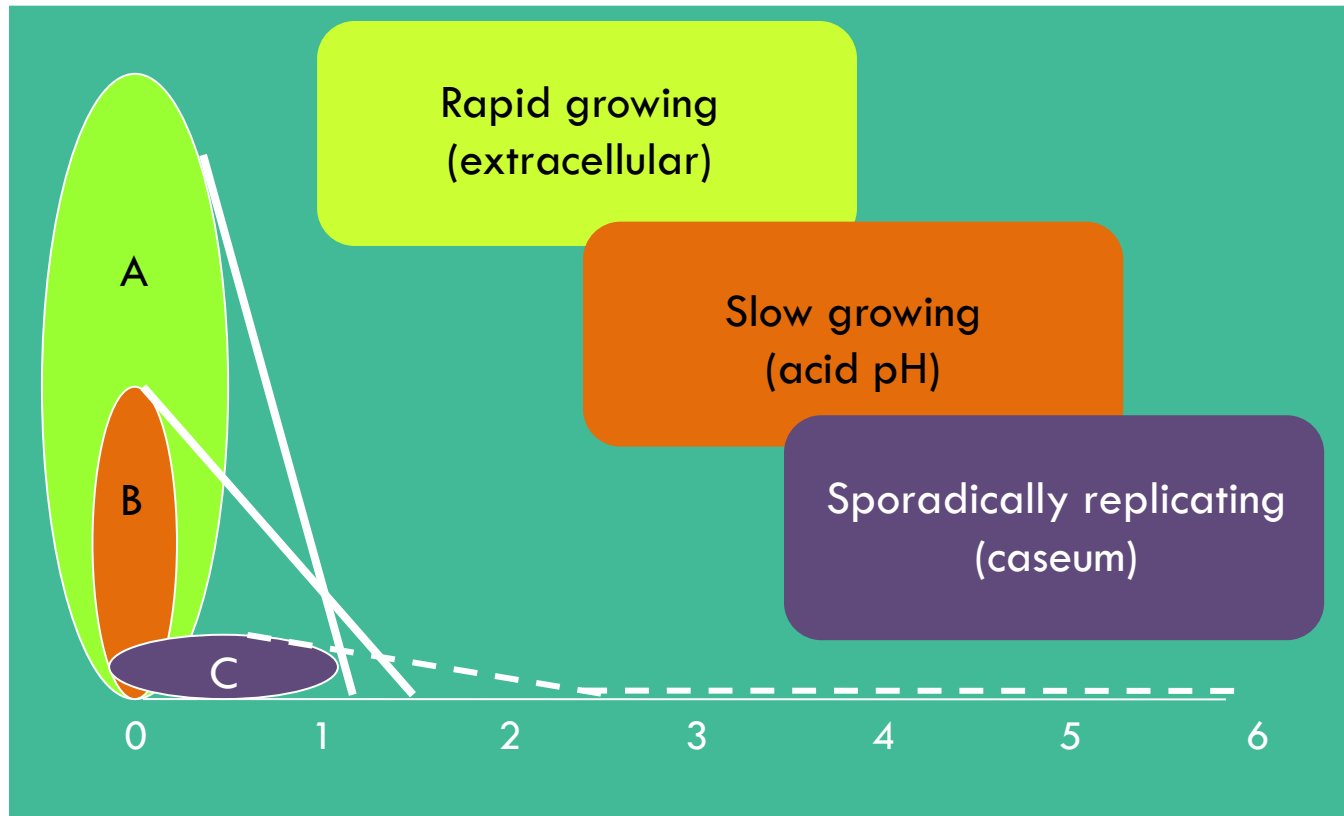
2.
Higher adverse events with higher doses

3.
Costs

OUTLINE

ACTIVITY OF ANTITUBERCULAR DRUGS

EBA AND VT50

Drug	EBA_{0-2}	EBA_{0-5}	EBA_{0-14}
Isoniazid 300	0.37-0.77	0.20-0.25	0.18-0.19
Rifampicin 600	0.17-0.63	0.28	0.11
Ethambutol 25	0.37	0.12	0.16
Pyrazinamide	0.04	-	0.11
Moxifloxacin	0.33-0.53	0.17-0.27	-
Streptomycin	0.04-0.13	-	-

Figure 1. Comparison of the bactericidal activity of anti-tuberculosis drugs using the time taken to reduce the sputum viable count by 50% (vt_{50}). (a) Isoniazid 300 mg, (b) isoniazid 600 mg, (c) ciprofloxacin 750 mg, (d) rifampicin 20 mg/kg, (e) rifampicin 10 mg/kg, (f) ethambutol 25 mg/kg, (g) streptomycin 1 g, (h) pyrazinamide 2 g, (i) thiacetazone 150 mg, (j) *para*-amino-salicylic acid 2 g. Points represent the mean and standard error of the mean (S.E.M.).

Donald PR and Diacon AH, Tuberculosis 2008; Gosling RD, et al. JAC 2003

PK TARGETS

Revisiting the mutant prevention concentration to guide dosing in childhood tuberculosis

Devan Jaganath[1]*, H. Simon Schaaf[2] and Peter R. Donald[2]

TABLE 2 Pharmacokinetic parameters of the anti-TB drugs[a]

Drug	Normal adult dose	Normal C_{max} (µg/ml)	Normal T_{max} (h)	Normal $t_{1/2}$ (h)
Isoniazid	300 mg daily	3–6	0.75–2	Polymorphic: Fast, 1.5; slow, 4
	900 mg BIW	9–15		
Rifampin	600 mg daily	8–24	2	2–3
Rifabutin	300 mg daily	0.45–0.90[b]	3–4	25–36
Rifapentine	600 mg daily[c]	8–30	5	15
Pyrazinamide	25–35 mg/kg daily	20–60	1–2	9
	50 mg/kg BIW	60–90		
Ethambutol	25 mg/kg daily	2–6	2–3	Biphasic: 2–4, then 12–14
	50 mg/kg BIW	4–12		
Cycloserine	250–500 mg daily or BID	20–35	2	7
Ethionamide	250–500 mg daily or BID	2–5	2	2
Streptomycin/ kanamycin/amikacin	15 mg/kg daily	35–45[d]	0.5- to 1.5-h i.m. dose or calculated to the end of i.v. infusion	3
	25 mg/kg BIW	65–80[d]		
PAS granules	4,000 mg BID	20–60	4–8	1
Levofloxacin	500–1,000 mg daily	8–13	1–2	9
Moxifloxacin	400 mg daily	3–5	1–2	7
Linezolid	300–600 mg most often once daily	12–26	1.5	5–6
Clofazimine	100 mg daily	0.5–2.0	2–7	Biphasic: several days, then many weeks

C_{max}

MPC

AUC/MPC$_{90}$

Mx 32, Lz 116

MIC

AUC

C_{max}/MIC > 10

AUC/MIC > 125

C_{max} Targets

Peloquin et al. Microbiol Spectrum, 2016

OUTLINE

PK AND EFFICACY

- High variability in plasma exposure of anti TB drugs
  - Food effect and gastric pH dependant (RH)

- Low anti-TB drug concentrations in PLWH (lower CD4 cell count), children and individuals with type 2 diabetes mellitus and with cystic fibrosis

- Low exposure associated with treatment failure and selection of drug-resistant strains
  - RFB dose and selection of RR MTB in PLWH

- RIF TDM and RIF dose increase successful in patients with slow response

- In a Study from Botswana (mostly PLWH) low Z concentrations were uncommon (5%) but associated (after correction for HIV status and CD4 cell count) with unfavorable outcome (aOR 3.38)

Berning SE, et al. NEJM 1992; Patel KB, et al. NEJM 1992; Ridzon R, et al. AJRCCM 1998; Mehta J, et al. Chest 2001; Chideya S, et al. CID 2009; Peloquion C. Microbiol Spectr 2017; Motta I, et al. Expert Opin Drug Metab Toxicol 2018

CUMULATIVE NUMBER OF LOW EXPOSURE DRUGS AND TREATMENT OUTCOMES

142 patients (10% PLWH) South Africa

Low rifampin and isoniazid peak and AUC concentrations preceded all cases of acquired drug resistance.

Table 2. Association Between Number of Drugs With Peak Concentration Above Classification and Regression Tree Analysis–Derived Threshold and 2-month Sputum Conversion

Drug	Odds Ratio of Success (95% confidence interval)	Sensitivity, %	Specificity, %
Pyrazinamide alone	6.9 (.9–54.4)	33.1	93.3
Pyrazinamide OR rifampin	10.3 (2.2–48.1)	61.4	86.7
Pyrazinamide AND rifampin	12.4 (1.6–99.1)	48.8	92.9
Pyrazinamide AND rifampin AND isoniazid	12.3 (2.7–56.8)	65.4	86.7

Table 3. Association Between Cumulative Number of Drugs Below Classification and Regression Tree Analysis–Derived Threshold AUC and Long-term Outcome
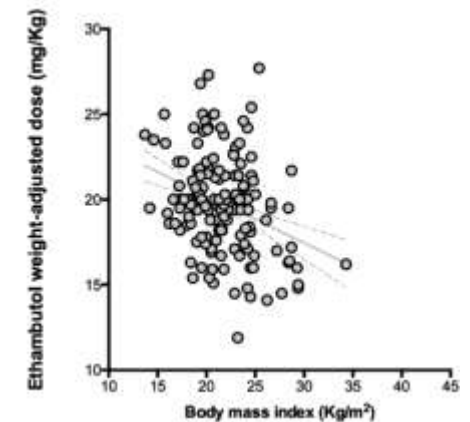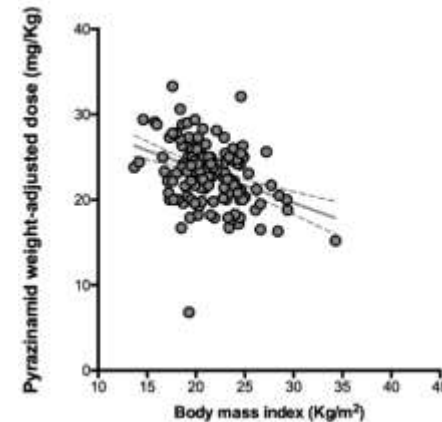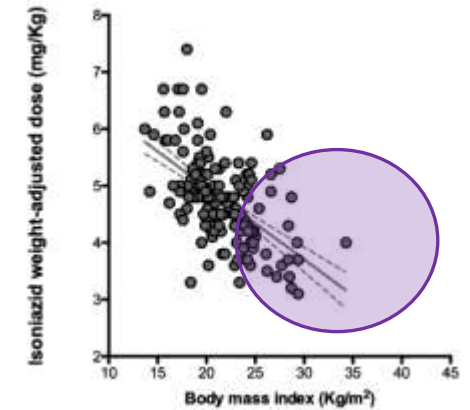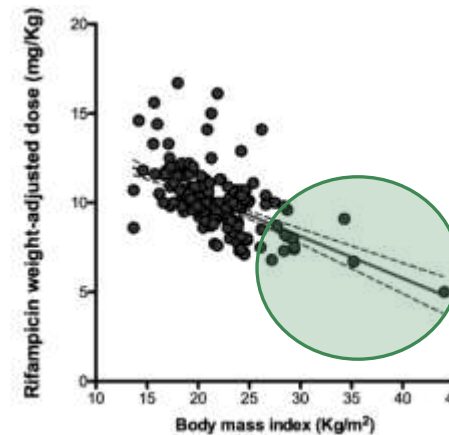
Drug AUCs	Long-Term Outcomes		Odds Ratio for Poor Outcome (95% confidence interval)
	Poor, %	Good, %	
No drug above threshold	1	2	(. . .)[a]
Any 1 drug above threshold	13 (52)	12 (48)	7.57 (2.57–22.34)
Any 2 drugs above threshold	14 (26)	40 (74)	2.65 (0.99–7.18)
All 3 drugs above threshold	7 (12)	53 (88)	Reference
Total	35 (100)	107 (100)	

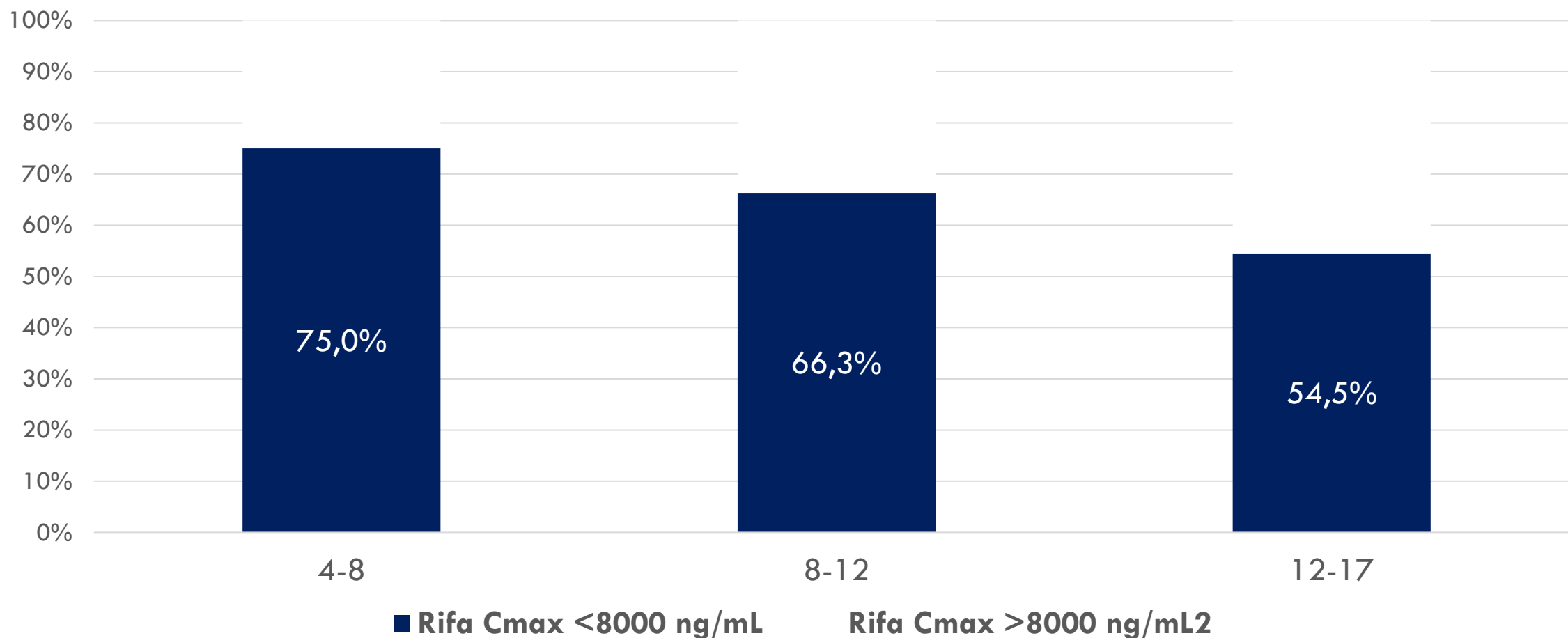Pasipanodya JG, et al. JID 2013

FACTORS ASSOCIATED WITH UNDERDOSING

- 199 participants (5% PLWH) on 1st line GL-based antiTB

- TDM at 2 and 4 weeks

- **60-66% had RIF Cmax <8000 ng/mL**

- **54-55% had INH Cmax <3000 ng/mL**

- 62-63.2% had more than 1 drug below target

Lower weight-adjusted doses, being born abroad and male gender
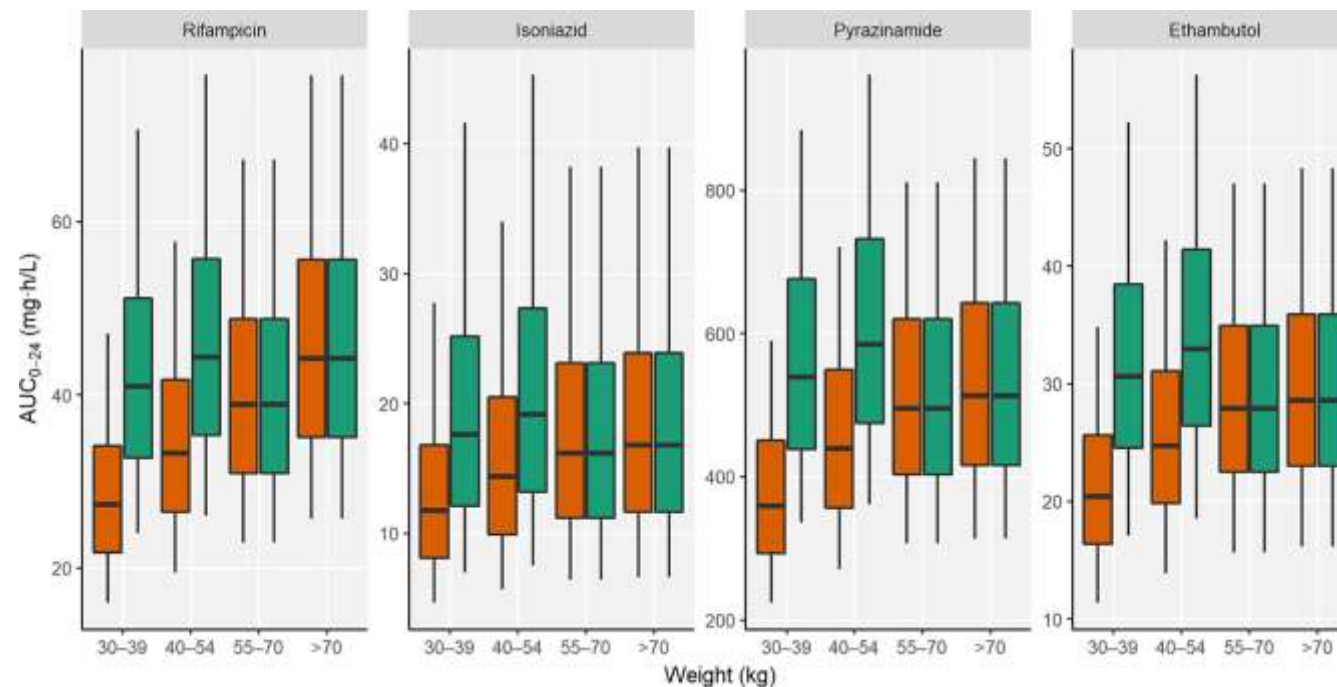
Lower weight-adjusted doses, older age, use of PPIs

Trentalange A, et al. Int J Antimicr Agents 2021

RIF WEIGHT ADJUSTED DOSE AND C_{MAX} TARGETS

Trentalange A, et al. Int J Antimicr Agents 2021

AMERICAN SOCIETY FOR MICROBIOLOGY
Antimicrobial Agents and Chemotherapy®

Low Antituberculosis Drug Concentrations in HIV-Tuberculosis-Coinfected Adults with Low Body Weight: Is It Time To Update Dosing Guidelines?

Christine Sekaggya-Wiltshire,[a] Maxwell Chirehwa,[b] Joseph Musaazi,[a] Amrei von Braun,[c] Allan Buzibye,[a] Daniel Muller,[d] Ursula Gutteck,[d] Ilaria Motta,[e] Andrea Calcagno,[e] Jan S. Fehr,[c] Andrew Kambugu,[a] Barbara Castelnuovo,[a] Mohammed Lamorde,[a] Paolo Denti[b]
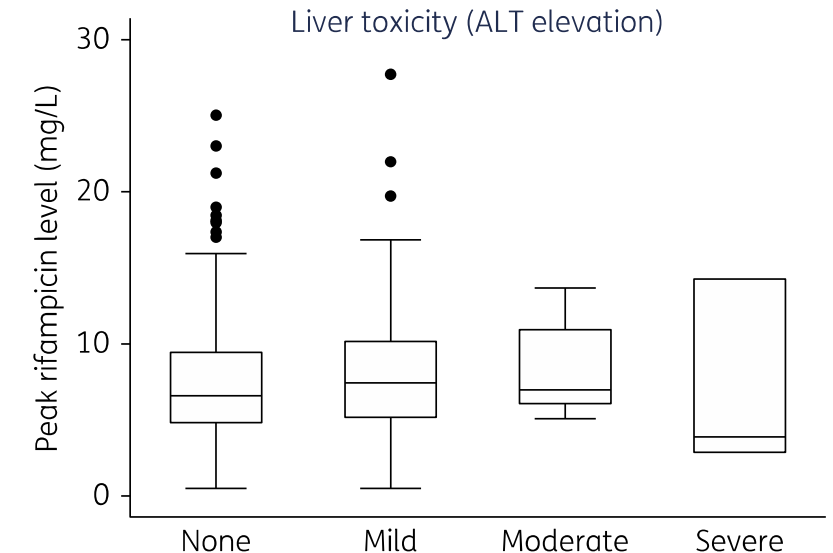

FIG 2 Comparison of simulated exposures using the current dosing strategy versus the suggested dose increment. Shown are box plots of simulated AUC_{0-24} values using the final models for rifampin, isoniazid, pyrazinamide, and ethambutol stratified by weight band. The orange boxes represent the exposure achieved with the currently WHO-recommended dose, while the green ones represent the adjusted dose. The box represents median (central line) and interquartile ranges (box boundaries), while the whiskers are the 2.5th and 97.5th percentiles.
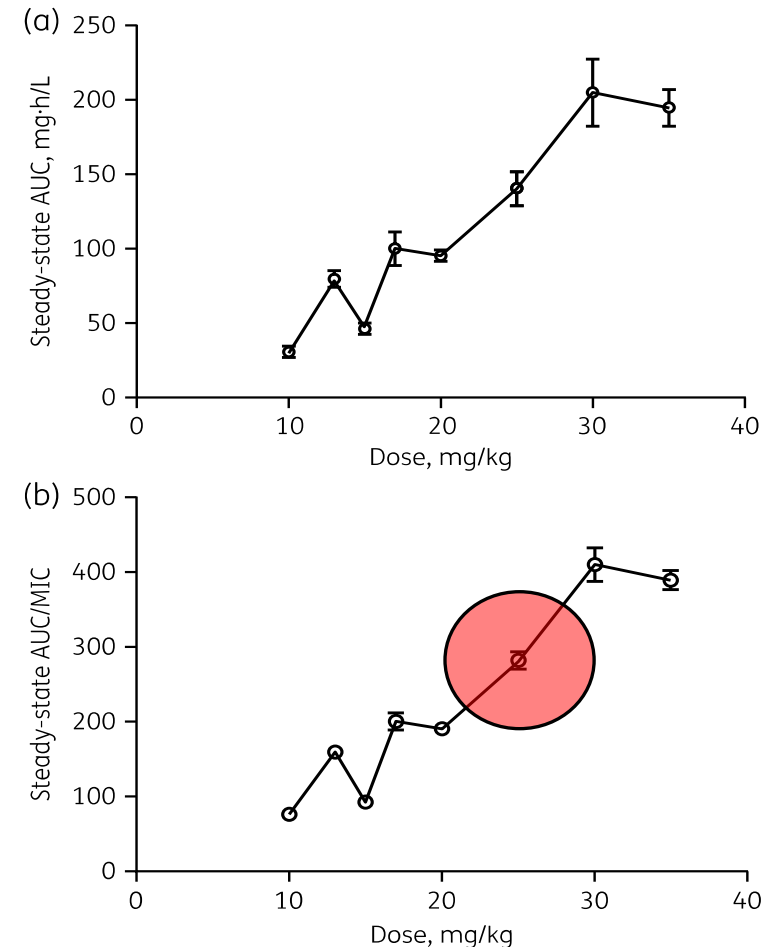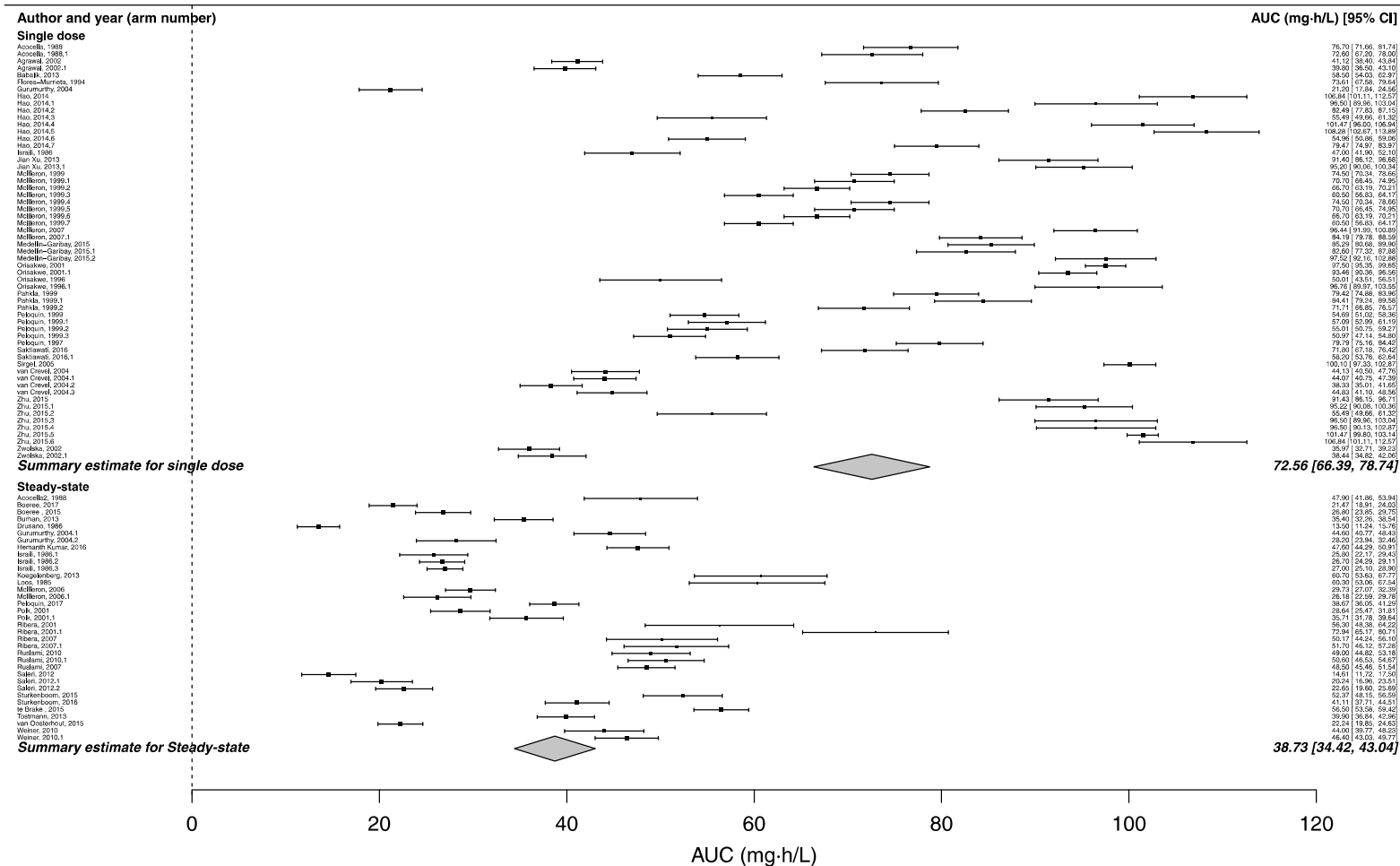
PK AND TOXICITY

Journal of Antimicrobial Chemotherapy

Anti-TB drug concentrations and drug-associated toxicities among TB/HIV-coinfected patients

C. Sekaggya-Wiltshire[1]*, A. von Braun[1], A. U. Scherrer[2,3], Y. C. Manabe[4], A. Buzibye[1], D. Muller[5], B. Ledergerber[2], U. Gutteck[5], N. Corti[6], A. Kambugu[1], P. Byakika-Kibwika[1,7], M. Lamorde[1], B. Castelnuovo[1], J. Fehr[2] and M. R. Kamya[7]
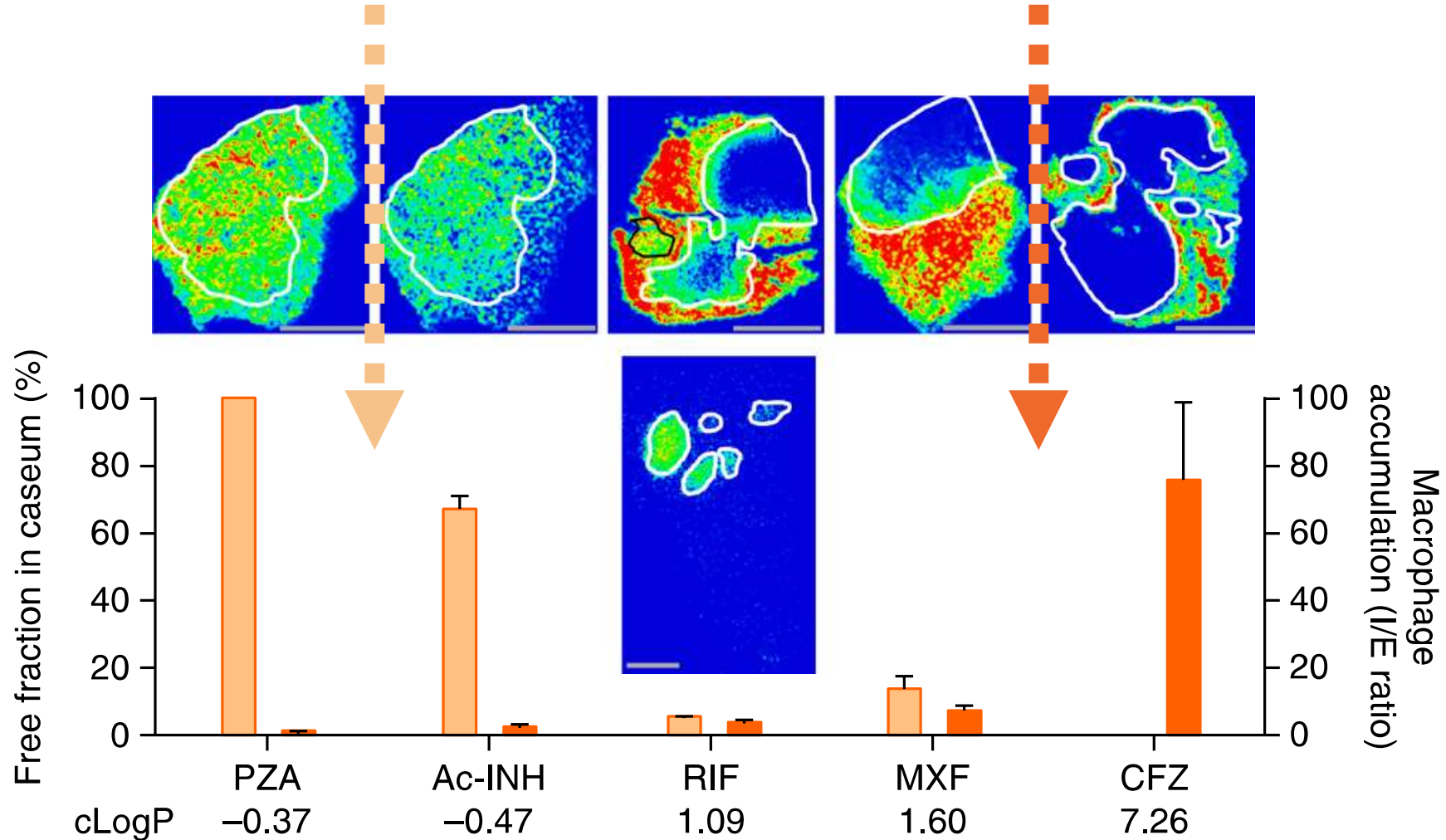
- Several adverse effects

- Mostly mild and reversible but some may be serious (optic neuropathy with E, uveitis with RFB) or life-threatening (severe liver toxicity with RHZ)

- Liver toxicity is most likely determined by multiple factors, including genetic (acetylator state for INH for instance) and non-genetic features

  - Drug exposure may be relevant at currently administered doses for INH-induced liver toxicity

  - Pyrazinamide at much higher doses in phase II studies

Liver toxicity (ALT elevation). Box plot of Peak rifampicin level (mg/L) versus None, Mild, Moderate, Severe.

Saukkonen JJ, et al Am J Respir Crit Care Med; Ramachandran G, et al. Pharmgenomics Pers Med 2012; Cojutti P, et al. J Antimicrob Chemother 2016; Sekaggya-Wiltshire C, et al. JAC 2017; Richardson M, et al. Syst Rev 2018

RIFAMPICIN UNDERDOSING

Stott KE, et al. JAC 2019

TISSUE PK: CASEUM VS. MACROPHAGES

Prideaux B, et al. Nat Med 2015

«THE PATH OF ANTI-TUBERCULOSIS DRUGS: FROM BLOOD TO LESIONS TO MYCOBACTERIAL CELLS»

OUTLINE

STUDIES WITH HD-RIF

SUMMARY OF STUDIES WITH HD-RIF

- Dose-proportional increase in EBA and in sputum conversion rates

Svensson RJ, JID 2018; Boeree MJ, et al. Lancet Infect Dis 2017; Svensson E, et al. CID 2018; Velasquez GE, et al. Am J Resp Crit Care Med 2018; Aarnoutse RE, et al. AAC 2017; Seijger C, et al. PlosOne 2019.

STUDIES WITH HD-RIF - EFFICACY

Study ID	RR (95% CI)	Events, High dose	Events, Standard dose	% Weight
Jindani (2016)	1.11 (0.97, 1.27)	142/171	69/92	16.09
Aarnoutse (2017)	1.08 (0.88, 1.31)	76/96	36/49	7.67
Boeree (2017)	1.06 (0.99, 1.14)	168/182	157/181	59.53
Velasquez (2018)	0.97 (0.81, 1.15)	89/120	46/60	9.72
Atwine (2020)	1.08 (0.88, 1.32)	50/58	24/30	6.99
Overall (I-squared = 0.0%, p = 0.827)	1.06 (1.01, 1.12)	525/627	332/412	100.00

NOTE: Weights are from random effects analysis

.755 — favours standard dose — 1 — favours high dose — 1.32

Onorato L, et al. CMI 2021

SUMMARY OF STUDIES WITH HD-RIF (2)

- Dose-proportional increase in EBA and in sputum conversion rates

- No increase in side effects up to 35 mg/Kg
  - Hyperbilirubinemia with doses >40 mg/Kg

TABLE 3 Summary of frequency of adverse events according to CTCAE criteria[a]

| AE grade | No. of AEs for subjects receiving: | | | | | | | | | |
| | All subjects (n = 150) | 600 mg rifampin (n = 50) | | | 900 mg rifampin (n = 50) | | | 1,200 mg rifampin (n = 50) | | |
		All	Related	Unrelated	All	Related	Unrelated	All	Related	Unrelated
Grade 1 (mild AEs)	821	273	120	153	239	110	129	309	105	204
Grade 2 (moderate AEs)	160	48	16	32	48	10	38	64	9	55
Grade 3 (severe AEs)	20	6	5	1	5	1	4	9	5	4
Grade 4 (life-threatening AEs)	0	0			0			0		
Grade 5 (death related to AE)	3	1		1	1		1	1		1

Rifampicin 1200mg

Rifampicin dose (mg/kg)

C_{max}*

AUC_{0-24}*

Rifampicin 1500mg

Rifampicin dose (mg/kg)

Rifampicin 1800mg

Rifampicin dose (mg/kg)

C_{max}

AUC_{0-24}

Rifampicin 2400mg

Rifampicin dose (mg/kg)

C_{max}

AUC_{0-24}

Svensson RJ, JID 2018; Boeree MJ, et al. Lancet Infect Dis 2017; Svensson E, et al. CID 2018; Velasquez GE, et al. Am J Resp Crit Care Med 2018; Aarnoutse RE, et al. AAC 2017; Seijger C, et al. PlosOne 2019.

STUDIES WITH HD-RIF – SIDE EFFECTS

Summary of meta-analysis results in the achievement of the outcomes in the higher-dose group and the standard group
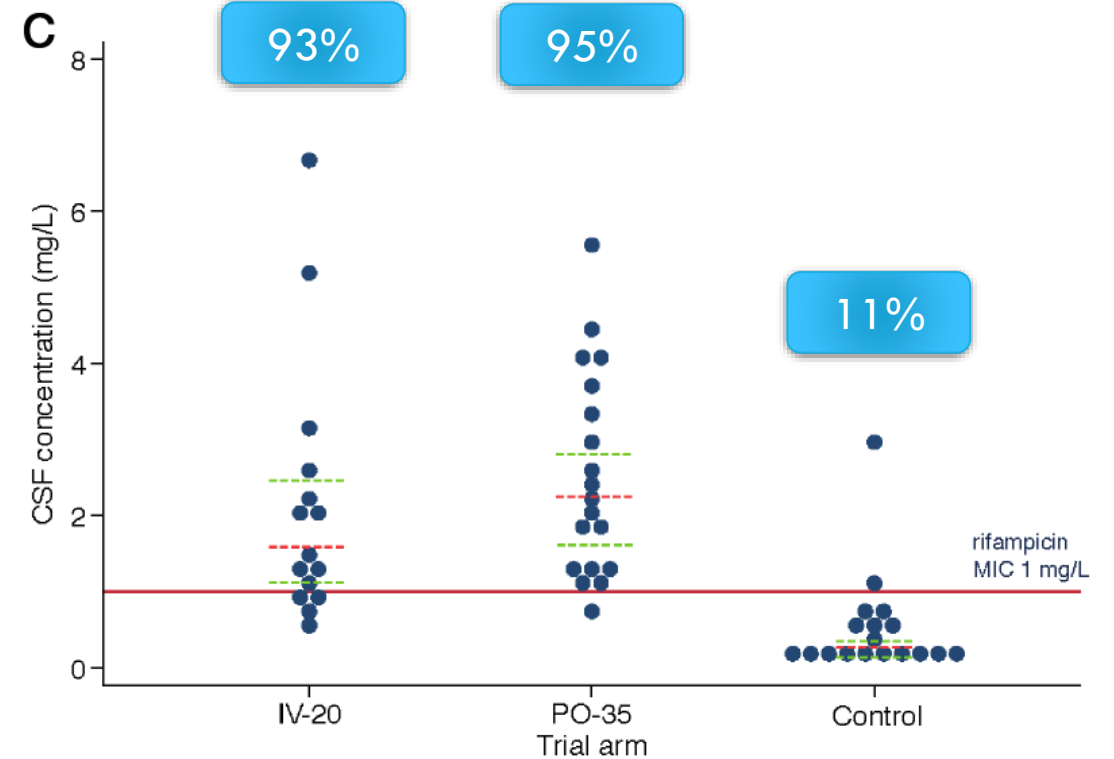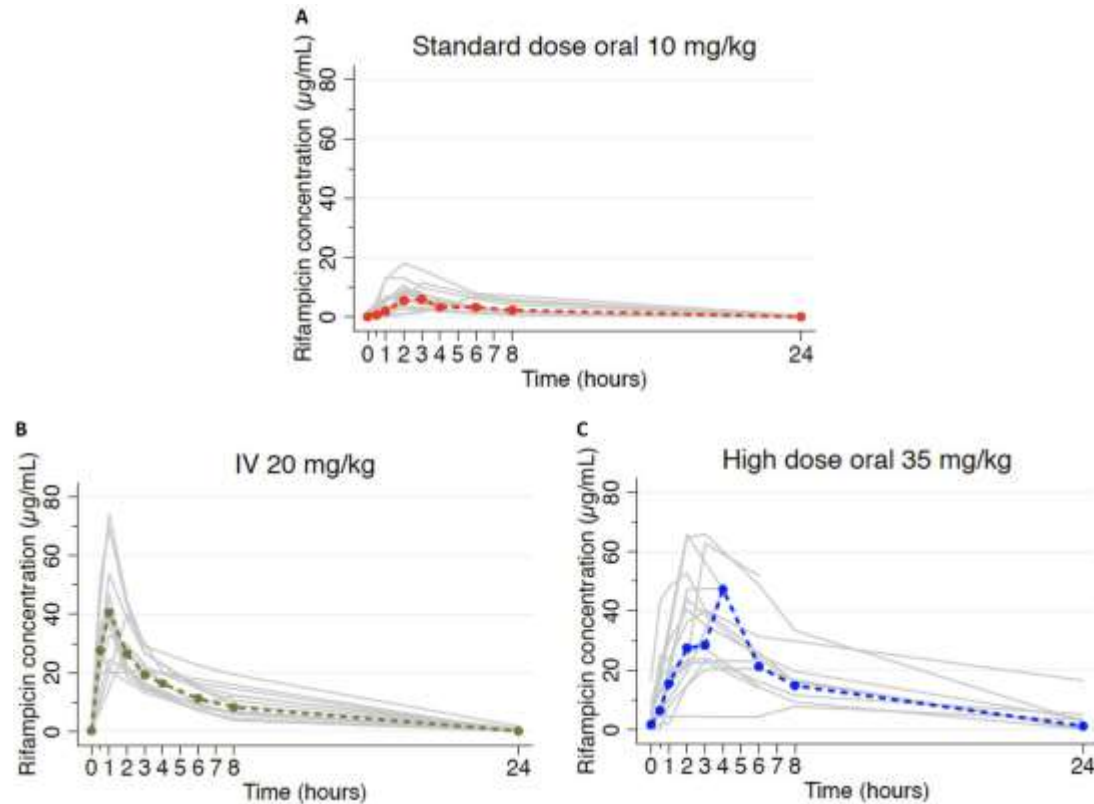
	No of studies [references]	No of patients higher/standard dose group	No of events higher/standard dose group	RR	95%CI	p	Heterogeneity test (I^2, %; p)
Sputum culture conversion at 8 weeks	5 [23–27]	627/412	525 (83.7)/332 (80.6)	1.06	1.01–1.12	**0.028**	0.0; 0.827
Sputum culture conversion at 8 weeks (rifampicin dosing 11–19 mg/kg)	3 [24–26]	188/201	147 (78.1)/151 (75.1)	1.05	0.91–1.17	0.412	0.0; 0.569
Sputum culture conversion at 8 weeks (rifampicin dosing ≥20 mg/kg)	5 [23–27]	439/412	378 (86.1)/332 (80.6)	1.07	1.01–1.13	**0.023**	0.0; 0.887
Treatment failure	4 [21,25,27,28]	554/460	57 (10.3)/51 (11.1)	0.84	0.59–1.21	0.362	0.0; 0.492
Treatment failure (rifampicin dosing 11–19 mg/kg)	2 [21,25]	83/84	15 (18.1)/20 (23.8)	0.65	0.21–2.05	0.464	0.0; 0.138
Treatment failure (rifampicin dosing ≥20 mg/kg)	3 [25,27,28]	471/436	42 (8.9)/44 (10.1)	0.89	0.6–1.32	0.549	0.0; 0.870
Mortality	5 [23,24,26–28]	1097/800	11 (1.0)/13 (1.6)	0.67	0.30–1.54	0.350	0.0; 0.757
Mortality (including 0 value)	8 [21–28]	1097/800	11 (1.0)/13 (1.6)	0.71	0.32–1.56	0.392	0.0; 0.948
Mortality (rifampicin dosing <20 mg/kg)	4 [21,24–26]	233/234	1 (0.4)/1 (0.4)	1.00	0.18–5.70	1.0	0.0; 1.000
Mortality (rifampicin dosing ≥20 mg/kg)	7 [22–28]	864/776	10 (1.2)/13 (1.7)	0.71	0.32–1.71	0.417	0.0; 0.869
Grade 3 or 4 liver toxicity	8 [21–28]	1109/813	65 (5.9)/43 (5.3)	1.15	0.79–1.67	0.479	0.0; 0.801
Grade 3 or 4 liver toxicity (rifampicin dosing 11–19 mg/kg)	4 [21,24–26]	239/241	15 (6.3)/13 (5.4)	1.19	0.59–2.39	0.625	0.0; 0.855
Grade 3 or 4 liver toxicity (rifampicin dosing ≥20 mg/kg)	7 [22–28]	870/782	50 (5.7)/38 (4.9)	1.17	0.77–1.76	0.460	0.0; 0.613
ADR leading to discontinuation	3 [23,26,27]	530/347	8 (1.5)/2 (0.6)	2.31	0.63–8.53	0.209	0.0; 0.959
ADR leading to discontinuation (including 0 value)	5 [21–23,26,27]	530/347	8 (1.5)/2 (0.6)	2.31	0.65–8.21	0.195	0.0; 0.986
ADR leading to discontinuation (rifampicin dosing ≥20 mg/kg)	4 [22,23,26,27]	407/323	8 (1.9)/2 (0.6)	2.63	0.71–9.76	0.148	0.0; 0.983

Onorato L, et al. CMI 2021

STUDIES WITH HD-RIF IN PATIENTS WITH TB MENINGITIS

1. 60 adults in Indonesia (12% HIV+) randomized to receive HZ (and dexamethasone) plus either oral RIF (10 mg/Kg) or iv RIF (13 mg/Kg) and Mx (400 or 800) or E (750 mg) for 14 days (then standard regimens)
   - **AUC, C_{max}, CSF-to-plasma ratio 3 times higher**
   - **Less chance of death (HR 0.42)** with iv RIF and GCS as independent predictors

2. 60 adult TBM patients in Bandung (Indonesia) randomized to 450 mg, 900 mg, or 1,350 mg (10, 20, and 30 mg/kg) oral RIF combined with other TB drugs for 30 days
   - **AUC and CSF-to-plasma ratios 3- and 5- folds higher**
   - **No increase in the incidence of grade 3 or 4 adverse events**
   - Non significant reduction in mortality in the 30 mg/kg arm (15% vs. 35% vs. 45%)

Ruslami R, et al. Lancet Infect Dis 2013

PLASMA VS. ORAL RIFAMPICIN IN TBM

RIFAPENTINE

Parameter	Rifampicin (600mg twice weekly)	Rifabutin (300mg twice weekly)	Rifapentine (600mg once weekly)
C_{max} (mg/L)	10.0	0.45	15.0
MIC in broth culture (mg/L)	0.15	0.06	0.04
C_{max}/MIC ratio	67	7.5	375
Estimated time over MIC at this dosage (h)	16	111	104
Binding to serum proteins (%)	85	71	97
Predicted C_{max} of the unbound drug (mg/L)	1.5	0.13	0.45
Estimated unbound C_{max}/MIC ratio	10	3.5	11
Ratio of intracellular : extracellular concentrations	5	9	24-60
Ratio of intracellular : extracellular MIC[a]	1-2, 6.7	2	1, 26

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens
with or without Moxifloxacin for Tuberculosis

S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley,
M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens,
N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham,
S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje,
E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson,
for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

ABSTRACT

BACKGROUND

Rifapentine-based regimens have potent antimycobacterial activity that may allow for a shorter course in patients with drug-susceptible pulmonary tuberculosis.

METHODS

In an open-label, phase 3, randomized, controlled trial involving persons with newly diagnosed pulmonary tuberculosis from 13 countries, we compared two 4-month rifapentine-based regimens with a standard 6-month regimen consisting of rifampin, isoniazid, pyrazinamide, and ethambutol (control) using a noninferiority margin of 6.6 percentage points. In one 4-month regimen, rifampin was replaced with rifapentine; in the other, rifampin was replaced with rifapentine and ethambutol with moxifloxacin. The primary efficacy outcome was survival free of tuberculosis at 12 months.

RESULTS

Among 2516 participants who had undergone randomization, 2343 had a culture positive for *Mycobacterium tuberculosis* that was not resistant to isoniazid, rifampin, or fluoroquinolones (microbiologically eligible population; 768 in the control group, 791 in the rifapentine–moxifloxacin group, and 784 in the rifapentine group), of whom 194 were coinfected with human immunodeficiency virus and 1703 had cavitation on chest radiography. A total of 2234 participants could be assessed for the primary outcome (assessable population; 726 in the control group, 756 in the rifapentine–moxifloxacin group, and 752 in the rifapentine group). Rifapentine with moxifloxacin was noninferior to the control in the microbiologically eligible population (15.5% vs. 14.6% had an unfavorable outcome; difference, 1.0 percentage point; 95% confidence interval [CI], −2.6 to 4.5) and in the assessable population (11.6% vs. 9.6%; difference, 2.0 percentage points; 95% CI, −1.1 to 5.1). Noninferiority was shown in the secondary and sensitivity analyses. Rifapentine without moxifloxacin was not shown to be noninferior to the control in either population (17.7% vs. 14.6% with an unfavorable outcome in the microbiologically eligible population; difference, 3.0 percentage points [95% CI, −0.6 to 6.6]; and 14.2% vs. 9.6% in the assessable population; difference, 4.4 percentage points [95% CI, 1.2 to 7.7]). Adverse events of grade 3 or higher occurred during the on-treatment period in 19.3% of participants in the control group, 18.8% in the rifapentine–moxifloxacin group, and 14.3% in the rifapentine group.
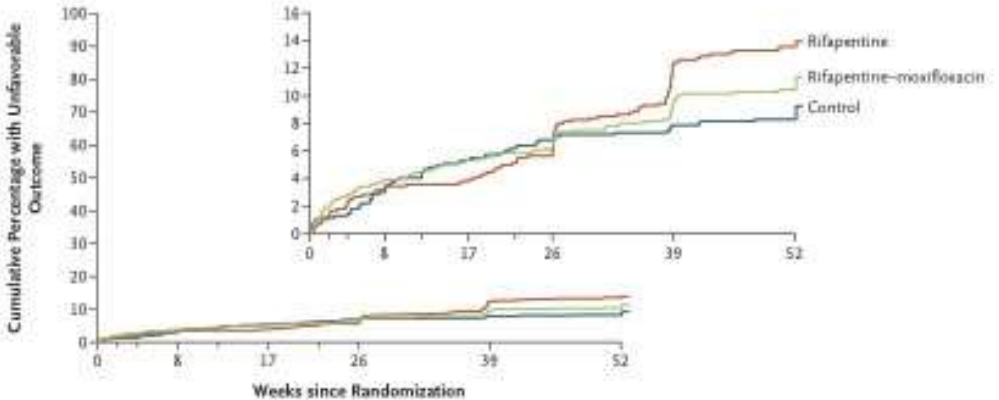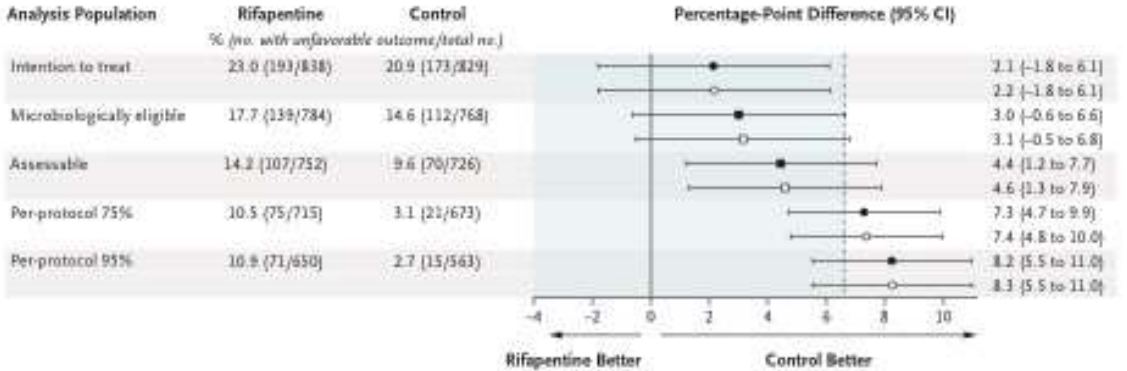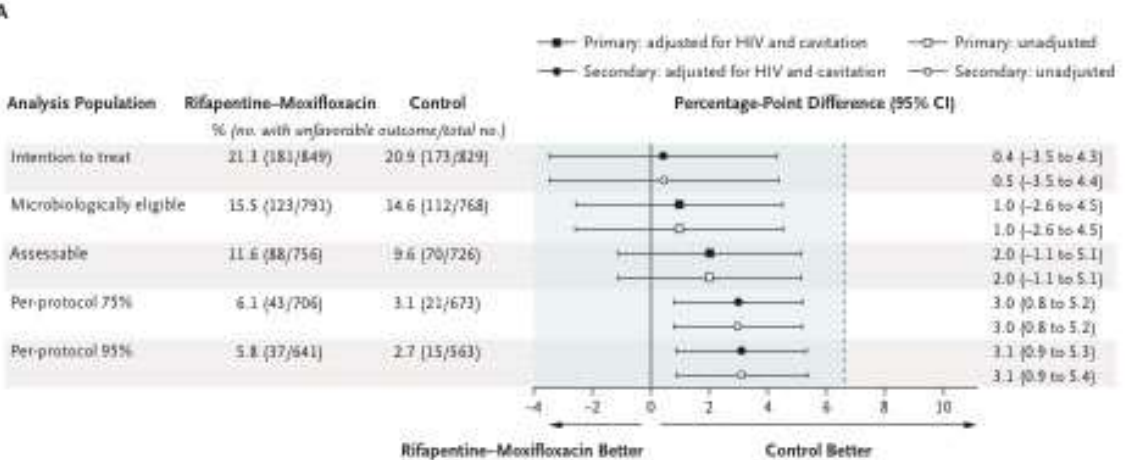
CONCLUSIONS

The efficacy of a 4-month rifapentine-based regimen containing moxifloxacin was noninferior to the standard 6-month regimen in the treatment of tuberculosis. (Funded by the Centers for Disease Control and Prevention and others; Study 31/A5349 ClinicalTrials.gov number, NCT02410772.)

OUTLINE

ISSUES WITH HD RIFAMPICIN

1. ## Disruption of fixed-dose combinations

2. ## DDIs?

Magis-Escurra C, et al. Lancet Resp Med 2018

Pound foolish and penny wise—when will dosing of rifampicin be optimised?

In September, 2017, the authors attended a tuberculosis conference in China where it became clear that resistance to anti-tuberculosis drugs could render the ambitious WHO targets for tuberculosis elimination unreachable.

The authors believe that the tuberculosis community should act swiftly and make smart and well founded choices to improve treatment success. Excellent studies have been published on optimal approaches to treat resistant tuberculosis, but unfortunately the tuberculosis community is transforming this knowledge into recommendations that change standard therapy at a slow pace. Effective interventions are needed more urgently than ever if the goals of the End TB Strategy are to be achieved. In 2013 and 2014, WHO made the courageous decision of making bedaquiline and delamanid available to the global community. This occurred at an early investigational stage when evidence from phase 3 trials was still absent; before that, bedaquiline and delamanid could not be included in standard therapy.

Although studies have shown that the dosing regimen for rifampicin currently recommended in all international guidelines is suboptimal,[2–4] a high-dose treatment strategy has still not been recommended; rather, the scientific community requested more studies.

The tuberculosis community's focus on a once daily, 600 mg dose of rifampicin is worrisome. This dose is at the low end of the dose–response curve and was selected in the past mainly for financial reasons.[2] Comparing the strength of evidence for the efficacy and safety of bedaquiline and delamanid, the authors do not understand why the demands of the scientific community are so much higher for a change in dosing of rifampicin (an old drug), when multiple studies have shown already that it is safe and more efficacious.

In vitro and in vivo pharmacokinetic and pharmacodynamic studies support a higher dosing strategy for rifampicin.[5–7] Bacteriological studies also indicate that the use of the standard once daily, 600 mg dose of rifampicin can increase the number of new multi-drug resistant tuberculosis cases, especially in case of isoniazid monoresistant strains or the Beijing genotype of M tuberculosis, both of which might be more tolerant to rifampicin than other strains.[8] Moreover, two phase 2 studies showed favourable outcomes with high-dose rifampicin ranging from 10 to 35 mg/kg orally per day in the absence of any relevant toxicity.[1,9,10] In Indonesian patients with tuberculous meningitis, high intravenous doses (about 13 mg/kg) of rifampicin yielded a 50% reduction in mortality.[11] Therefore, why not reassess the original data[2] to make an evidence-based decision to recommend a high dose of rifampicin in tuberculosis treatment?

The ambition of WHO to eliminate tuberculosis between 2035 and 2050 requires effective interventions and our suggestion could be one of them. The most important first-line drug against tuberculosis is underdosed and we suggest taking a firm decision to change this situation.

It is time for the rapid programmatic introduction of a high dose of rifampicin (30–35 mg/kg, which a phase 2 trial indicated would improve efficacy)[1,9] for at least four high-risk groups that are not well treated by the standard dose—ie, patients with tuberculosis meningitis, HIV, diabetes, and severe illness characterised by a low body mass index (<18 kg/m²). These patients are characterised by high rates of absorption problems, acquired drug resistance, relapses, and mortality. The decision to increase the dose of the first-line tuberculosis therapy and prevent further development of resistance should not be postponed.

A rapid roll-out of high-dose rifampicin in these high-risk groups should be organised in a centrally controlled way, similar to the WHO bedaquiline and delamanid roll-out. A large phase 3 trial of higher dose rifampicin (20 and 30 mg/kg) is underway (NCT02581527).[3] Although results will only be available in 3–5 years, phase 3 trials will provide much needed data to optimise the duration of first-line treatment.

Introduction should be accompanied by appropriate monitoring according to the US Food and Drug Administration, European Medicines Agency, and WHO guidelines for early market release of drugs. Because rifampicin, unlike bedaquiline and delamanid, is already off-patent, we call on WHO, the American Thoracic Society, and the European Respiratory Society in consultation with the US Food and Drug Administration and European Medicines Agency, to act quickly.

In our opinion, saving pennies on a 600 mg, once daily, rifampicin dose while losing lives of patients with tuberculosis, does not pay off.

*Cecile Magis-Escurra,
Richard M Anthony,
Adri G M van der Zanden,
Dick van Soolingen,
Jan-Willem C Alffenaar
cecile.magis-escurra@radboudumc.nl

Radboud University Medical Centre -TB Expert Centre Dekkerswald, Nijmegen-Groesbeek, 6561KE, the Netherlands (CM-E); Mycobacteria Reference Laboratory, RIVM, Bilthoven, the Netherlands (RMA, DvS); Department of Medical Microbiology, VieCuri Medical Center, Venlo, the Netherlands; Medical Microbiology, Laurentius Hospital, Roermond, the Netherlands; Laboratory of Medical Microbiology and Public Health, Hengelo, the Netherlands (AGMvdZ); University of Groningen, University Medical Centre Groningen, UMCG, Groningen, the Netherlands (J-WCA)
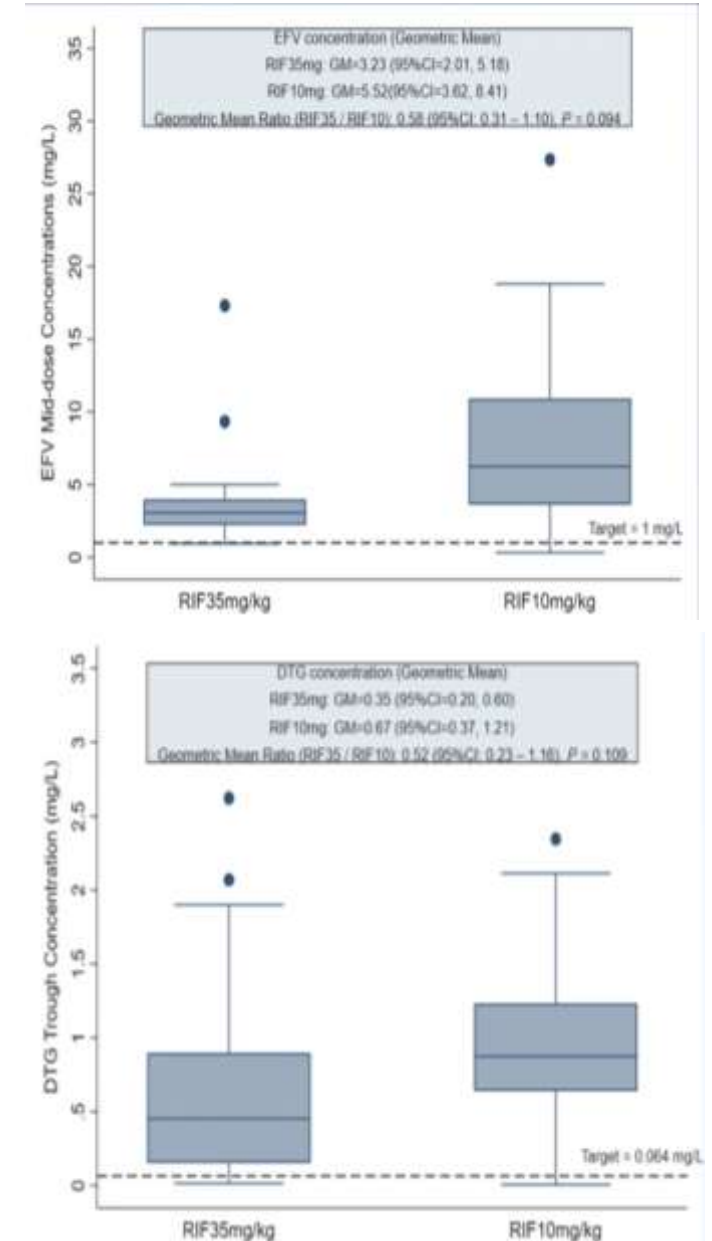
1 Boeree MJ, Diacon AH, Dawson R, et al. A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. Am J Respir Crit Care Med 2015; 191: 1058–65.

2 van Ingen J, Aarnoutse RE, Donald PR, et al. Why do we use 600 mg of rifampicin in tuberculosis treatment? Clin Infect Dis 2011; 52: e194–99.

ENZYME INDUCTION WITH HD RIF?

	R10 EFV600	R20 EFV600	R20 EFV800
n	31	28	31
Week 8 AUC_{0-24}	40198	47505	44466
Week 28 AUC_{0-24}	38918	49574	35169
GMR AUC_{0-24}	0.96 (0.84-1.10)	0.87 (0.75-1.00)	1.12 (0.96-1.30)
Week 8 C_{min}	1078	1163	1032
Week 28 C_{min}	1137	1496	1028
GMR C_{min}	0.92 (0.79-1.08)	0.83 (0.72-0.96)	1.16 (0-97-1.39)

EFV concentration (Geometric Mean)
RIF35mg: GM=3.23 (95%CI=2.01, 5.18)
RIF10mg: GM=5.52 (95%CI=3.62, 8.41)
Geometric Mean Ratio (RIF35 / RIF10): 0.58 (95%CI: 0.31 – 1.10), P = 0.094

DTG concentration (Geometric Mean)
RIF35mg: GM=0.35 (95%CI=0.20, 0.60)
RIF10mg: GM=0.67 (95%CI=0.37, 1.21)
Geometric Mean Ratio (RIF35 / RIF10): 0.52 (95%CI: 0.23 – 1.16), P = 0.109

Atwine D, et. al. JAC 2020; Sekaggya-Wiltshire C, et al. CROI 2021 #90
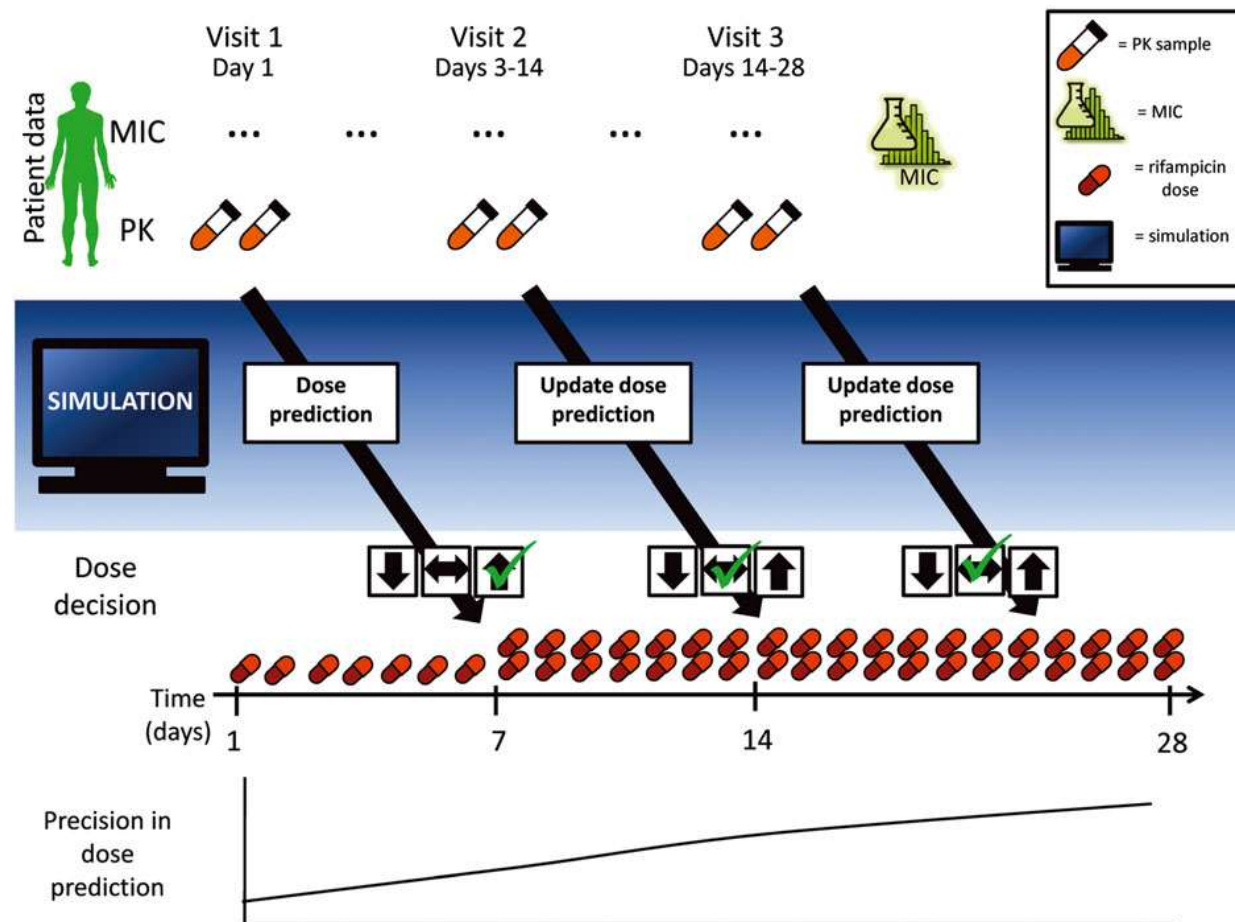
OUTLINE

BJCP   BRITISH PHARMACOLOGICAL SOCIETY

Individualised dosing algorithm and personalised treatment of high-dose rifampicin for tuberculosis
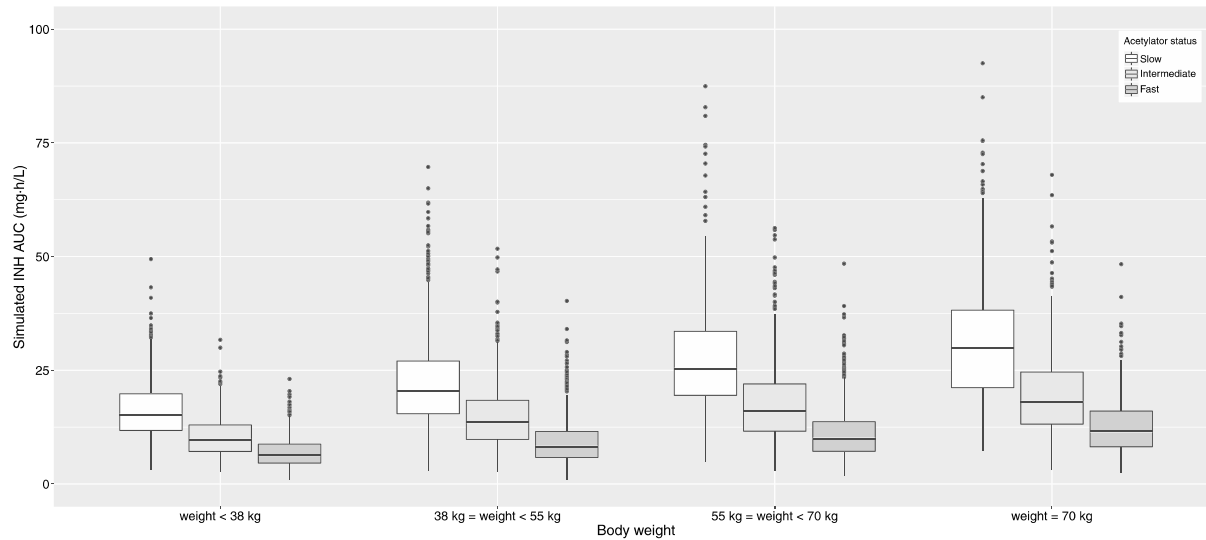
Robin J. Svensson[1] | Katarina Niward[2,3] | Lina Davies Forsman[4,5] | Judith Bruchfeld[4,5] |
Jakob Paues[2,3] | Erik Eliasson[6] | Thomas Schön[7,8] | Ulrika S.H. Simonsson[1] (ID)

INH DOSE AND PHARMACOGENETICS

Patients <38 kg → lower 30.4% (RIF AUC), 45.9% (INH AUC) and 18.0% (PZA AUC)
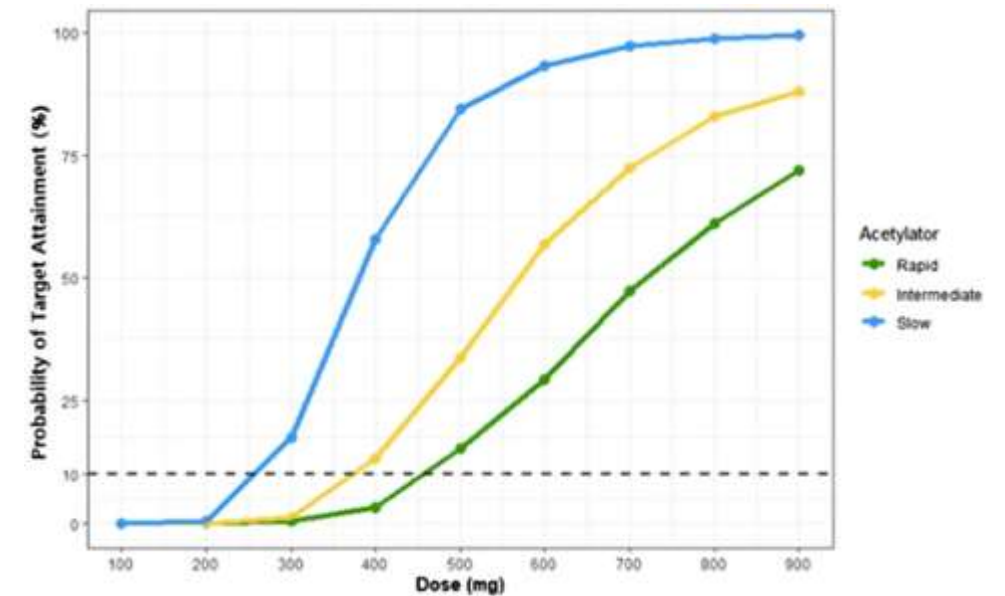
→ Higher doses + one fixed-dose combination tablet or + 150 mg INH

Proposed dose in Korean patients

| 200 mg | 300 mg | 400 mg |

Probability of achieving a C_{max} of ≥6 for the simulated INH dosing regimens according to the NAT2 acetylator phenotype.

Gao Y, et al. BJCP 2020; Cho Y-S, et al. J Clin Pharm 2021

CONCLUSIONS

- Current 1st-line antitubercular drugs doses were chosen according to patients' features (body weight, PK exposure), experience (fear of adverse events) and costs that changed over time (and need to be challenged with the risks of selecting DR strains)

- Isoniazid, Ethambutol and Pyrazinamide may have significant toxicities with higher doses

- RIF is **underdosed** and higher doses (up to 35 mg/kg) may increase bactericidal activity, prevent the selection of resistant strains and would not increase side effects

- The adoption of higher doses may lead to some implementation issues so it may be **prioritized** in hard-to-treat patients (cavities, extensive disease, extrapulmonary TB) and in those with a higher chance of low exposure (PLWH, diabetics, children, low BMI)

  - The effect of higher RIF doses on enzyme induction and DDIs still need to be thoroughly assessed

- The combination of HD-RIF with newer drugs may favour shorter regimens (as observed for rifapentine) thus allowing for better treatment adherence

ACKNOWLEDGEMENTS