Therapeutic Drug Monitoring for TB

Eric R. Houpt MD,
Chief, Division of Infectious Diseases Int'l Health
University of Virginia

No disclosures

UNIVERSITY of VIRGINIA

CDC Guidelines provide guidance when to consider TDM

Table 9. Conditions or Situations in Which Therapeutic Drug Monitoring May Be Helpful

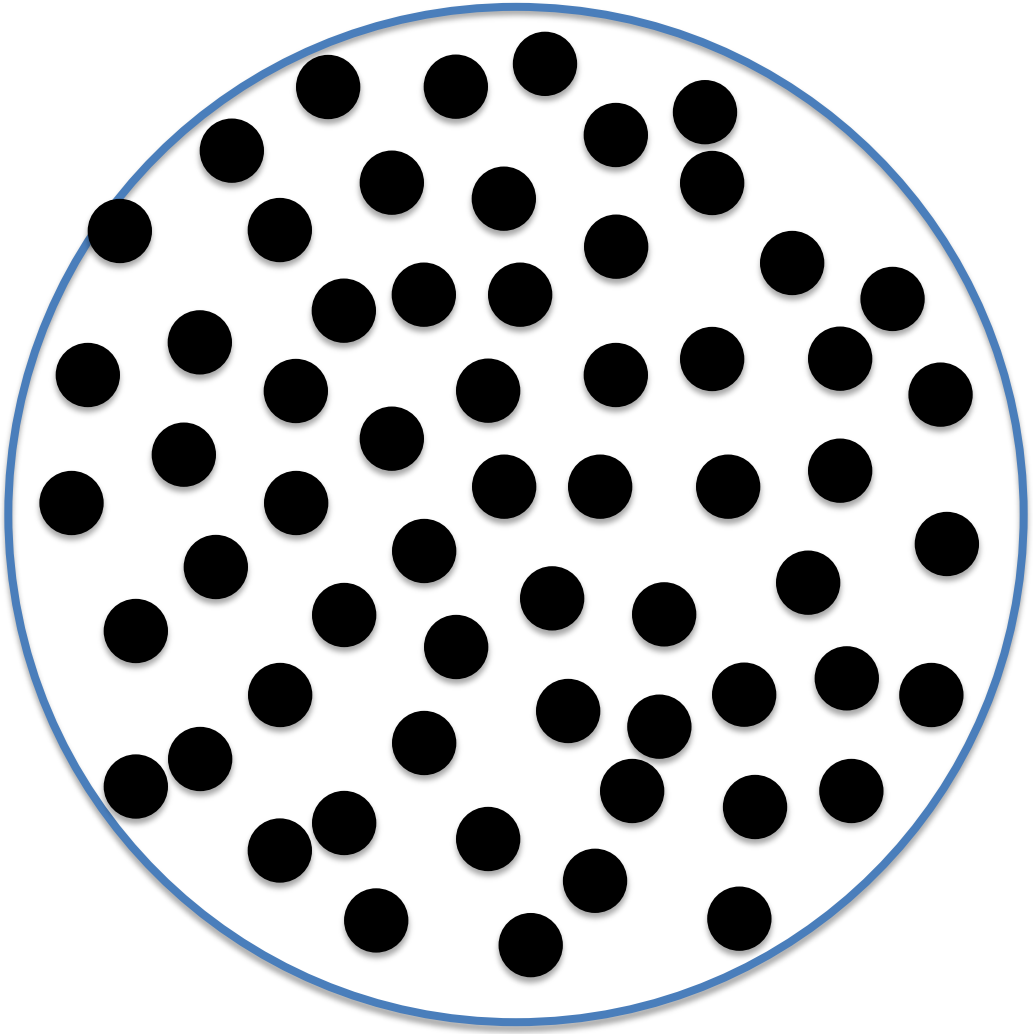
Poor response to tuberculosis treatment despite adherence and fully drug-susceptible *Mycobacterium tuberculosis* strain
Severe gastrointestinal abnormalities: severe gastroparesis, short bowel syndrome, chronic diarrhea with malabsorption
Drug–drug interactions
Impaired renal clearance: renal insufficiency, peritoneal dialysis, critically ill patients on continuous renal replacement
HIV infection
Diabetes mellitus
Treatment using second-line drugs

Abbreviation: HIV, human immunodeficiency virus.

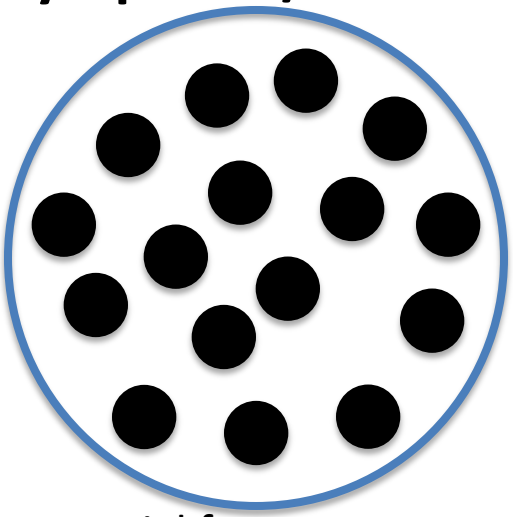
Nahid et al, *Clin Infect Dis* 2016

Outcomes with active TB

Most do well (>90%)



Some don't
"slow response" = persistent symptoms/smear+



Many potential factors may contribute

Extensive disease

Drug resistance

HIV

Other comorbidities

Adherence

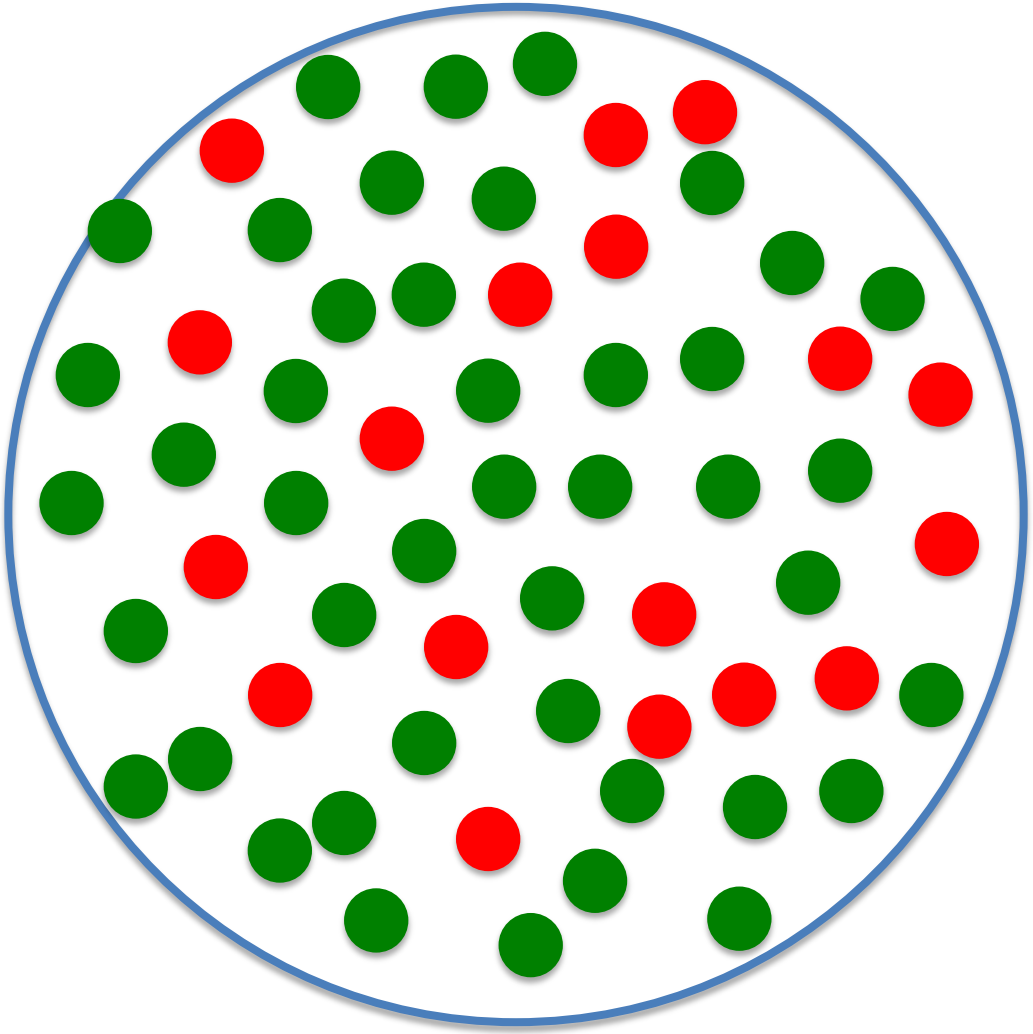
Low drug levels

Diabetes

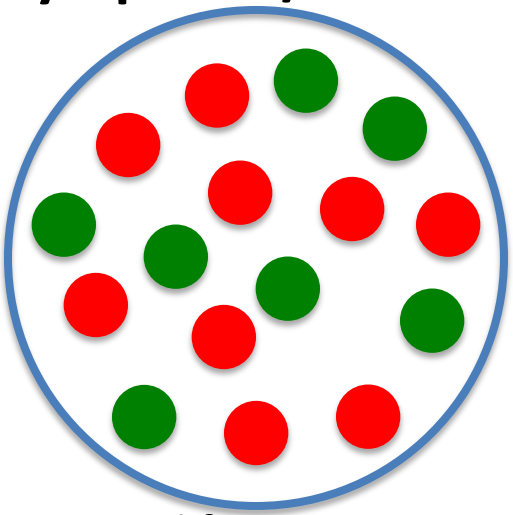
……

Outcomes with active TB

Most do well (>90%)



Some don't
"slow response" = persistent symptoms/smear+



Many potential factors may contribute

Extensive disease

Drug resistance

HIV

Other comorbidities

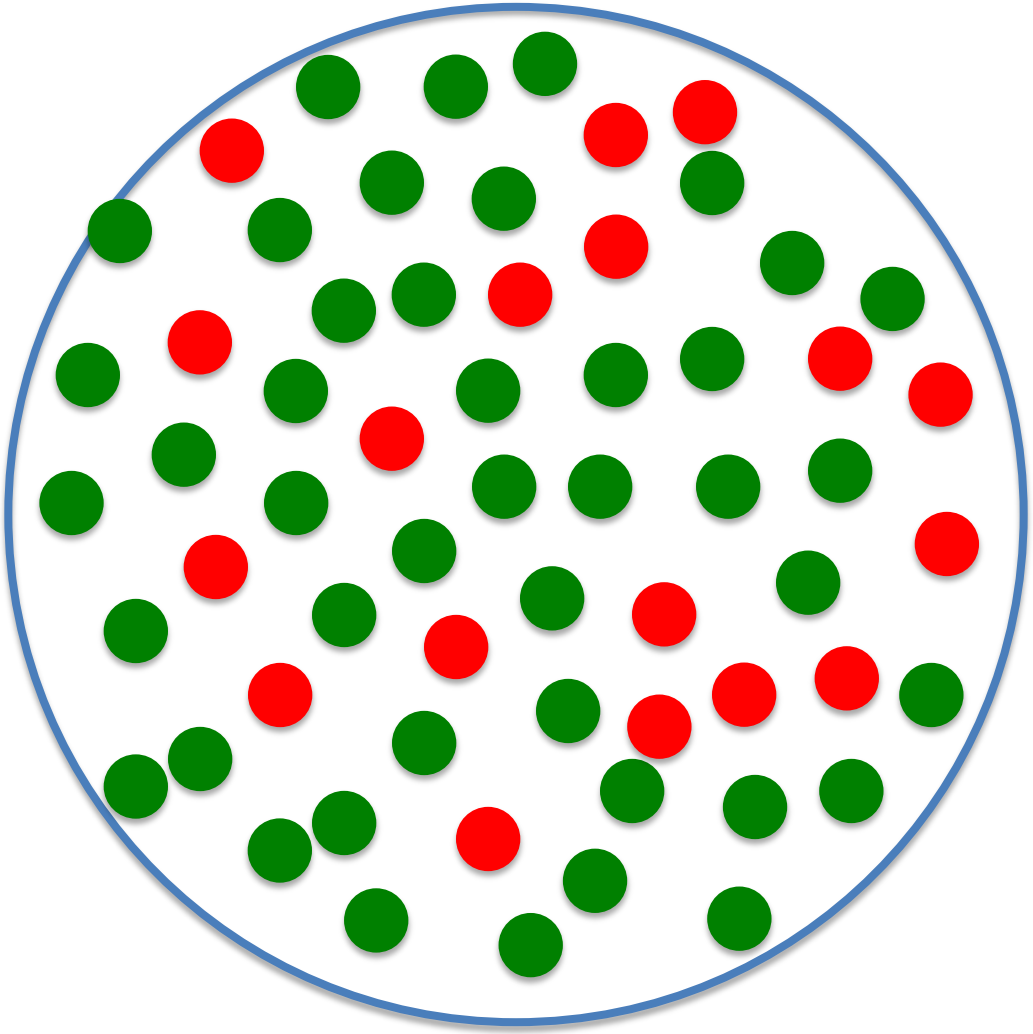
Adherence

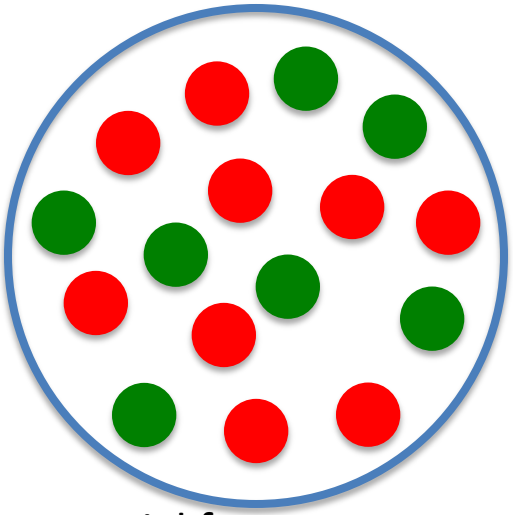
Low drug levels

Diabetes

……

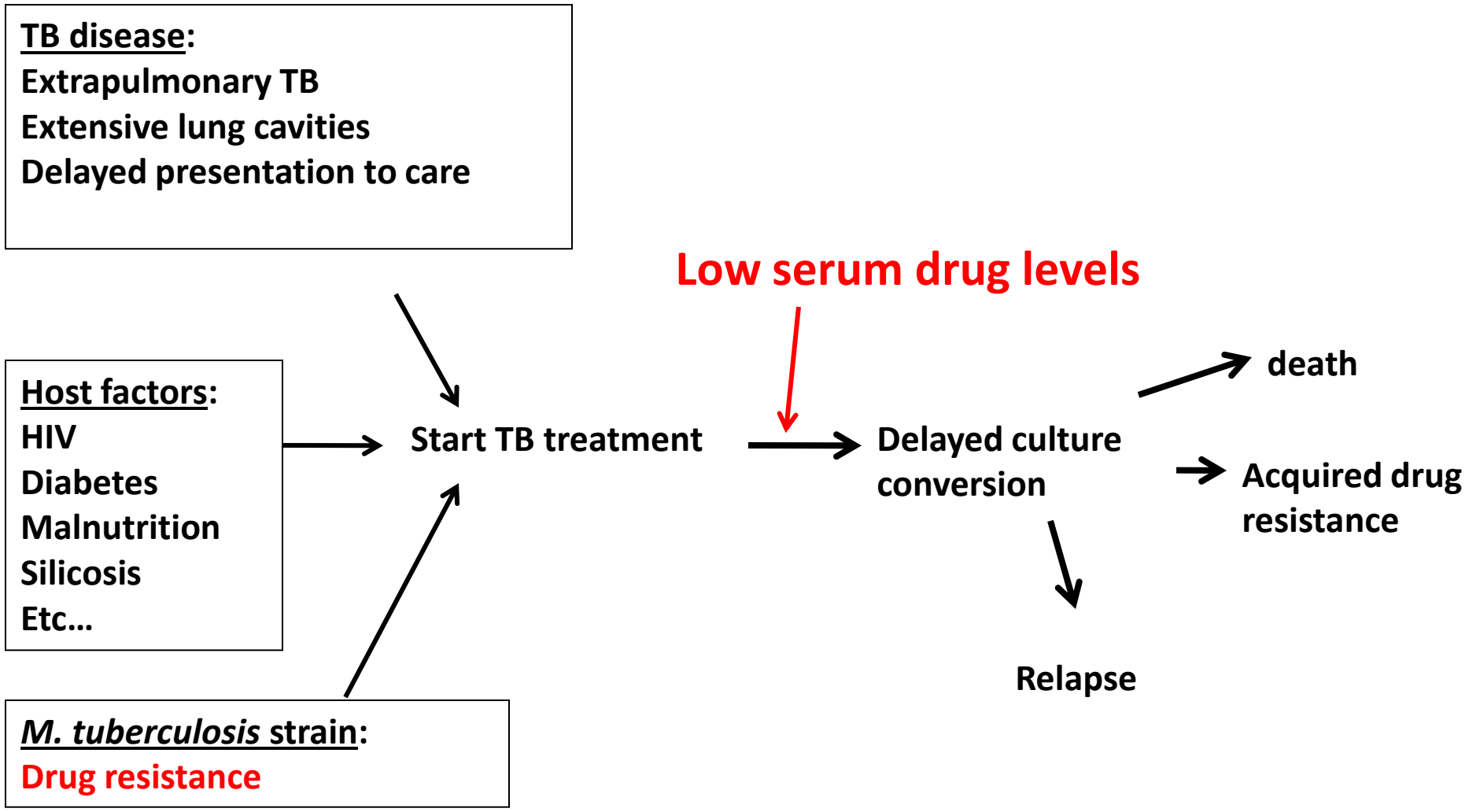
Not all slow responders have low levels (might be other factors)
AND many with low levels will do fine
So prefer the term "Expected" Drug Levels over "Therapeutic"





Many potential factors may contribute
Extensive disease
Drug resistance
HIV
Other comorbidities
Adherence
Low drug levels
Diabetes
……

Worse outcomes…..What can we do about it?



Background on TDM

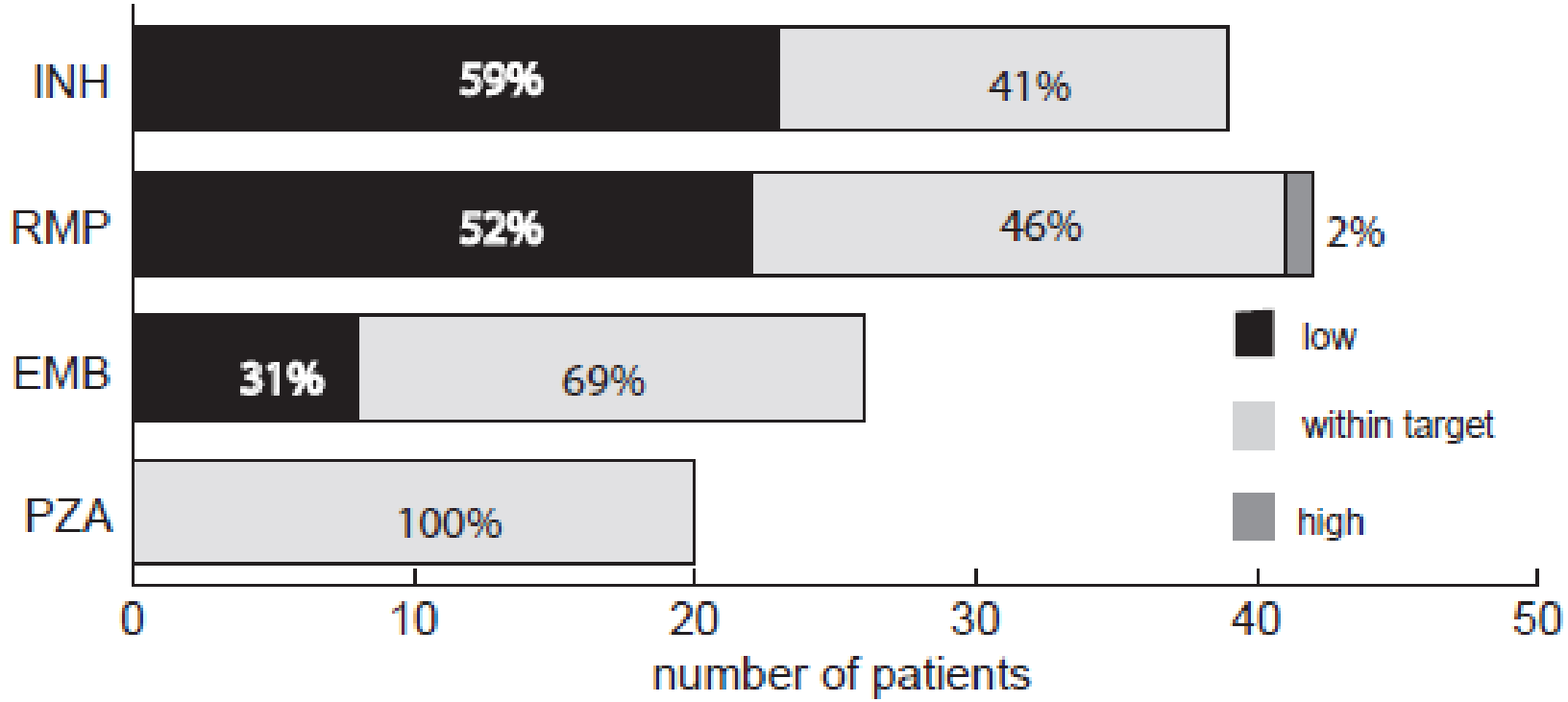
- We have been routinely checking serum TB drug concentrations in "slow responders" since ~2007
- ~14% of all Tb patients, defined as no improvement in sx or persistent smear +

- Diabetics were **6.3 times more likely to be slow responders** ($p<0.001$) ~40% of diabetics

- Furthermore, **diabetics had significantly lower serum rifampin levels** (estimated peak C_{2h})

Heysell et al. *Emerg Infect Dis* 2010

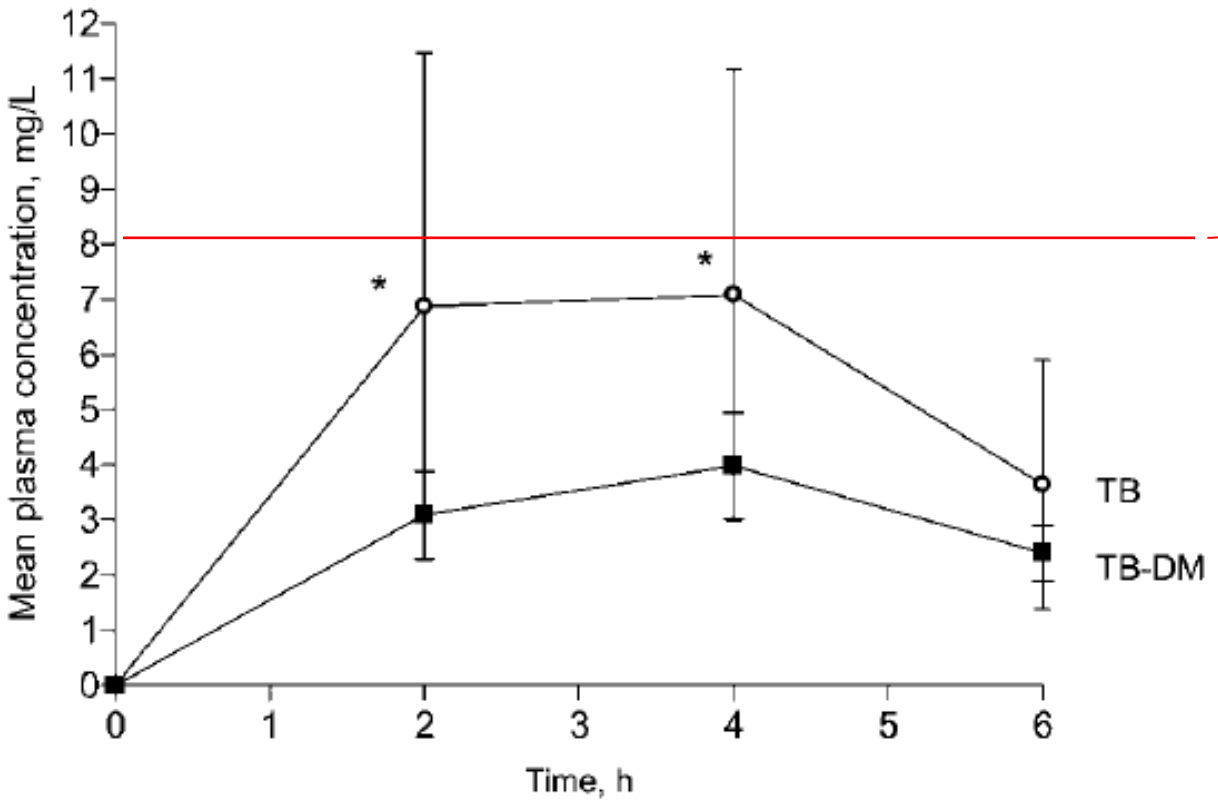
Majority of Virginia slow responders had low C_{2hr} levels of INH and rifampin



82% had low levels to one of INH or RMP, couldn't predict which

Heysell et al, *Emerg Infect Dis*, 2010

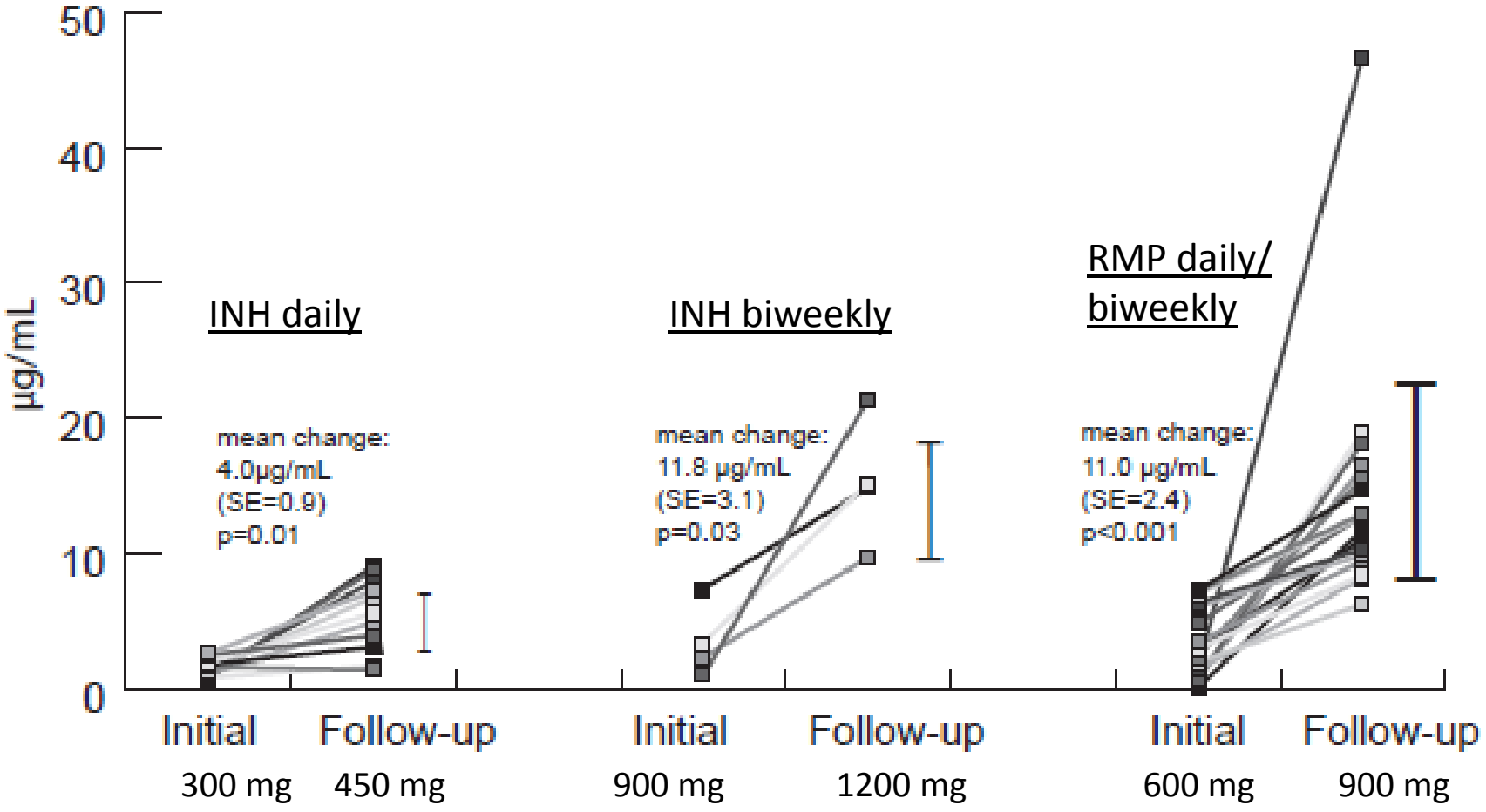
Low rifampin levels is not new
Rifampin exposure significantly reduced in diabetics from Indonesia



8-24 ug/mL expected C_{max} range

Nijland et al. *Clin Infect Dis* 2006

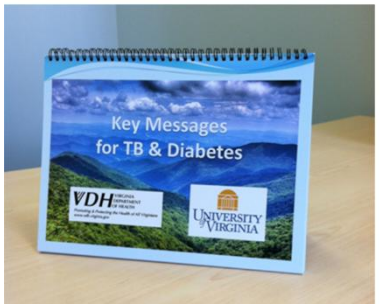
Drug levels usually improve, or correct, after one incremental dose adjustment



I spans C_{2hr} expected range

Heysell et al, *Emerg Infect Dis* 2010

- **In 2011, an initiative was started to measure isoniazid and rifampin levels in all diabetics at 2 weeks of TB therapy**
  - **these 2 drugs only, b/c PZA usually fine, EMB usually dropped**
  - **instead of waiting for ~40% to be slow responders**
  - **Also HbA1c check on all, TB Diabetes flipchart**



Outcomes improved in diabetics during the study period compared to baseline

Table 2 Clinical outcomes of adults with drug-susceptible tuberculosis and documented sputum time to culture conversion in days

Outcome	All patients *N* = 363			Non DM *N* = 307			DM *N* = 56		
	2009-10 *N* = 215	2013-14 *N* = 148	*p*-value	2009-10 *N* = 185	2013-14 *N* = 122	*p*-value	2009-10 *N* = 30	2013-14 *N* = 26	*p*-value
Time to culture conversion (days, mean ± SD)	56 ± 35	43 ± 28	<0.001	51 ± 36	43 ± 30	0.003	61 ± 32	42 ± 22	0.02
2 months culture conversion No. (%)	126 (59)	110 (74)	0.002	111 (60)	89 (73)	0.02	15 (50)	21 (80)	0.03
Death No. (%)	5 (2)	2 (1)	0.71	4 (2)	1 (1)	0.65	1 (3)	1 (4)	1.00

Alkabab et al BMCID2017

As expected many had low levels

- Of the 21 diabetics, **16 (76%) had a C_{2hr} value below the expected range for isoniazid** (mean 2.1±1.5 µg/ml; expected 3-5), **rifampin** (mean 6.6 ±4.3 µg/ml; expected 8-24) **or both**

Levels generally correct with single incremental increase

- 15 patients had follow-up concentrations after dose adjustment, all increased and 12 to the expected range (including all for rifampin).
- Effectively, our algorithm shunts most diabetics to at least 3x weekly therapy during continuation phase, with INH 900/RIF 900, while keeping to a 6 month total duration

May limit the need for prolonged treatment and program resources

- **total statewide burden of slow response decreased** from 1.6 patients/mo (40% diabetic) to 1.2 patients/mo (12.5% diabetic)

Virginia guidelines for therapeutic drug monitoring

http://www.vdh.virginia.gov/content/uploads/sites/112/2017/11/2017-Recommendations-and-Procedures-for-the-use-of-Therapeutic-Drug-Monitoring-TDM-112107.pdf

Virginia Department of Health Recommendations and Procedures for the use of Therapeutic Drug Monitoring (TDM)

Background

Slow response to TB treatment can be caused by several factors; non adherence, drug resistance, inadequately prescribed regimens, intolerance to TB medications and poor absorption often due to co-morbidities. Poor clinical response to TB therapy may lead to prolonged infectiousness or acquired drug resistance and further burden public health systems by extending treatment duration. Measurement of serum drug levels at the time of estimated peak concentration (C_{max}), termed therapeutic drug monitoring (TDM), has been performed for clients with poor clinical response to tuberculosis (TB) treatment in Virginia since 2007 [3] .

Procedure for requesting Therapeutic Drug Monitoring

- Obtaining approval for TDM must be received prior to scheduling, collecting and shipping of samples to the Infectious Disease Pharmacokinetics Laboratory (IDPL) in Gainesville, Florida. Other laboratories are not included in this program. If a decision to use an alternative lab is made, the cost of testing will be the responsibility of the district.
- Approval is obtained by calling 804-864-7906 and speaking with one of the nurse consultants. Some approvals require the recommendation of one of the TB clinical consultants.
    - Denise Dodge, RN – 804-864-7968
    - Debbie Staley, RN– 804-864-7972
    - Lisa McCoy, MD – 804-864-7920
- Approvals will be consistent with the recommendations outlined in this document. Consultation is recommended for any second dose adjustment and for any client taking second-line medications.
- If approved, the laboratory requisition slip will be faxed to the district with the medications approved and will include a specimen authorization number.
- Follow the directions on the requisition slip regarding the specific timing requirements of testing. Most blood draws will be 2 hours after the last full dose. **Specimens can only be shipped Monday through Thursday so that they arrive on a weekday.** Specimens are not accepted on weekends.

Procedures for Collecting Serum Drug Level

- The daily medication dose is administered to the client by directly-observed therapy. Assure that the dose is not given within 12 hours of the prior dose.
- Consistent with recommendations for treatment with anti-tuberculosis medications, clients should avoid antacids, milk products or vitamin supplements within 2 hours of taking medications.
- The exact time and date of administration is recorded on the lab authorization.
- Complete each column under each drug. The reliability of results is directly related to the accuracy of this information.
- Four drugs can be included on one slip as long as they are drawn at the same time.
- Two tests can be performed using one plain red top 10 ml tube if completely filled and both medications are **drawn at the same time**. (5 mls of blood [2 mls serum] are required *per drug tested*.) For example, if drawing isoniazid and rifampin at 2 hours one large red top tube filled to the top is sufficient.

TDM: who to consider

Table 1: Groups considered for TDM

Group	Definition	Drugs to check	Follow-up
1 - Slow responder (failure to clinically improve as expected)	Clients with smear positive pulmonary TB for a prolonged period of time without improvement (defined as a steady decrease from 4+ to 2+; 3+ to 1+; 2+/1+ to smear negative)	Isoniazid and Rifampin **ONLY**:	Dose increases in consultation with DTBNH staff and medical consultants. **Follow-up drug levels can be checked.**
2 - All diabetics (HbA1c $\geq$ 6.5)	Ideally test **2 weeks** after treatment begins. If a recent HbA1c (<3mo) result is not available, perform HbA1c to avoid delaying TDM upon intake. After 8 weeks the window of opportunity is lost so we do not perform TDM (unless slow response or another reason is identified)	Isoniazid and Rifampin **ONLY**:	Automatic dose adjustment for low level (See Table 2). **No follow-up drug levels checked.**
3 - All HIV positive (regardless of CD4 count or viral load)	Ideally test within **1- 2 weeks** after a stable regimen begins.	Isoniazid and Rifampin/Rifabutin **ONLY**:	Dose increase in consultation with DTBNH staff. **Follow-up drug levels can be checked.**
4 - Others	Other scenarios in discussion with TB consultants (e.g., new clinical deterioration, receiving second-line TB medications, sudden relapse, severe illness, other co-morbidities)	Case-by-case	Case-by-case

What to do with “low” SDL

Virginia Department of Health Recommendations and Procedures for the use of Therapeutic Drug Monitoring (TDM)

Table 2. Expected peak concentrations for Isoniazid and Rifampin with VDH recommended automatic dose adjustment

Medication (expected C_{max} range)	Dose adjustment when below expected peak
Isoniazid: daily (3-6 µg/ml)	Increase daily dose from 300 mg to 450 mg
Rifampin: (8-24 µg/ml)	Increase dose from 600 mg to 900 mg (both daily and intermittent therapy)

Table 3. Dose adjustment for diabetics and HIV/AIDS infected populations

	Normal drug levels	Sub-target INH Normal RIF	Normal INH Sub-target RIF	Sub-target INH and Sub-target RIF
Initiation Phase regimen*	Continue INH 300 mg and RIF 600 mg M-F	Increase INH 450 mg Continue RIF 600 mg M-F	Continue INH 300 mg Increase RIF 900 mg M-F	Increase INH 450 mg and RIF 900 mg M-F
Continuation Phase regimen	Continue INH and RIF M-F or thrice weekly	INH 900 mg RIF 600 mg M-F or thrice weekly	INH 900 mg RIF 900 mg M-F or thrice weekly	INH 900 mg and RIF 900 mg, M-F or thrice weekly

Raises the question: what is the "right" dose of rifampin?

*In 1971 the dose of **10 mg/kg** was arbitrarily chosen without a maximum tolerated dose study. 20mg/kg and 35 mg/kg now being evaluated: earlier culture conversion (in liquid media)

	Control	$RIF_{35}HZE$	RIFQHZ	$RIF_{20}QHZ$	$RIF_{20}MHZ$
MGIT culture censored at 8 weeks (post hoc)					
Cumulative probability of culture conversion by 8 weeks	32%	49%	34·5%	27·8%	46·2%
Adjusted hazard ratio (95% CI)*	..	2·06 (1·26–3·38) p=0·004	1·04 (0·59–1·81) p=0·90	0·91 (0·49–1·67) p=0·76	1·67 (1·01–2·67) p=0·05
Unadjusted hazard ratio (95% CI)	..	1·73 (1·07–2·82) p=0·03	1·07 (0·62–1·86) p=0·81	0·87 (0·48–1·58) p=0·64	1·47 (0·90–2·40) p=0·13
Solid LJ culture censored at 8 weeks (post hoc)					
Cumulative probability of culture conversion by 8 weeks	80·9%	88·0%	83·9%	82·6%	82·7%
Adjusted hazard ratio (95% CI)*	..	1·17 (0·83–1·64)	1·00 (0·70–1·42)	1·06 (0·74–1·52)	0·76 (0·54–1·07)
Adjusted log-rank test*	..	p=0·38	p=1·00	p=0·75	p=0·12
Unadjusted hazard ratio (95% CI)	..	1·24 (0·88–1·73)	1·09 (0·77–1·55)	1·12 (0·79–1·60)	0·88 (0·63–1·24)
Unadjusted log-rank test	..	p=0·22	p=0·62	p=0·53	p=0·48
Solid LJ culture censored at 12 weeks excluding without a positive culture on LJ solid media before or within the 2 weeks of randomisation (post hoc)					
Number in analysis (total=207)	101	46	45	47	58
Cumulative probability of culture conversion by 8 weeks	96·7%	100·0%	92·8%	93·3%	97·8%
Adjusted hazard ratio (95% CI)*	..	1·37 (0·95–1·99)	0·84 (0·58–1·23)	1·00 (0·69–1·45)	0·88 (0·62–1·24)
Adjusted log-rank test*	..	p=0·19	p=0·78	p=0·62	p=0·37
Unadjusted hazard ratio (95% CI)	..	1·37 (0·95–1·98)	0·92 (0·64–1·34)	1·05 (0·73–1·51)	0·95 (0·67–1·33)
Log-rank test, unadjusted	..	p=0·07	p=0·65	p=0·76	p=0·73

LJ=Löwenstein-Jensen. MGIT=mycobacteria growth indicator tube. $RIF_{35}HZE$=rifampicin 35 mg/kg, isoniazid, pyrazinamide, ethambutol. RIFQHZ=rifampicin 10 mg/kg, isoniazid, pyrazinamide, SQ109 300 mg. $RIF_{20}QHZ$=rifampicin 20 mg/kg, isoniazid, pyrazinamide, SQ109 300 mg. $RIF_{20}MHZ$=rifampicin 20 mg/kg, isoniazid, pyrazinamide, moxifloxacin 400 mg. Doses of concomitant drugs are detailed in Procedures. *Analysis adjusted for HIV status, GeneXpert cycle threshold (<16, ≥16), and site. MGIT analyses also adjusted for baseline time to positivity.

***Table 3*: Summary of analyses of time to culture conversion in MGIT and on LJ culture to 8 weeks (post hoc), and on LJ culture excluding patients without positive LJ at baseline (post hoc)**

Hepatitis 2% > 8%

Boeree, Lancet ID, 2017

It would not surprise me if soon we use 900mg RIF routinely, or in high risk pts……

Local case: Unmasked MDR in HIV

23 y/o man originally from the Philippines

Presented with R neck mass (lymphadenopathy), voice change

HIV + (CD4 124)

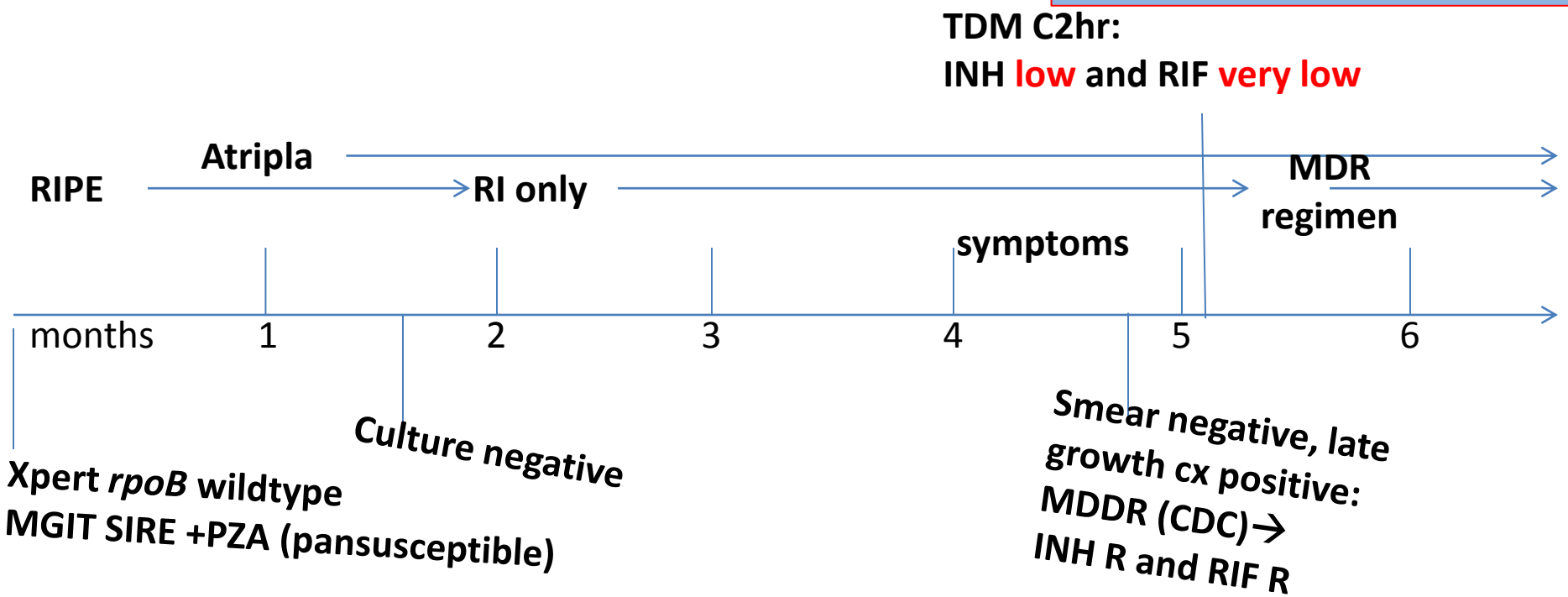
Sputum and R neck biopsy→ smear (4+ from sputum) and cult

Interestingly CXR was normal (laryngeal TB?)

Pretreatment *M tb* isolate:
embB L355L (silent)
embB G378A (neutral)

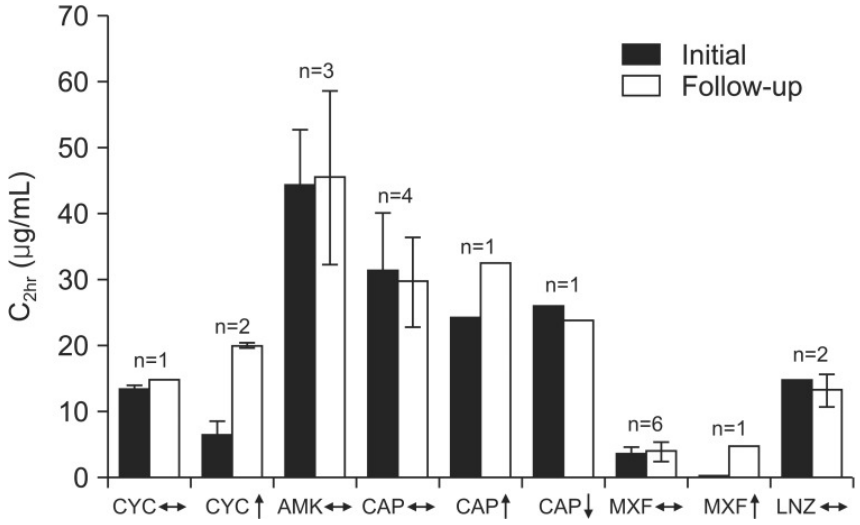
4 month treatment isolate:
embB L355L (silent)
embB G378A (neutral)

inhA C-15T→ R by MGIT
rpoB D518Q→ R by MGIT



TDM in MDR

- Since 2009, regularly check TDM in all MDR patients to all drugs (except bedaquiline)
- Cycloserine: 4/7 have been “low”
- Moxifloxacin: 1/5 “low”
- Capreo: 3/5 “low”
- PAS: 0/5 “low”
- Linezolid: 1/3 “low”
- Amikacin: 1/2 “low”



Heysell SK et al., Tuberc Respir Dis (Seoul). 2015 Apr; 78(2): 78–84.

Tb drug side effects

- INH: transaminitis
- PZA: transaminitis, arthralgias
- RIF: hyperbilirubinemia, hypersensitivity = fever+ rash
- EMB: optic neuritis (acuity, red-green)
- All drugs: Rash
- Linezolid: neuropathy, cytopenia: use 50-100mg B6
- Cycloserine: psychiatric, sleep; use B6
- Moxifloxacin, Clofazimine, Bedaquiline: QT prolongation, OK up to QTc 500-550
- Aminoglycosides: ototoxicity (use NAC), nephrotoxicity, keep trough low/undetectable

Why NAC with aminoglycosides?

ORIGINAL ARTICLE

A systematic review and meta-analysis of the efficacy and safety of *N*-acetylcysteine in preventing aminoglycoside-induced ototoxicity: implications for the treatment of multidrug-resistant TB

Katharina Kranzer,[1,2] Wael F Elamin,[1] Helen Cox,[3] James A Seddon,[4] Nathan Ford,[5] Francis Drobniewski[1,6]

ABSTRACT

Background Ototoxicity is a severe side effect of aminoglycoside antibiotics. Aminoglycosides are recommended for the treatment of multidrug-resistant TB (MDR-TB). *N*-Acetylcysteine (NAC) appears to protect against drug- and noise-induced hearing loss. This review aimed to determine if coadministering NAC with aminoglycoside affected ototoxicity development, and to assess the safety and tolerability of prolonged NAC administration.

Methods Eligible studies reported on the efficacy of concomitant NAC and aminoglycoside administration for ototoxicity prevention or long-term (>6 weeks)

Key messages

What is the key question?

- Does coadministration of *N*-acetylcysteine (NAC) with aminoglycosides prevent the development of ototoxicity and is it safe?

What is the bottom line?

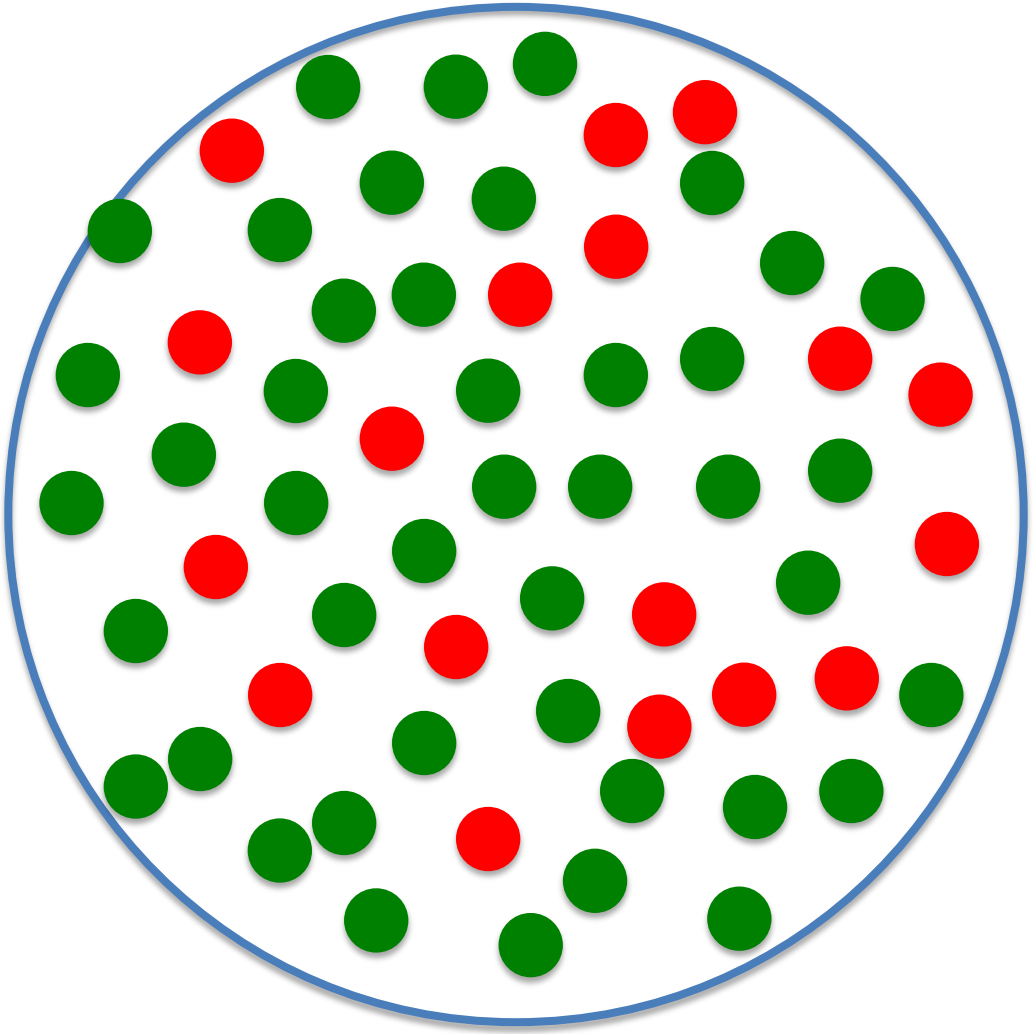
- Coadministration of NAC reduces the risk of ototoxicity by 80% and was found to be safe.

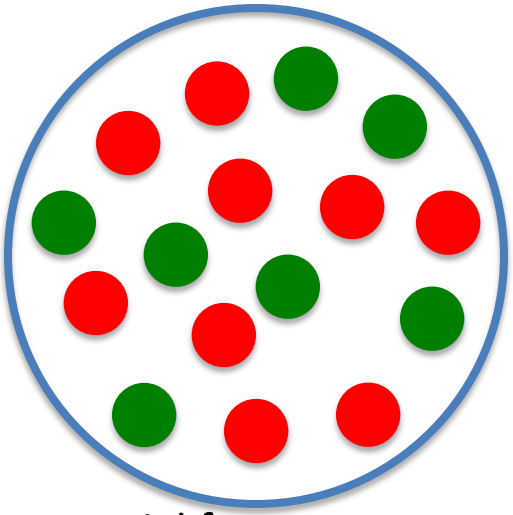
Kranzer K, *et al*. *Thorax* 2015;**70**:1070–1077.

Remember

Not all slow responders have low levels (might be other factors)

AND many with low levels will do fine





Many potential factors may contribute

Extensive disease

Drug resistance

HIV

Other comorbidities

Adherence

Low drug levels

Diabetes

……

Thank you

- UVA
  - Scott Heysell, Tania Thomas
- VDH
  - Denise Dodge, Amanda Khalil
- University of Florida
  - Chuck Peloquin
- Virginia TB Foundation