Diagnosis and Management of Extrapulmonary TB

Andrew DiNardo, MD, PhD

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Has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this activity

Diagnosis and Management of Extrapulmonary TB

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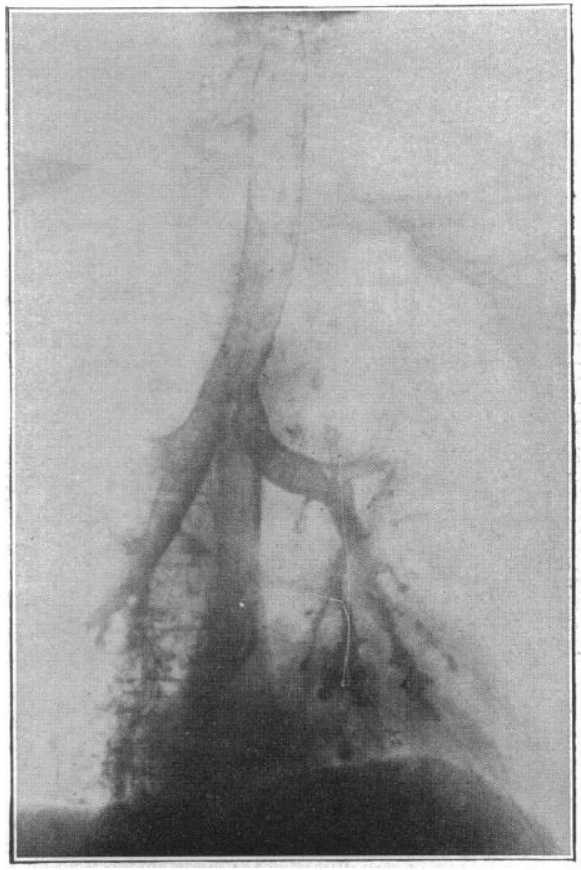
Take home points:

- Extra-pulm TB diagnosis is diagnosis is more challenging
  - Send multiple PCRs
- Make use of Therapeutic Drug Monitoring (TDM)!
- Use your Clinical pharmacists!
- Steroids help: Antibiotics are required, but not sufficient
  - Don’t be afraid to add additional immunotherapy if steroid recalcitrant
- TB endotypes: Both Hyper-inflammatory +/- anergic
- Cure ≠ improved health

All TB is extra-pulmonary



Iodized poppy-seed oil was injected into the trachea by means of a catheter passed between the vocal cords. This shows the iodized oil in both the tracheobronchial tree and the esophagus. There is an actual spilling over of the iodized oil from the trachea into the esophagus. The patient did not cough at any time.

Detection of *Mycobacterium tuberculosis* complex DNA in CD34-positive peripheral blood mononuclear cells of asymptomatic tuberculosis contacts: an observational study

Muluget a Belay, Begna Tulu, Sidra Younis, David A Jolliffe, Dawit Tayachew, Hana Manwandu, Tenagnework Abozen, Emawayish A Tirfie, Metasebia Tegegn, Aboma Zewude, Sally Forrest, Jonathan Mayito, Jim F Huggett, Gerwyn M Jones, Denise M O'Sullivan, Henny M Martineau, Mahdad Noursadeghi, Aneesh Chandran, Kathryn A Harris, Vlad Nikolayevskyy, Julie Demaret, Stefan Berg, Martin Vordermeier, Taye T Balcha, Abraham Aseffa, Gobena Ameni, Markos Abebe, Stephen T Reece, Adrian R Martineau**

Summary

Background Haematopoietic stem cells expressing the CD34 surface marker have been posited as a niche for *Mycobacterium tuberculosis* complex bacilli during latent tuberculosis infection. Our aim was to determine whether *M tuberculosis* complex DNA is detectable in CD34-positive peripheral blood mononuclear cells (PBMCs) isolated from asymptomatic adults living in a setting with a high tuberculosis burden.

Reticulo-endothelial system: Monocytes/ macrophage phagocytose Mtb (and other NTMs and endemic mycosis and the "B" bacteria)→ spleen, liver, bone marrow, lymph organs.

27 Yr old M with no PMH presents with 2 weeks of headaches and fevers progressing to confusion and somnolence over last 2 days. He works as a granite cutter and has no eoth during the week, but >8 beers on Friday and Saturday. BMI 17; A1c 11. CXR and Chest CT have no disease. LP: 80 WBCs, 65% lymphocytes, glucose 20, protein 85. CSF AFB smear and Mtb PCR both negative. QuantIFERON (QFT) negative. ADA 13.

1. QFT, and Mtb PCR are negative: it’s not TB
2. QFT values don’t matter
3. Repeat LP including large volume (20-30mL) of CSF
4. QFT and Mtb PCR both have imperfect sensitivity; empirically start RHZE

1919 age 35:
Pleurisy

1962: age 78
fevers, night sweats, GI bleed, severe anemia

BmBx: grew Mtb weeks later

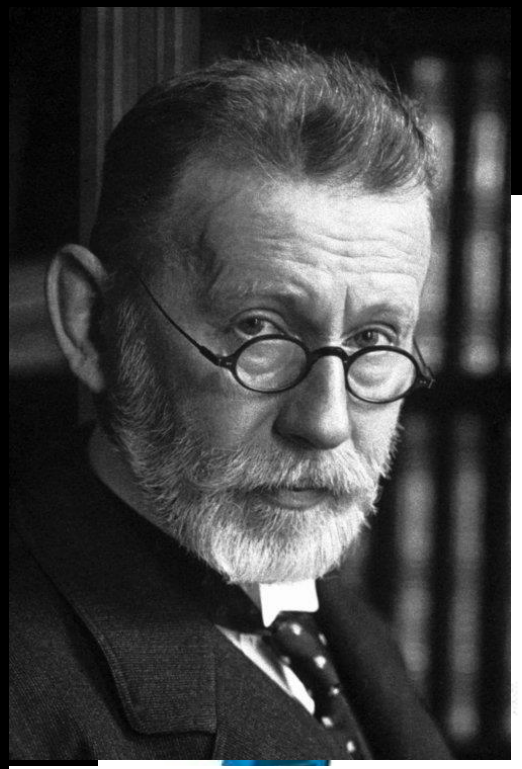
Diagnostic accuracy depends on:

1. Specimen quality

2. Quantity of specimens evaluated

Diagnosis, 1882 to 2006…

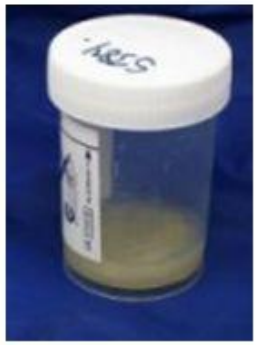
Test	Turn around time	LOD (organisms/ mL)	Sensitivity
AFB smear	< 2 hours	5,000	Low
Culture	14-42 days	1-10	Good Not perfect
PCR (Xpert ultra)	1h 42 min	112 in US 15 (Ultra)	Good Not perfect



Gene Xpert work-station At Baylor-Eswatini TB Clinic

Overview of the procedure

1 Mix



2 Add

3 Insert

4 Detect

Cochrane Database of Systematic Reviews | Review - Diagnostic

Xpert Ultra versus Xpert MTB/RIF for pulmonary tuberculosis and rifampicin resistance in adults with presumptive pulmonary tuberculosis

Jerry S Zifodya, Jonah S Kreniske, Ian Schiller, Mikashmi Kohli, Nandini Dendukuri, Samuel G Schumacher, Eleanor A Ochodo, Frederick Haraka, Alice A Zwerling, Madhukar Pai, Karen R Steingart, David J Horne
Authors' declarations of interest

Version published: 22 February 2021 Version history

Gene Xpert (ULTRA) on Sputum

Specimen Type	Summary Sensitivity
Smear-positive	99%
Smear-negative	77%
All	91%
PLWHIV	87%

7 studies; 2834 patients

Original Gene Xpert LOD 112 CFU/mL

Ultra LOD 15 CFU/mL

Ultra Xpert for Extra-pulm TB

Xpert MTB/RIF Ultra and Xpert MTB/RIF assays for extrapulmonary tuberculosis and rifampicin resistance in adults (Review)

Kohli M, Schiller I, Dendukuri N, Yao M, Dheda K, Denkinger CM, Schumacher SG, Steingart KR

Cochrane Database of Systematic Reviews

Specimen Type	# Studies	Number evaluated	Summary Sensitivity
CSF Xpert	33	3774	71%
CSF Ultra	6	475	89%
CSF 1 specimen*	4	496	63%
Pleural fluid Ultra	4	398	70%
Lymph node	14	1588	88%
Urine	9	943	85%
Bone	6	471	97%
Peritoneal fluid	13	580	59%
Pericardial fluid	5	181	61%

* Culture vs composite reference standard; 1 vs multiple samples

Single PCR + 3 smears is for rule out, not if high suspicion

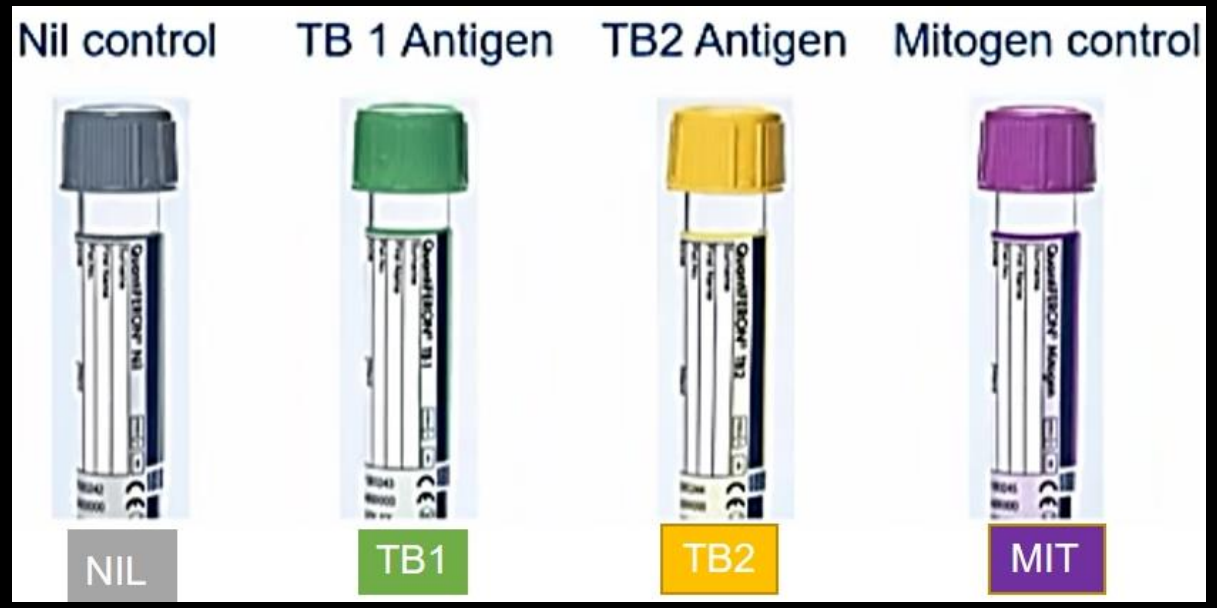
Send multiple specimens *for PCR* if high suspicion

27 Yr old M with no PMH presents with 2 weeks of headaches and fevers progressing to confusion and somnolence over last 2 days. He works as a granite cutter and has no eoth during the week, but >8 beers on Friday and Saturday. CXR and Chest CT have no disease. LP: 80 WBCs, 65% lymphocytes, glucose 20, protein 85. CSF AFB smear and Mtb PCR both negative. QuantIFERON (QFT) negative. ADA 13.

Why is the QFT negative?

1. The test failed
2. The lab tech messed up
3. The immune system failed
4. The test measures ESAT-6 and CFP-10 induced IFNγ. In the setting of severe illness, immune anergy results, decreasing TB-specific and mitogen non-specific IFNγ production.

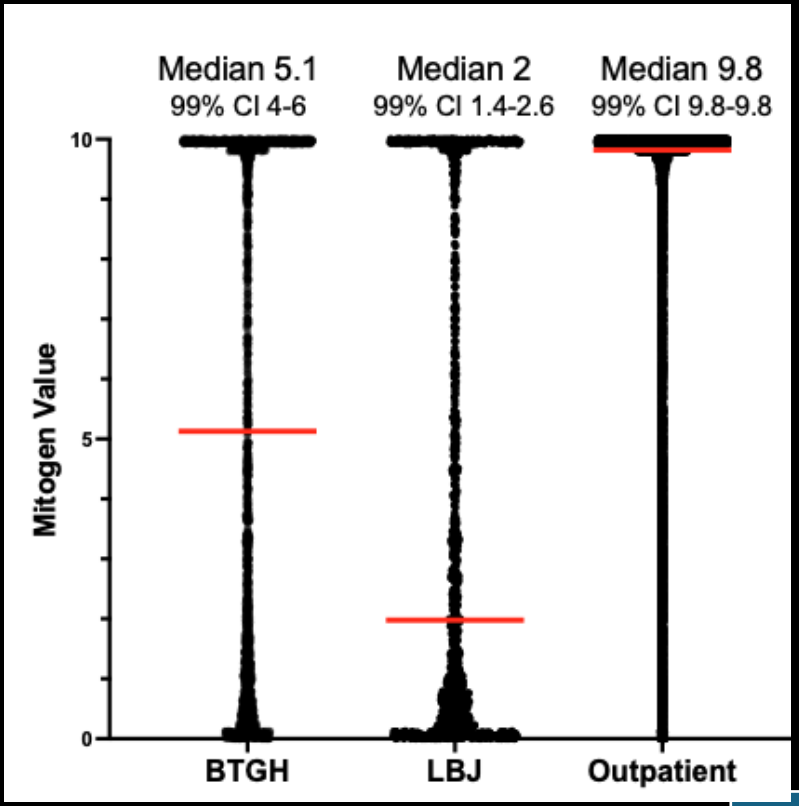
Anergy & tests of infection



ESAT-6, CFP-10
RD1 overlap

5-45% of microbiologically confirmed TB patients are anergic at diagnosis. Good or bad?

Secret data… your eyes only!!!



>14,000 QFT results

1m ago All Rows Time Mark

	2022 12/22/22 04:46	2023 1/4/23 05:40	1/7/23 11:51	1/22/23 04:13	3/28/23 13:15
ROUTINE CHEMISTRI…					
C-Reactive Prot	23.3 ▲		11.7 ▲		3.4
IMMUNOLOGY					
NIL value		3.02 *		4.38 *	
TB1 Ag Minus NIL		0.56 *		0.74 *	
TB2 Ag Minus NIL		0.82 *		0.58 *	
Mitogen Minus NIL		0.40 *		1.68 *	

Ben Taub 6-8 2025	n	Nil (median; 95%CI)	Mitogen (median; 95%CI)
Occup. Health	869	0.06 (0.05-0.06)	10.00 (10-10)
Out-Patient	1461	0.07 (0.06-0.07)	10.00 (10-10)
In-Patient (non-ICU)	132	0.06	3.7 (2.7-6.4)
ICU	28	0.045	2.9 (0.3-10)

27 Yr old M with no PMH presents with 2 weeks of headaches and fevers progressing to confusion and somnolence over last 2 days. He works as a granite cutter and has no eoth during the week, but >8 beers on Friday and Saturday. CXR and Chest CT have no disease. LP: 80 WBCs, 65% lymphocytes, glucose 20, protein 85. CSF AFB smear and Mtb PCR both negative. QuantIFERON (QFT) negative. ADA 13. Patient worsens. Repeat large volume LP is Mtb PCR+ and rpoB resistance not detected. What next?

1. Start RHZE with RIF 10mg/kg
2. Start RHZE with RIF 35mg/kg
3. Start RHZE with RIF 20mg/kg
4. Include Dexamethasone
5. Include infliximab
6. Include anakinra

Steroids for TB meningitis

- Only for non-HIV?
- 30% reduction in death (Thwaites 2004)
- Prevents neurologic progression
- Does not regress existing neurologic deficits (START EARLY)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 12, 2023 VOL. 389 NO. 15

Adjunctive Dexamethasone for Tuberculous Meningitis in HIV-Positive Adults

Joseph Donovan, Ph.D., Nguyen D. Bang, Ph.D., Darma Imran, M.D., Ho D.T. Nghia, Ph.D., Erlina Burhan, Ph.D., Dau T.T. Huong, M.Sc., Nguyen T.T. Hiep, M.D., Lam H.B. Ngoc, B.Sc., Dang V. Thanh, M.D., Nguyen T. Thanh, M.D., Anna L.S. Wardhani, B.Sc., Kartika Maharani, M.D., Cakra P. Gasmara, M.D., Nguyen H.H. Hanh, M.D., Pham K.N. Oanh, M.D., Riwanti Estiasari, Ph.D., Do D.A. Thu, B.Sc., Ardiana Kusumaningrum, M.D., Le T. Dung, M.D., Do C. Giang, Ph.D., Dang T.M. Ha, Ph.D., Nguyen H. Lan, M.D., Nguyen V.V. Chau, Ph.D., Nguyen T.M. Nguyet, B.Sc., Ronald B. Geskus, Ph.D., Nguyen T.T. Thuong, Ph.D., Evelyne Kestelyn, M.P.H., Raph L. Hamers, Ph.D., Nguyen H. Phu, Ph.D., and Guy E. Thwaites, F.R.C.P., for the ACT HIV Investigators*

12 months of follow-up:

- Dex group: mortality 116 of 263 (44.1%)
- Placebo: mortality 126 of 257 (49.0%)
- No benefit

What is the right dose of RIF?

Dose	% w CSF RIF MIC>1
10mg/kg (~600mg)	11%
20 mg/kg (~1200 mg)	93%
35 mg/kg (~2400 mg)	95%

Clinical Infectious Diseases, Volume 73, Issue 5, 1 September 2021, Pages 876–884, https://doi.org/10.1093/cid/ciab162

ORIGINAL ARTICLE

Trial of High-Dose Oral Rifampin in Adults with Tuberculous Meningitis

D.B. Meya,[1,2] F.V. Cresswell,[1,3,4] B. Dai,[5] N. Engen,[5] K. Naidoo,[6,7] A.R. Ganiem,[8,9] D. Imran,[10] M. Kabahubya,[1] R.J. Lessells,[6,11] V. Yunivita,[9,12] R. Estiasari,[10] L. Tugume,[1] B. Hlabisa,[6] M.Y. Kurniawati,[13,14] N. Sagita,[15] E. Kagimu,[1] K. Maharani,[10] J. Gakuru,[1] M.N. Gaharu,[16] T. Mugabi,[1] S. Kimuda,[1] S. Namombwe,[1] L. te Brake,[17] R. Aarnoutse,[17] E.M. Svensson,[17,18] A.S. Bangdiwala,[5] S. Namanda,[1] N.C Bahr,[5] A.K. Musubire,[1] M.Y.S. Moosa,[19] R.L. Hamers,[20,21] S. Marais,[22,23] D.R. Boulware,[2] R. van Crevel,[21,24,25] and R. Ruslami,[9,12] for the HARVEST Trial Team*

Why is more not better?

Three hypothesis on why more is not better?

6 months of follow-up:

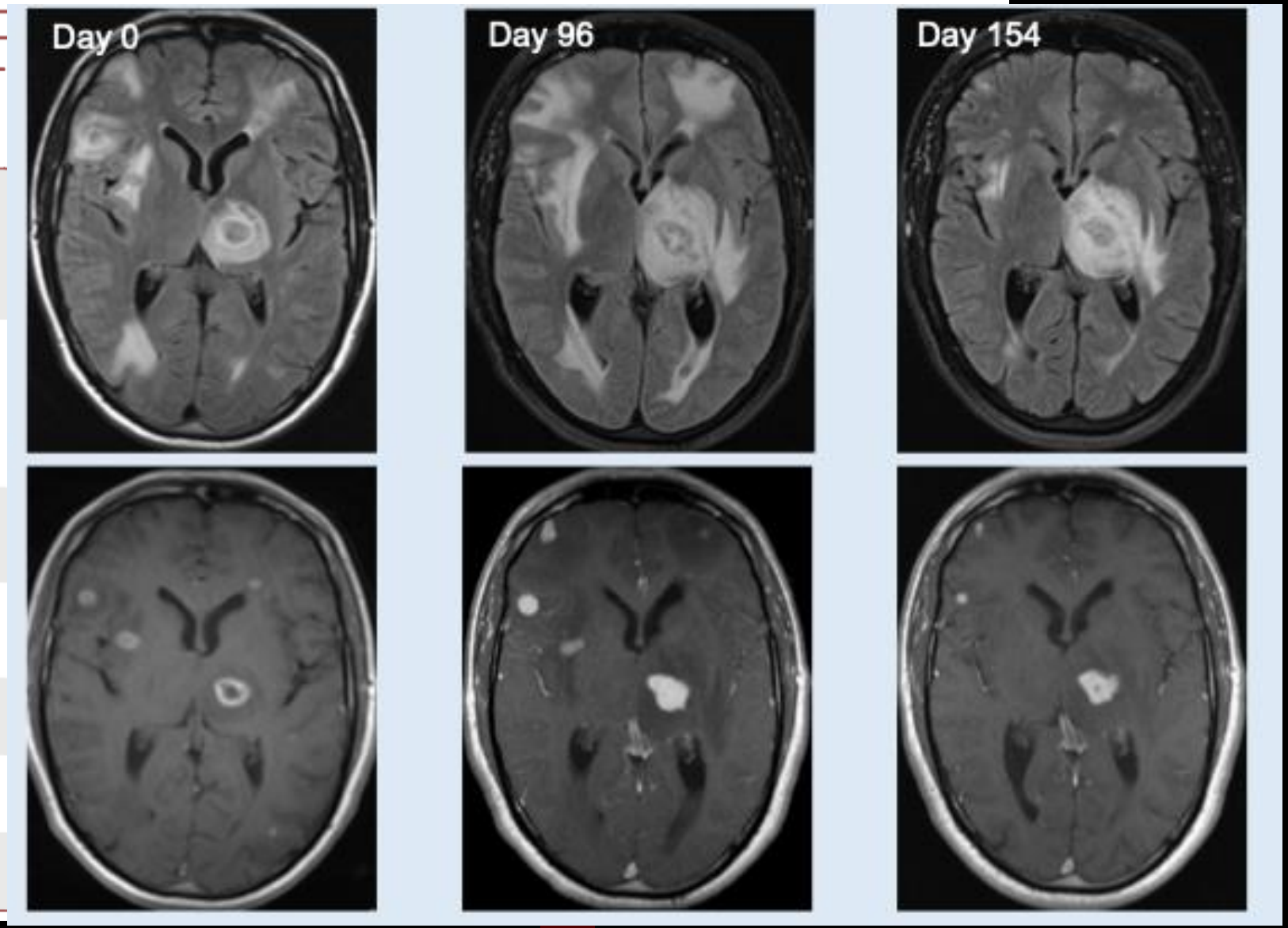
- 10mg/kg: 100 deaths (40%)
- 35mg/kg: 109 deaths (43%)
- No benefit

Case Report

Interleukin-1 receptor antagonist anakinra as treatment for paradoxical responses in HIV-negative tuberculosis patients: A case series

Table 1. Patient characteristics

Patient #	Gender/age/origin	Tuberculosis manifestation
1	male 39 years old Romania	pulmonary
2	male 66 years old Indonesia	pulmonary
3	male 44 years old Bulgaria	pulmonary and laryngeal/hepatic
4	male 45 years old the Netherlands	meningitis
5	male 28 years old Eritrea	meningitis and pulmonary TB
6	female 20 years old Somalia	disseminated (abscesses)
7	male 41 years old Suriname	pericardial tuberculosis

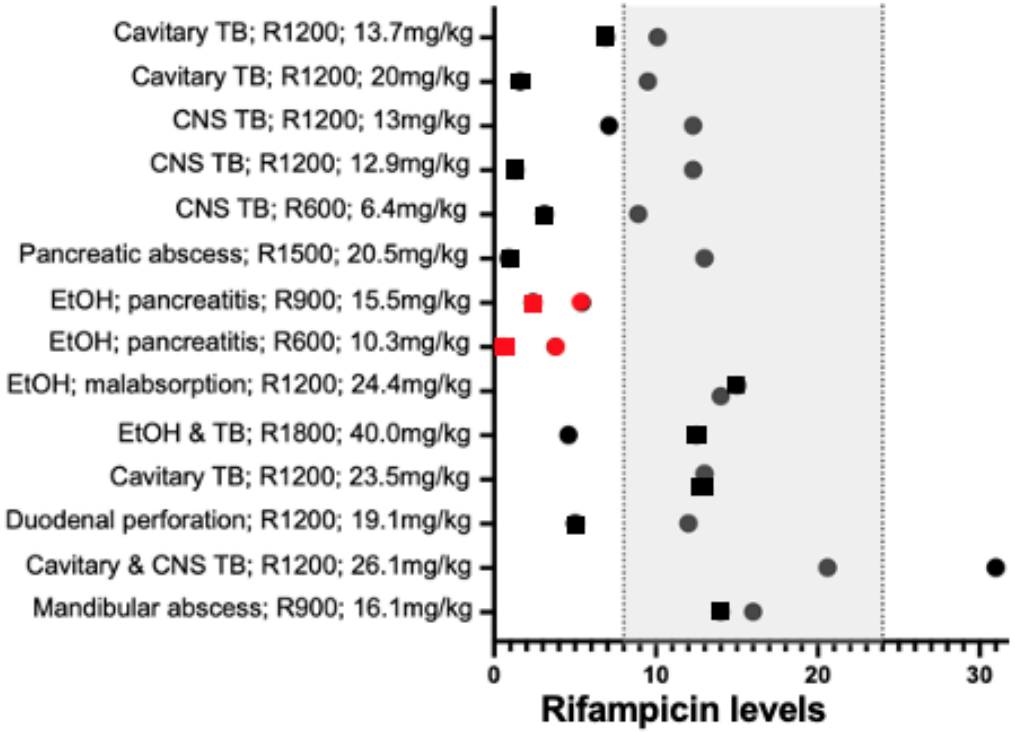


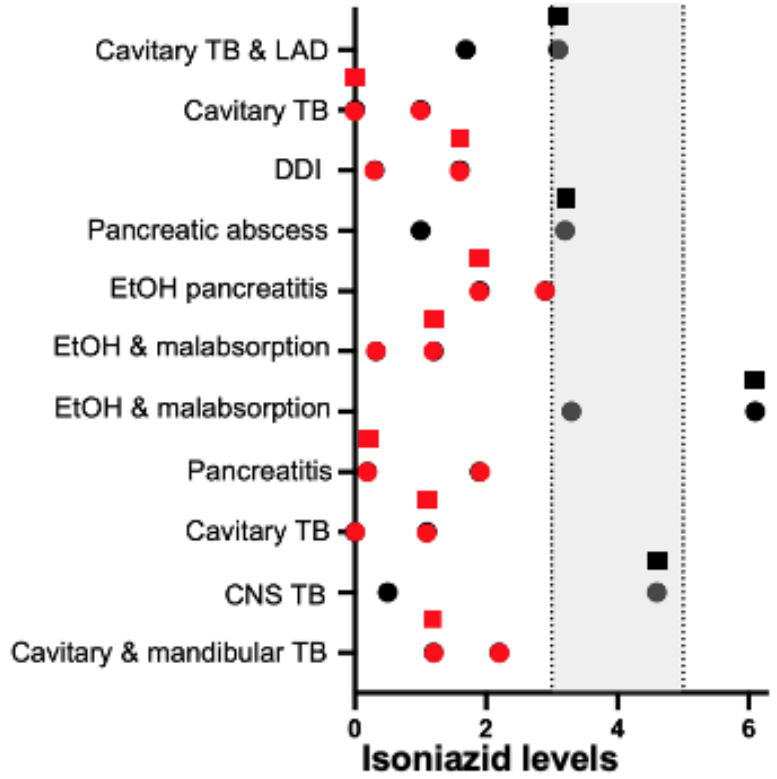
Role of TDM

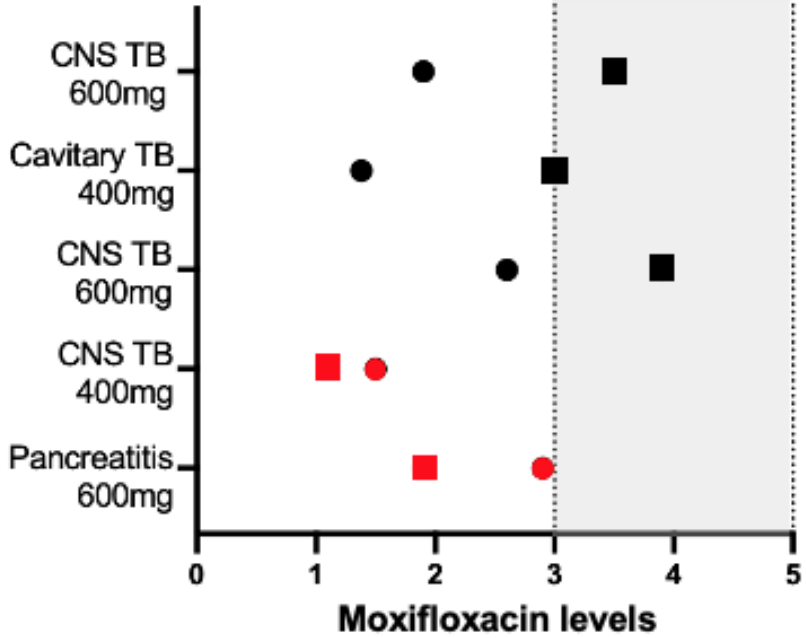
TABLE 1 Patients who especially may benefit from TDM

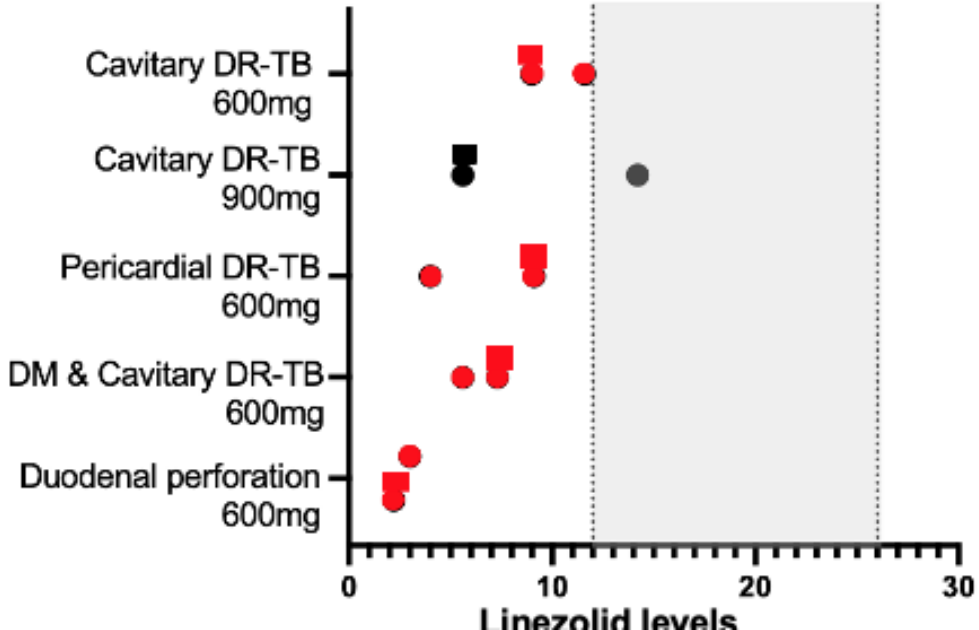
Critically ill patients
Meningitis patients
Osteomyelitis patients
HIV-coinfected patients
Diabetic patients
Patients with a history of gastrointestinal disease or gastrointestinal surgery
Renal failure patients
Hepatic disease patients
Patients receiving multiple interacting drugs

Sub-therapeutic









40-50% of TB patients have sub-therapeutic drug levels.

PMID: 39754280

Therapeutic Drug Monitoring

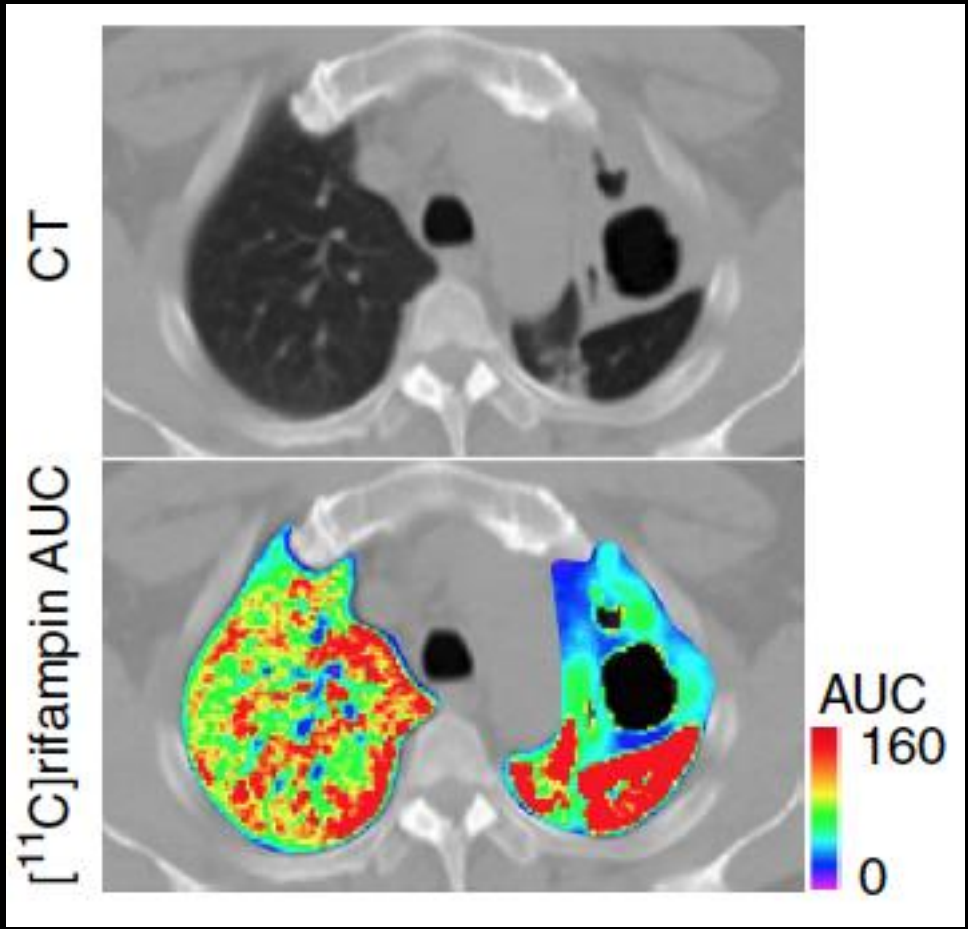
TEXAS Health and Human Services

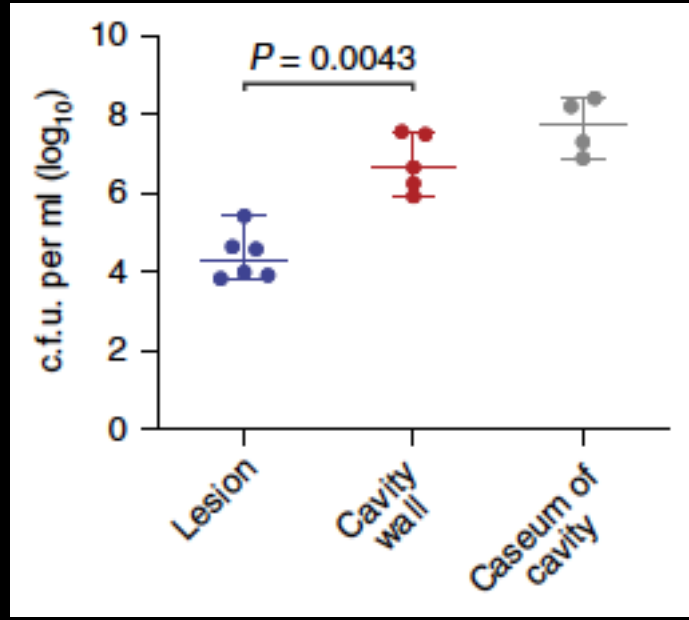
Bacteriological Criteria (consider at 8 weeks of therapy)	**Medical Criteria** (consider at 2-4 weeks of therapy)	**Clinical Criteria** (consider at 8 weeks of therapy)	**Criteria based on TB Diagnosis****
Slow response to adequate therapy at **8 weeks** of treatment, evidenced by the following: • Patient remains AFB sputum smear positive 2+ or greater (unless easily explained) And/or • Sputum smear results not decreasing as expected (4+ to 3+, 2+, etc.)	• TB/poorly controlled diabetes comorbidity • Mal-absorption due to chronic or acute co-morbidity • Chronic or excessive vomiting or diarrhea • HIV infection and CD-4 count <100** • Low or high body mass index (>10% above or below ideal body weight)	• No improvement of TB symptoms (i.e. no weight gain, no reduction in cough, etc.) at 8 weeks • Worsening CXR anytime during course of adequate therapy • New clinical deterioration, likely related to TB (i.e. new evaluation for TB relapse or concern for drug resistance**)	• Patient Relapse: When signs and symptoms of TB return within two years of a prior episode of disease and there was a good possibility that relapse was due to low drug levels (exclude previous poor adherence, missed doses, or N/V) • When second line drugs need monitoring, as per consult recommendations • TB meningitis

>50% TB pts need dose adjustment when starting HRZE w 1200mg RIF

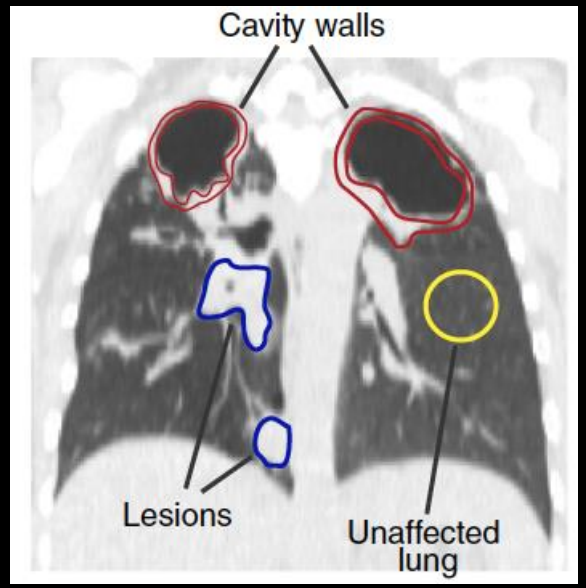
https://www.dshs.texas.gov/sites/default/files/IDCU/disease/tb/forms/PDFS/TherapeuticDrugMonitoringProcess.p

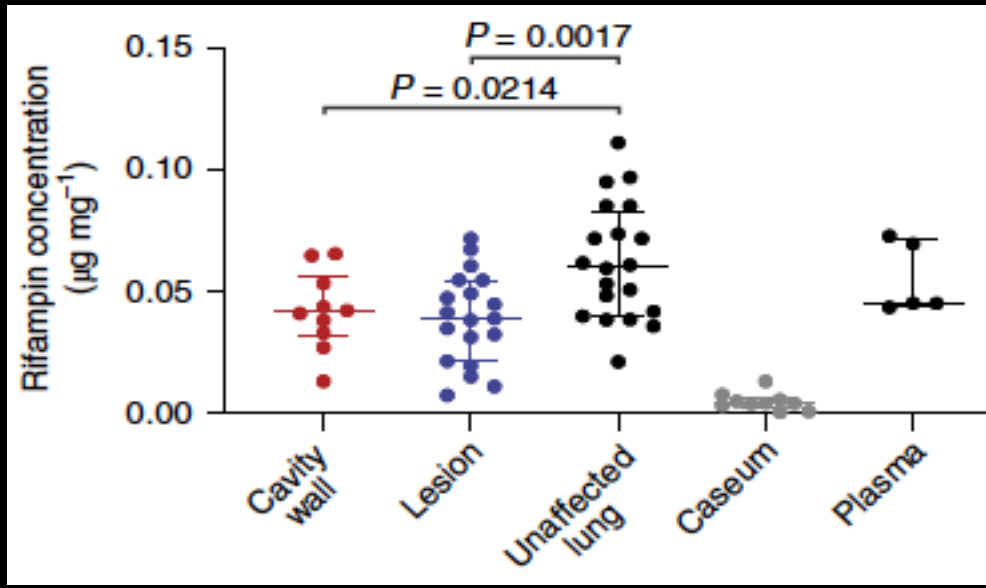
Ordonez & Jain 2020





Caseum - highest CFU
- lowest drugs





Dose rifampicin 20mg/kg; liver toxicity is not dose dependent

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

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

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

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http://dx.doi.org/10.1016/
S2213-2600(18)30044-4

Q2: Treatment of Nonsevere, Presumed Isoniazid-Susceptible, Rifampin-Susceptible TB in Children

2025 TB Treatment Guidelines

Recommended Regimen	Intensive Phase (*8 wk*)‡	Continuation Phase (*8 wk*)
Isoniazid†	10–15 mg/kg	10–15 mg/kg
Rifampin	10–20 mg/kg	10–20 mg/kg
Pyrazinamide	35 (30–40) mg/kg	None
Ethambutol§	20 (15–25) mg/kg (included/excluded based on local guidelines)	None

32 yr M, recently emigrated from Venezuela via the Darrien Gap, presented with 20lb weight loss, anorexia, productive cough, diarrhea, and abdominal pain. Diffuse 1-2 cm violaceous lesions on skin.

New diagnosis of HIV/ AIDS w VL log5, CD4 of 12, HLA-b5701 negative, HBsAg+, Gene Xpert+, Stool AFB smear+. Sub-cm nodules seen in RUL CT. What therapy should be started now?

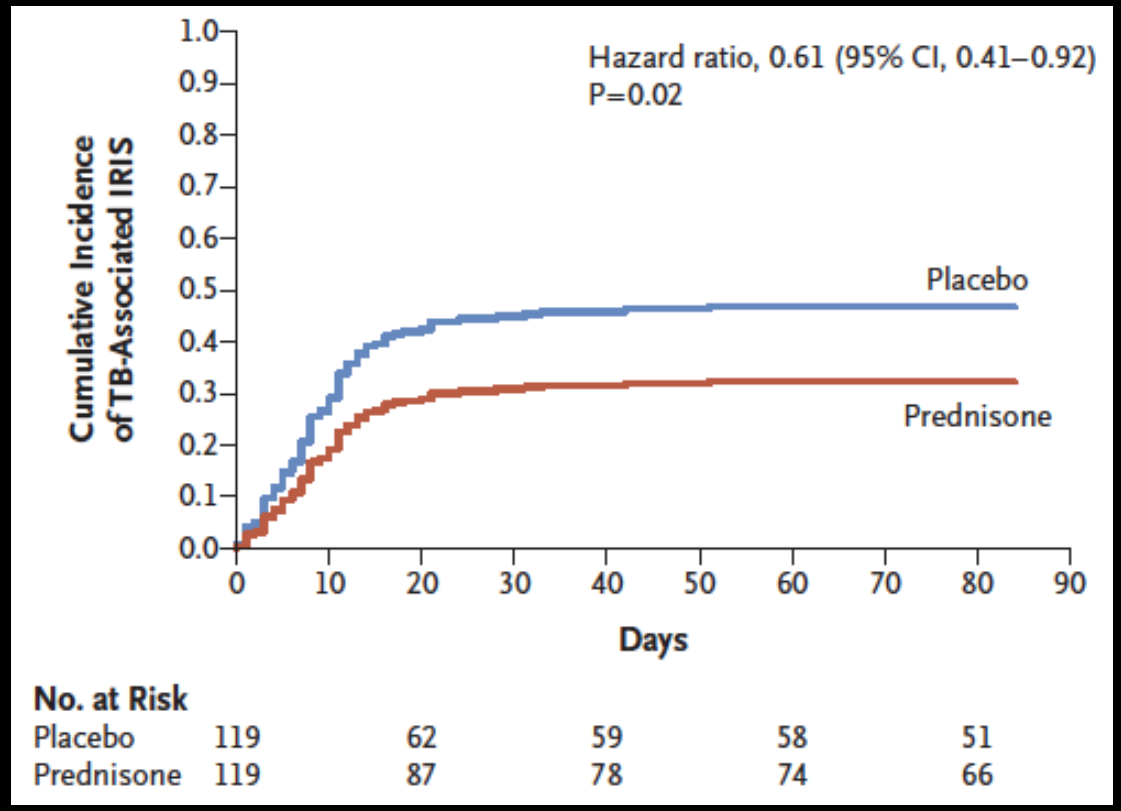
- RHZE with RIF 600mg
- RHZE with RIF 1200mg
- RHZE + ART (BID DTG + TNF/3TC)
- RHZE + ART (BID DTG + TNF/3TC) + Prednisone

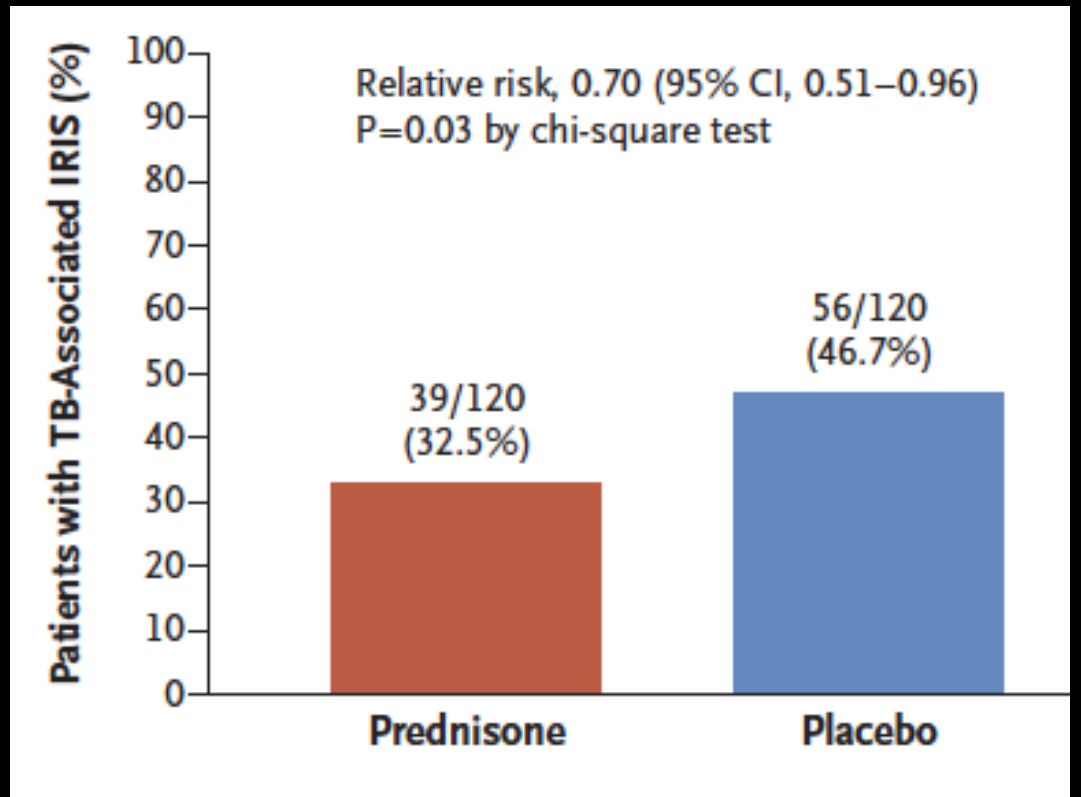
ORIGINAL ARTICLE

Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS

G. Meintjes, C. Stek, L. Blumenthal, F. Thienemann, C. Schutz, J. Buyze, R. Ravinetto, H. van Loen, A. Nair, A. Jackson, R. Colebunders, G. Maartens, R.J. Wilkinson, and L. Lynen, for the PredART Trial Team

For high-risk individuals, should we be giving prophylactic prednisone to prevent IRIS?



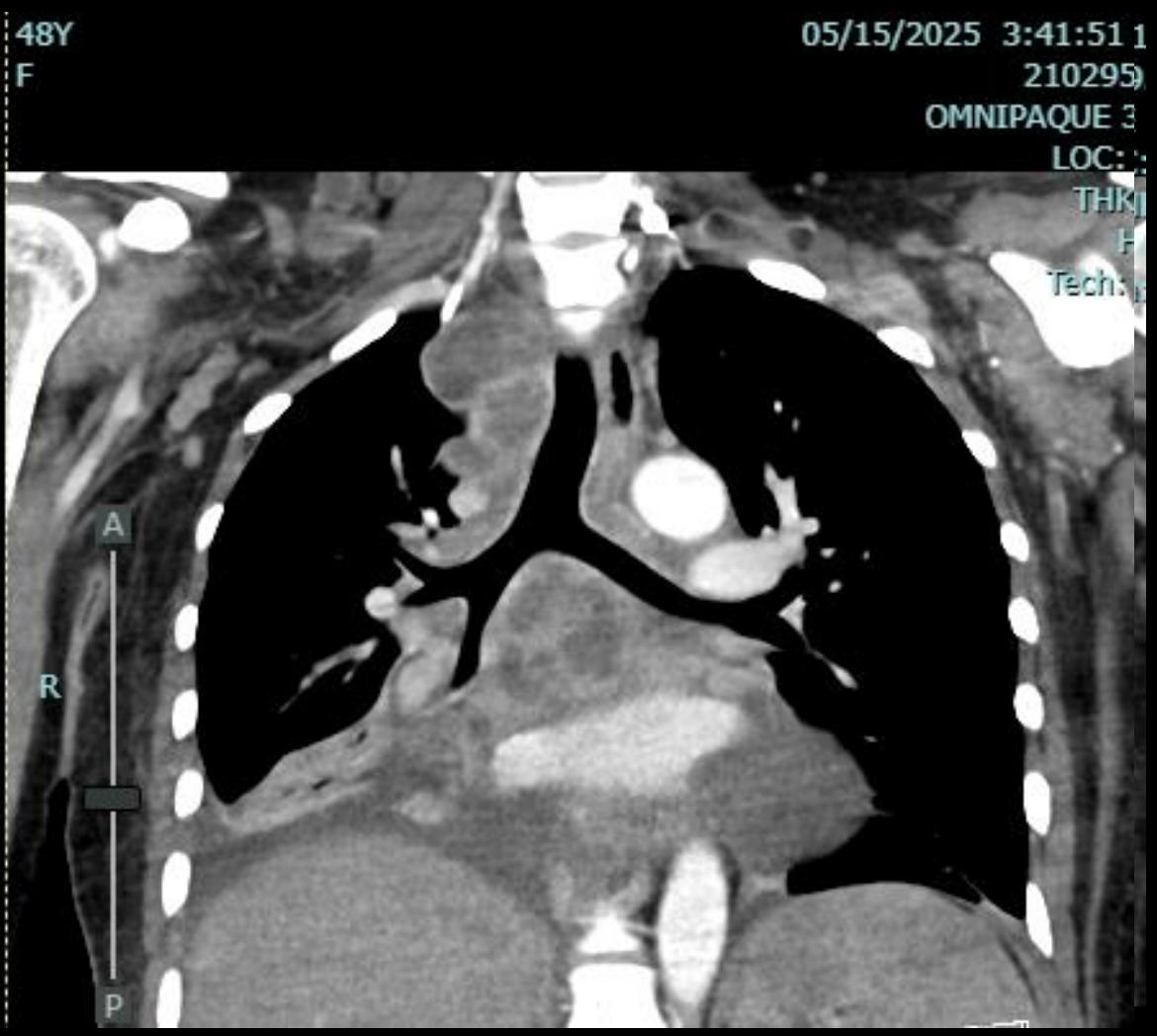


32 yr M, recently emigrated from Venezuela via the Darrien Gap, presented with 20lb weight loss, anorexia, productive cough, diarrhea, and abdominal pain. Diffuse 1-2 cm violaceous lesions on skin.

Pulmonary and GI TB diagnosed. New HIV/ AIDS diagnosed. RHZE (1200mg RIF) started. 2 weeks later ART Started. 3 weeks later TB IRIS resulting in duodenal perforation and CNS tuberculomas with seizures.

- Could we have prevented IRIS?
- Can we identify IRIS faster?
- How should we treat IRIS?
- → role of TDM & giving IV vs PO Abxs if GI absorption is too poor

When to start ART during TB?



- TB diagnosed
- 2 weeks later ART started with Prednisone
- Insomnia and mania

32 yr M, recently emigrated from Venezuela via the Darrien Gap, presented with 20lb weight loss, anorexia, productive cough, diarrhea, and abdominal pain. Diffuse 1-2 cm violaceous lesions on skin.

Pulmonary and GI TB diagnosed. New HIV/ AIDS diagnosed. RHZE (1200mg RIF) started. 2 weeks later ART Started. 2 weeks later TB IRIS resulting in duodenal perforation and CNS tuberculomas with seizures.

Nine months into therapy, he developed bilateral neck swelling with drainage of the right anterior cervical lymph node. Repeat cultures and biopsies demonstrated AFB+, caseating granulomas and culture negative.

Management?

- Surgical resection
- Prednisone
- Change RH to BPaLM

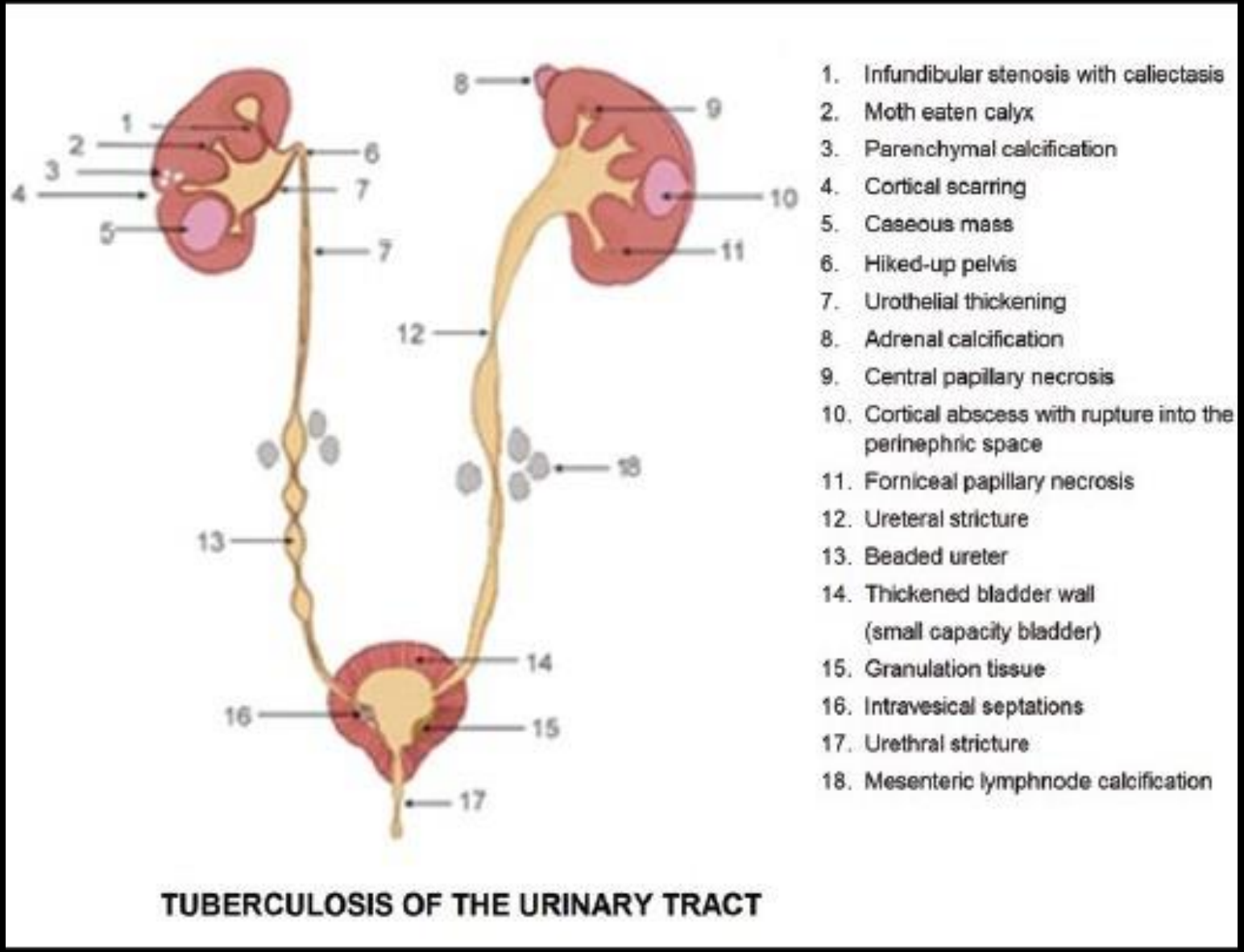
Management of TB Lymphadenitis

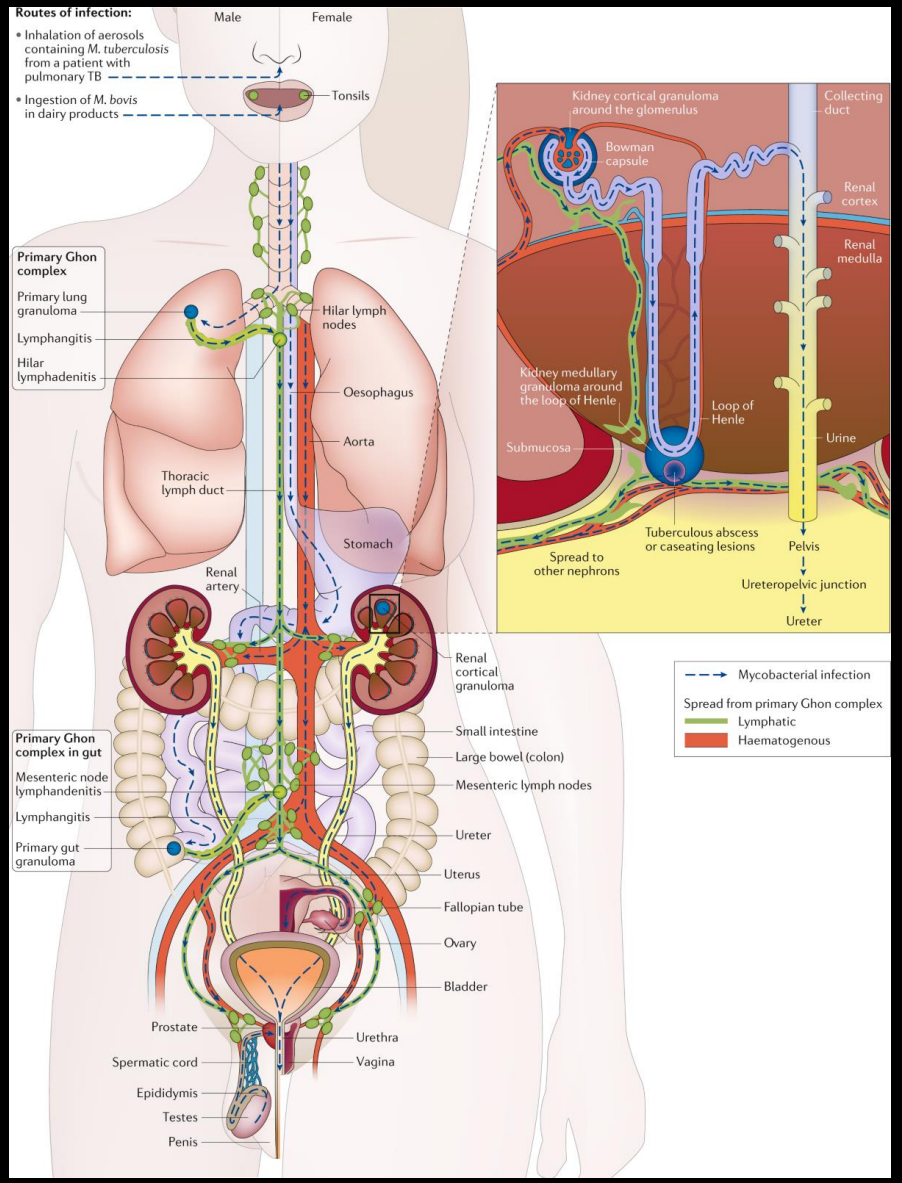
- 6 months of Abxs is as good as 9 months
- Standard 2 RHZE / 4HR
- Paradoxical reactions common (~20-30%) in both HIV and non-HIV associated scrofula
  - AFB+ (dead organisms), PCR positive, culture negative (42 days later)
  - MBLA test still in development… jeesh our field is slow…
- *Usually*, No added benefit of surgery in clinical trial
  - Surgery is recalcitrant to steroids
  - TDM & steroids!
- Biopsy warranted to rule out lymphoma

57 yr old female with DM (A1c 6.8) presents with nausea, abdominal pain, anorexia, cough, fevers, and weight loss. Cr is 4 (up from <1 1 yr ago). Diagnosed with urogenital peritoneal, CNS (tuberculoma), and pulmonary (miliary pattern) TB. She is started on ATT. TDM demonstrated good levels on RHZE). A month later she has worsening nausea, emesis, anorexia. What next?

1. Change RHZE to BPaLM
2. Diagnose the problem?
    1. LFTs are normal; Renal Fxn worse; Imaging cw Urethral and ureteral strictures;
3. Add Linezolid and Moxifloxacin to RHZE
4. Place percutaneous nephrostomy tubes and foley catheter, add steroids, check urine Mtb PCR (including rpoB) and culture.

LAM





PMID: 23986618

Preventing Renal failure in urogenital TB

- Multiple mechanisms
  - Parenchymal disease either from endarteritis, amyloidosis, interstitial nephritis, glomerulonephritis.
    - Are these preventable with anti-inflammatory drugs? (Steroids, anti-TNF or IL1b?)
  - Strictures resulting in obstruction; preventable if steroids given early
- Increased rates of squamous metaplasia
- Monitor renal function closely
- Get urology involved early to help w stenting
- Weekly urine AFB to confirm Abxs working
- TDM

32 yr old transgender male with >10 yr history of suicidal ideation and failed attempts, IVDU, incarcerations with T10-T11 osteomyelitis by imaging and peri-bronchial nodules (tree-in bud). Bone bx negative for Mtb PCR. QFT positive. PMH of lumbar MRSA OM. 3 weeks after RHL+minocycline he had his first period in 10 yrs.

- RIF: Activation of Pregnane X receptor (PXR)→ CYP inducer. Increased testosterone metabolism.
- Also on methadone…
- Management: shared decision making: Rifabutin, increased testosterone, longer duration on non-RIF based regimen

32 yr old transgender male with >10 yr history of suicidal ideation and failed attempts, IVDU, incarcerations with T10-T11 osteomyelitis by imaging and peri-bronchial nodules (tree-in bud). Bone bx negative for Mtb PCR. QFT positive.

- Duration of therapy?
- 6, 9, or 12 months?
- MRC studies in 1970s-1980s: RIF regimens of 6 & 9 months as successful as 12-18 months.
- 1980s-1990s: Indian (CMCV) studies: no difference in 6 vs 9 months for vertebral TB→ WHO recommends 6 months; many clinicians prefer 9-12 months

TB & Diabetes

- Surpassed HIV as most common comorbidity assoc w TB worldwide
- Hyper-active lymphocytes with myeloid immune deficiency
- Diminished glutathione stores; manage ROS worse

- Worse outcomes; increased mortality
- More MDR TB on primary infection. Why???

TB, diabetes & metformin

- Decreases all cause mortality!
- Maybe improves lung healing (Met-RIF study India)
- Improved time to culture conversion?

- Be cautious with nausea
  - 250mg daily x 3-5 days, then increase very gently
  - Make sure GFR >45

55 yr M with poorly controlled DM (A1c 9.5), HIV presents with 2 weeks chest pain and pericardial effusion, which is Mtb PCR-positive. Management?

- RHZE without prednisone
- RHZE without prednisone

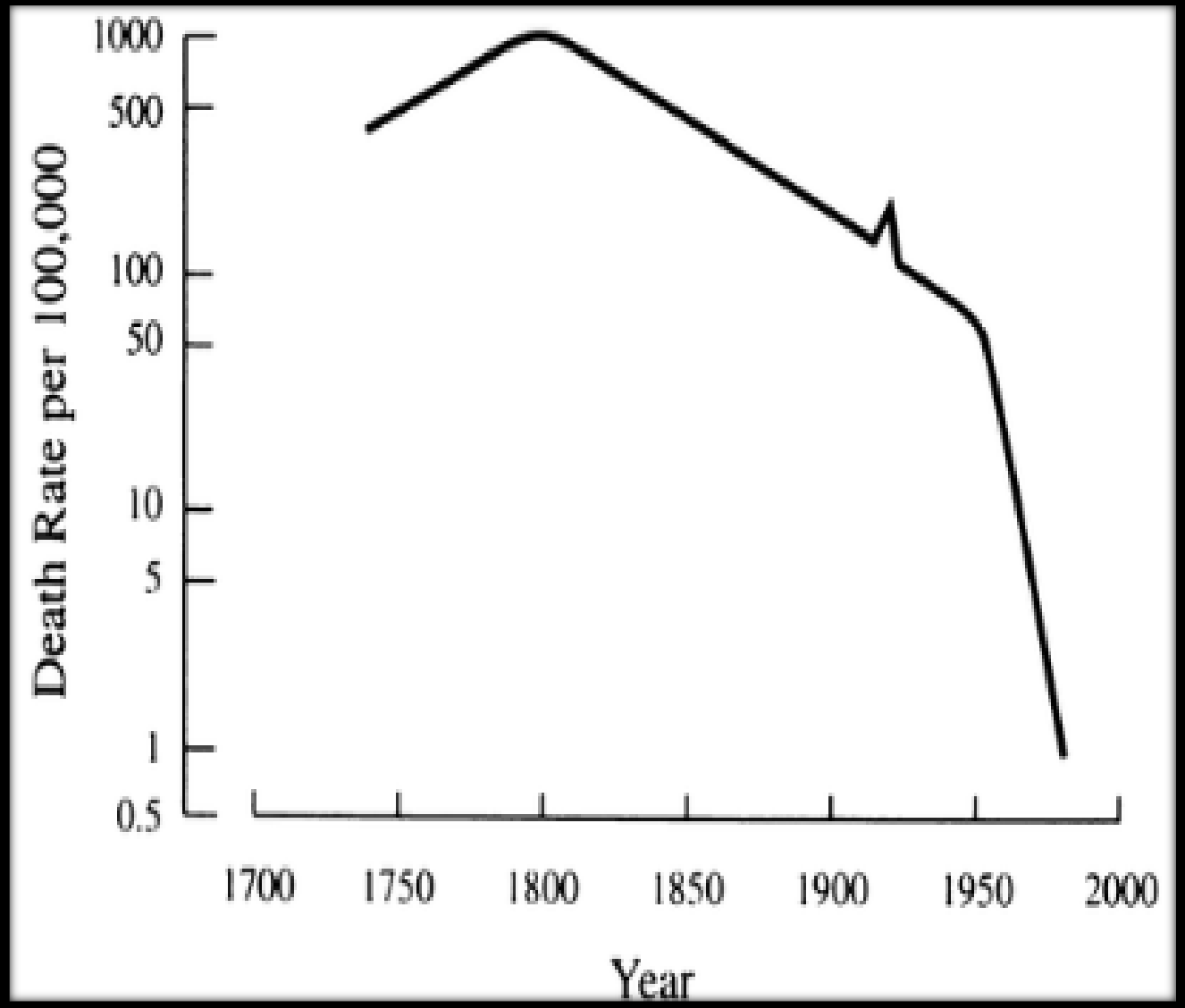
55 yr M with DM (A1c 9.5), HIV presents with 2 weeks chest pain and pericardial effusion, which is Mtb PCR-positive.

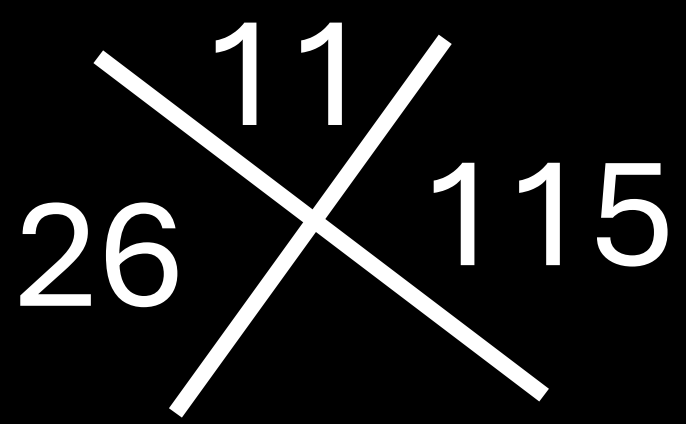
CD4 count 455; HIV VL < 20; ferritin 1200. CRP 23; QFT Nil 2.1; TB1 0; TB2 0; Mitogen 0.5. Management?

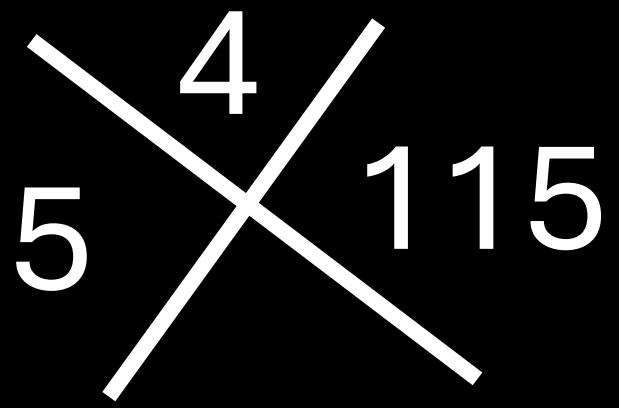
- RHZE without prednisone
- RHZE without prednisone

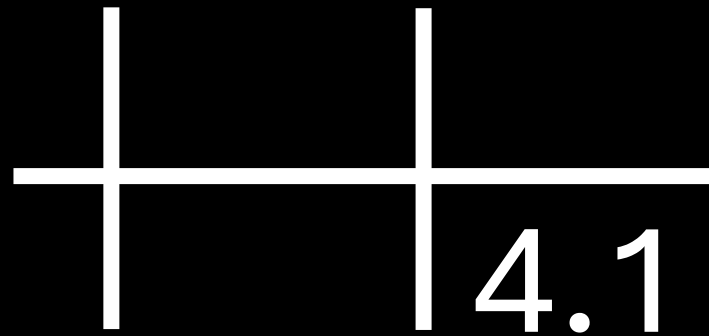
Ready for the 3rd era?

Tuberculosis Mortality Rate









CRP 12

IL6 650 pg/ml

Ferritin 1200

QFT

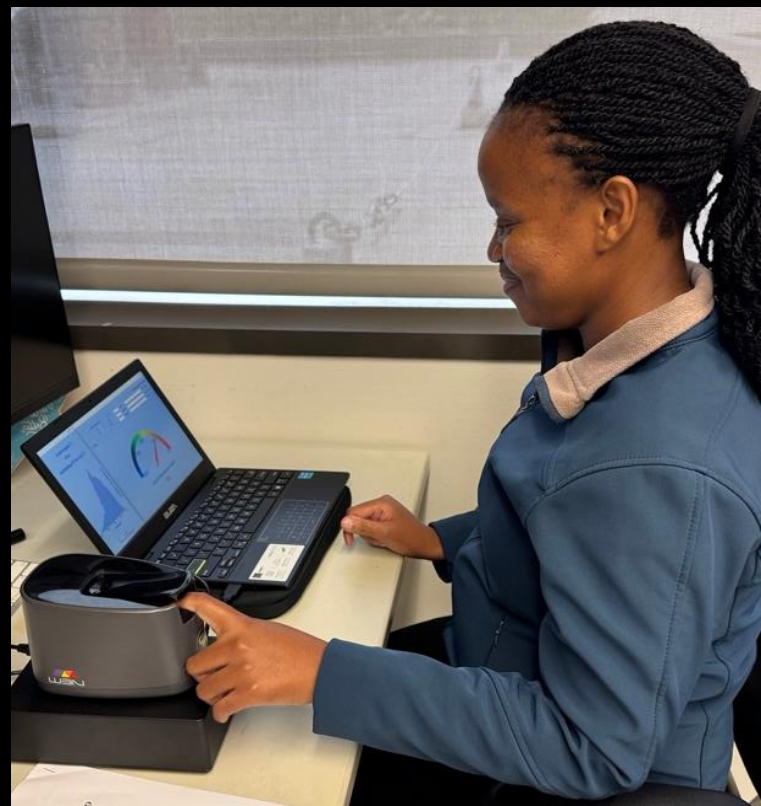
Nil 1.3; TB1 0.5; mitogen 0.5

What are TB endotypes?

- TB can be caused by immune paralysis (low CD4 counts, TNF or JAK inhibitors)
  - → intracellular Mtb proliferation→ miliary disease progression; needs Abxs and recovery of immune function
- TB can be caused by immune over-activation. Best described example is HLH
  - Over-activated macrophages: immune induced pathology; needs immune suppression (myeloid focused immunosuppression)
- There is no single pathophysiology for TB
- Ergo, there is no single treatment for TB
- Our community problem: advance the field so that the clinician at the bedside can discriminate the etiology of the pathophysiology

Post-Tb after extra-pulmonary TB

- TB survivors have 3.7-fold increased risk of mortality
- Increased mortality due to cardiovascular disease, cancers, respiratory lung damage, and recurrent infections
- Transition to primary care
- Work on smoking cessation
- Review modifiable risks
- VeggieMeter
- Exercise for everyone



cure ≠ improved health

Thank you….

Questions and comments?

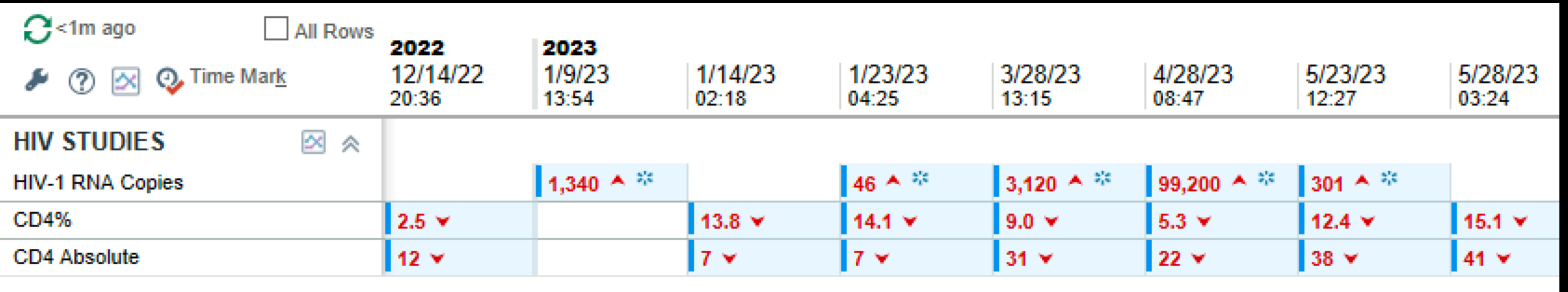
Jan 2023

- Worsening abd pain, re-admitted, found to have contained perforated duodenum, and CT concerning for multiple enteric-enteric fistulas.
- GI EGD & c-scope: no evidence of KS by endoscopy
- Previous stool & sputum cultures both with M. bovis. Repeat sputum and stool cultures later culture positive.
- Switched to LZD, Moxi, RIF, Amikacin. (INH discontinued due to hepatotoxicity).
- Persistent fevers, anorexia, and Abd pain.
- Management? Steroids, tocilizumab, or anakinra?

- Antibiotics kill bacteria
- Antibiotics do not adequately address inflammation
- Add anti-inflammatories if necessary
  - NSAIDS
  - Steroids
  - Anakinra
  - Infliximab

May clinic

- Ryan White paperwork not filled out; ART held for >1 month and then restarted
- Weeks after restarting ART, he has worse headache of his life
- Re-admitted & diagnosed with CNS histoplasmosis; s/p 3 wks amBisome and transitioned to itraconazole
- Sputum & stool AFB smear & culture negative since Feb
- ATT on itraconazole? TB pan-sensitive. DILI on INH. Switched to Linezolid and moxifloxacin



TB & HIV; some DDI

- Engage a clinical pharmacist if possible!
- Dr. Dominque Brewster at Quinton Meese clinic
- RHZE: BID dolutegravir
  - Is Biktarvy ok? INSIGHT. Avoid for now.
- BPLM
- RIF: CYP450 induction: ↓ Azoles: switch to non-RIF regimen; consider isavuconazole; PharmD; TDM

CG: Finishing Case 1

- Scrofula IRIS at month 12 of ATT→ more prednisone
- ~2-3 yrs later: permanent neuropathic pain
- Working landscaping
- Smiling!
- HIV VL undetectable
- No further KS treatment other than ART

HIV & TB summary

- Often disseminated
- Often multiple organs
- Frequent IRIS, can be fatal or debilitating
- Get TDM
- Don’t be afraid of steroids
- Diagnosis more challenging due to “paucibacillary sputum”
- Don’t rely on diagnostic tests requiring immunity (TST, QFT, Tspot)

Duration of ATT for HIV/TB?

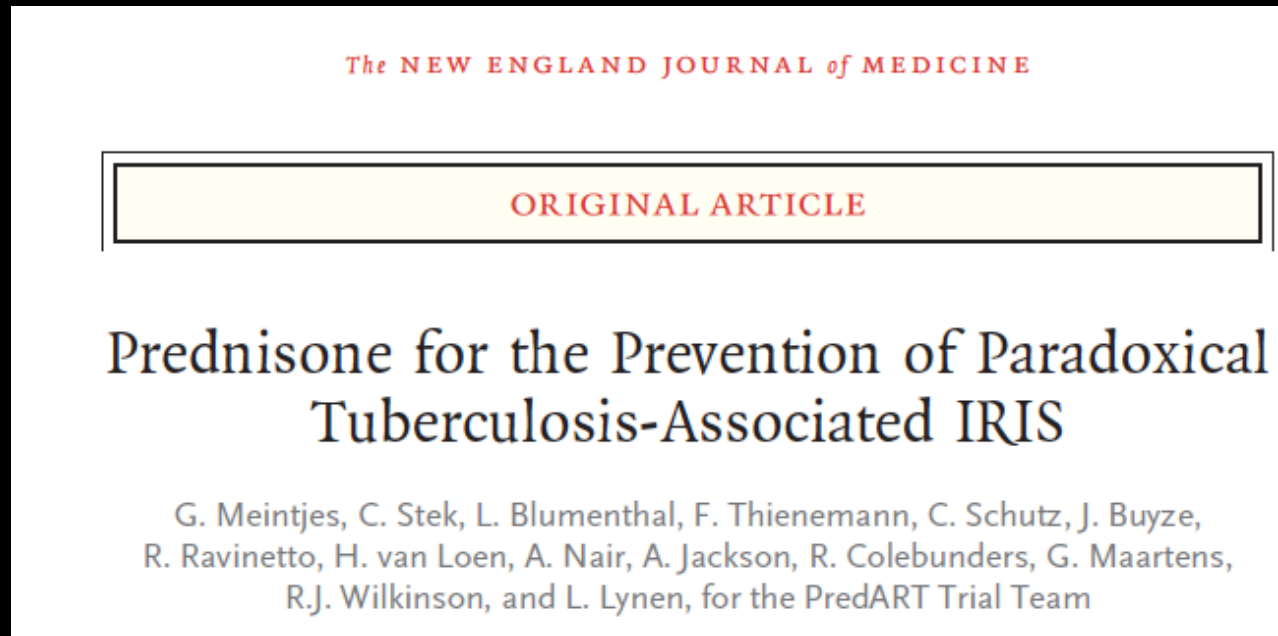
- Do all cases need 9 months?
- Only pulmonary or extrapulmonary
- Follow up imaging to confirm abscesses resolve

When to start ART during TB?

- CNS TB: beware fatal IRIS: start
- Severe disease near certain organs

- If “simple” HIV-TB: 1-2 weeks pending ADAP

- If not simple, especially CNS
  - Delay 4-6 weeks
  - Consider pre-emptive steroids



IRIS: How much steroids is enough?

- Dexamethasone 8mg q 8 hours, taper 1 mg per week for 24 weeks

Or

- Prednsione 40mg/ day x 2 weeks x 2 weeks; 20mg x 2 weeks

Or

- Based on symptoms, signs, and response to steroids?

Rifamycins and Anti-Diabetic Agents: Drug-Drug Interactions

General Tuberculosis (TB) Therapy Information

Developed by Kelly Bujnoch, PharmD Candidate 2011 with the assistance of Regina Tabor, RPh, DPh, Robert Petrossian and Barbara Seaworth, MD

Many diabetic medications are metabolized via the Cytochrome P450 (CYP450) enzymatic system in the liver. Rifampin is a potent inducer of the Cytochrome P450 and accounts for many of the drug interactions that occur during TB therapy.

Rifabutin is a weaker inducer of the Cytochrome P450 system, potentially interacting with some of the same medications as Rifampin.

Enzyme induction effects can last 2-4 weeks after discontinuation of rifampin. Glucose levels should be monitored and diabetic medications should be readjusted at the end of treatment.

Brand	Generic	Clinical Effect	Rifampin (RIF) Drug-Drug Interactions	Recommendations
Biguanide (Metformin) Based				
Glucophage®	**Metformin**	↓Production of glucose by the liver ↓Absorption of glucose by intestines ↑Insulin sensitivity	None noted	No contraindications
Glucovance®	**Glyburide+ Metformin**	Glyburide: ↑Secretion of insulin from the pancreas Metformin: ↓Production of glucose by the liver ↓Absorption of glucose by intestines ↑Insulin sensitivity	↓Glyburide levels 39% Metformin: None noted	•Consider glipizide as first choice sulfonylurea to minimize interactions •Increase monitoring •Consider dose adjustment of antidiabetic agents or alternative glucose control therapy. Metformin: •No contraindications
Metaglip®	**Glipizide+ Metformin**	Glipizide: ↑Secretion of insulin from the pancreas Metformin: ↓Production of glucose by the liver ↓Absorption of glucose by intestines ↑Insulin sensitivity	↓Glipizide levels 22% Metformin: None noted	
Janumet®	**Sitagliptin+ Metformin**	Sitagliptin: ↑Secretion of insulin from the pancreas • delays gastric emptying ↓Appetite ↓Glucagon release after meals Metformin: ↓Production of glucose by the liver ↓Absorption of glucose by intestines ↑Insulin sensitivity	May ↓ sitagliptin levels Metformin: None noted	Sitagliptin: • Increase monitoring; interaction may be minimal and require no adjustments Metformin: •No contraindications
Sulfonylurea Based				
Micronase®	**Glyburide**	↑Secretion of insulin from the pancreas	↓Glyburide levels 39%	•Consider glipizide as first choice sulfonylurea to minimize interactions •Increase monitoring •Consider dose adjustment of antidiabetic agents or alternative glucose control therapy.
Amaryl®	**Glimepiride**	↑Secretion of insulin from the pancreas	↓Glimepiride levels 30%	
Glucotrol®	**Glipizide**	↑Secretion of insulin from the pancreas	↓Glipizide levels 22%	
Glucovance®	**Glyburide + Metformin**	Glyburide: ↑Secretion of insulin from the pancreas Metformin: ↓Production of glucose by the liver ↓Absorption of glucose by intestines ↑Insulin sensitivity	↓Glyburide levels 39% Metformin: None noted	•Consider glipizide as first choice sulfonylurea to minimize interactions •Increase monitoring •Consider dose adjustment of antidiabetic agents or alternative glucose control therapy. Metformin: •No contraindications
Metaglip®	**Glipizide+ Metformin**	↑Secretion of insulin from the pancreas Metformin: ↓Production of glucose by the liver ↓Absorption of glucose by intestines ↑Insulin sensitivity	↓Glipizide levels 22% Metformin: None noted	
Avandaryl®	**Pioglitazone + Glimepiride**	Pioglitazone: ↑Insulin sensitivity (body and liver cells) Glimepiride: ↑Secretion of insulin from the pancreas	↓Pioglitazone levels 54% ↓Glimepiride levels 30%	Pioglitazone: •Increase monitoring •Consider dose adjustment of antidiabetic agents or alternative glucose control therapy. •Consider glipizide as first choice sulfonylurea to minimize interaction Metformin: •No contraindications
Duetact®	**Rosiglitazone + Glimepiride**	Rosiglitazone: ↑Insulin sensitivity (body and liver cells) ↓Production of glucose by the liver ↑Cell uptake of glucose Glimepiride: ↑Secretion of insulin from the pancreas	↓Rosiglitazone levels 54-65% ↓Glimiprde levels 30%	Rosiglitazone: •Increase monitoring •Consider dose adjustment of antidiabetic agents or alternative glucose control therapy. •Consider glipizide as first choice sulfonylurea to minimize interaction Metformin: •No contraindications

Rifamycins and Cardiovascular Agents: Drug - Drug Interactions

General Tuberculosis (TB) Therapy Information

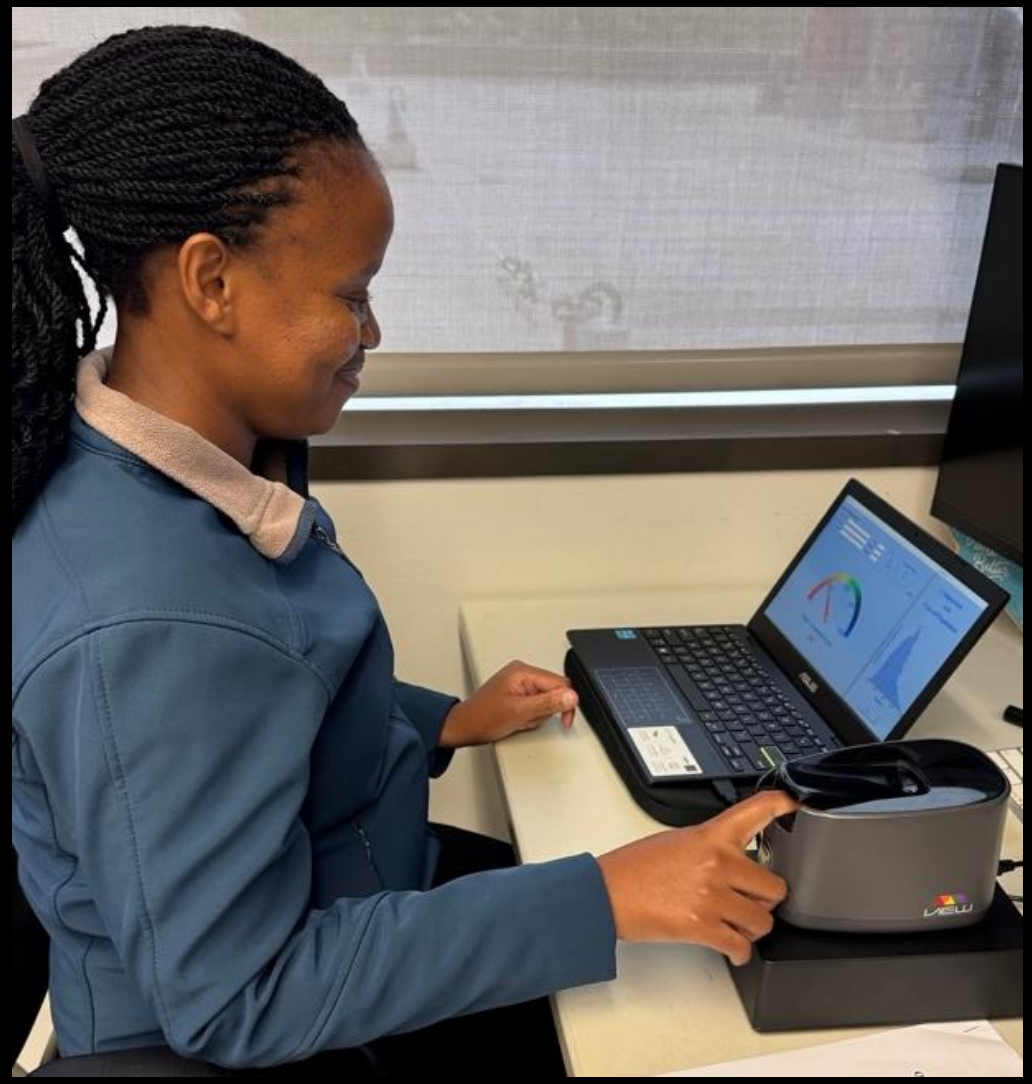
Many cardiovascular agents are metabolized via the Cytochrome P450 (CYP450) enzymatic system in the liver . Rifampin is a potent inducer of the Cytochrome P450 and accounts for many of the drug interactions that occur during TB therapy.

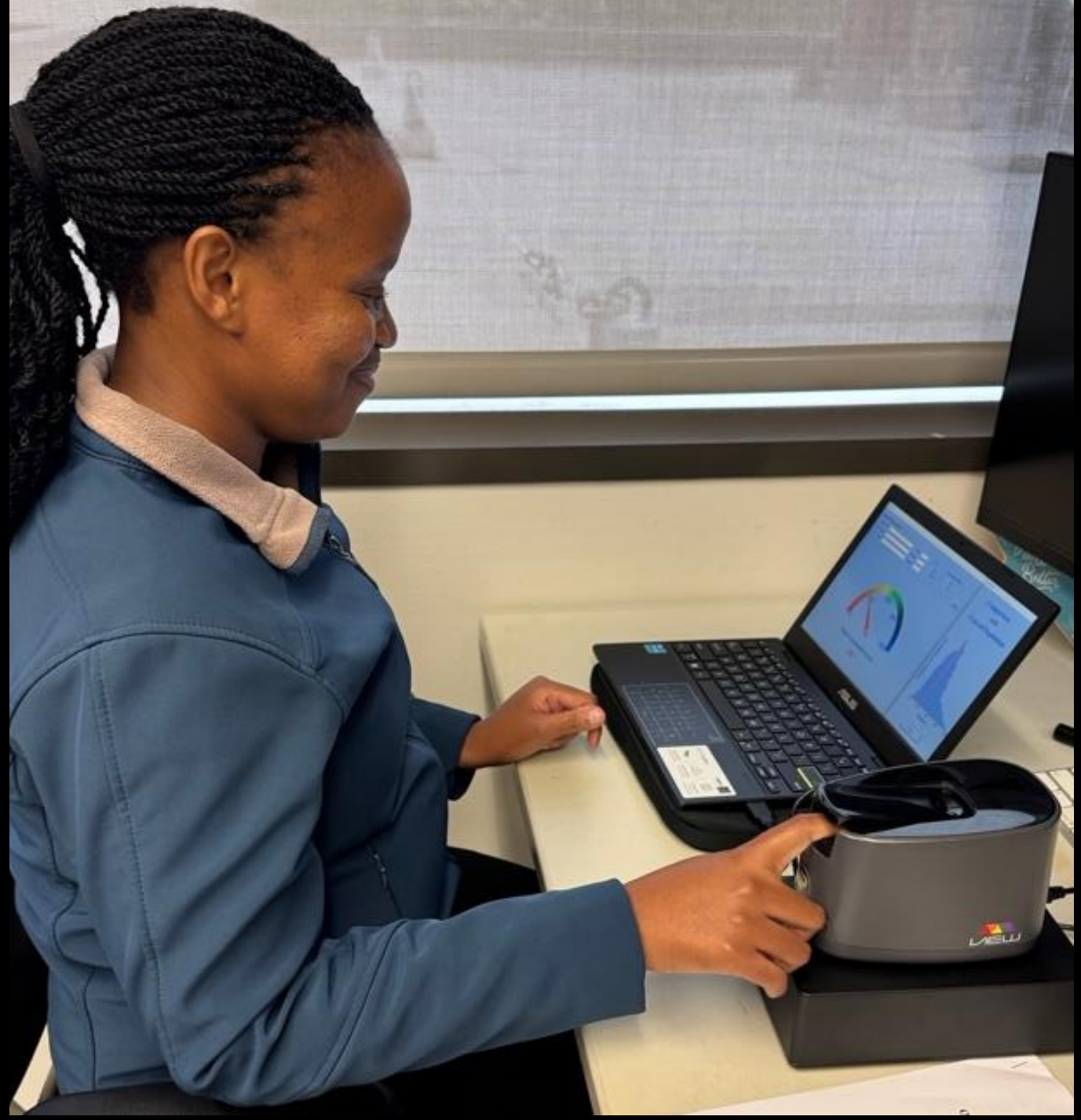
Rifabutin is a weaker inducer of the Cytochrome P450 system, potentially interacting with some of the same medications as Rifampin.
Rifapentine is also a potent inducer of CYP450 enzymatic system in the liver with drug-drug interactions of a severity similar to those of rifampin.

Generic	Clinical Effect	Interactions	Recommendations
Angiotensin Converting Enzyme (ACE) Inhibitors			
(Class Effect)	↓blood pressure	RIF: ↓ACEI levels ~30% (poor evidence, no studies)	Increase BP monitoring; Consider ACEI dose adjustment.
Angiotensin Receptor Blockers (ARBs)			
(Class Effect)	↓blood pressure •renoprotective	RIF: ↓ARB levels ~35% (poor evidence, no studies)	Increase BP monitoring; Consider ARB dose adjustment.
Beta Blockers			
metoprolol	↓blood pressure	RIF: ↓metoprolol levels 33%	Increase BP monitoring; Consider dose adjustment.
propranolol	↓blood pressure	RIF: doubled apparent oral clearance	Increase BP monitoring; Consider dose adjustment.
bisoprolol	↓blood pressure	RIF: ↓bisoprolol levels 34%	Increase BP monitoring; Consider dose adjustment.
Calcium Channel Blockers (CCBs)			
nifedipine	↓blood pressure	RIF: ↓nifedipine levels 92-97% (Contraindicated *)	Increase BP monitoring; Consider dose adjustment; Consider switching to other antihypertensive agents with less interaction. *Major interactions occurr between orally administered nifedipine and rifampin. IV administration significantly reduces the potency of the interactions.
amlodipine	↓blood pressure	RIF: theoretically ↓ amlodipine levels	Increase BP monitoring; Consider dose adjustment; Consider switching to other antihypertensive agents with less interaction.
diltiazem	↓blood pressure	RIF: ↓diltiazem levels	Increase BP monitoring; Consider dose adjustment; Consider switching to other antihypertensive agents with less interaction.
verapamil	↓blood pressure	RIF: ↓verapamil levels 93-99%	Increase BP monitoring; Consider dose adjustment; Consider switching to other antihypertensive agents with less interaction.
Thiazide Diuretics			
(Class Effect)	↓blood pressure	none noted	no contraindications
HMG CoA Inhibitors (Statins)			
atorvastatin	↓cholesterol levels ↓stroke •cardioprotective	RIF: ↓atorvastatin levels 80%	Increase BP monitoring; Consider alternate lipid lowering agent to minimize effect; Consider increasing Statin dose; Consider using Rifabutin in place of Rifampin.
rosuvastatin	↓cholesterol levels ↓stroke •cardioprotective	RIF: may ↓rosuvastatin levels	Increase BP monitoring; Consider increasing Statin dose; Consider using Rifabutin in place of Rifampin.
simvastatin	↓cholesterol levels ↓stroke •cardioprotective	RIF: ↓simvastatin levels 82-97%	Increase BP monitoring; Consider alternate lipid lowering agent to minimize effect; Consider increasing Statin dose; Consider using Rifabutin in place of Rifampin.
pravastatin	↓cholesterol levels ↓stroke •cardioprotective	RIF: theoretically ↓statin levels	Increase BP monitoring; Consider alternate lipid lowering agent to minimize effect; Consider increasing Statin dose; Consider using Rifabutin in place of Rifampin.
lovastatin	↓cholesterol levels ↓stroke •cardioprotective	RIF: theoretically ↓statin levels	Increase BP monitoring; Consider alternate lipid lowering agent to minimize effect; Consider increasing Statin dose; Consider using Rifabutin in place of Rifampin.
fluvastatin	↓cholesterol levels ↓stroke •cardioprotective	RIF:↓statin levels ~50%	Increase BP monitoring; Consider alternate lipid lowering agent to minimize effect; Consider increasing Statin dose; Consider using Rifabutin in place of Rifampin.
Ionotropic/Chronotropic Agents			
digoxin	↑cardiac output •heart rate control with atrial arrhythmias	RIF: ↓levels ~30%	Measure digoxin levels prior to rifampin therapy and then intermittently thereafter. Increase digoxin dose as necessry to maintain therapeutic levels.
Antiplatelet Agents			
clopidogrel	↓platelet adhesion	↑metabolism of clopidogril to active metabolite	Monitor for increased antiplatelet effects such as bruising or bleeding.

TB, diabetes & malabsorption

- Check TDM early: ~10-14 days
- Start with 1200mg RIF (maybe 1800 if known poor absorption)
- Talk to patients about fruits and Veggies every visit
- Encourage exercise every visit
- B6 to decrease neuropathy





Case Study # 2

- 55 yr M w HTN develops new ESRD
  - 2019-2020: testicular abscess not improved s/p 2 courses Abxs
  - March 2021: mild fevers and weight loss
  - November 2021: further weight loss and new renal failure
    - Peri-renal abscess; CXR no disease
    - QFT: indeterminant
    - Urine Gene Xpert positive w Ct 18; Culture TTP 19 days
  - Started on RHZE
    - Symptoms first improve and then 2 months later:
      - Nausea, anuric→ found to have bilateral hydronephrosis
      - Urine Gene Xpert positive w Ct 17; Culture Negative
      - Improved on prednisone

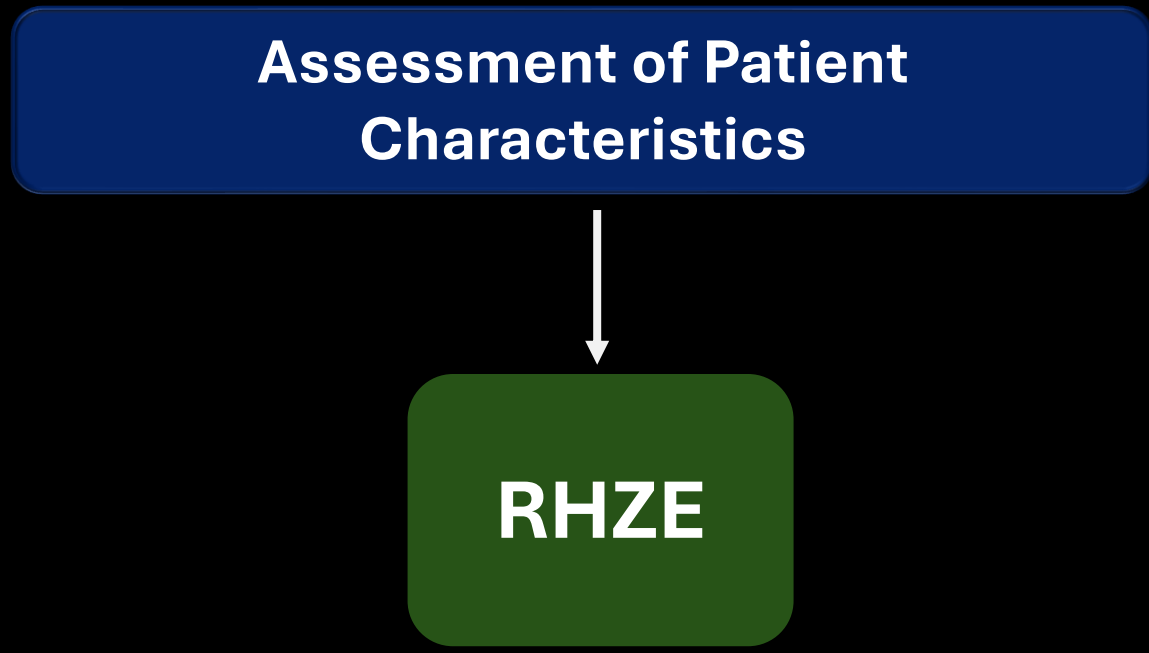
Case Study # 2

- 55 yr M w HTN develops new ESRD
  - 2019-2020: testicular abscess not improved s/p 2 courses Abxs
  - March 2021: mild fevers and weight loss
  - November 2021: Diagnosed w TB; started RHZE
    - Peri-renal abscess; CXR no disease; 2cm scrotal fluid collection; TB+
  - Jan 2022: Developed IRIS
  - *Jan 2023*
    - *Anorexia not resolved*
    - *Still with 2cm fluid collection in scrotum → Abxs won't treat an abscess*
    - *What is the right time to allow for Abx resolution before draining?*

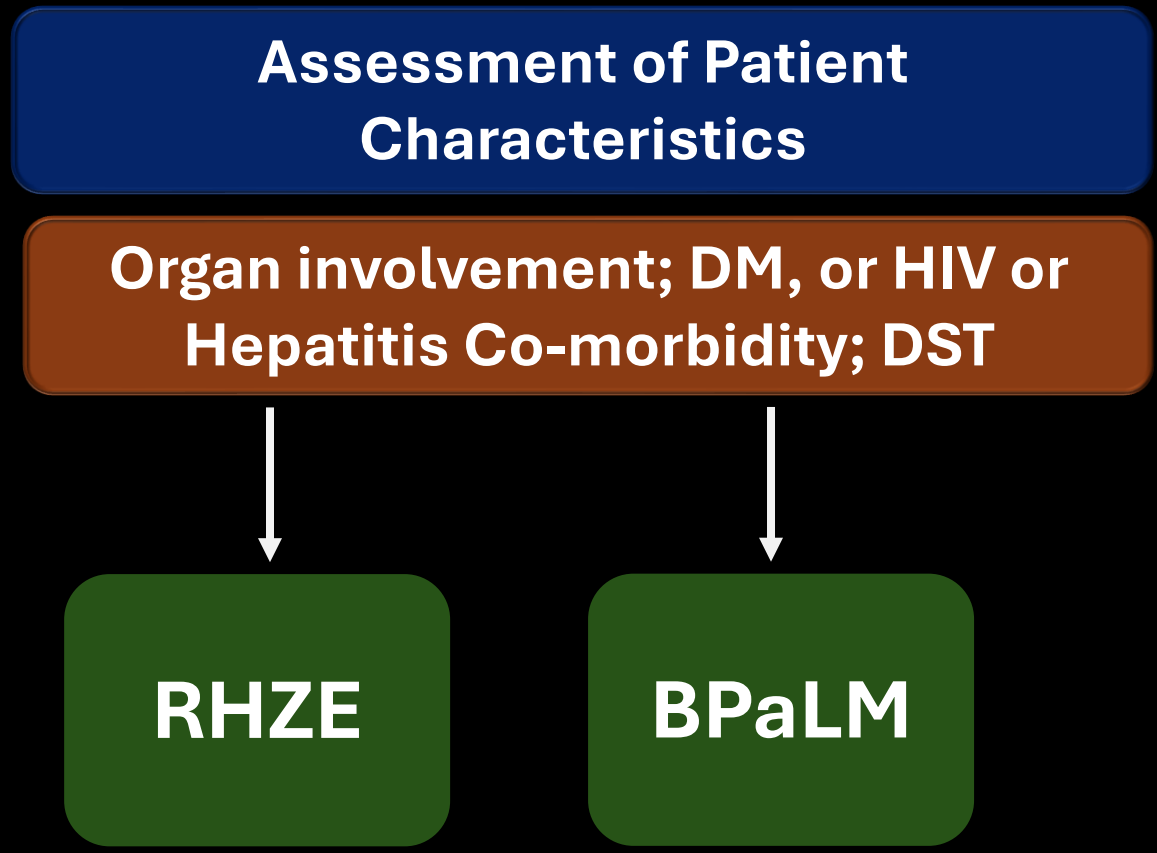
Case Study # 2: Abxs & Kidney disease

- Chronic kidney disease increases risk of TB
  - How? Malnutrition? Anergy?
- Symptoms often atypical due to disseminated disease
  - Fever only!
- Screen with TST or IGRA
  - (?preferably IGRA for patient effort? And mitogen?)
- Xpert can be used on almost any specimen type!
  - Sputum
  - Stool
  - Urine
  - CSF

Treatment algorithm for TB in 1972



General TB therapy 2025



Select circumstances:

1. DM→ metformin
2. ART
3. Steroids for TBM/ masses
4. Steroids to prevent IRIS
5. Pulm Rehab
6. Smoking cessation
7. Nutritional assessment
8. Deworming
9. EtOH mitigation
10. Rituximab for IFNg AutoAbs

What are we still missing?

We are over-dosing TB antibiotics

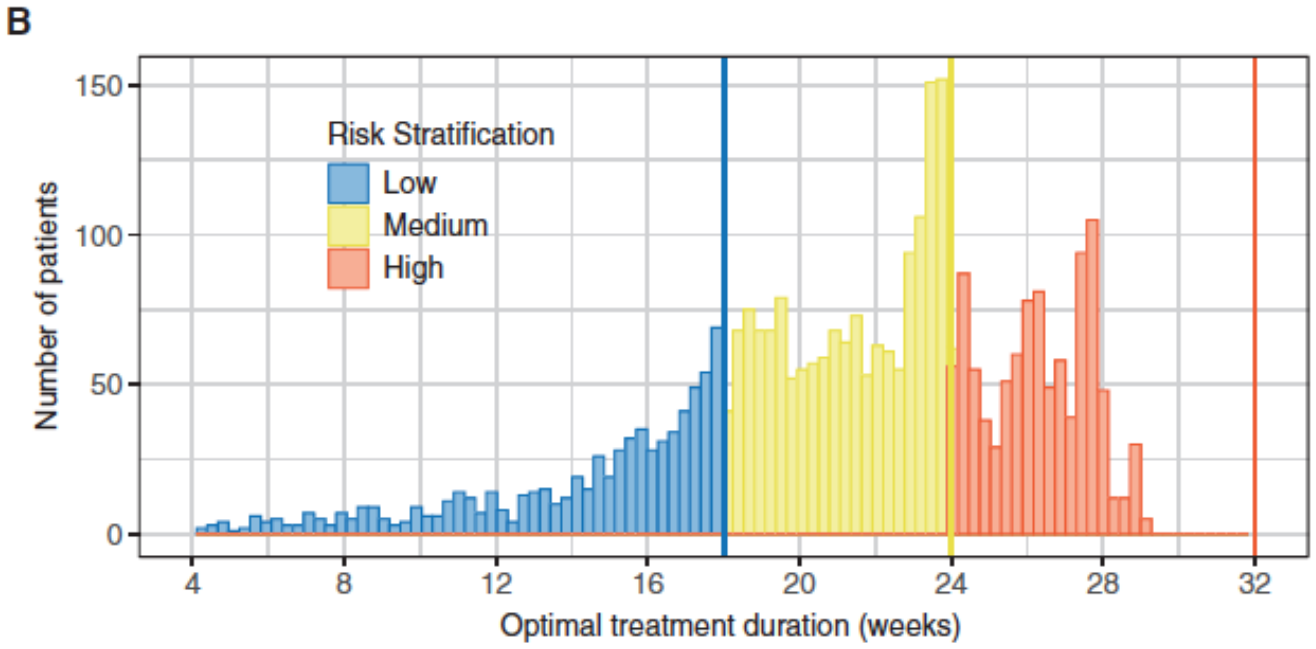
ESTABLISHED IN 1812 OCTOBER 23, 2014 VOL. 371

Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis

Stephen H. Gillespie, M.D., D.Sc., Angela M. Crook, Ph.D., Timothy D. McHugh, Ph.D., Carl M

Precision-Enhancing Risk Stratification Tools for Selecting Optimal Treatment Durations in Tuberculosis Clinical Trials

Ilips[2,3], Payam Nahid[2,3], and Radojka M. Savic[1,2,3]



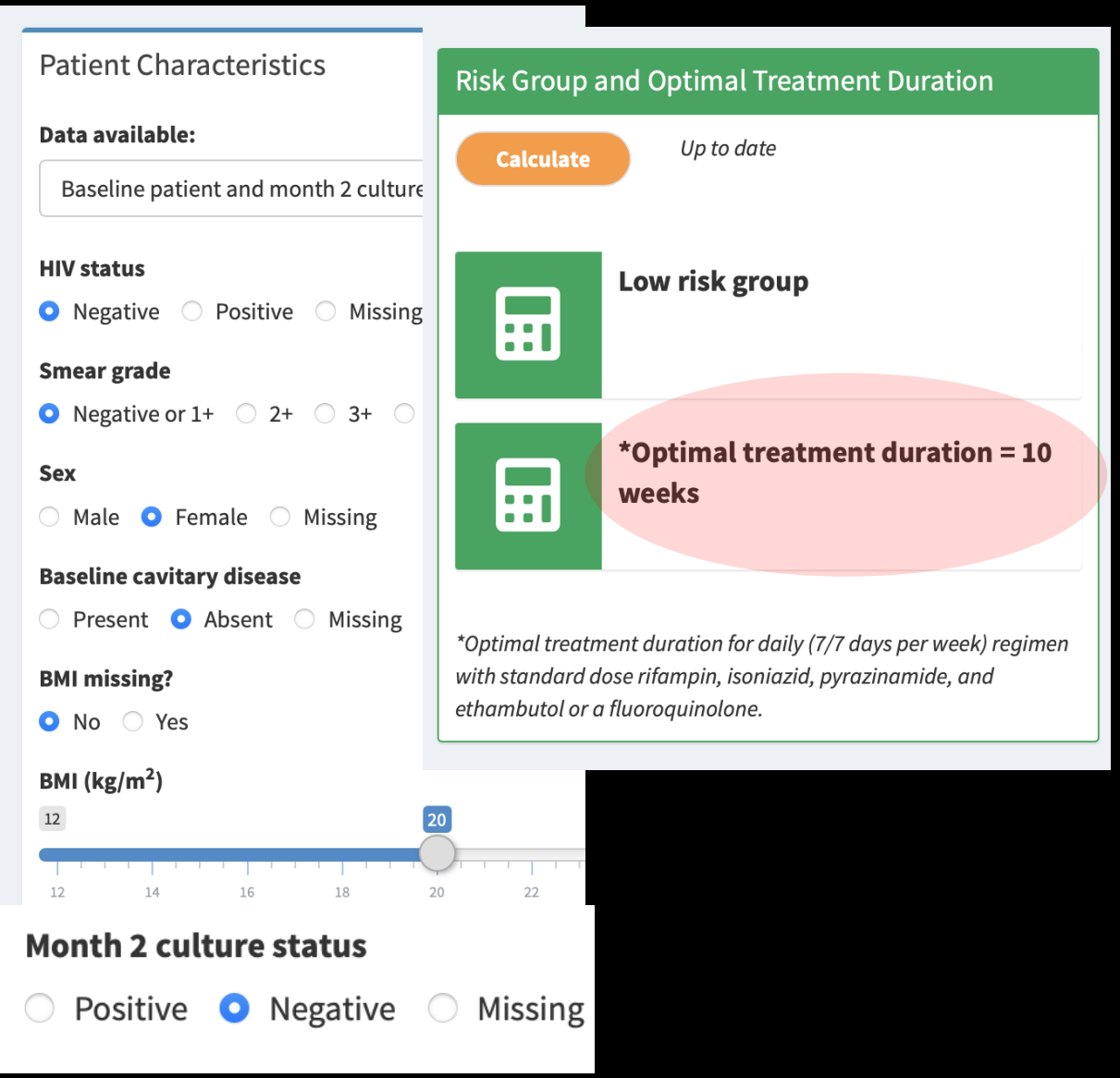
sceptible

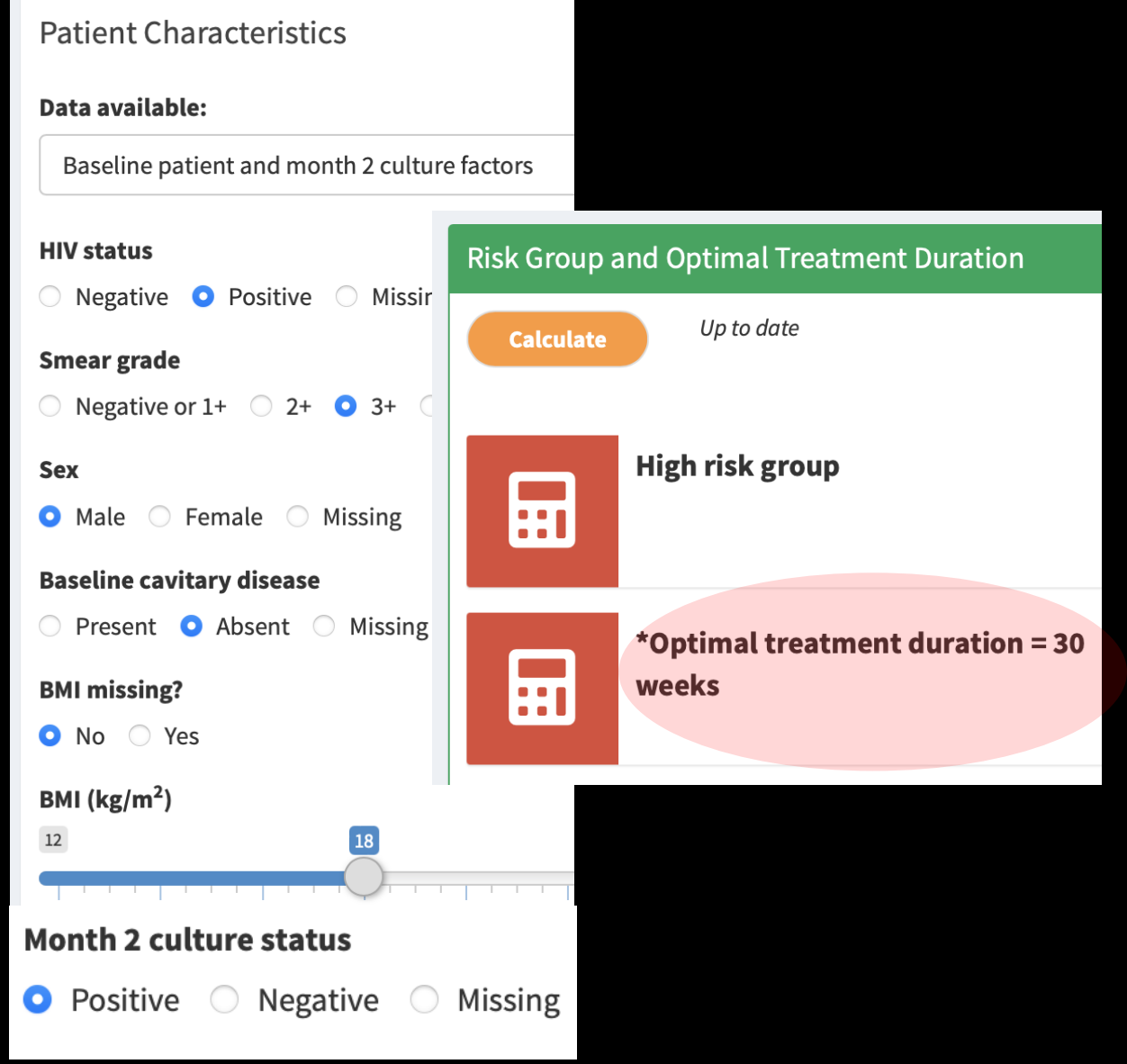
a Suresh, B.Sc.,

Cavity size

BMI

only need 2-4 mo of ATT



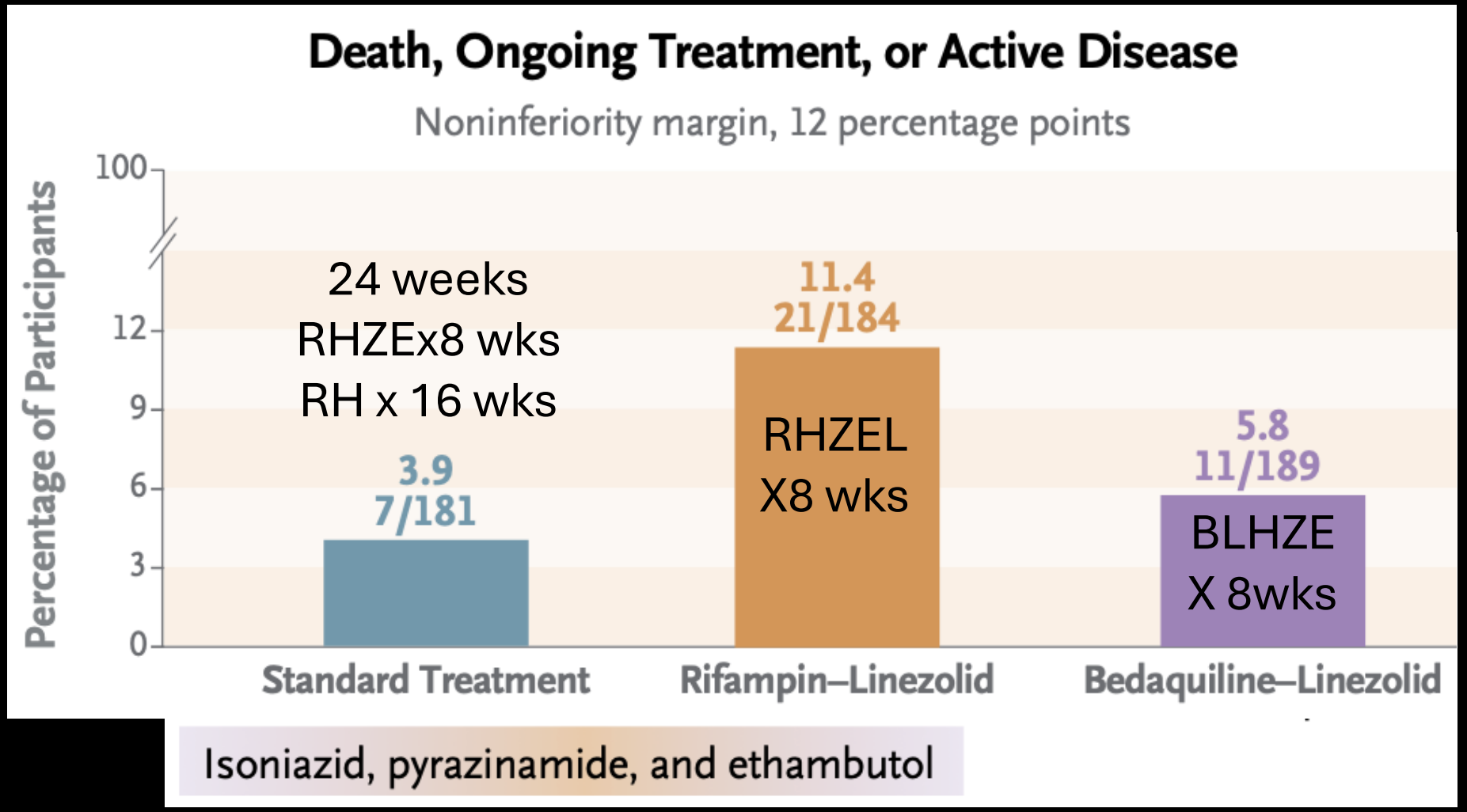


http://saviclab.org/tb-risk/

Multiple clinical trials on going.
*Modeling based on 2013 ART

Treatment Strategy for Rifampin-Susceptible Tuberculosis

Nicholas I. Paton, M.D., Christopher Cousins, M.B., Ch.B., Celina Suresh, B.Sc.,

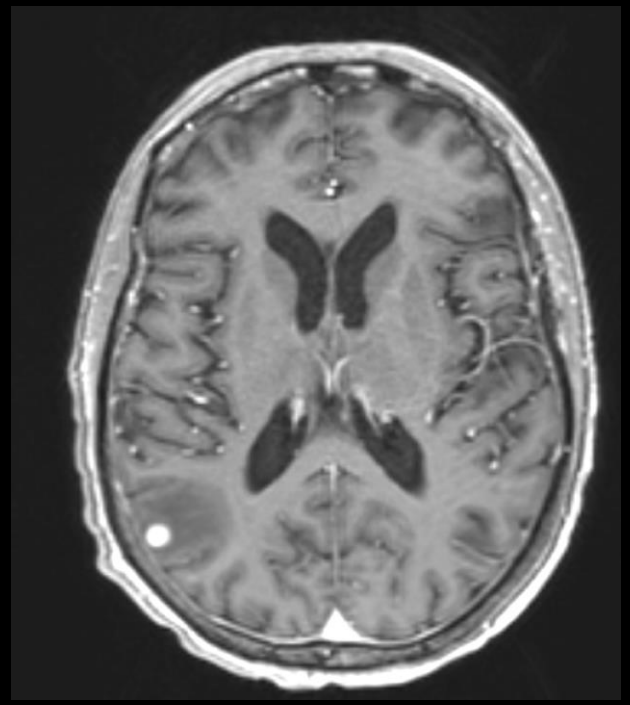


Low dose (10mg/kg) RIF used

Assessing Inflammation & Immune responsive now

Inflammation

- CRP, ESR
- Cytokine panel*



ARUP 13 cytokine panel; $150 USD

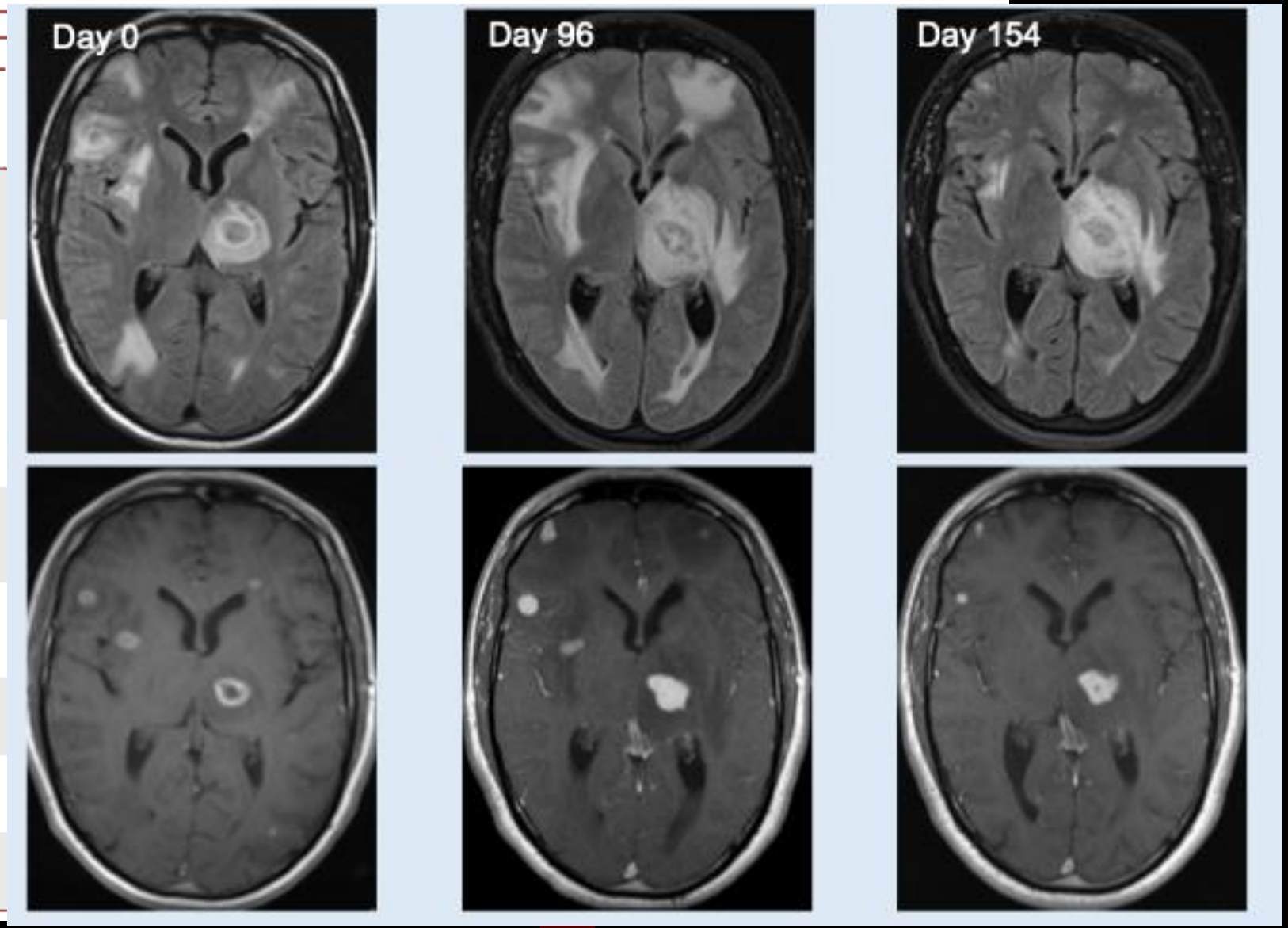
Components	
Interleukin 2 Receptor, Soluble, Serum	→ Dexamethasone
Interleukin 12, Serum	
Interferon gamma, Serum	
Interleukin 4, Serum	
Interleukin 5, Serum	
Interleukin 10, Serum	
Interleukin 13, Serum	
Interleukin 1 beta, Serum	→ Anakinra
Interleukin 6, Serum	→ Tocilizumab
Interleukin 8, Serum	
Tumor Necrosis Factor - alpha, Serum	→ Infliximab
Interleukin 2, Serum	
Interleukin 17, Serum	

Case Report

Interleukin-1 receptor antagonist anakinra as treatment for paradoxical responses in HIV-negative tuberculosis patients: A case series

Table 1. Patient characteristics

Patient #	Gender/age/origin	Tuberculosis manifestation
1	male 39 years old Romania	pulmonary
2	male 66 years old Indonesia	pulmonary
3	male 44 years old Bulgaria	pulmonary and laryngeal/hepatic
4	male 45 years old the Netherlands	meningitis
5	male 28 years old Eritrea	meningitis and pulmonary TB
6	female 20 years old Somalia	disseminated (abscesses)
7	male 41 years old Suriname	pericardial tuberculosis



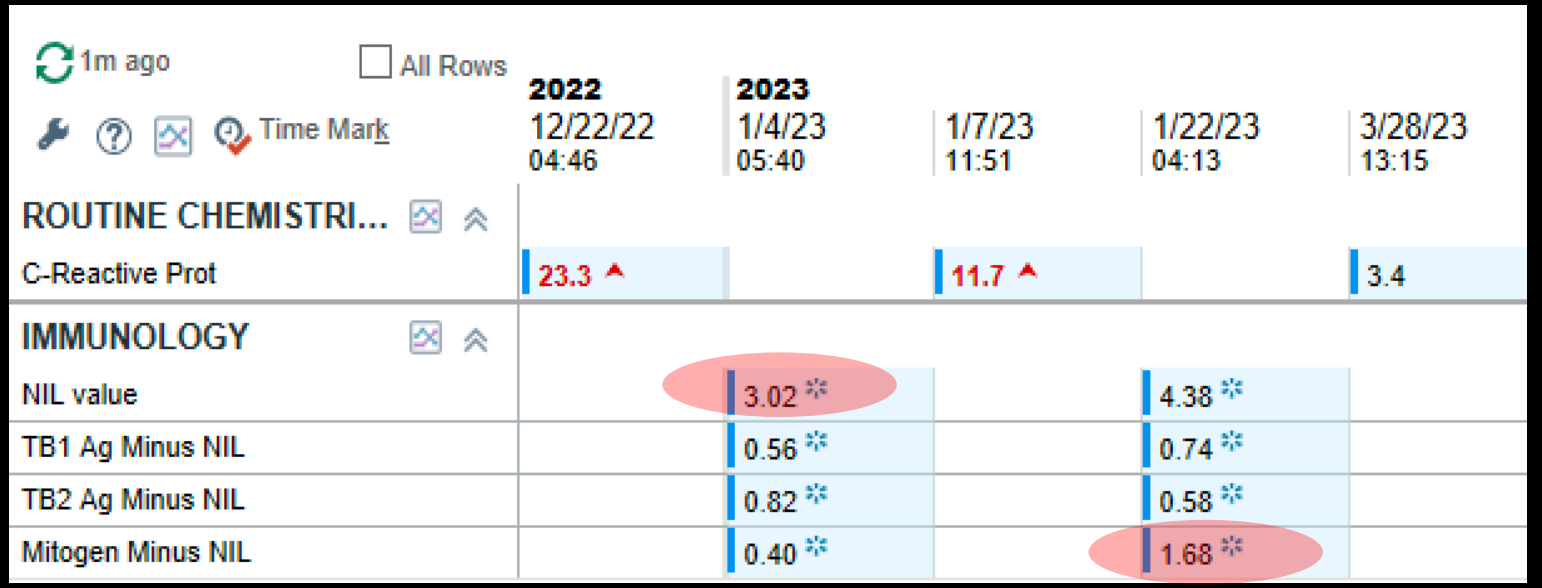
Assessing Inflammation & Immune responsive now

Inflammation

- CRP, ESR
- Cytokine panel

Immune Responsiveness

- QuantiFERON



1m ago | All Rows | Time Mark

	2022 12/22/22 04:46	2023 1/4/23 05:40	1/7/23 11:51	1/22/23 04:13	3/28/23 13:15
ROUTINE CHEMISTRI...					
C-Reactive Prot	23.3 ▲		11.7 ▲		3.4
IMMUNOLOGY					
NIL value		3.02 ✲		4.38 ✲	
TB1 Ag Minus NIL		0.56 ✲		0.74 ✲	
TB2 Ag Minus NIL		0.82 ✲		0.58 ✲	
Mitogen Minus NIL		0.40 ✲		1.68 ✲	

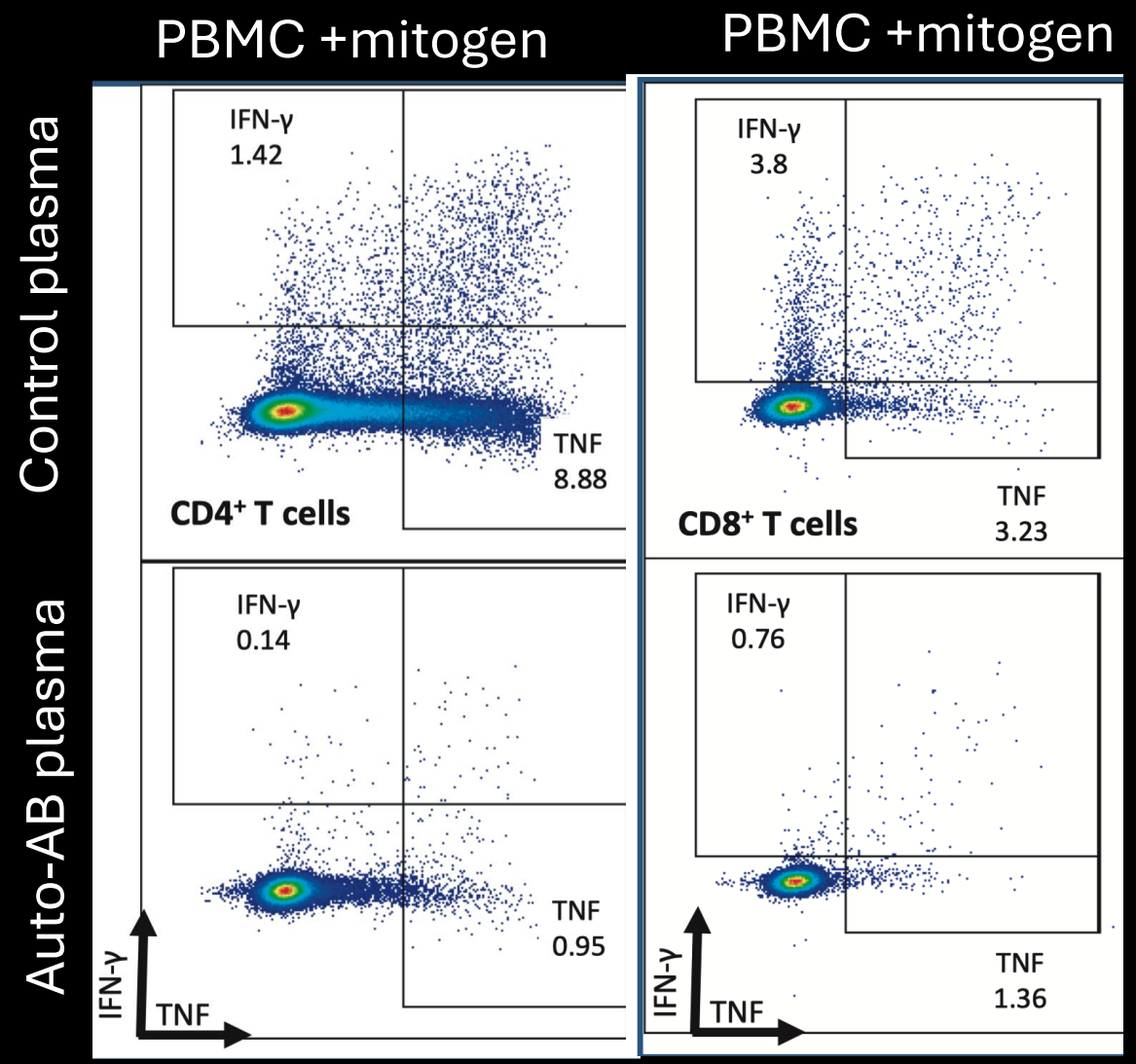
Assessing Inflammation & Immune responsive now

Inflammation

- CRP, ESR
- Cytokine panel

Immune Responsiveness

- QuantiFERON
- Fxnal Flow Cytometry*



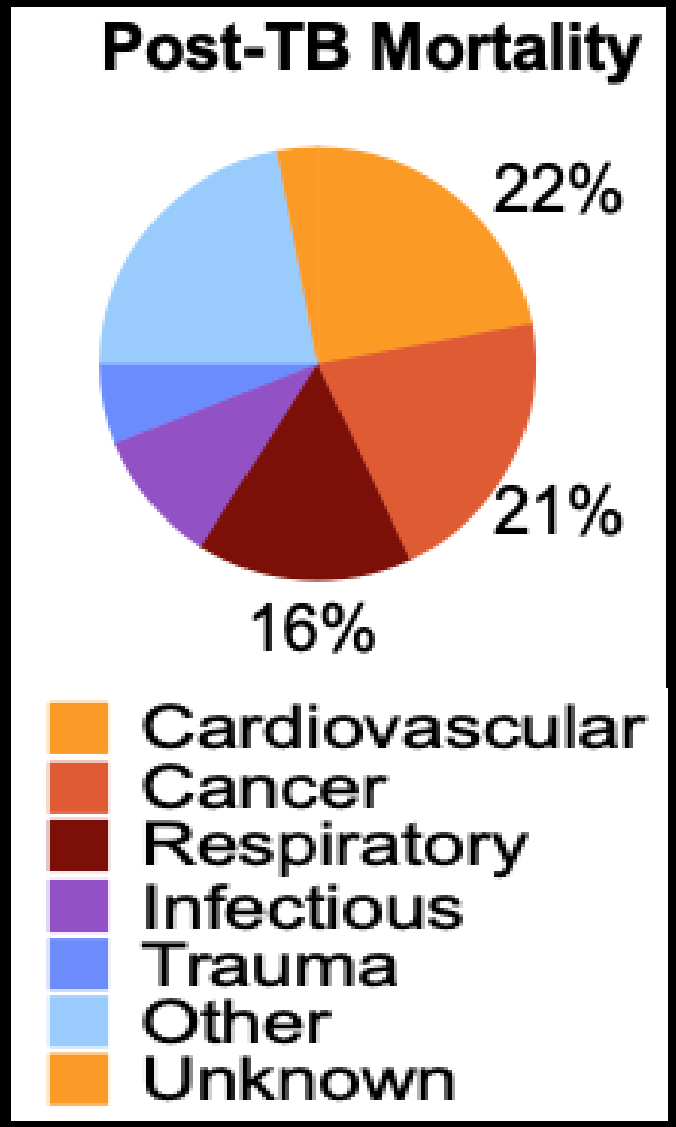
But these are super extreme cases.

How does this apply to “regular” TB cases?

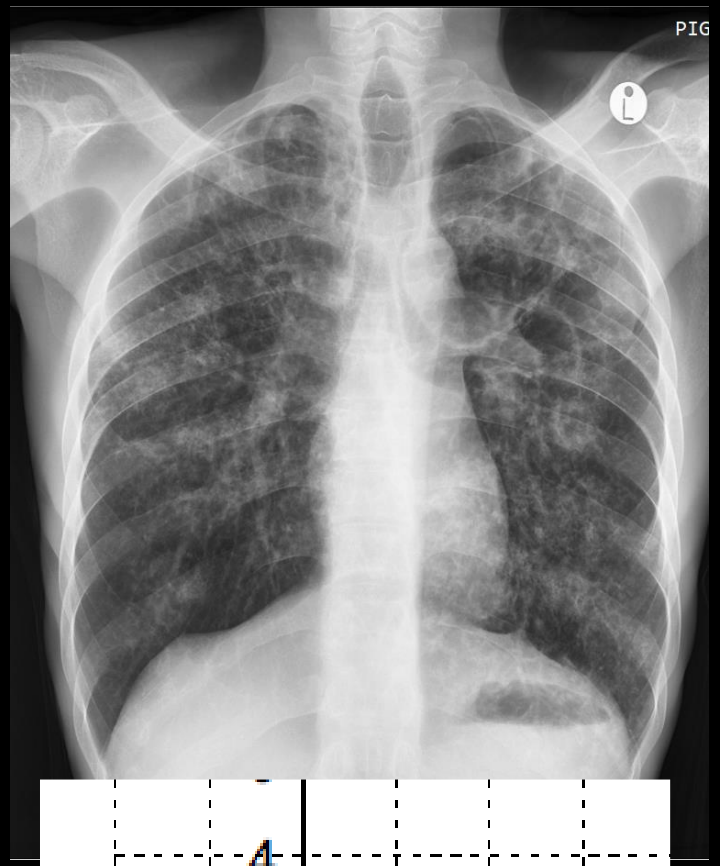
Is TB curable with antibiotics?

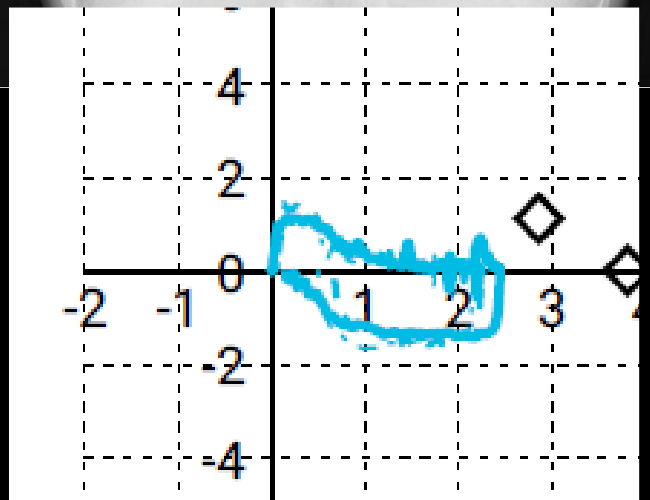
Microbiologic cure ≠ health

3.7-fold Risk Death post-TB

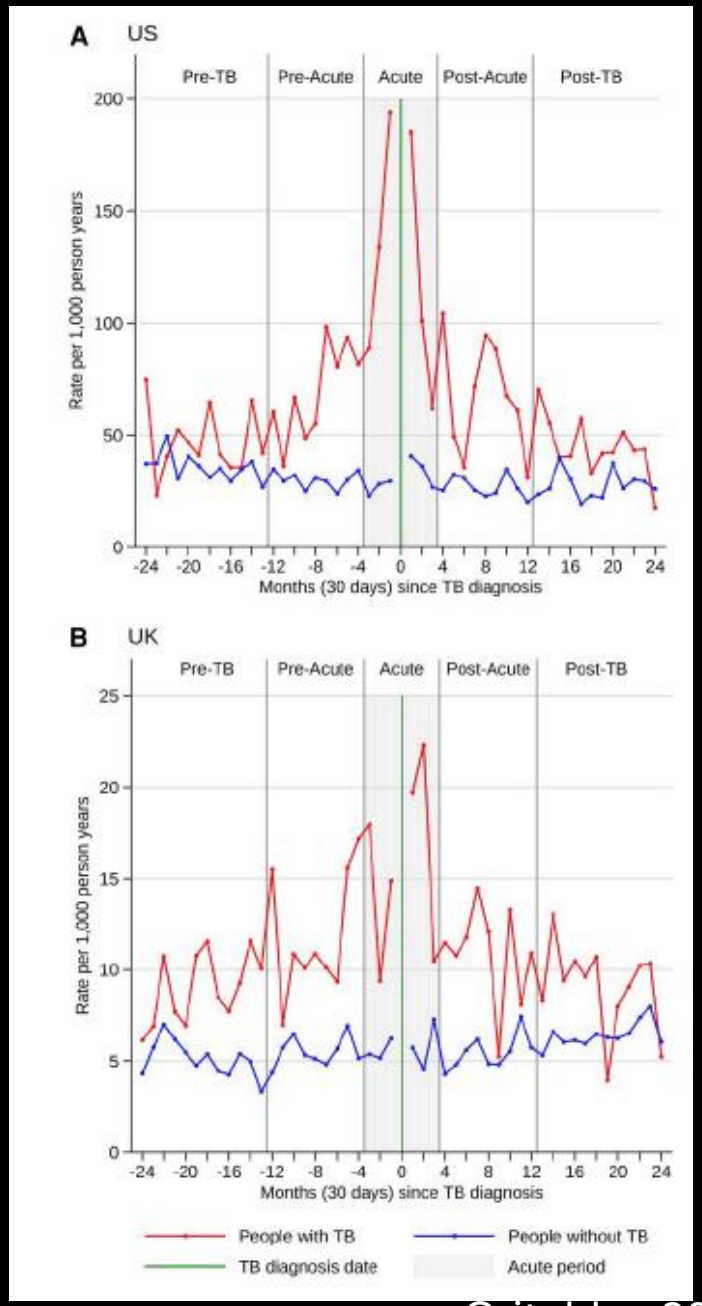


Romanowski 2019





CVD incidence & TB



Critchley 2024

Epidemiology of PTLD

- Estimated >150 million TB survivors with lung damage
- TB survivors have 7 years of life lost post-TB, with half estimated to be related to PTLD
- 15% of TB survivors estimated to have severe PTLD
- 50-75% of all TB survivors estimated to have some persistent lung damage

INT J TUBERC LUNG DIS 25(10):797–813

http://dx.doi.org/10.5588/ijtld.21.0425

CLINICAL STANDARDS FOR LUNG HEALTH

Clinical standards for the assessment, management and rehabilitation of post-TB lung disease

- Assess lung function in all TB patients
- Identify patients who would benefit from pulm rehab
- Adapt pulm rehab to specific settings and evaluate its effectiveness
- Education and counselling to help manage
- Public health standard to record
- Research to improve PTLD

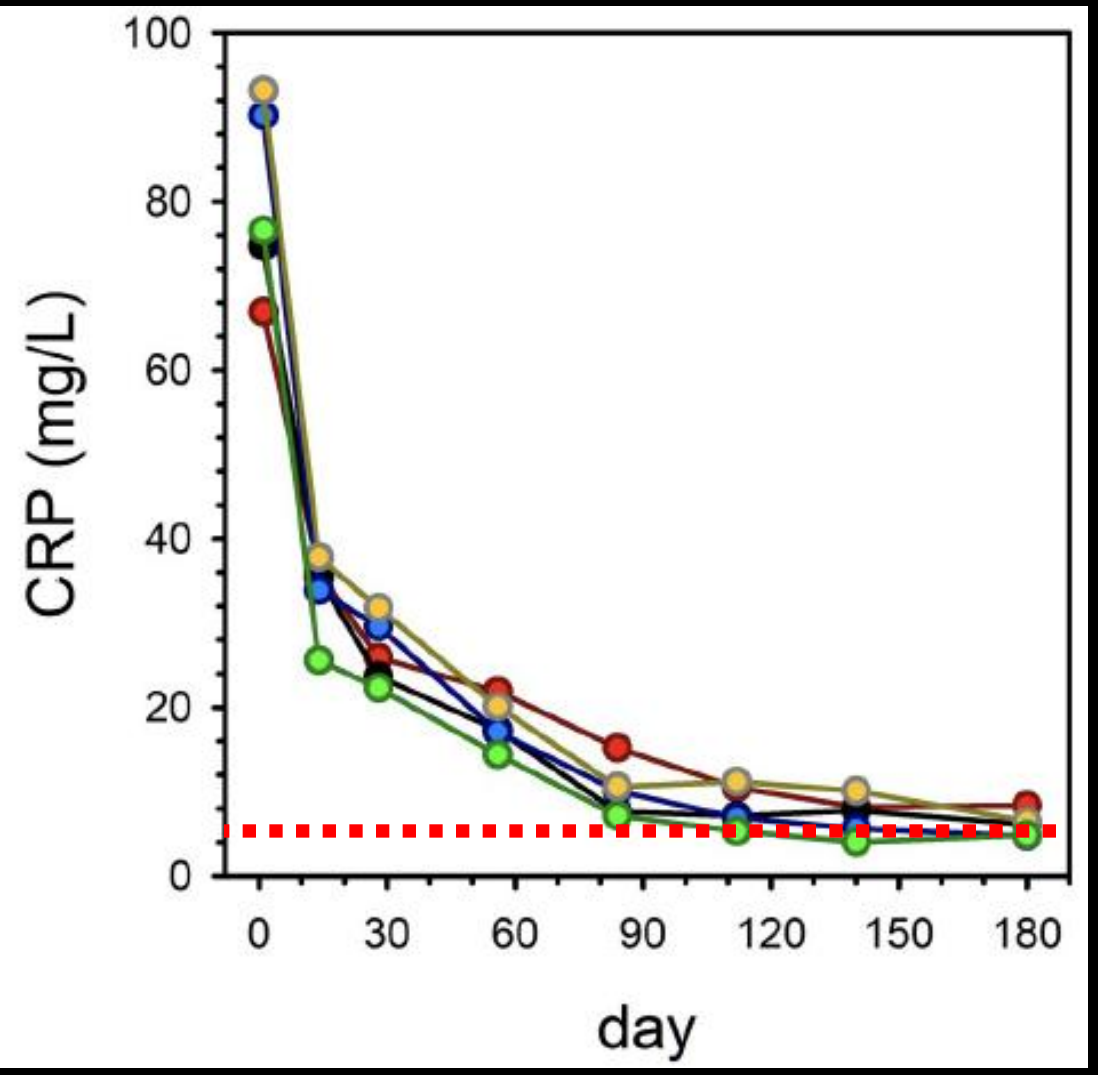
Adjunctive host-directed therapies for pulmonary tuberculosis: a prospective, open-label, phase 2, randomised controlled trial

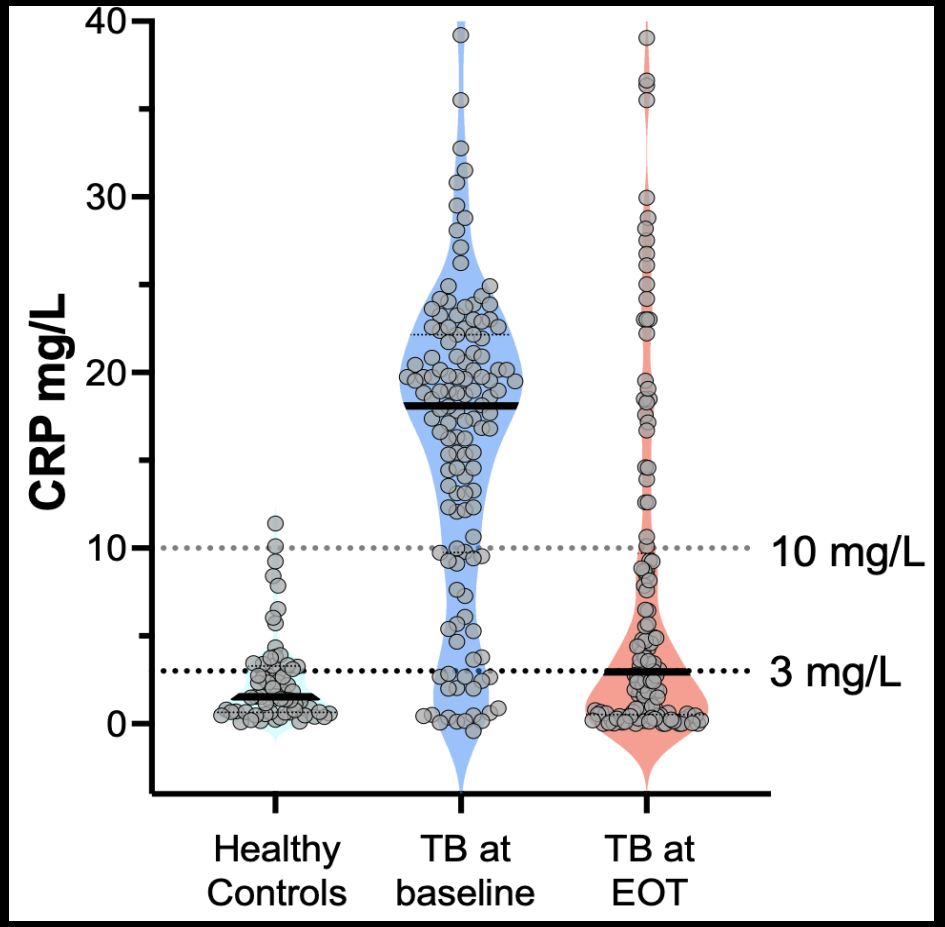
Robert S Wallis, Sibuse Ginindza, Trevor Beattie, Nishanee Arjun, Morongwe Likoti, Vinodh A Edward, Mohammed Rassool, Khatija Ahmed, Katherine Fielding, Bintou A Ahidjo, Mboyo D T Vangu, Gavin Churchyard

Randomized Trial of Metformin With Anti-Tuberculosis Drugs for Early Sputum Conversion in Adults With Pulmonary Tuberculosis

Chandrasekaran Padmapriydarsini,[1] Megha Mamulwar,[2,a] Anant Mohan,[3,a] Prema Shanmugam,[1] N. S. Gomathy,[1] Aarti Mane,[2] Urvashi B. Singh,[3] Nathella Pavankumar,[1] Abhijeet Kadam,[2] Hemanth Kumar,[1] Chandra Suresh,[1] Devaraju Reddy,[1] Poornaganga Devi,[1] P. M. Ramesh,[4] Lakshmanan Sekar,[1] Shaheed Jawahar,[5] R. K. Shandil,[5] Manjula Singh,[6] Jaykumar Menon,[5] Randeep Guleria[3]; and the METRIF Team

~half TB survivors remain hyper-inflammatory

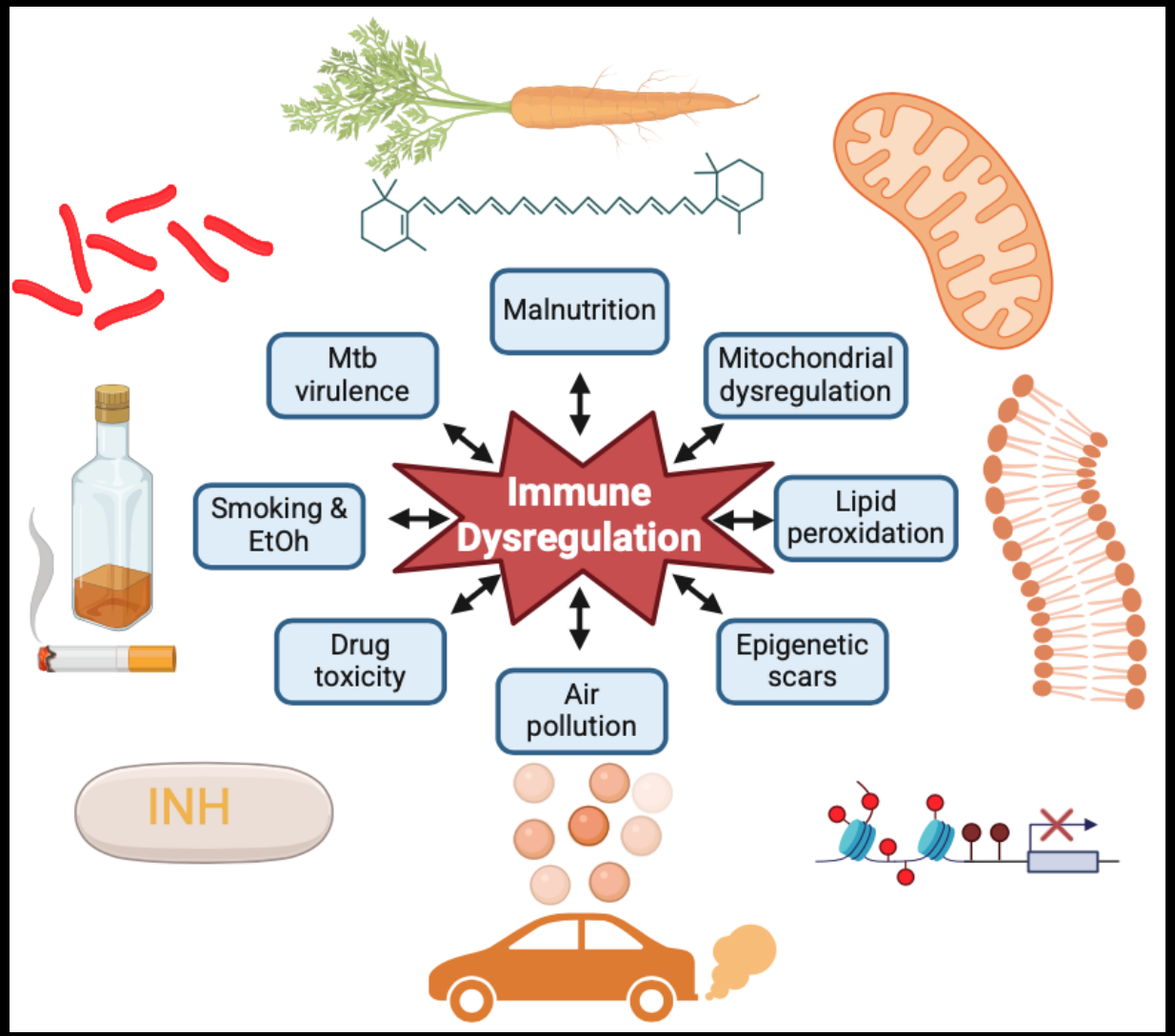


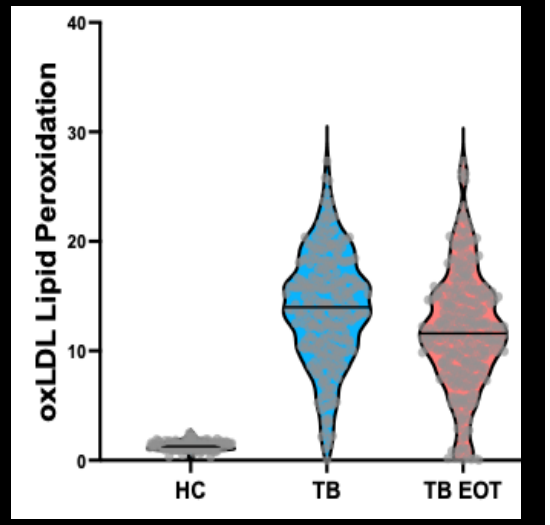


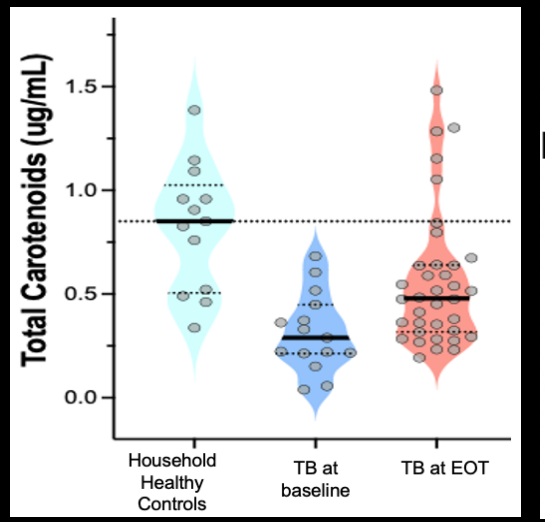
Unpublished Eswatini

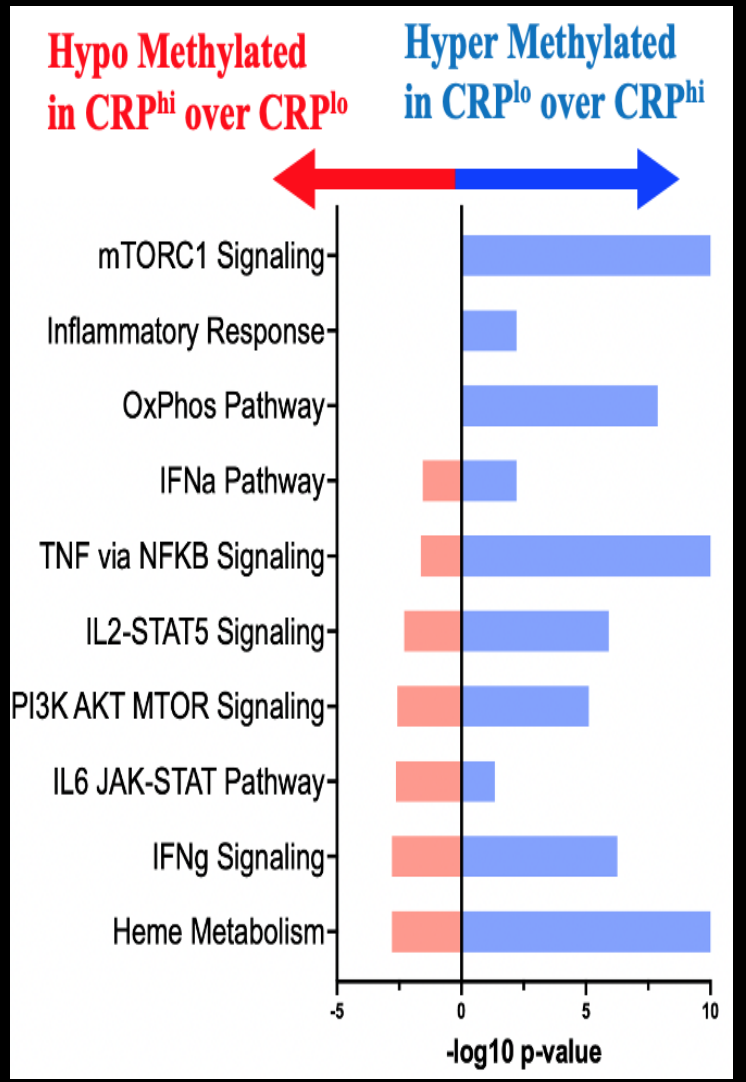
CRP > 3mg/L Increased Risk CVD

Why does inflammation persist despite successful Abxs?



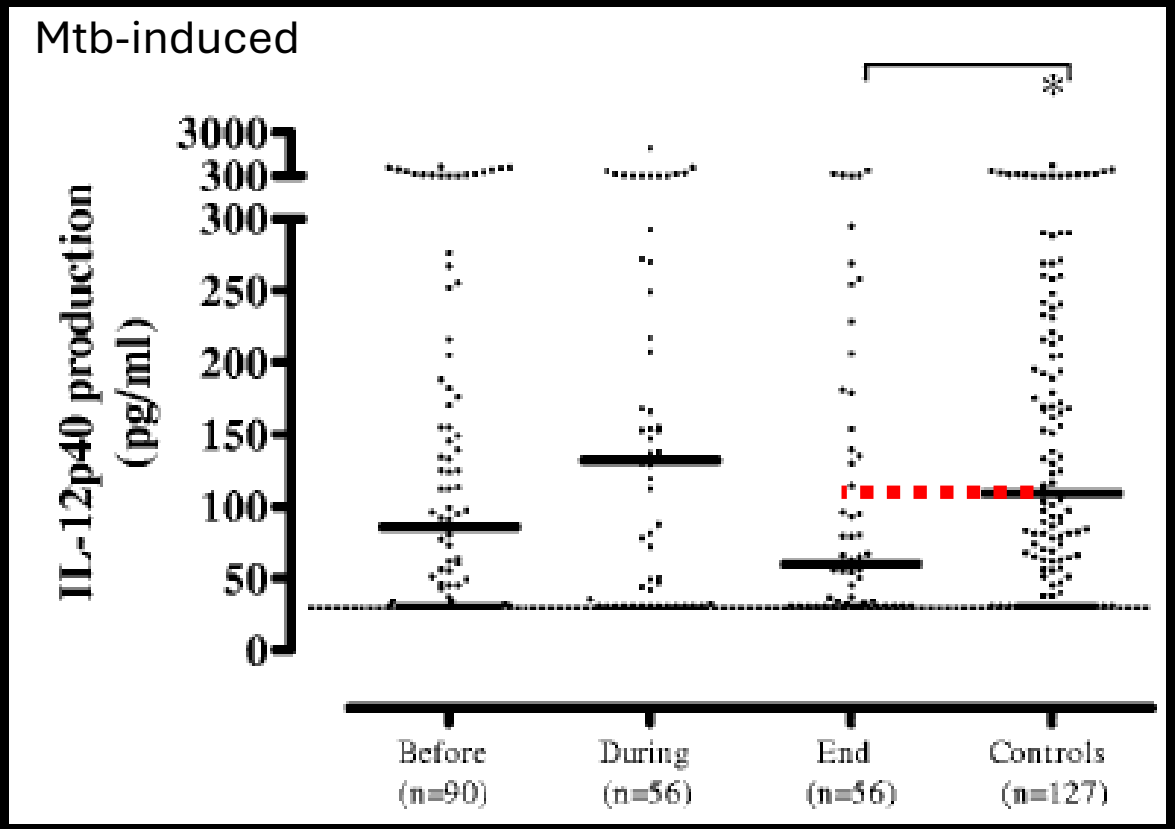


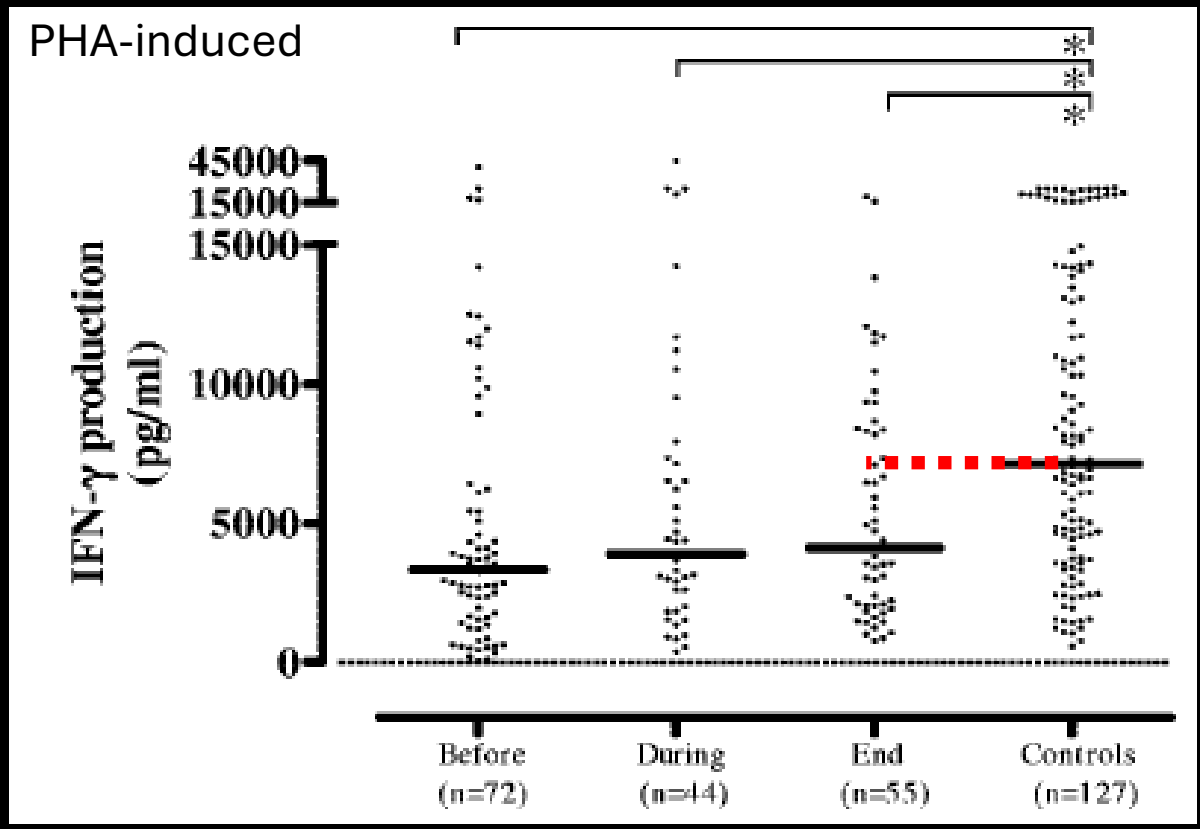




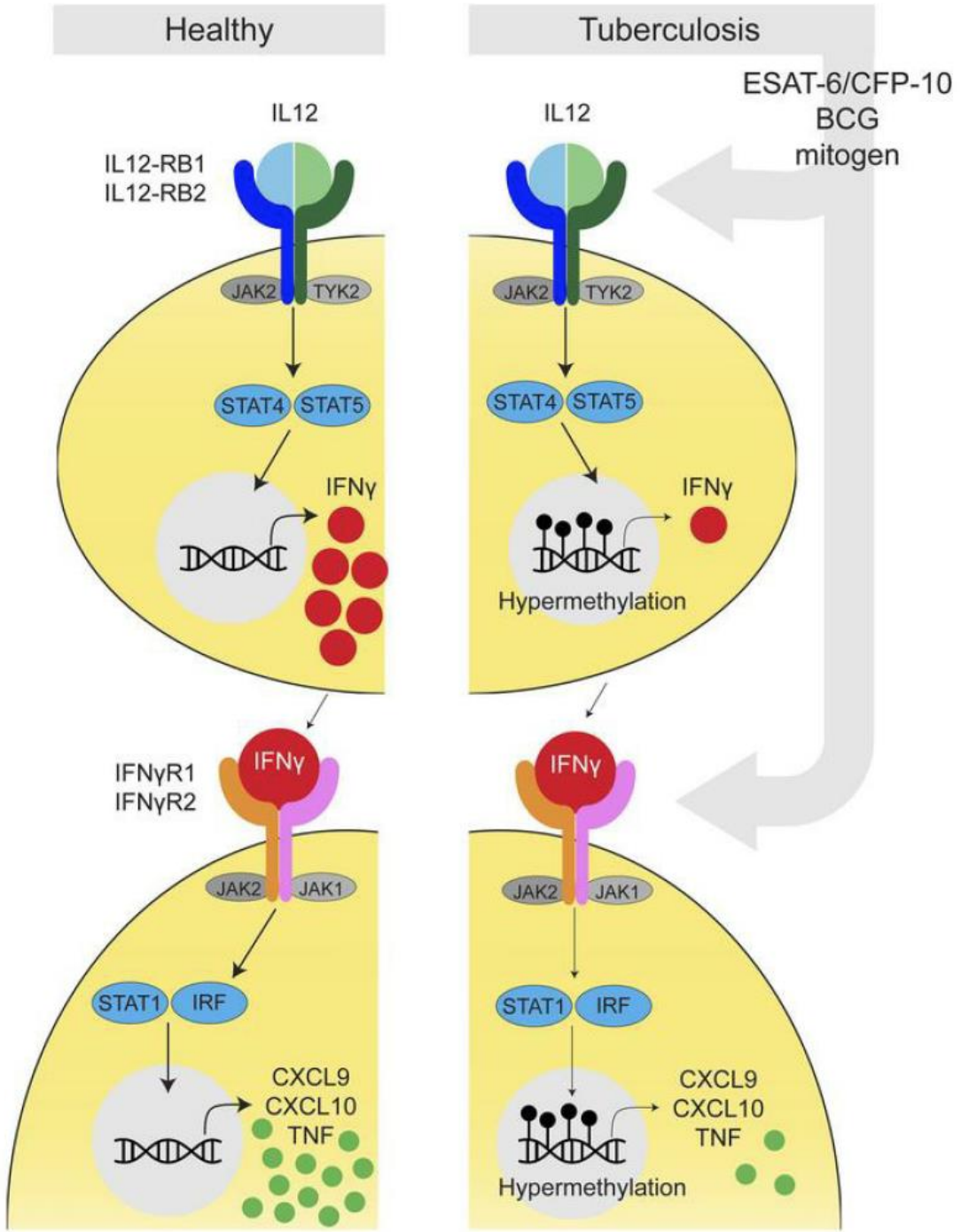
Dynamic Changes in Pro- and Anti-Inflammatory Cytokine Profiles and Gamma Interferon Receptor Signaling Integrity Correlate with Tuberculosis Disease Activity and Response to Curative Treatment[▽]

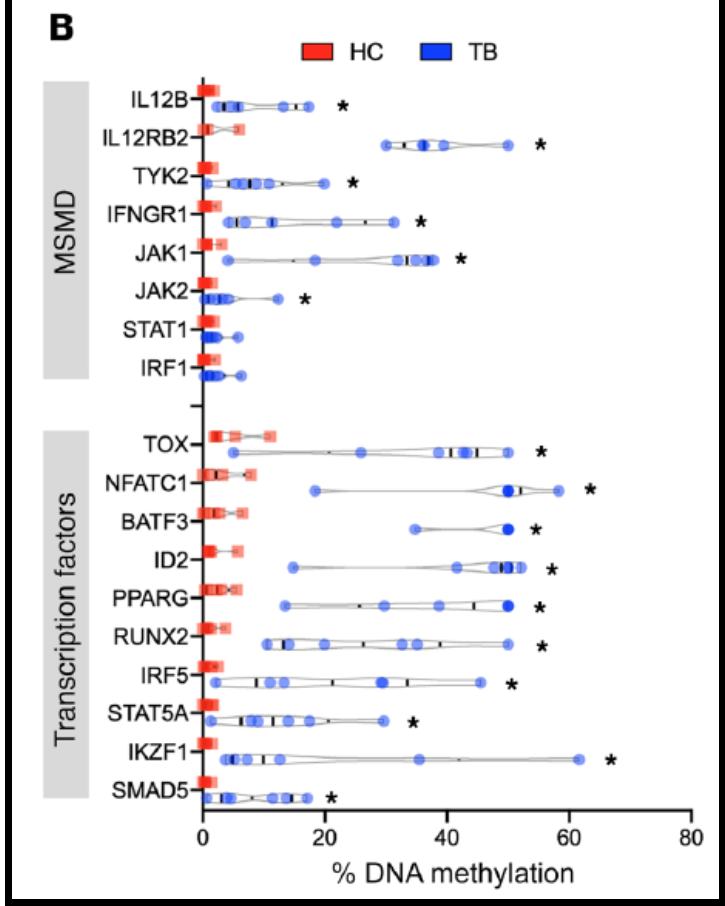
Edhyana Sahiratmadja,[1,2] Bachti Alisjahbana,[3] Tjitske de Boer,[1] Iskandar Adnan,[2] Anugrah Maya,[4] Halim Danusantoso,[4] Ronald H. H. Nelwan,[5] Sangkot Marzuki,[2] Jos W. M. van der Meer,[6] Reinout van Crevel,[6] Esther van de Vosse,[7] and Tom H. M. Ottenhoff[1]*



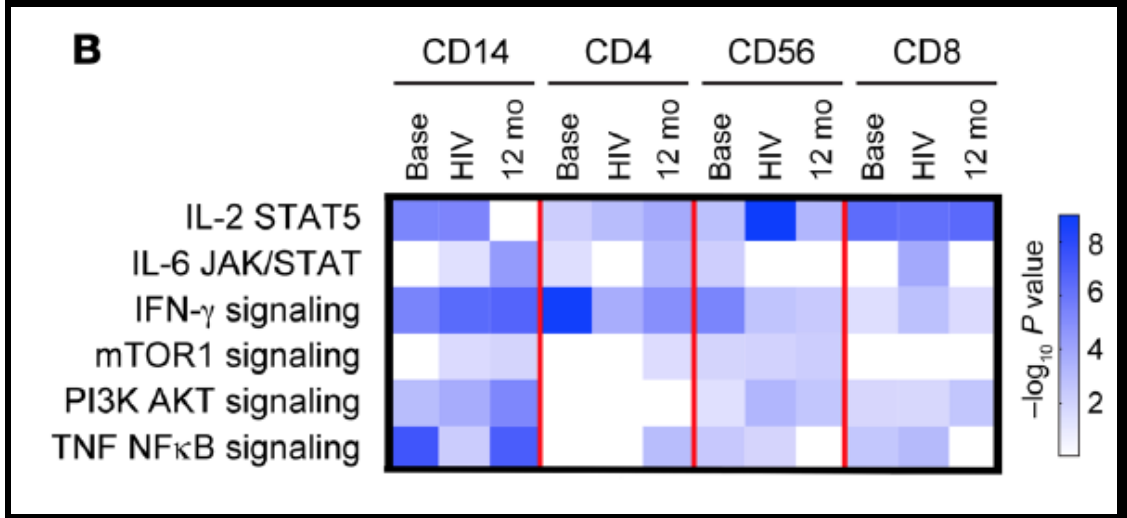


~half TB survivors remain hypo-responsive





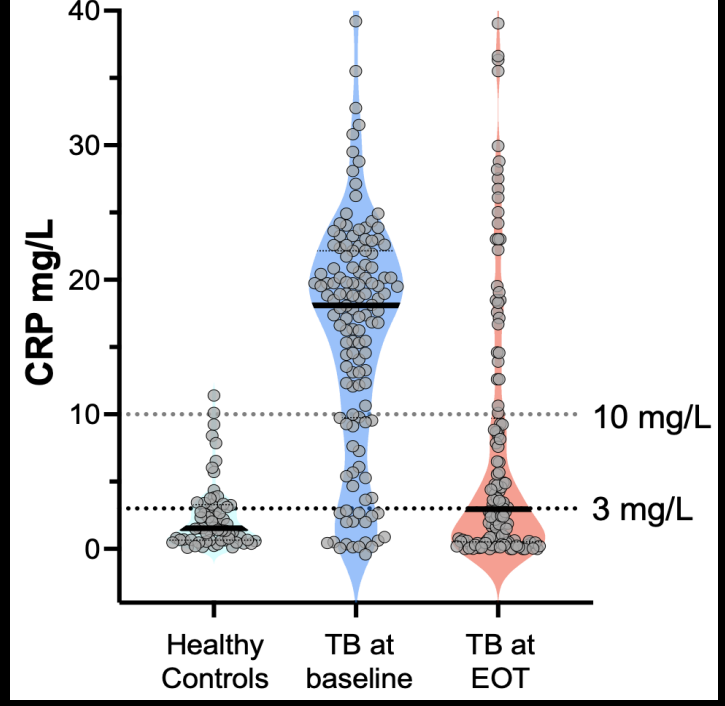
DNAm changes persist despite successful treatment

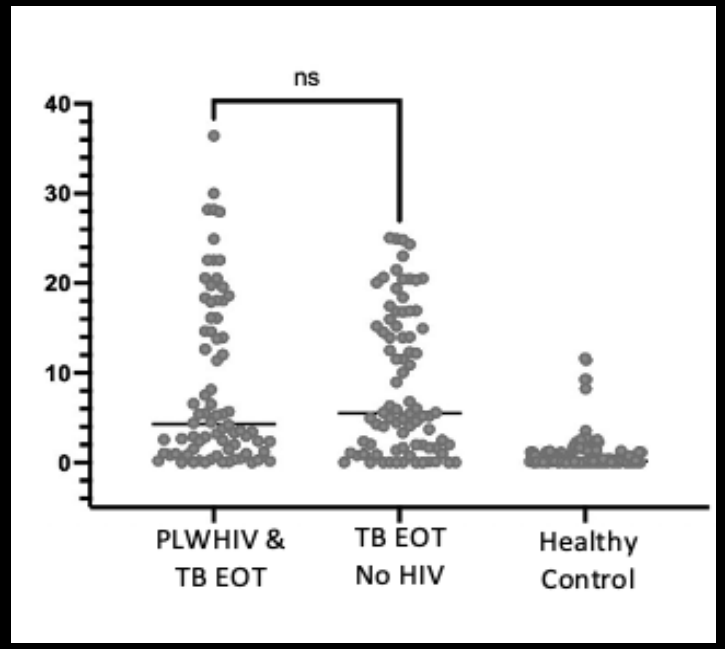


JCI 2020

Summary

- ATT is too long (over-dosing):
  - new regimens coming!
- Use TDM to prevent under-dosing
- Microbial cure ≠ health
- PFTs are SOC
- CVD, Cancer, Recurrent infections
- Antibiotics don’t resolve inflammation
- Antibiotics don’t resolve anergy
- Endotype specific HDT

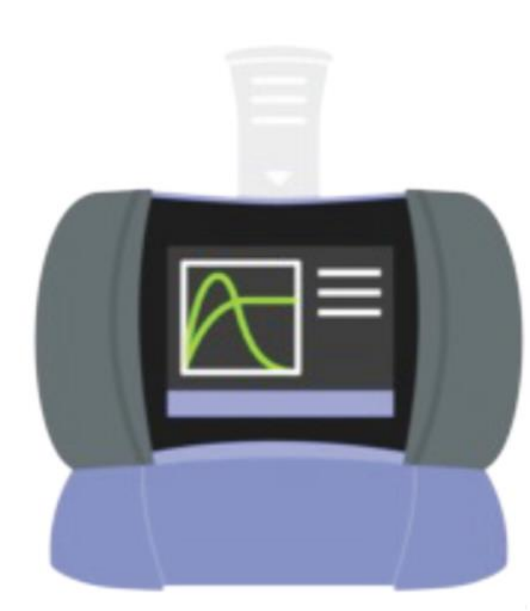

CRP mg/L
40
30
20
10
0
10 mg/L
3 mg/L
Healthy Controls
TB at baseline
TB at EOT

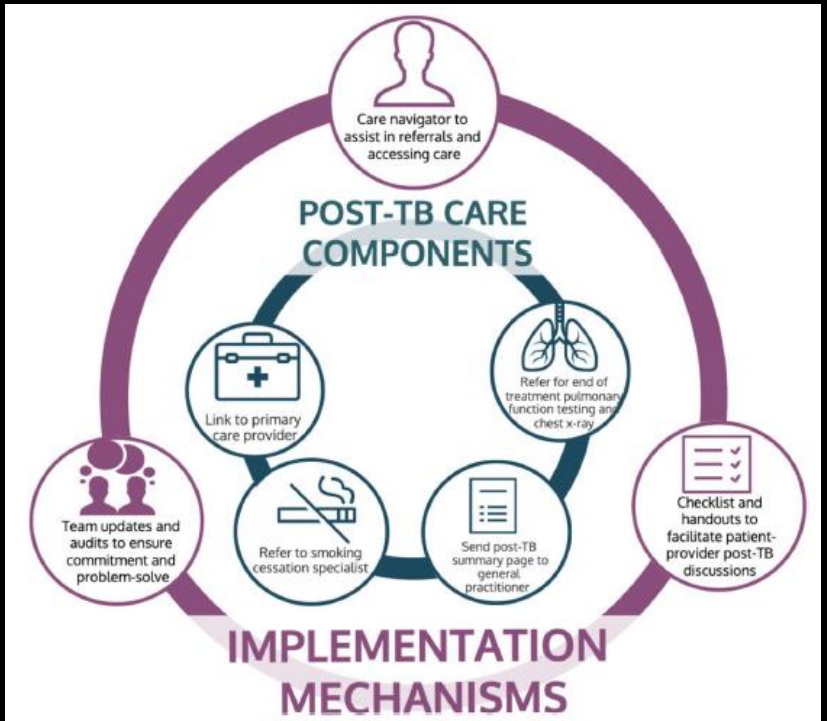

ns
40
30
20
10
0
PLWHIV & TB EOT
TB EOT No HIV
Healthy Control

93% VL < 100 EOT

How does Texas help close the gap in treatment monitoring?

- Continue follow up for 10 years
- Universal roll-out of lung function evaluation as SOC
- TX-specific post-TB care package
- Who benefits from rehab or HDT?





RESEARCH Open Access

Using a theory-informed approach to guide the initial development of a post-tuberculosis care package in British Columbia, Canada

Kamila Romanowski[1,2*], Victoria Jane Cook[1,2], Mark Gilbert[3,4] and James Cameron Johnston[1,2]

Pulmonary Rehab

Benefits for COPD or ILD

- Decreased breathlessness
- Increased daily function & Quality of life
- Decreased re-admission/ health care utilization

Benefits for Tuberculosis

- Improved 6MWT
- Less chest pain and cough
- Improved QoL

PMID: 30872556

PMID: 29270007

PMID: 38589115

Rifampicin

- Development guided by high cost and concern for toxicity
- Dose response studies were not done
- Minimum effective dose was approved 10 mg/kg

- Trials in 1970s using rifampicin and PZA allowed treatment to be shortened from 18 to 6 months.

- Multiple trials have explored higher doses of rifampin in treatment of pulmonary TB and meningitis.
- Cmax – 8-24 mcg/ml

Efficacy and Safety of High-Dose Rifampin in Pulmonary Tuberculosis

A Randomized Controlled Trial

Gustavo E. Velásquez[1,2], Meredith B. Brooks[2], Julia M. Coit[2], Henry Pertinez[3,4], Dante Vargas Vásquez[5], Epifanio Sánchez Garavito[6], Roger I. Calderón[7], Judith Jiménez[7], Karen Tintaya[7], Charles A. Peloquin[8], Elna Osso[2], Dylan B. Tierney[9], Kwonjune J. Seung[9,10], Leonid Lecca[2,7], Geraint R. Davies[3,4]*, and Carole D. Mitnick[2,9,10]*

- Rifampin at 10, 15, 20 mg/kg with standard dose INH, PZA, EMB during intensive phase
- Primary outcome: change in elimination rate of M TB $\log_{10}$ CFU
- Primary safety endpoint: grade 2 or higher rifampin-related AE

- Per protocol analysis: more rapid sputum sterilization with similar toxicity using higher dose rifampin
- Serum drug concentration - C_{max}
  - 81% achieved Cmax > 8 in 20 mg/kg
  - 33% achieved Cmax > 8 in 10 mg/kg

AJRCCM 2018

Systematic review

Standard versus high dose of rifampicin in the treatment of pulmonary tuberculosis: a systematic review and meta-analysis

Lorenzo Onorato [1], Valeria Gentile [1], Antonio Russo [1], Giovanni Di Caprio [1], Loredana Alessio [1], Paolo Chiodini [2], Nicola Coppola [1,*]

8 RCTs –

- compared rifampin 10 mg/kg/d to higher doses up to 35 mg/kg/d during first 8 weeks of treatment
- 1897 participants
- Primary outcome – culture conversion at 8 weeks

Clin Microbiol Infect 2021

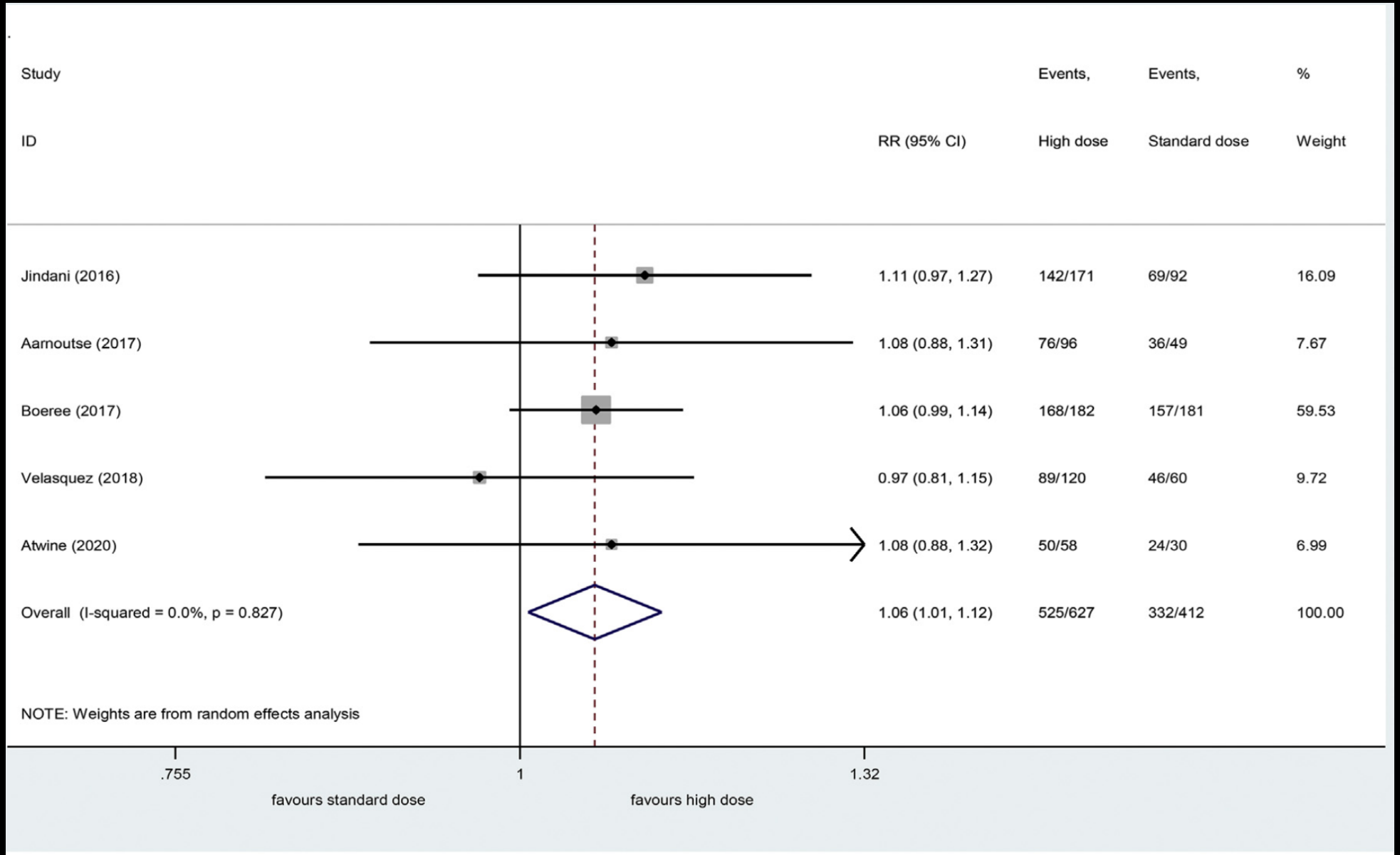


Fig. 2. Forest plot of RRs of sputum culture conversion at 8 weeks in patients receiving a high or standard dose of rifampicin.

Onorato, L et al. Clin Microbiol Infect

- No difference in treatment failure rate (RR 0.84; 95% CI 0.59 – 1.21)
- No difference in mortality rate (1% vs 1.6%: high vs standard dose)
  - RR 0.71; (95% CI 0.32 -1.56)
- Grade 3-4 liver toxicity rates were not different

- Higher dose rifampin alone is unlikely to shorten TB treatment
- Perhaps - combined with other medications and intensive dosing frequency

Onorato, L et al. Clin Microbiol Infect 2021