Therapeutic Drug Monitoring for Improving TB Treatment Outcomes: A Concept for a Randomized Clinical Trial before Clinical Implementation

Randall Reves, MD, MSc
TB Consultant
Professor of Medicine and Public Health
University of Colorado Denver

Conflicts of Interest for Randall Reves

- No real or potential commercial conflicts of interest.
- Employers have at times paid portions of my salary and travel expenses using funds provided by the US Government through the Centers for Disease Control and Prevention.

Objectives

1. Describe the why the data are inadequate to support recommendations for obtaining blood levels of first-line TB drugs.
2. Discuss whether a randomized trial to to evaluate treatment outcomes using individual therapeutic drug monitoring (TDM) for first-line drugs should be a research priority.

Theoretically. . .

TDM for TB could be an effective strategy if:

1. Variation in blood levels occur in patients receiving standard treatment doses
2. If increasing doses results in “acceptable” levels
3. If treatment failure, relapse and/or acquired resistance are more frequent among patient with “low” compared to “acceptable” levels
4. If increasing doses for patient with “low” levels improves overall outcomes, including toxicity

TDM for TB: effective strategy assessment

No.	Criteria	Score
1	Variation in blood (plasma) levels demonstrated	True
2	Levels “improved” with dose-adjustment	Mixed
3	Treatment failure/relapse/acquired resistance associated with “low” levels	
4	Outcomes improved with dose adjustment based on levels	

Case 1: 43 y.o. woman, poorly controlled diabetes mellitus

- Cavitary pulmonary TB
  - Smear & culture positive, drug-susceptible
  - Smear positive at 4 weeks
  - Plasma glucose levels 200-300's

What would you do?

1. Obtain blood drug levels & increase doses if indicated.
2. Obtain levels, increase does as needed and repeat levels with further increases if indicated.
3. Use standard doses for 6 months
4. Use standard doses for 9 months

Case 1: 43 y.o. woman on daily DOT

Wk	INH	3-6	RIF	8-24	EMB	N D	PZA	20-60	Sm	Cult
0	300		600		2000	-	1600		4+	POS
2	→ 600	**0.7**	→ 900	**5.8**	2000 => d/c	-	1600	34.6		
6	600	**2.3**	→ 1200	**4.5**	-	-	1600	ND	N	N
8	600		1200		-		-		N	N
14	600	3.3	1200	**5.2**			-		N	N

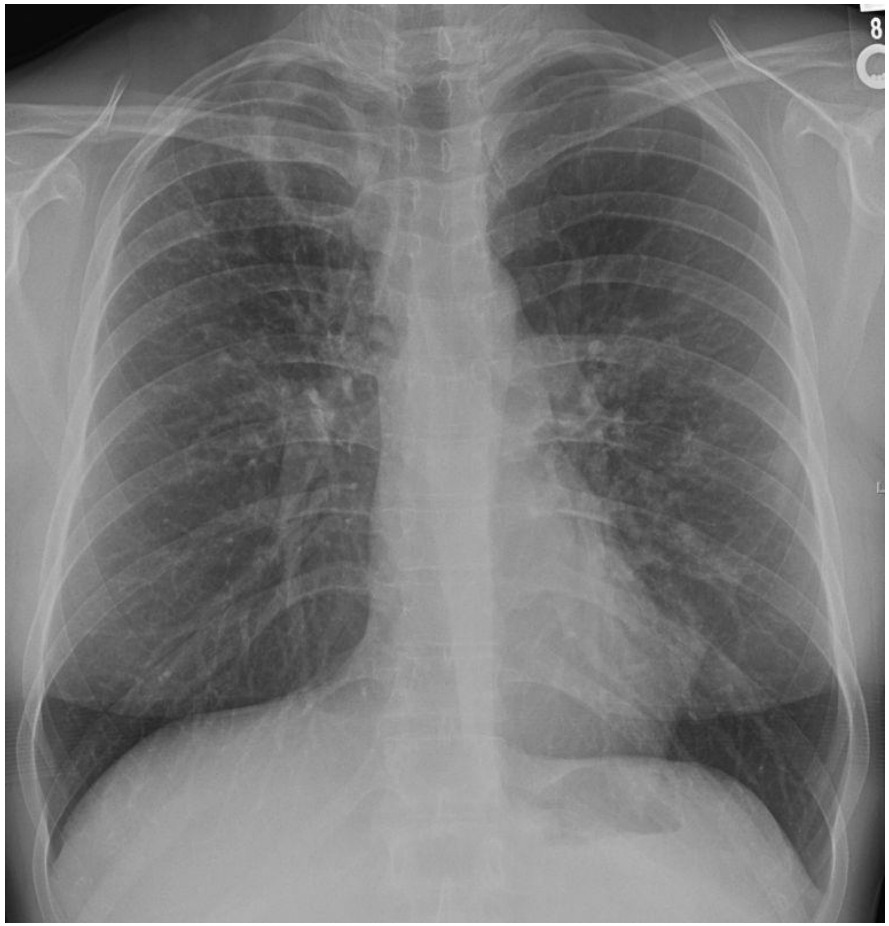
1. S & C conversion at 6 wks on 2-fold higher INH & RIF.
2. RIF levels not increased & < 8 even on 1200 mg daily.

43 y.o. woman: 6-wk. culture (-), Wk 14 of INH 600 RIF 1200 & low RIF level

What do you recommend?

1. Increase RIF to 1500 or 1800 mg daily
2. Ignore level and continue current meds
3. Something else? – see later slide

The Anecdote Problem: Case 2 Nursing student with cough



- 3 (+) smear positive
- Travelled all around S. Africa in 2006 – including Kwazulu Natal
- No resistance with rapid molecular testing
- Would you recommend:
  - TDM for some / all drugs?
  - "regimen optimization"?

Case 1: Nursing student 8 wk resolution of cavity & culture-conversion

Treatment & outcome

- Rifamycin dose increased 2.5-fold over FDA approved dose

Sputum AFB smear/cult.

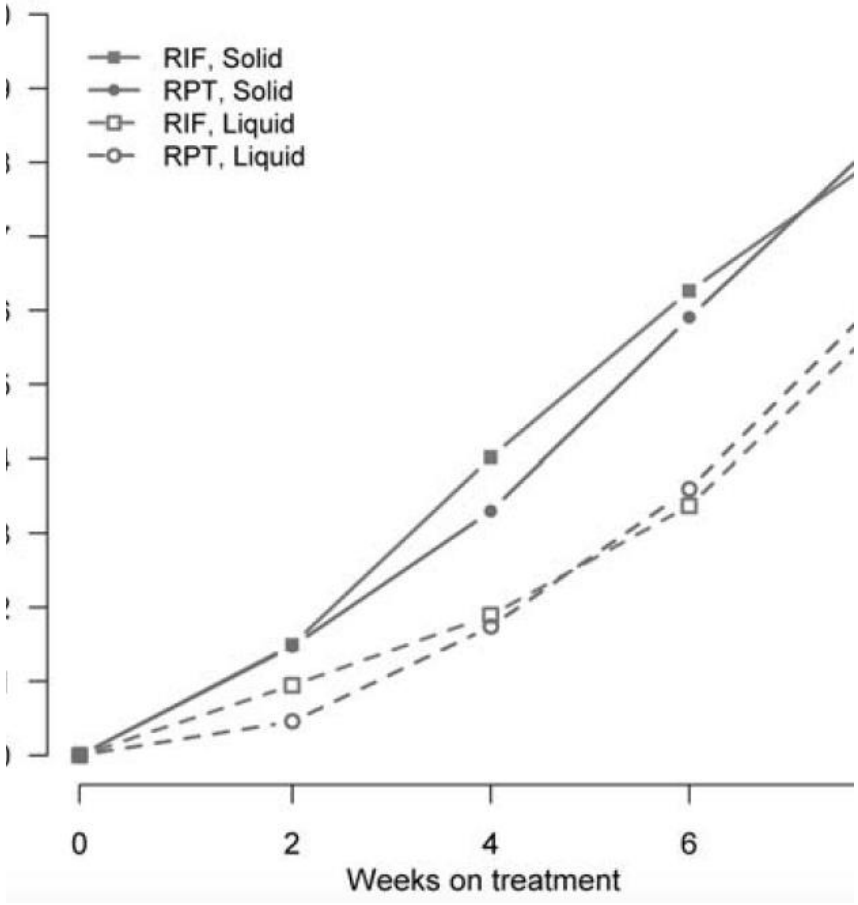
- Base 4+/4+
- 2 wks 3+/1+
- 4 wks 1+/3 colonies
- 6 wks N/rare
- 8 wks N/N & Cavity closed

Your interpretation?

1. Supports “optimizing” regimen
2. Who knows without seeing the blood levels?
3. Eight weeks is too short to say.
4. I have no idea & blood levels wouldn’t help me.

Would you have recommended obtaining baseline or selective TDM in such a patient?

Case 2: One of 531 RCT participants in TBTC Study 29 of 8-wk sputum conversion



- Daily 5/wk DOT IZE+
  - RIF 600mg
  - rifapentine 600 mg (FDA appr. 600 BIW)
- Conclusions:
  - RPT well tolerated
  - No increased activity
  - Higher doses to be considered in RCT

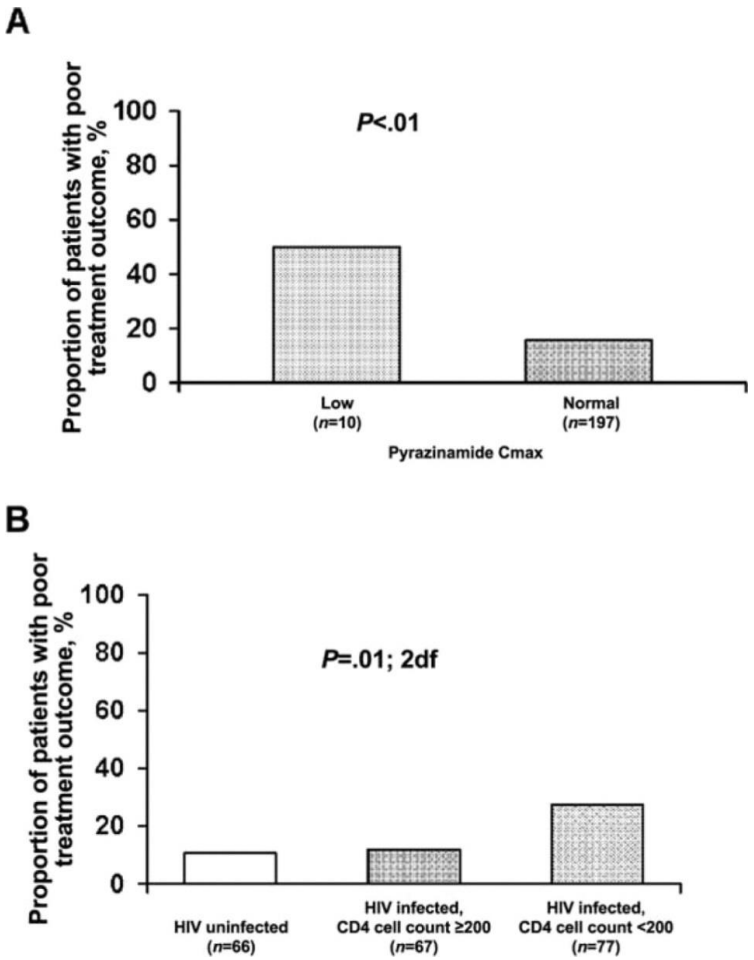
TBTC 29: S. Dorman, et. al, JID 2012

"Maybe 8-wk outcomes are not enough" What about baseline levels & all outcomes?

- Prospective study of 225 patients in Botswana, 69% HIV+
- Baseline 1,2 & 6 hr levels of IRZE, 300 vs 400 mg INH
- Poor treatment outcomes: 36 (16%) with 14 deaths
- Levels: "low" C_{max} in many patients at baseline
  - INH 37%
  - RIF 84%
  - EMB 39%
  - PZA 5% (n=11)
- Question: Will baseline levels predict outcomes & support increasing doses?

Chideya S. TB drugs and treatment outcomes. CID 2009;48:1685-94.

Proportion of patients with poor tuberculosis treatment outcome, by maximum serum concentration (Cmax) of pyrazinamide (n=207; A) and human immunodeficiency virus (HIV) status and CD4 cell count category (n=210; B).



Answer -not really:

- Only low PZA levels in 10 patients associated with poor outcomes.
- Would you really test over 200 patients to increase PZA in 10?

Chideya S et al. Clin Infect Dis. 2009;48:1685-1694

Serum Drug Concentrations Predictive of Pulmonary Tuberculosis Outcomes

JID 2013

Jotam G. Pasipanodya,[1] Helen McIlleron,[2] André Burger,[3] Peter A. Wash,[3] Peter Smith,[3] and Tawanda Gumbo[1,4]

[1]Office of Global Health, University of Texas Southwestern Medical Center, Dallas, Texas; [2]Division of Pharmacology, Department of Medicine, University of Cape Town, Observatory; and [3]The Brewelskloof Hospital, Worcester, South Africa; and [4]Department of Medicine, University of Texas Southwestern Medical Center, Dallas

Sizeable study in South Africa: 142 patients (64% prior TB): 15 died, 19 relapsed, 1 failed treatment & 3 had ADR. The only pertinent finding for this discussion was referred to on p. 1467

(OR = 51.90; CI, 3.04–886). Table 3 further demonstrates that the lower the cumulative number of drugs above the cutoff AUC threshold, the higher the odds of poor long-term outcomes ($P = .001$). To put this into context, we also examined the association with failure of the drug concentrations currently used in the field for therapeutic drug monitoring [18]: the ORs for poor long-term outcome were as shown in Supplementary Table 2.

Serum Drug Concentrations Predictive of Pulmonary Tuberculosis Outcomes

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JID 2013

My suggested title: SDC **NOT** Predictive of Pulmonary TB Outcomes

Supplementary Table 2. Association between currently utilized target concentrations of first line anti-TB drugs and long-term outcome.

	Long-term outcome Odds ratio (95% CI)	*p*-value
Pyrazinamide ≤20 mg/L	0.14 (<0.01-3.45)	0.30
Rifampin ≤8 mg/L	0.88 (0.34-2.24)	1.00
Isoniazid ≤3 mg/L	0.84 (0.07-9.54)	1.00

Bottom line: measuring blood levels as currently done was **not** predictive of poor outcomes.

Only post-hoc calculation of 8-level, 4-drug "CART-derived 24 hr AUC" thresholds was "significant."

TDM for TB: effective strategy assessment

No.	Criteria	Score
1	Variation in blood (plasma) levels demonstrated	True
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3	Treatment failure/relapse/acquired resistance associated with “low” levels	False
4	Outcomes improved with dose adjustment based on levels	No interpretable data (no RCT of strategy)

43 y.o. woman: 6-wk. culture (-) on Wk 14 of INH 600 RIF 1200 - low RIF level

My recommendation?

1. Stop drawing blood levels.
2. Place the patient on INH 300, RIF 600 5 day/wk, or INH 900, RIF 600 TIW to compete 6 or 9 months.
3. Stop strategy of TDM until RCT of the strategy proves benefit outweighs risk and cost.

In conclusion: The low blood levels we should be most concerned about caused by a standard dose of TB drugs failing to pass though the lips.

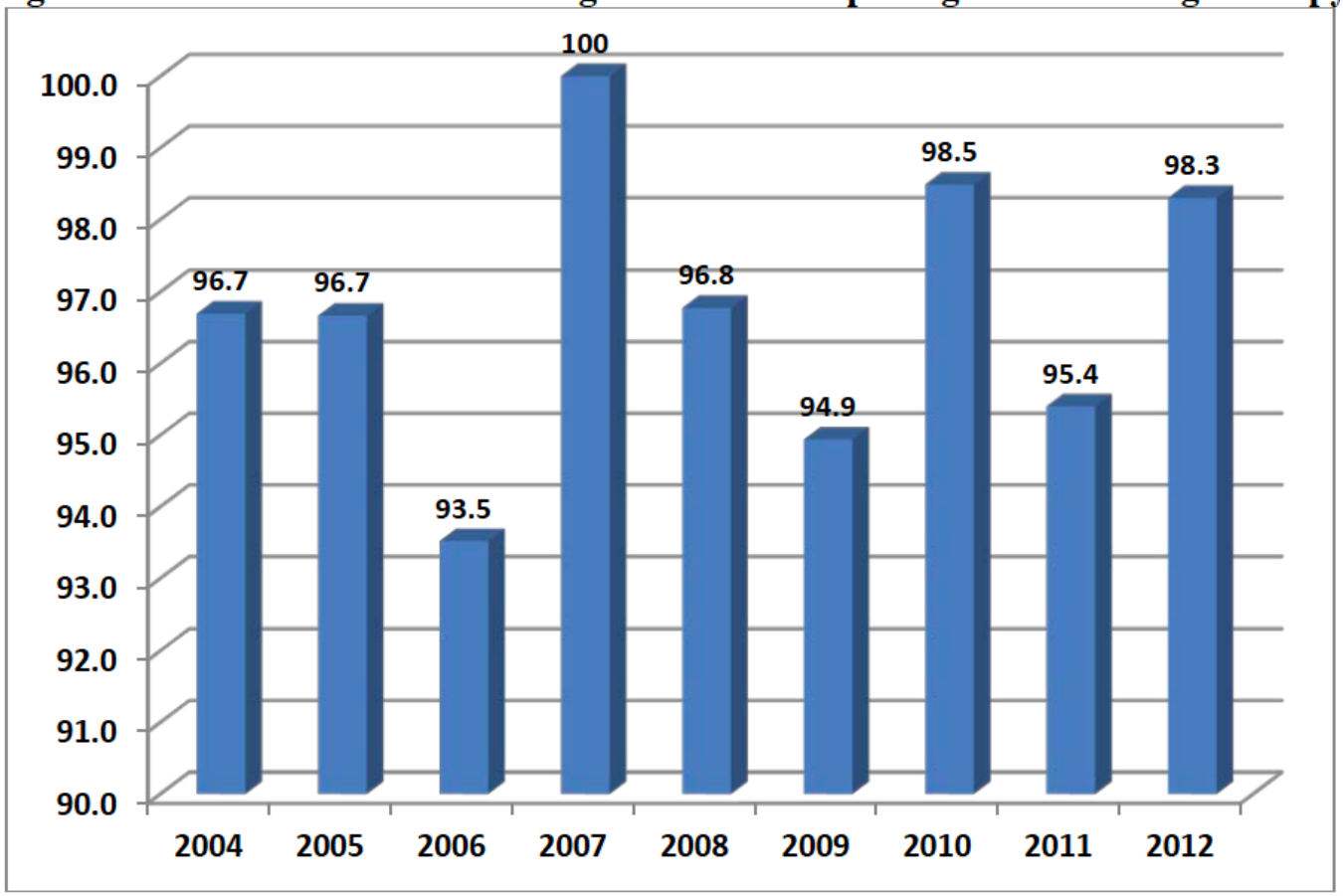
Rationale for TDM: Lack of data no barrier for strong recommendations

- If we assume that TB treatment costs $US10,000–12,000 per patient for a 6-month course, it certainly costs an additional $US3,000 to extend the treatment to 9 months . .
- . . checking 2- and 6-h post-dose samples for four drugs would cost approximately $US 600
- Not all of the extended durations could be prevented by TDM, but it seems likely, based on the available reports, that many of them could be prevented, and at a considerable cost savings. **Prospective studies are needed to confirm or modify these estimates.**

A Alsultan, C Peloquin, Drugs 2014

CO TB treatment completion in ≤ 12 mo.: universal DOT with no TDM

Figure 11. 2004-2012: Percent of Eligible Cases Completing Anti-TB Drug Therapy



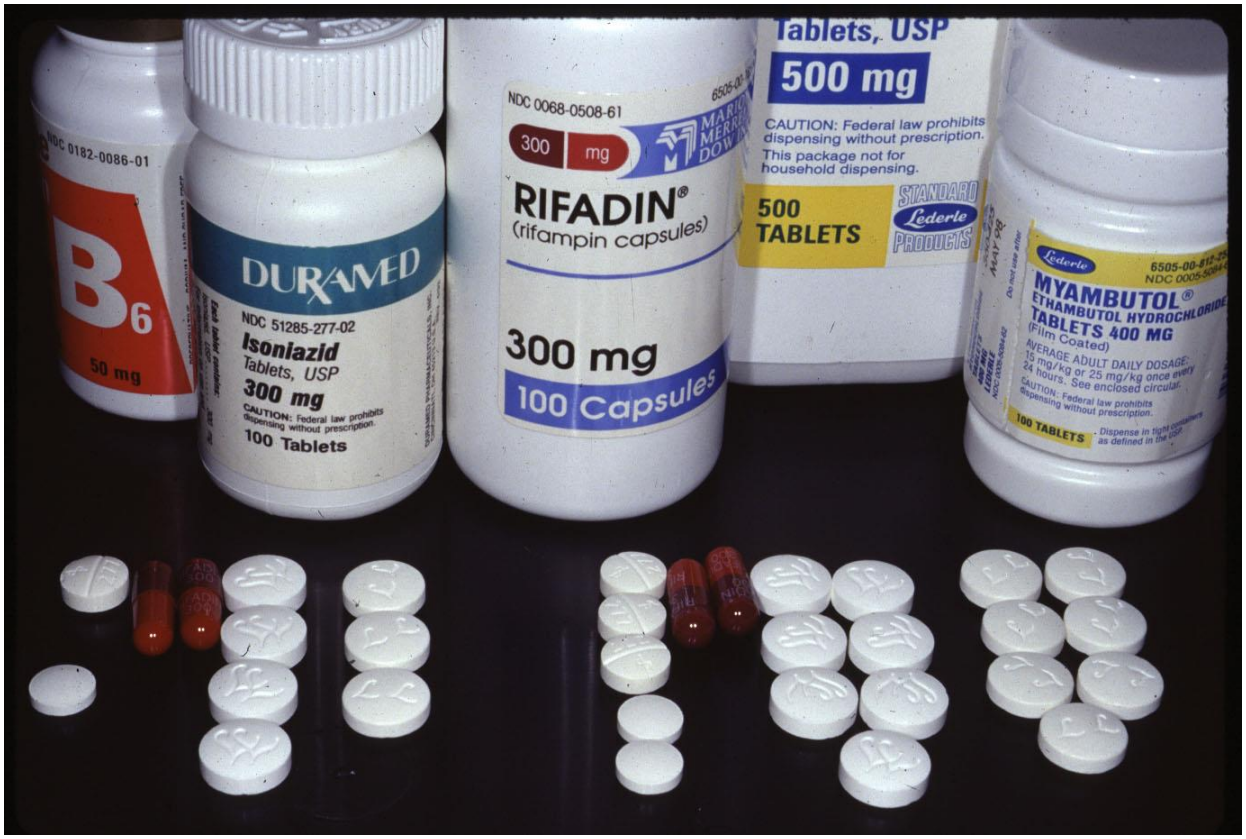
https://www.colorado.gov/pacific/sites/default/files/DC_TB-Surveillance-Report-13.pdf

Extra slides: for rebuttal, time permitting

Once-daily, single-pill combination HIV regimens in use 2014

Once-daily, 11-pill/capsule TB regimen in use since 1993

- BIW IRZE – 21 units per dose
- TIW IR – 17 units per dose



Daily

BIW : twice-weekly