Therapeutic Drug Monitoring for Tuberculosis

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No disclosures

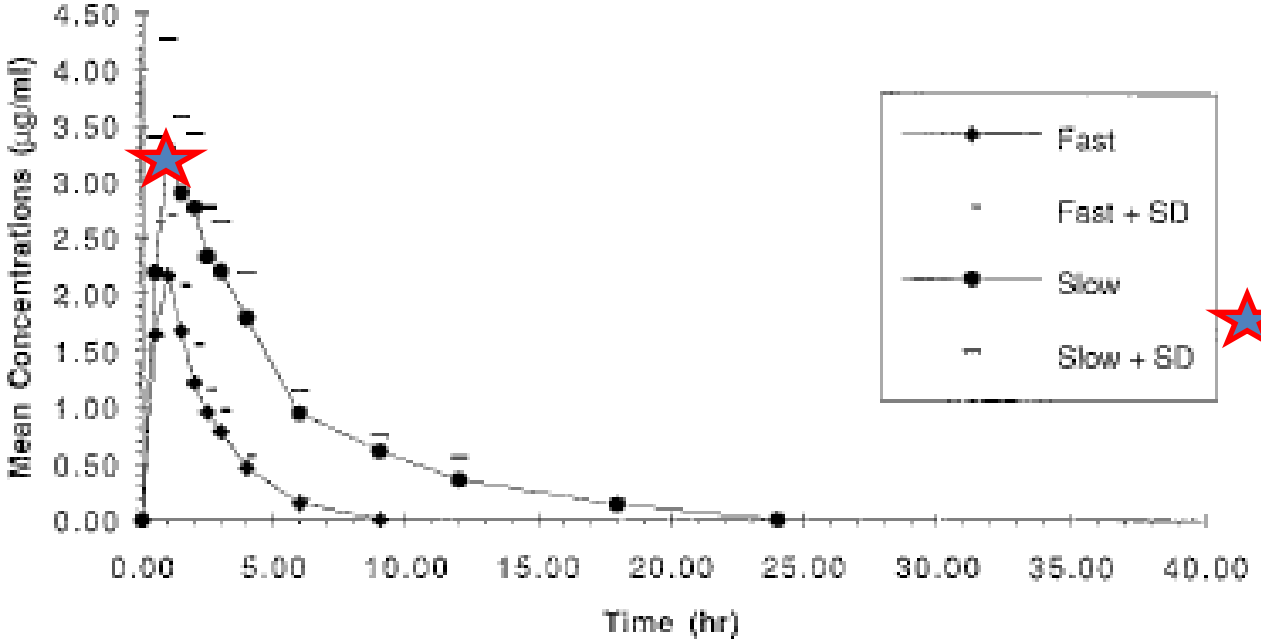
1) **Pharmacokinetic (PK) variability**

2) Increased dose → “acceptable” levels

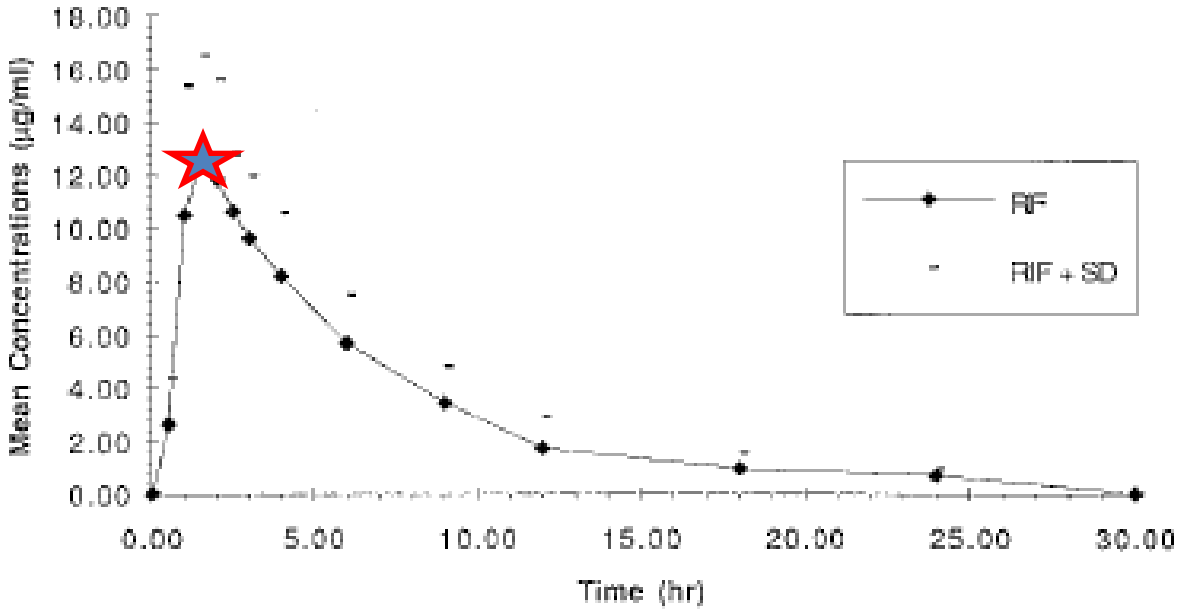
3) Poor outcomes more frequent with “low” levels

4) Increasing doses for low levels→ better outcomes

Current "expected ranges" *in part* derived from healthy controls



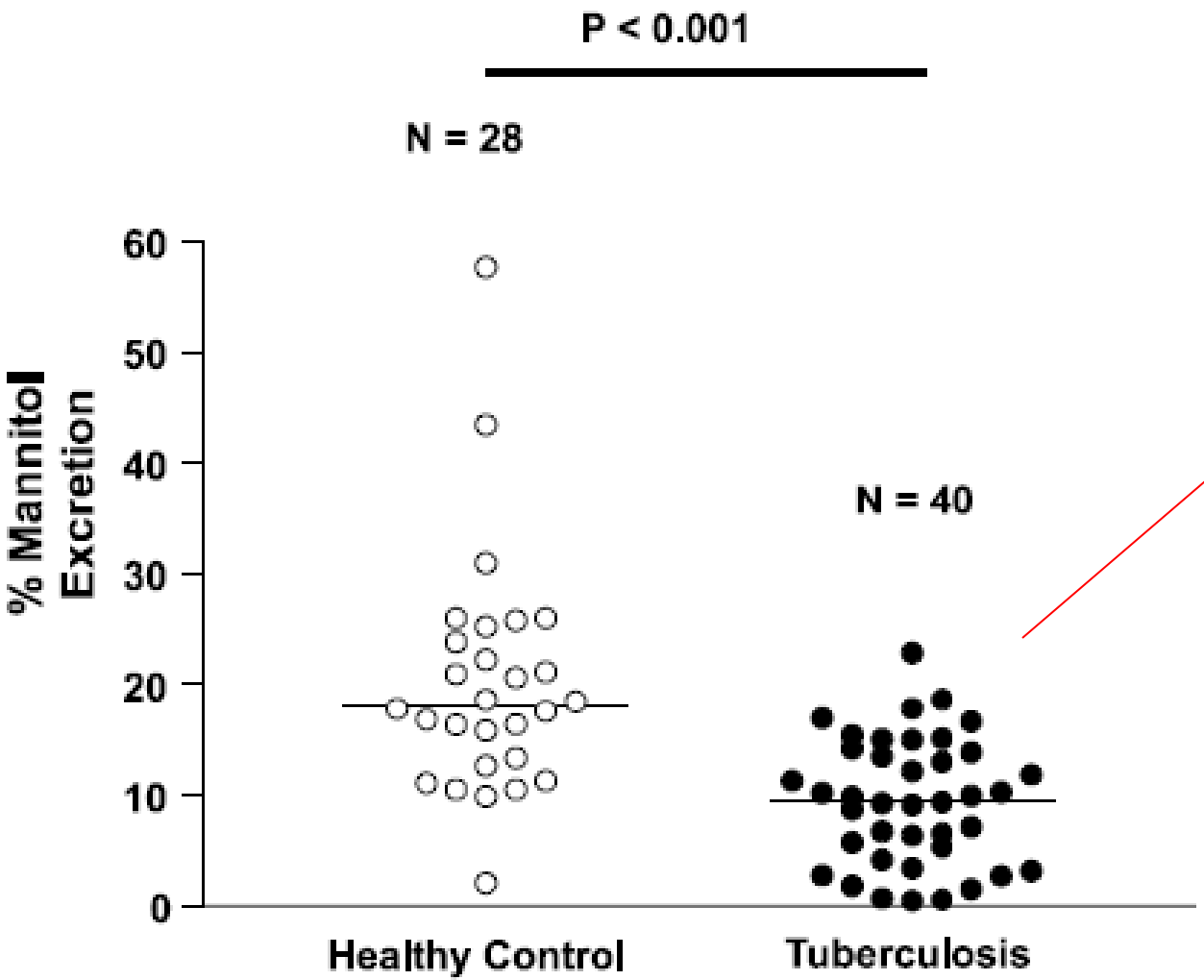
INH: C_{max} 3-6 µg/ml



RIF: C_{max} 8-24 µg/ml

Peloquin et al, *AAC* 1997

Intestinal absorptive area is decreased in TB patients



Subset of TB patients→
12/18 low RIF C_{2hr}
13/18 low INH C_{2hr}

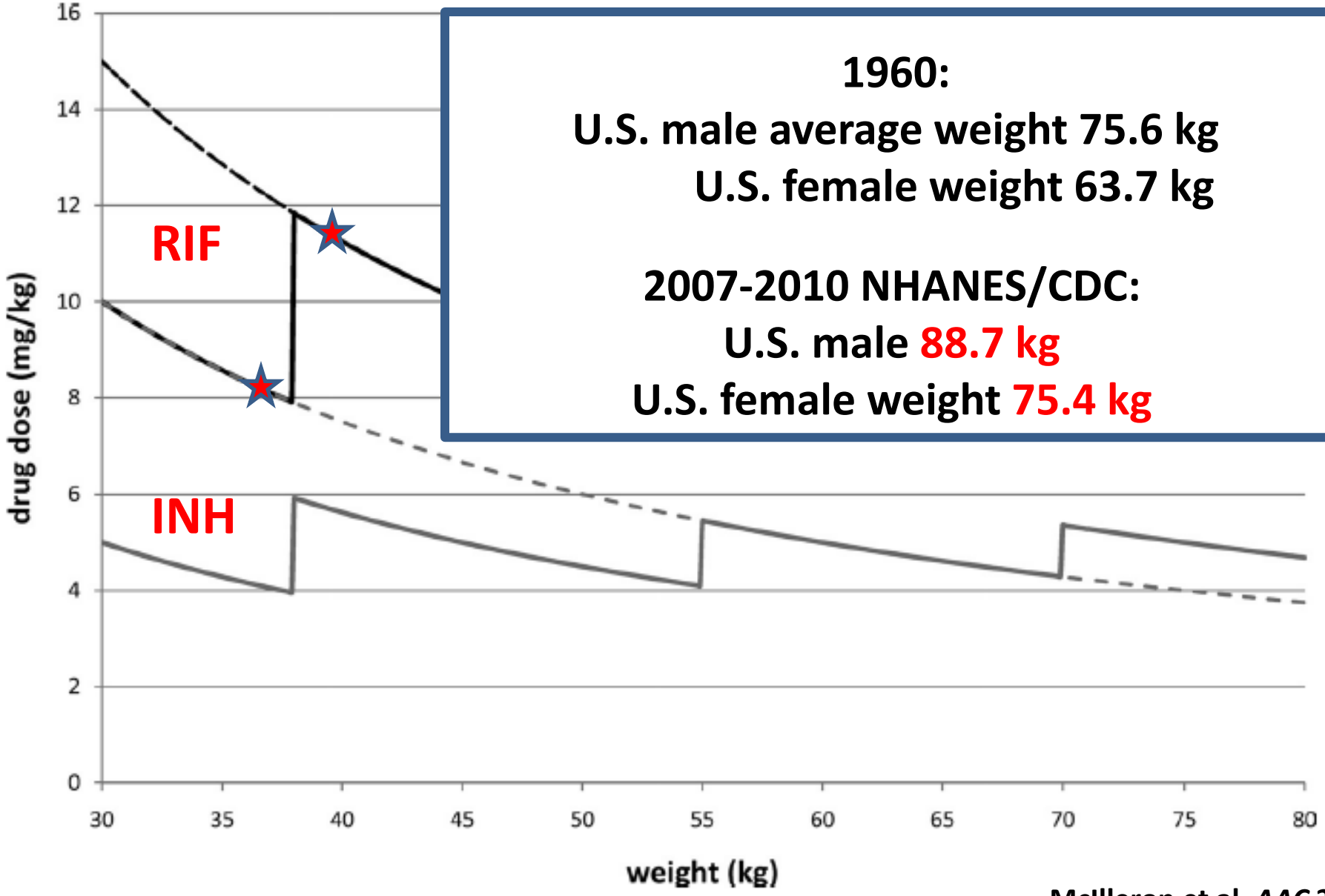
Pinheiro, *Brazil J Infect Dis* 2006

Barroso, *Am J Trop Med Hyg* 2009

Choudhri, *Clin Infect Dis* 1997

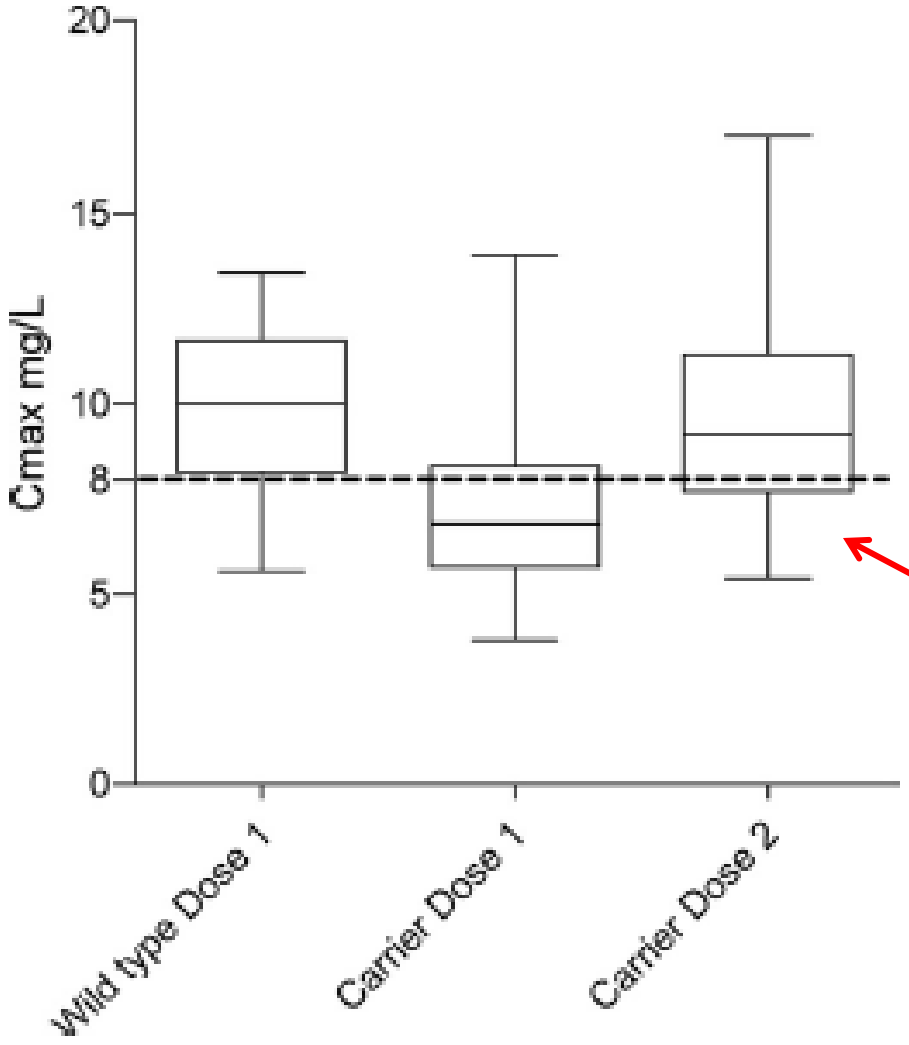
Gurumurthy, *Clin Infect Dis* 2004

Fixed dose categories may ‘under-dose’



McIlleron et al, *AAC* 2012

SLCO1B1 polymorphism→ low rifampin exposure is the *norm* in a South African population



Allelic frequency 0.70

Reduced rifampin AUC 18-28%

63% with C_{max} below 8 µg/ml

Increasing rifampin dose by 150 mg

Chigutsa et al, *AAC* 2011

PK variability is common* at standard dosing

TABLE 2 Plasma concentrations of antituberculosis drugs at 14 or 30 days after initiation of the short-course drug treatment regimen

	Plasma concn (μg/ml) for TB patient group on indicated day			
	Nondiabetic		Diabetic	
Serum drug	14	30	14	30
Isoniazid	3.2 ± 0.2	2.9 ± 0.2	1.5 ± 0.2[a]	1.2 ± 0.2[a]
Rifampin	5.1 ± 0.5	5.4 ± 0.5	2.9 ± 0.2[a]	3.2 ± 0.5[a]
Pyrazinamide	23.4 ± 2.0	27.9 ± 1.6	25.9 ± 1.4	23.4 ± 1.9
Ethambutol	2.81 ± 0.30	3.6 ± 0.3	3.70 ± 0.64	4.3 ± 0.7

[a] Value is significantly ($P < 0.05$) lower than the values observed in nondiabetic TB patients on the corresponding days.

Babalik, *AAC* 2013

Mean C_{2hr} INH and RIF below 'expected' range

No **diabetic had 'normal' C_{2hr} INH or RIF**

*Fahimi, *IJTLD* 2013

*Requena-Mendez, *AAC* 2012

1) **Pharmacokinetic (PK) variability**

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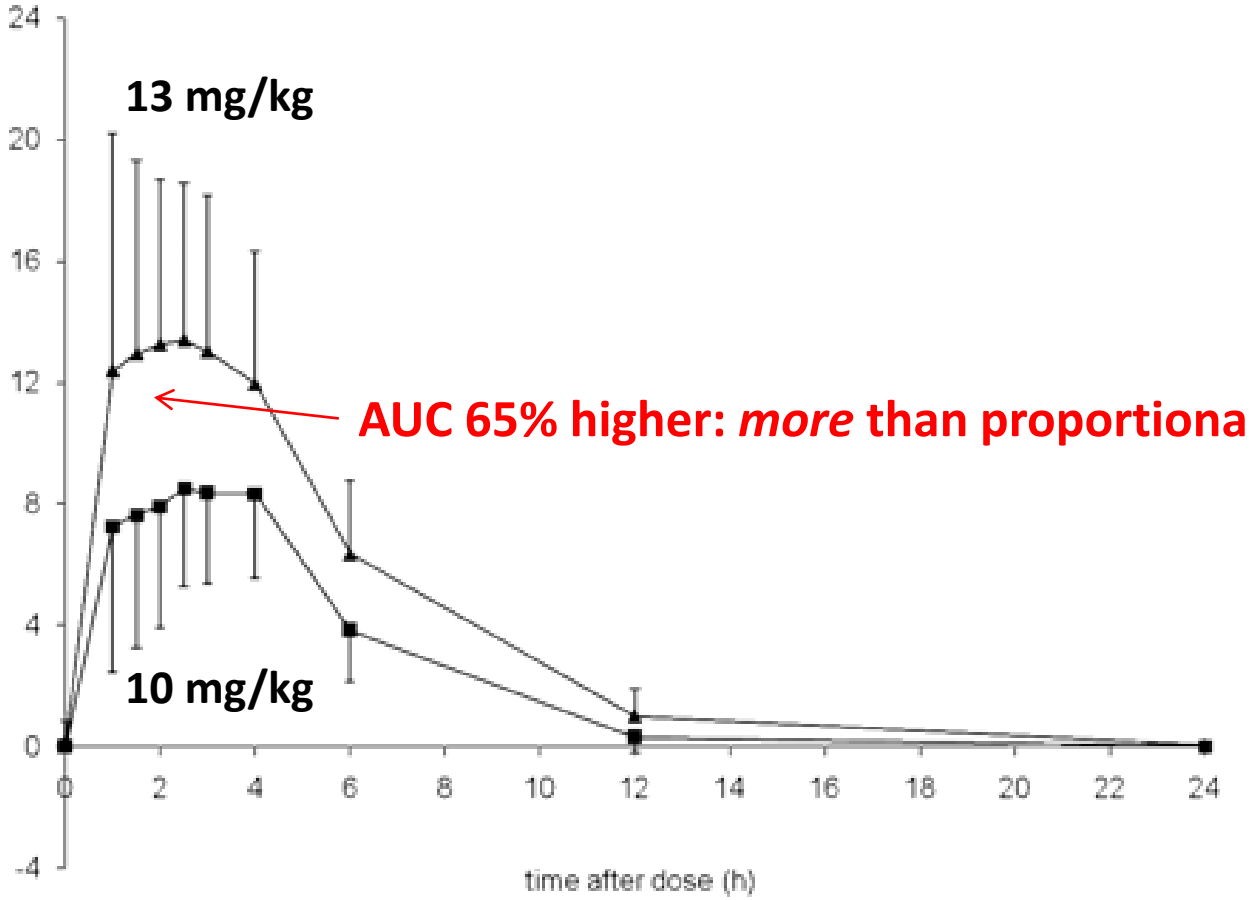
4) Increasing doses for low levels→ better outcomes

Dose increase → higher concentrations, near "expected range"



Ruslami, *AAC* 2007

- **Montreal (slow responders):**

  Mean dose increase **INH** 61%→ 127% C_{2hr} increase

Babalik, *Can Resp J* 2011

Rarely a concentration does not increase post adjustment

Vancouver

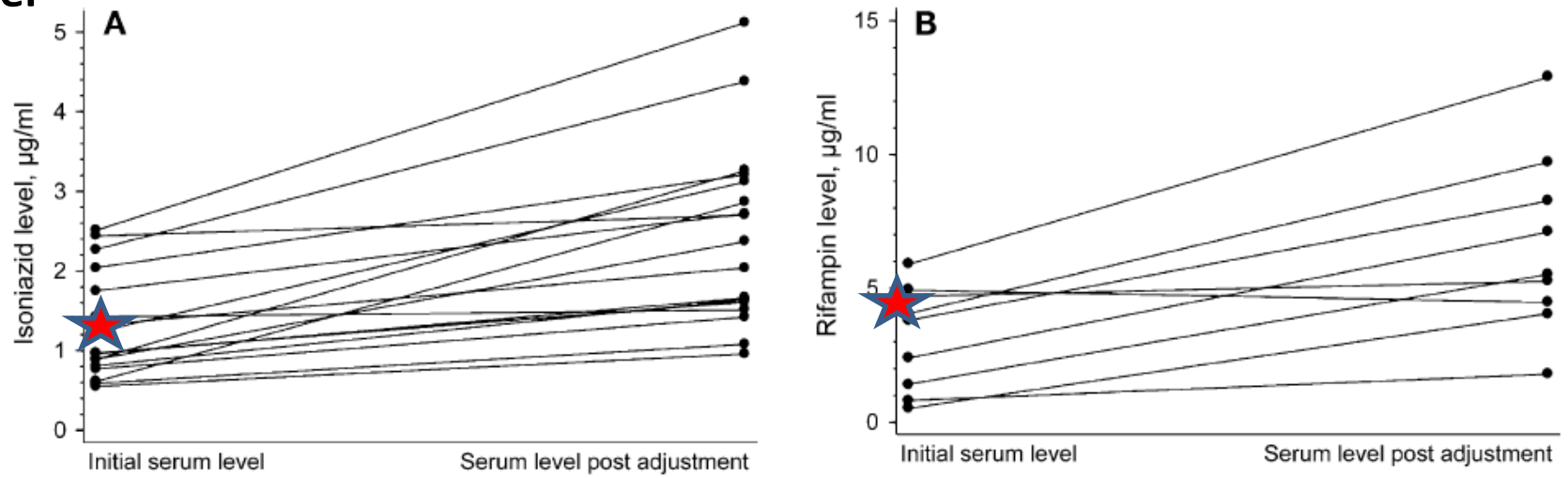
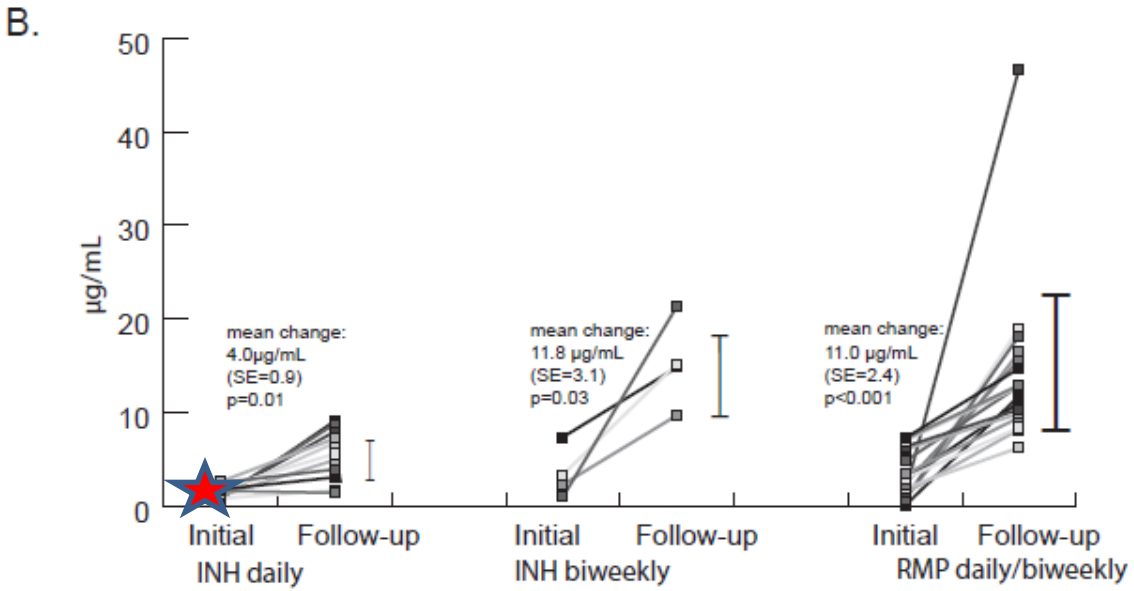


Figure Serum response per 100 mg increase in dosage. **A.** Serum isoniazid levels, $n = 17$. **B.** Serum rifampicin levels, $n = 9$.

Virginia



van Tongeren, *IJTLD* 2013

(similar overall mean increase)

Heysell, *Emerg Infect Dis* 2010

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Do we need to reset our 'expected' ranges?

Failure (N=5)	Success (N=23)	P value
Mean C_{2hr} (range)	**Mean C_{2hr} (range)**	
INH 1.0 (0.4-2.2)	INH 2.6 (2.0-3.3)	0.004
RIF 4.0 (2.2-7.6)	RIF 7.3 (5.1-10.5)	0.129
EMB 2.5 (0.7-9.2)	EMB 2.0 (1.4-2.8)	0.551
PZA 26.4 (14.0-50.0)	PZA 35.2 (28.8-43.1)	0.232

Adjust for median C_{2hr} values

Below median values → % failure	Above median values → % failure	P value
RIF 33%	RIF 0%	0.04
INH 36%	INH 0%	0.04
Both 45%	Both 0%	0.005

Success: cure or treatment complete;
Failure: death (n=3) or relapse within 1 year (n=2)

Prahl et al, *J Antimicrob Chemother* 2014

Some observational studies *cannot* demonstrate a clinical impact of poor drug exposure

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C_{max}/ MIC > 175 prevents resistance development*

C_{max} 6.0 (below "expected") / MIC 0.06 = 100

C_{max} 10.0 (within "expected") / MIC 0.5 = 20

*ex vivo hollow-fiber model, mimics early animal studies

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Other studies (*with more treatment failure*) demonstrate significant association with low drug concentrations and poor outcome

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)**	

South Africa: top 3 predictors of poor outcome were AUC (drug concentrations) for PZA, RIF and INH

Pasipanodya, *J infect Dis* 2013

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Dose increase for "low" concentrations in slow-responders: well-tolerated*, favorable outcomes if timely TDM?, but understudied

	Vancouver N= 52	Virginia N= 42	Montreal N= 20
Population	1-2% total, 2000-10	14% total, 2007-09	7% total, 2005-10
Low C_{2hr}	47 (90%)	32 (89% w testing for INH + RIF)	17 (85%)
Outcomes	45% failure; 11% relapse; acquired drug-resis (ADR)	No ADR; if low RIF corrected→shorter tx. duration	No ADR; all cured
Caveats	Late referrals?	TDM at 4-6 weeks	Barriers to implement

*Mehta, *Chest* 2001

*Kimmerling, *Chest* 1998

van Tongeren, *IJTLD* 2013

Heysell, *EID* 2010

Babalik, *Can Respir J* 2011

Next best step?

The Case for Using Higher Doses of First Line Anti-Tuberculosis Drugs to Optimize Efficacy

Goutelle, *Curr Pharm Des* 2014

→ RCTs currently defining rifampin dose; need for pharmacogenomics (NAT-2)?

New Susceptibility Breakpoints for First-Line Antituberculosis Drugs Based on Antimicrobial Pharmacokinetic/Pharmacodynamic Science and Population Pharmacokinetic Variability[▽]

Gumbo, *AAC* 2010

→ 4-fold increase in MDR-TB?

Diabetics were **6.3 times more likely to have slow response** ($p<0.001$):

*goal= minimize over-testing
maximize benefit

*Heysell, *Tuberc Res Treat* 2013

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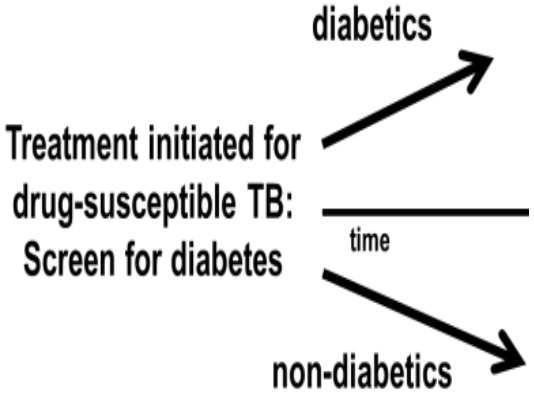

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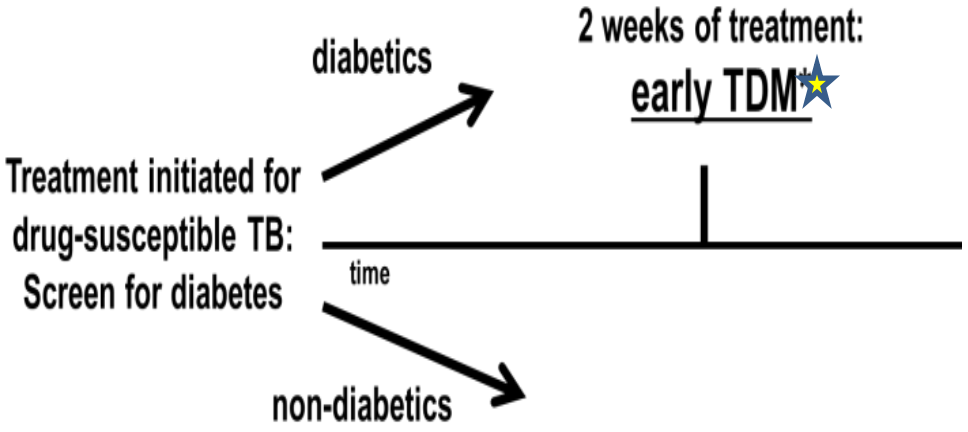

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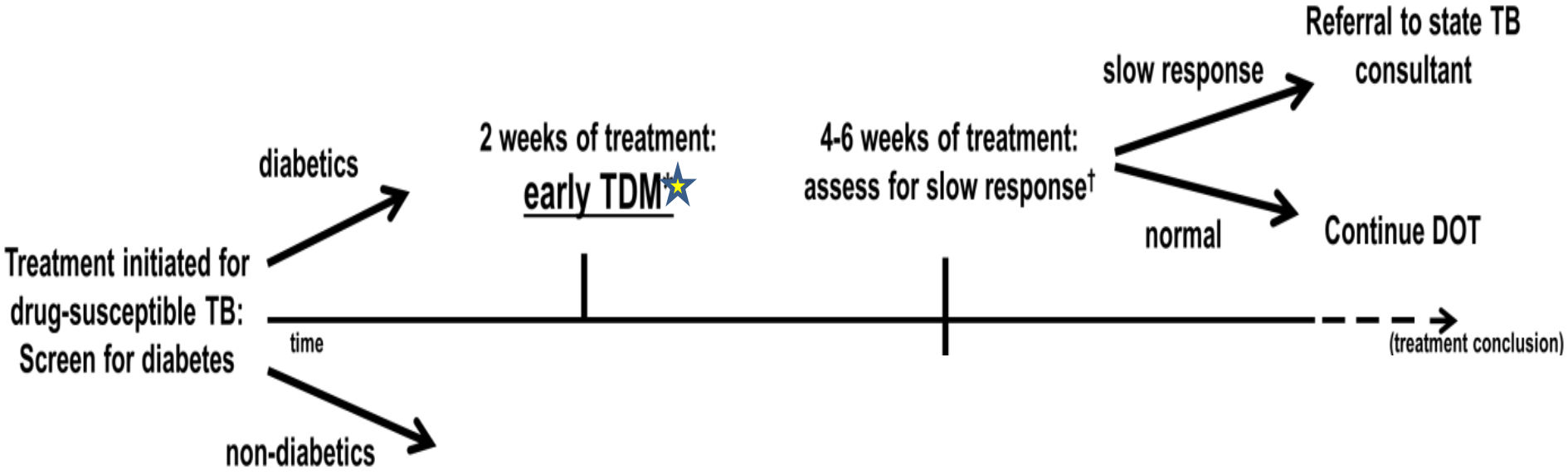

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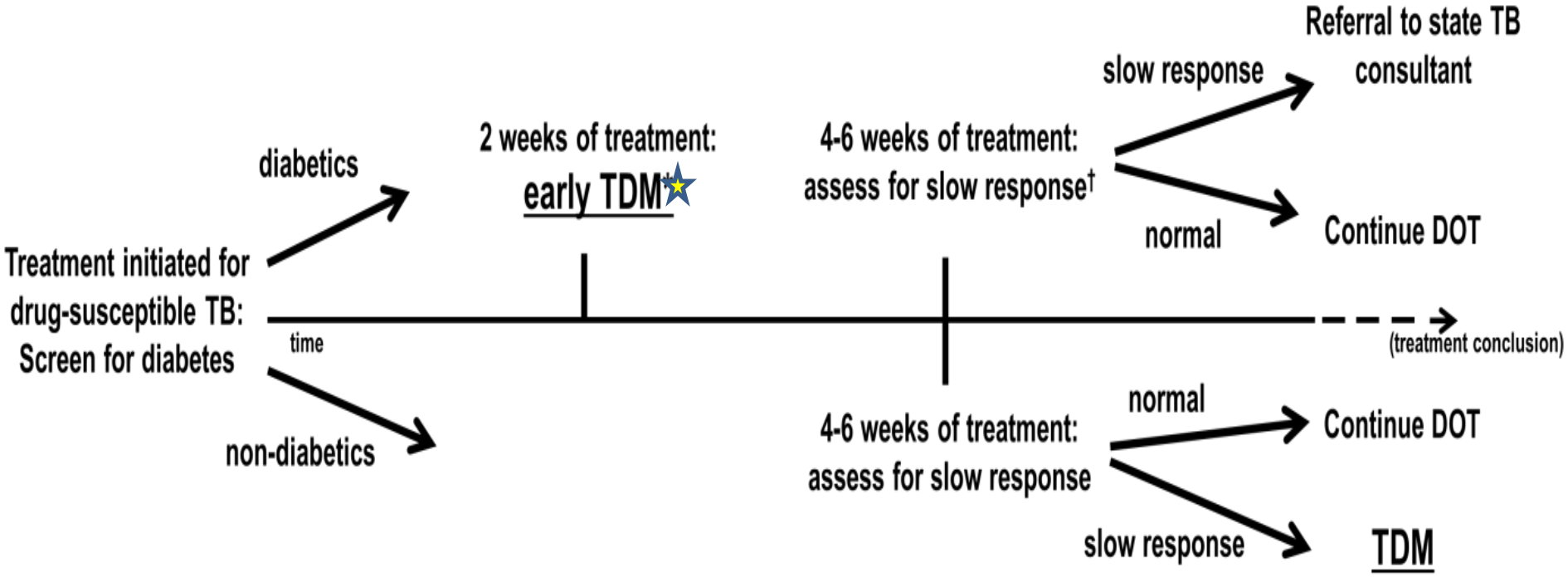


*Heysell, *Tuberc Res Treat* 2013

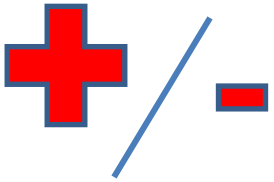
1) **Pharmacokinetic (PK) variability**

Further define host predisposition/ role pharmacogenomics

2) **Increased dose → "acceptable" levels**

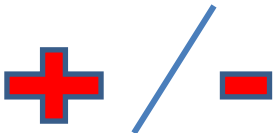
Optimal dose increase/ relative to MIC

3) **Poor outcomes more frequent with "low" levels**



Further define/ validate thresholds in diverse populations

4) **Increasing doses for low levels→ better outcomes**



RCT? Delivery models (ie. dried blood spot)?

Thank You

VDH VIRGINIA DEPARTMENT OF HEALTH
Protecting You and Your Environment

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