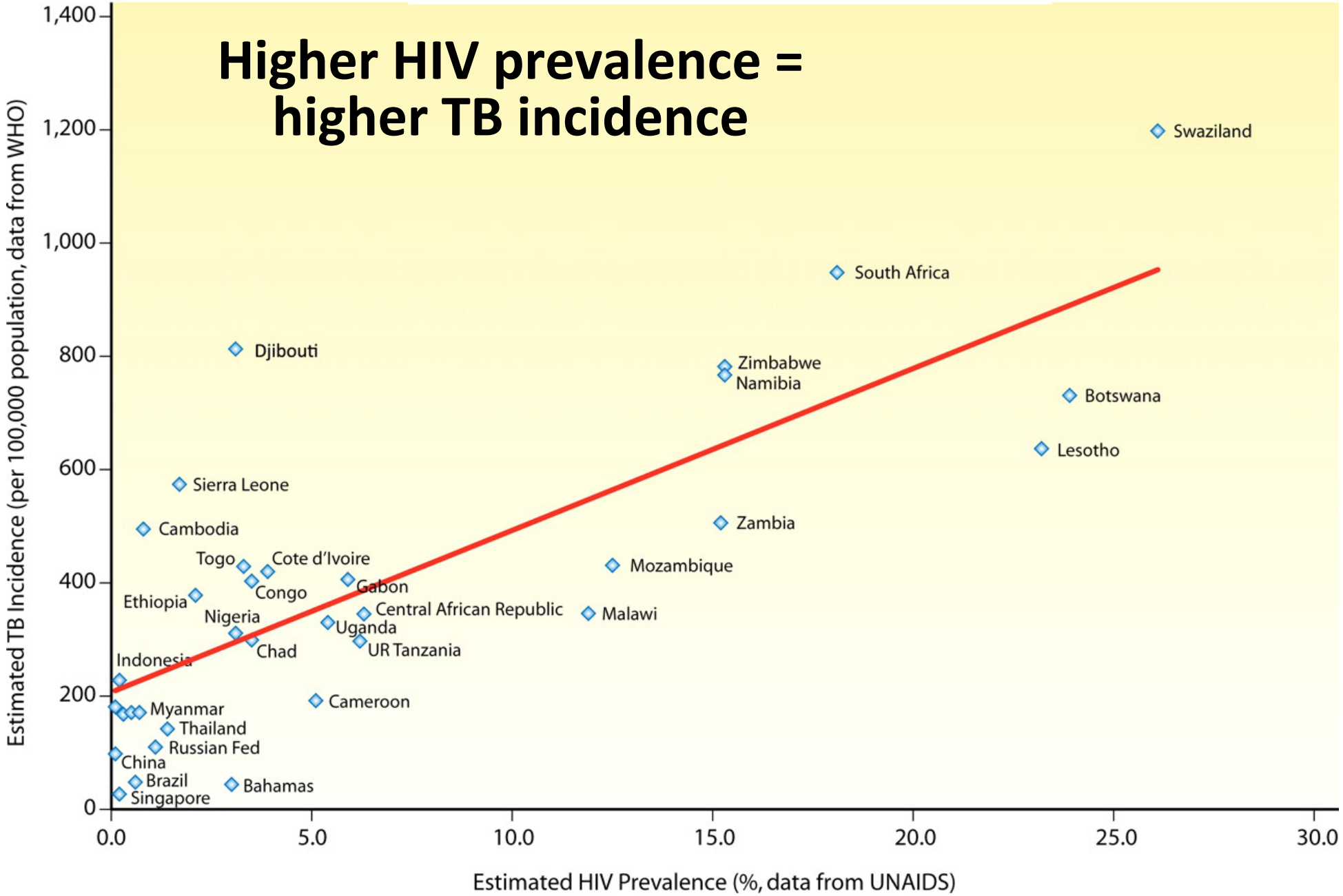
Tuberculosis in people living with HIV and/or diabetes

Scott Heysell MD, MPH
Professor, Medicine and Infectious Diseases
Director, Center of Global Health Equity
Co-director, UVA Health Bronchiectasis and NTM Care Center Network
VDH medical consultant, tuberculosis
University of Virginia

When a virus and a bacteria can work so well together, why can’t we?

Practical guide HIV and TB Integration: South Africa Ministry of Health

Higher HIV prevalence = higher TB incidence



Kwan, *Clin Microbiol Rev* 2011

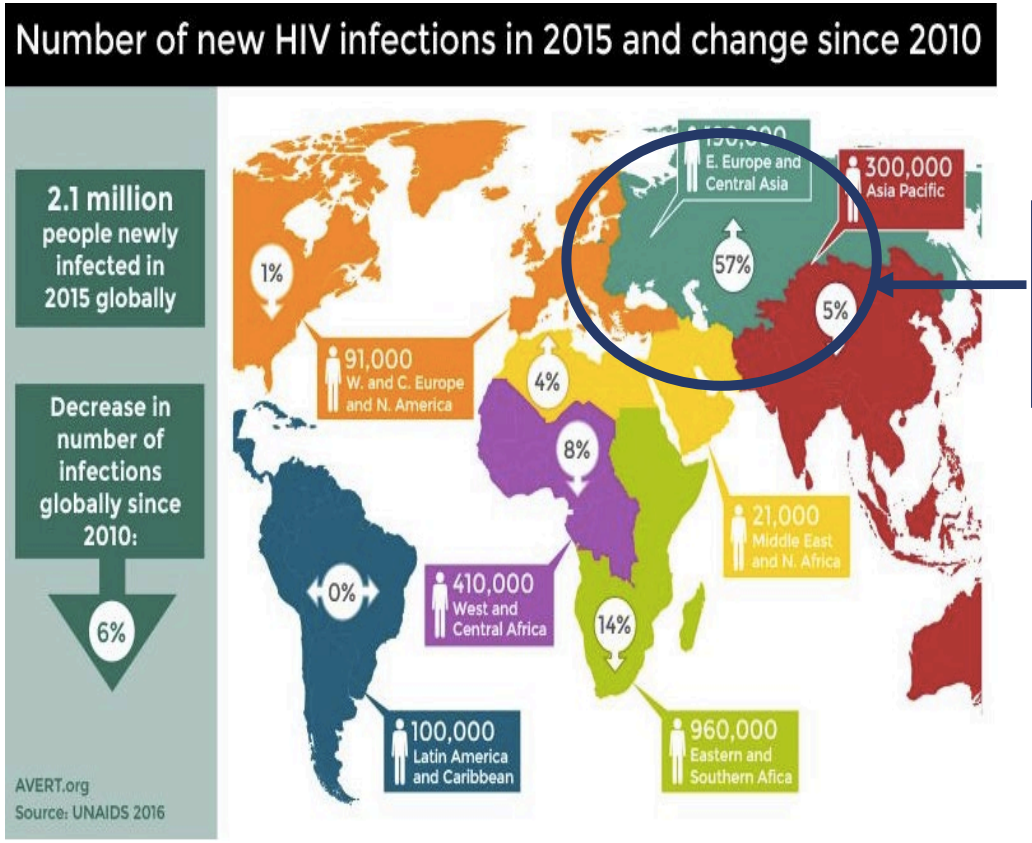
What region of the world has the greatest percent increase in new HIV infections over the last decade?

a. Latin America

b. Eastern and Southern Africa

c. Caribbean

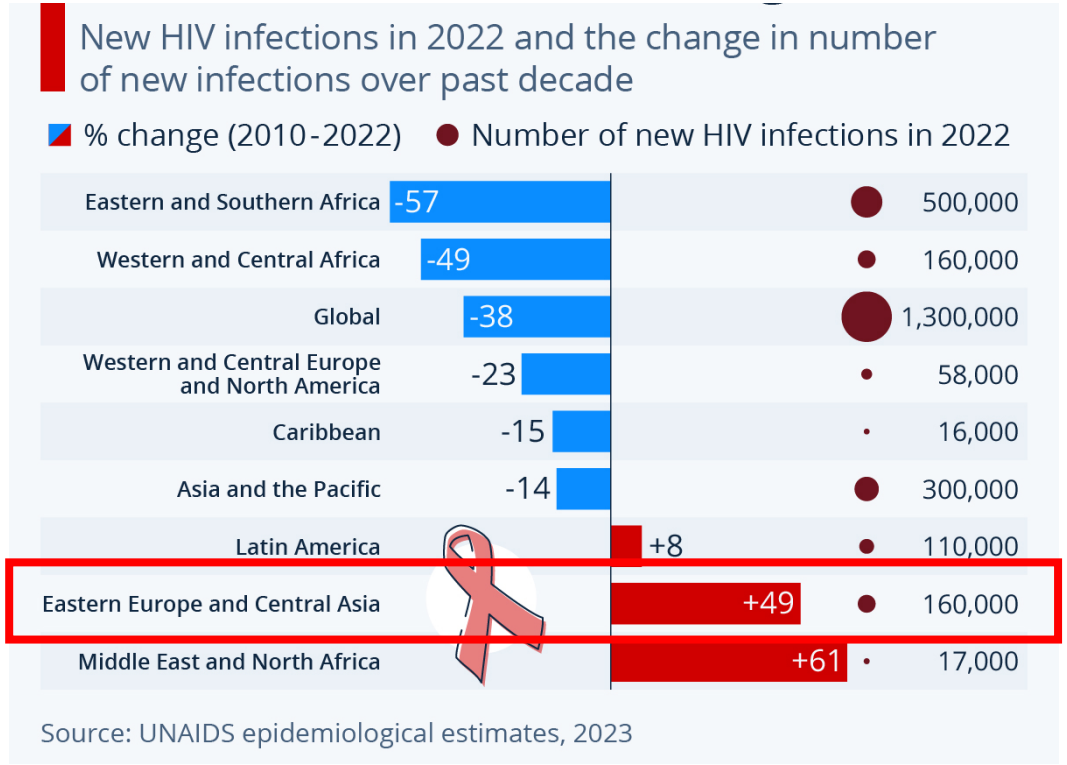
d. Eastern Europe and Central Asia



~80% of new HIV diagnoses in Russian Federation

TB is the leading killer:

1. by a single bacterial pathogen
2. by a curable infectious disease
3. of HIV patients and
4. of all adults in South Africa

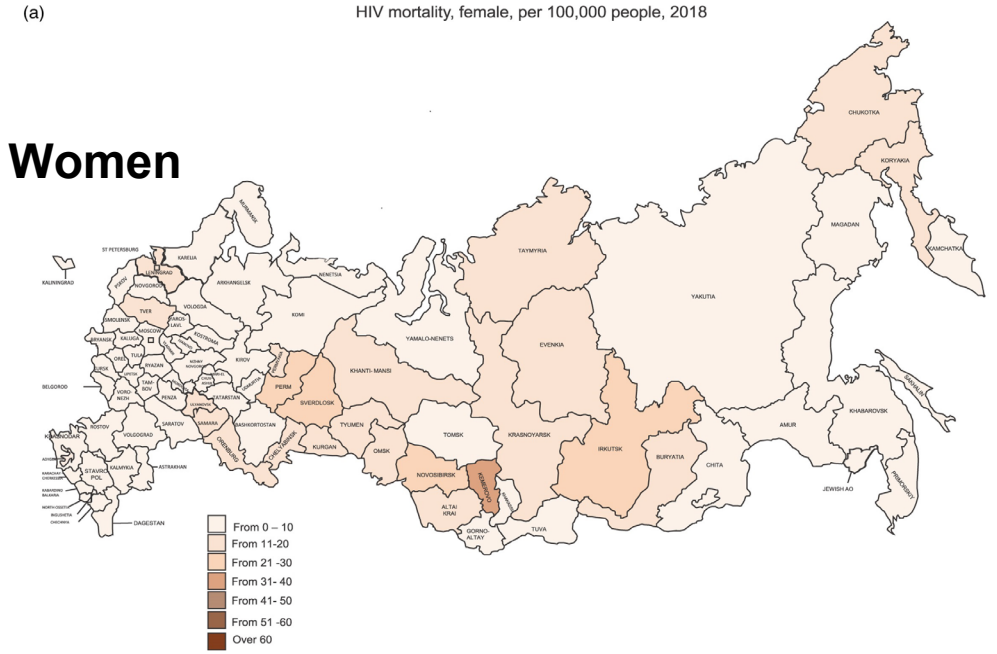


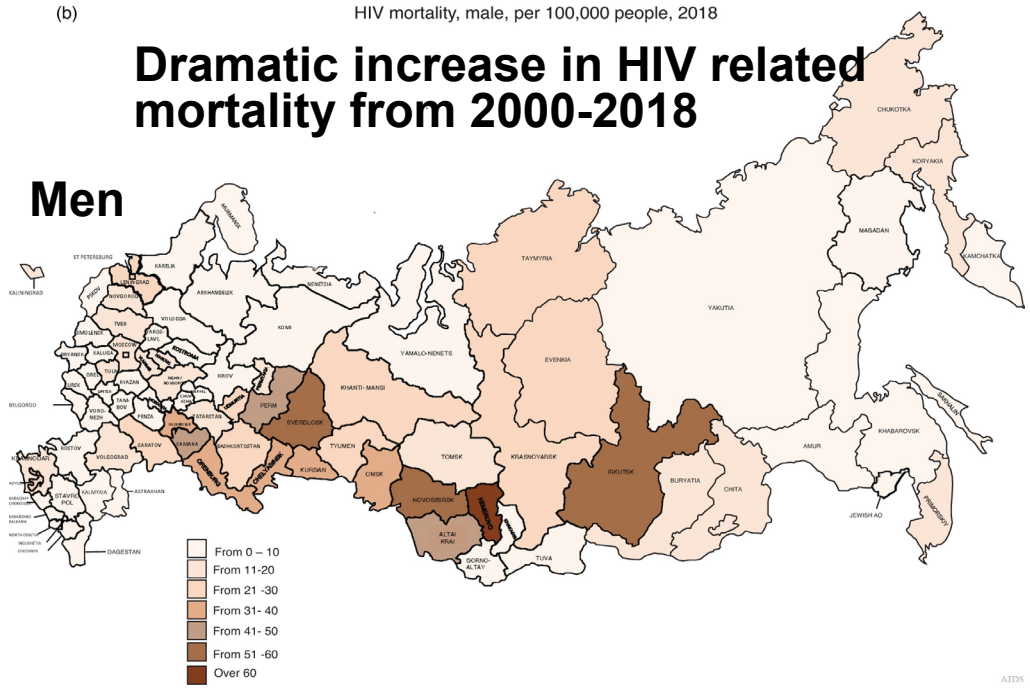
RR-TB: resistant to rifampin

MDR-TB: resistant to isoniazid and rifampin

XDR-TB: MDR-TB plus resistance to a fluoroquinolone and another Group A agent (bedaquiline or linezolid)

HIV related mortality a major health issue in Russian Federation





Dramatic increase in HIV related mortality from 2000-2018

Table 1 - HIV-associated mortality among male and female individuals in the Russian Federation.

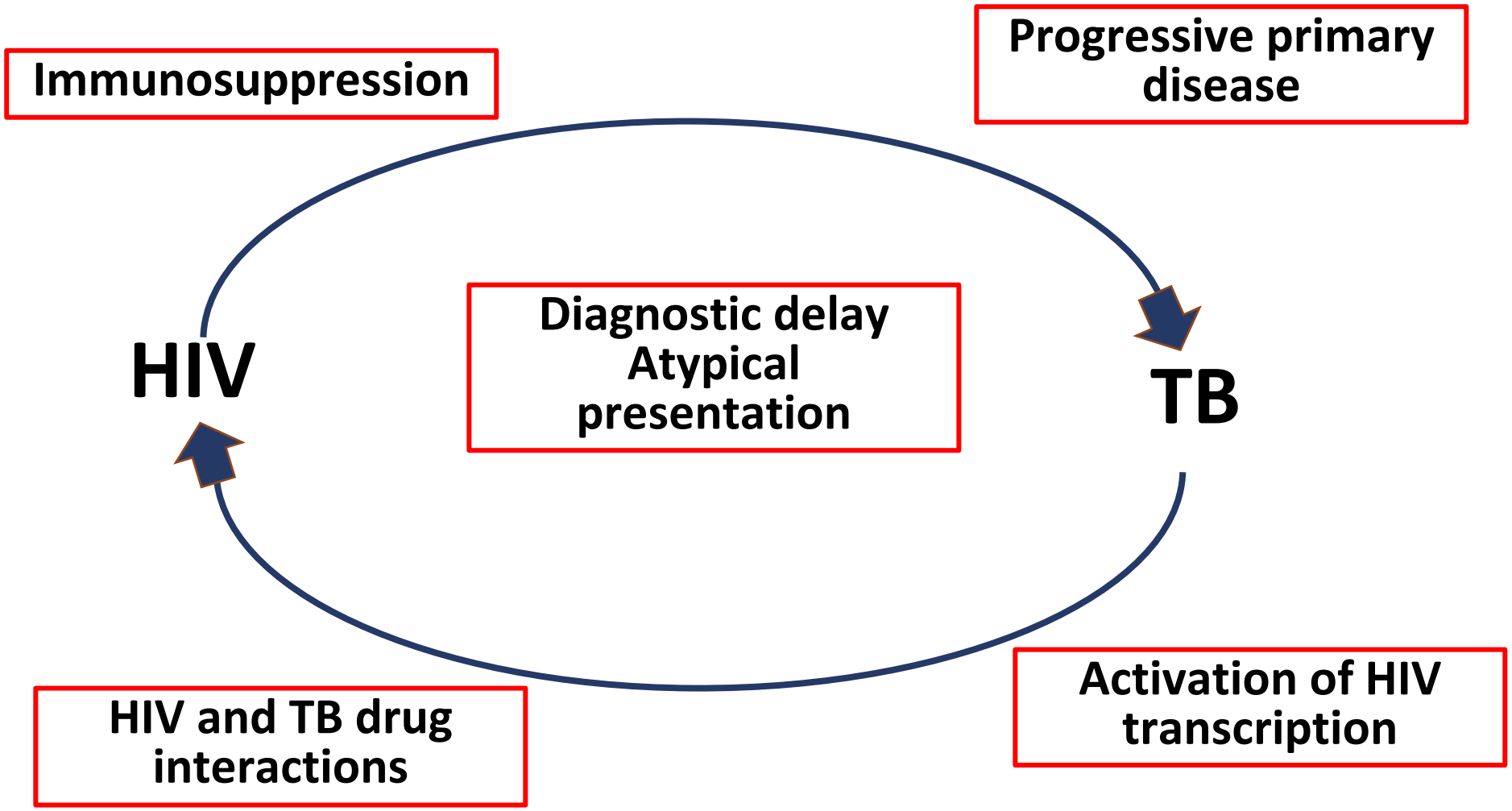
	2000	2018
HIV/AIDS mortality per 100 000 (males)	0.2	18.5
HIV/AIDS mortality per 100 000 (females)	0.0	8.7

Sources: Russian Fertility and Mortality database (RusFMD) and the authors' calculations.

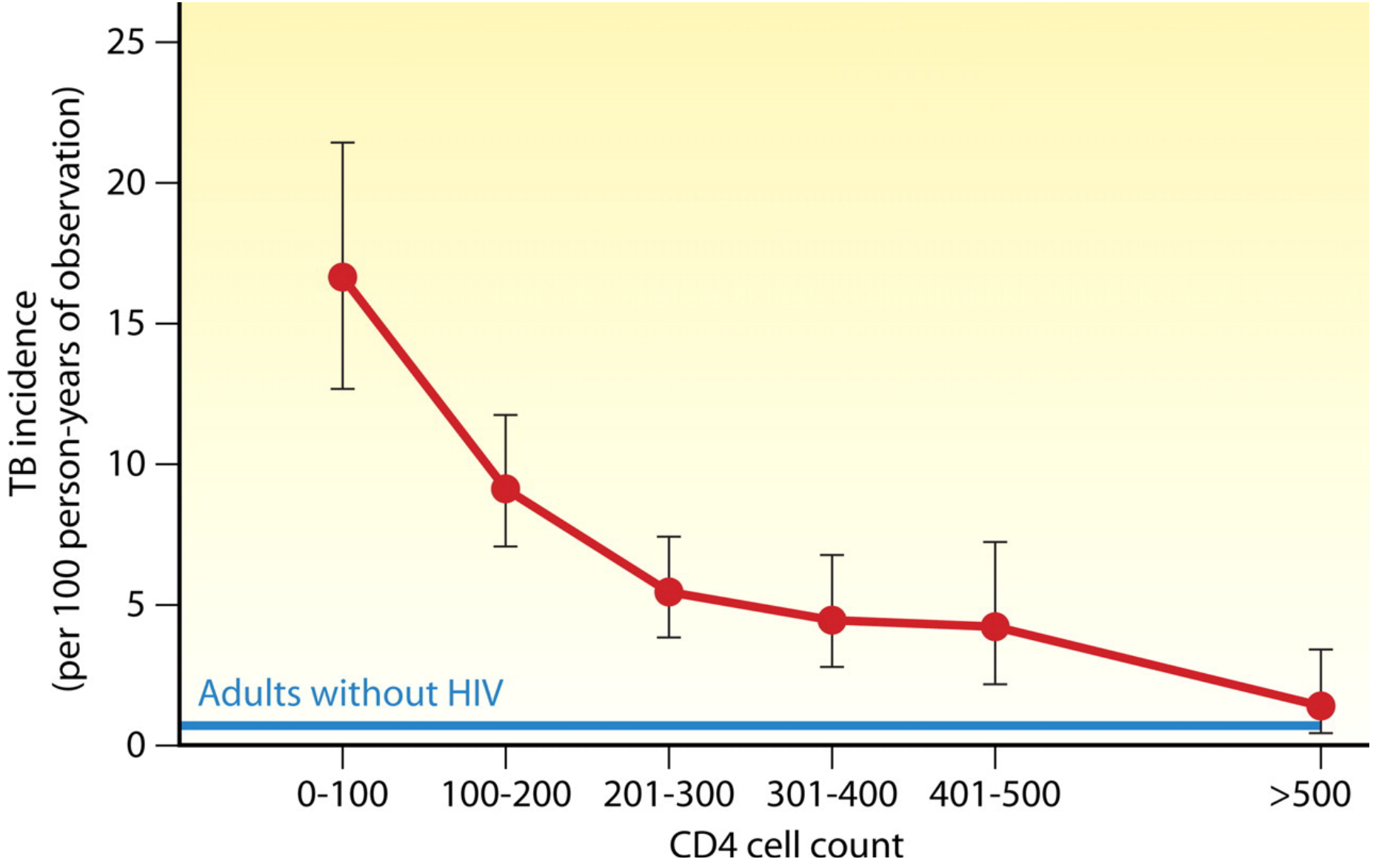
AIDS

Nikoloski et al, *AIDS* 2023

Higher TB related mortality among people living with HIV compared to those without HIV



Treatment of HIV prevents TB reactivation



Lawn et al AIDS 2009

Antiretroviral therapy (ART) is critical to TB treatment success

Early initiation of antiretroviral therapy in people living with HIV (PLWH) and drug-susceptible TB (especially those with low CD4+ T cell counts) is strongly supported by randomized trials.

Accumulating evidence suggests **lower mortality among PLWH with MDR-TB who are treated for both conditions concurrently**→

Brust, *Clin Infect Dis* 2018

Substudy of patients with MDR-TB in the SAPiT trial, in which ART delay (associated with mortality rate of 56 per 100 person-years) was reduced by 86% to 11 per 100 person-years when **ART was introduced early**.

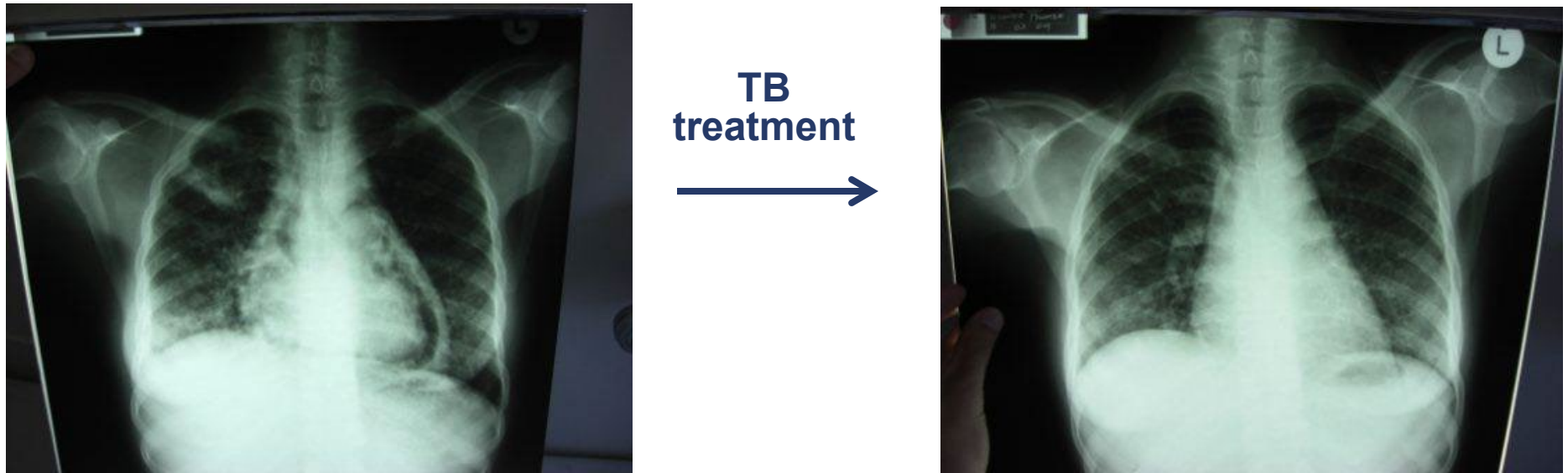
Padayatchi, *IJTLD* 2014

General international consensus→ in ART naïve PLWH, start ART early (approximately 2 weeks after TB treatment if tolerating anti-TB therapy) if:

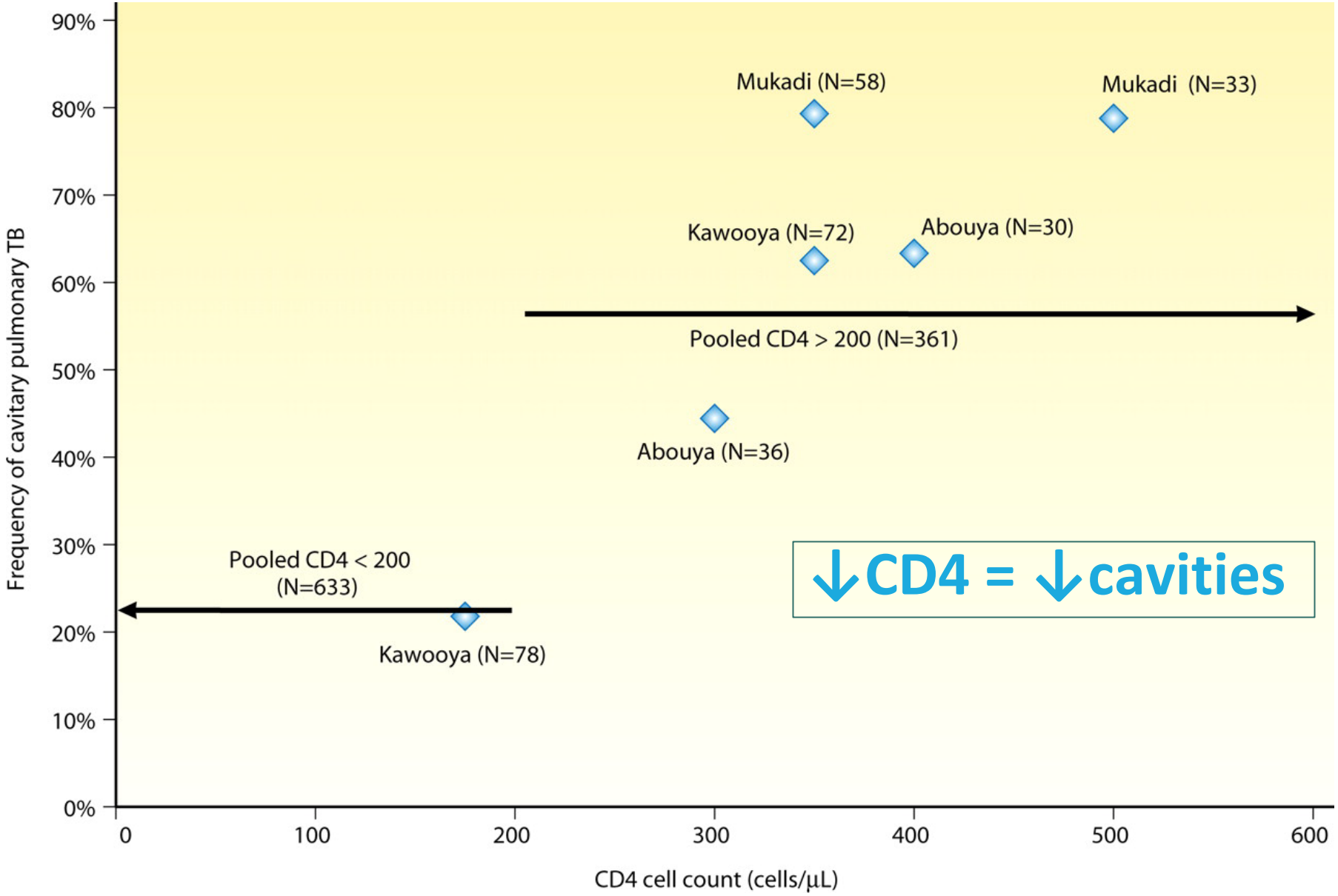
RR-TB
CD4</= 50
Bedbound (low Karnofsky score)

Active TB diagnosis is challenging people living with HIV

- Extrapulmonary TB is more common, including TB bacteremia/sepsis
- Chest x-rays are more likely to be non-cavitary, particularly at lower CD4 counts
- Sputum smear microscopy is lower yield in people with HIV compared to those without HIV
- This low sputum burden compromises the sensitivity of the newer molecular diagnostics

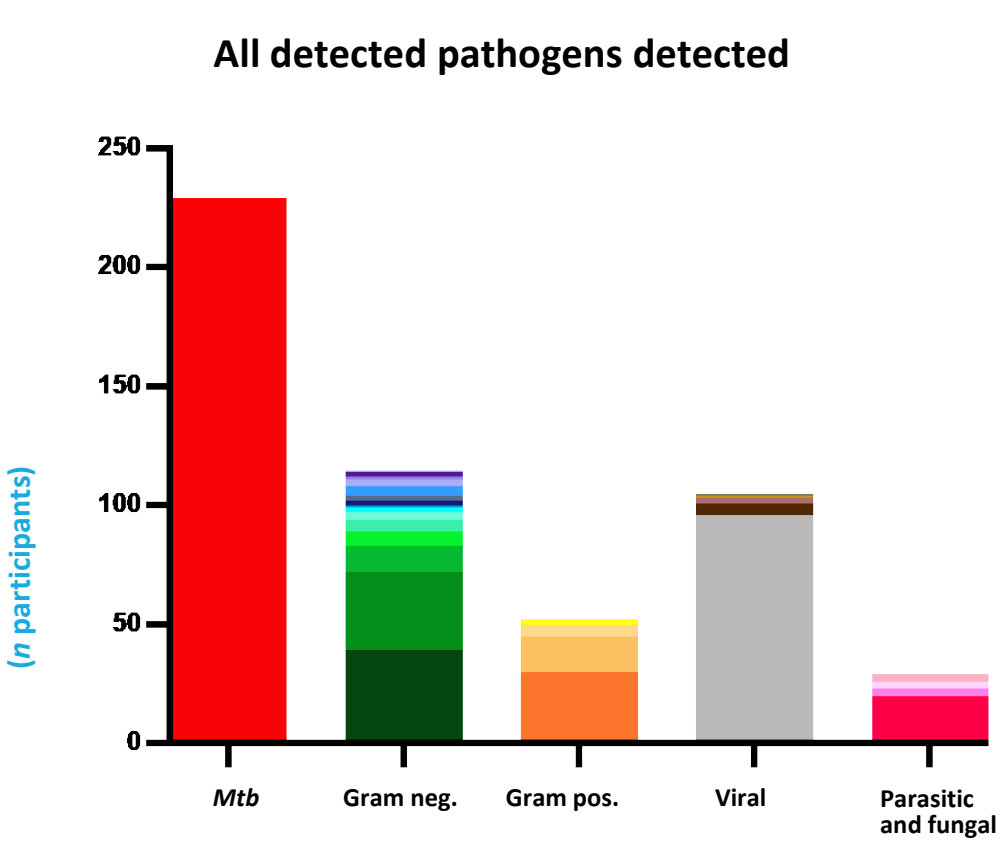


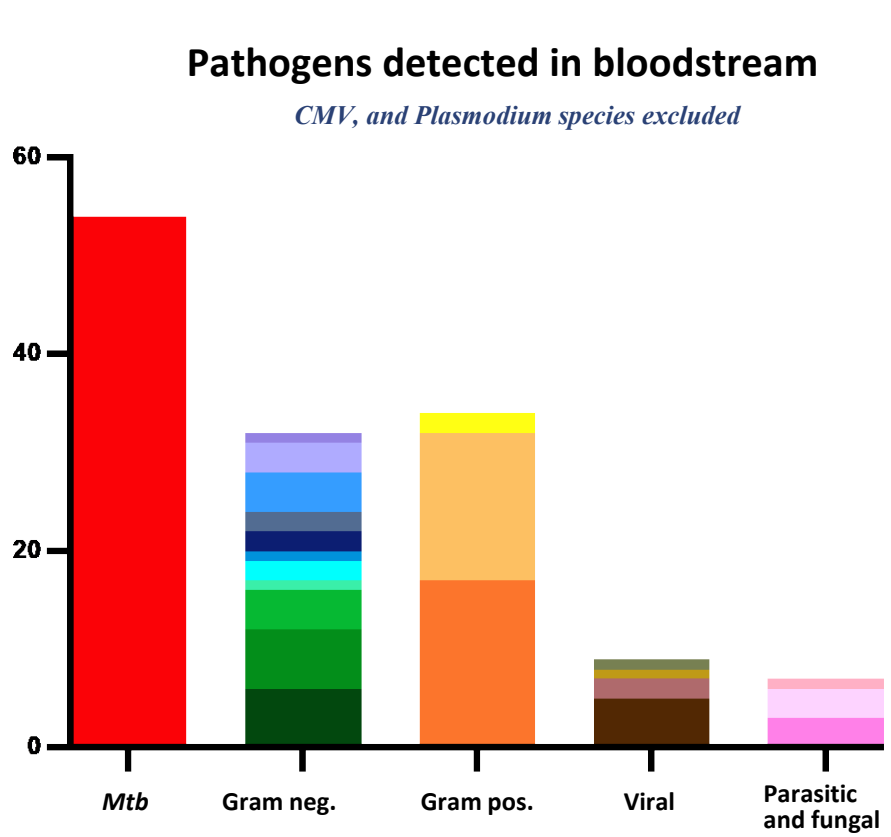
Pulmonary TB presents atypically in HIV with low CD4 count

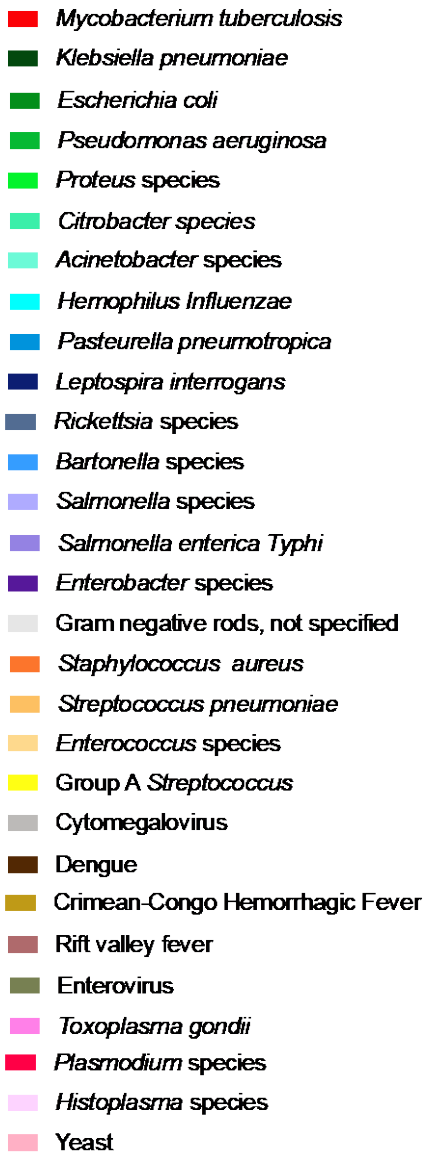


Kwan C K , Ernst J D Clin. Microbiol. Rev. 2011;24:351-376

In HIV related sepsis (Uganda and Tanzania), *M. tuberculosis* was the most common pathogen detected overall, and most common among bloodstream pathogens





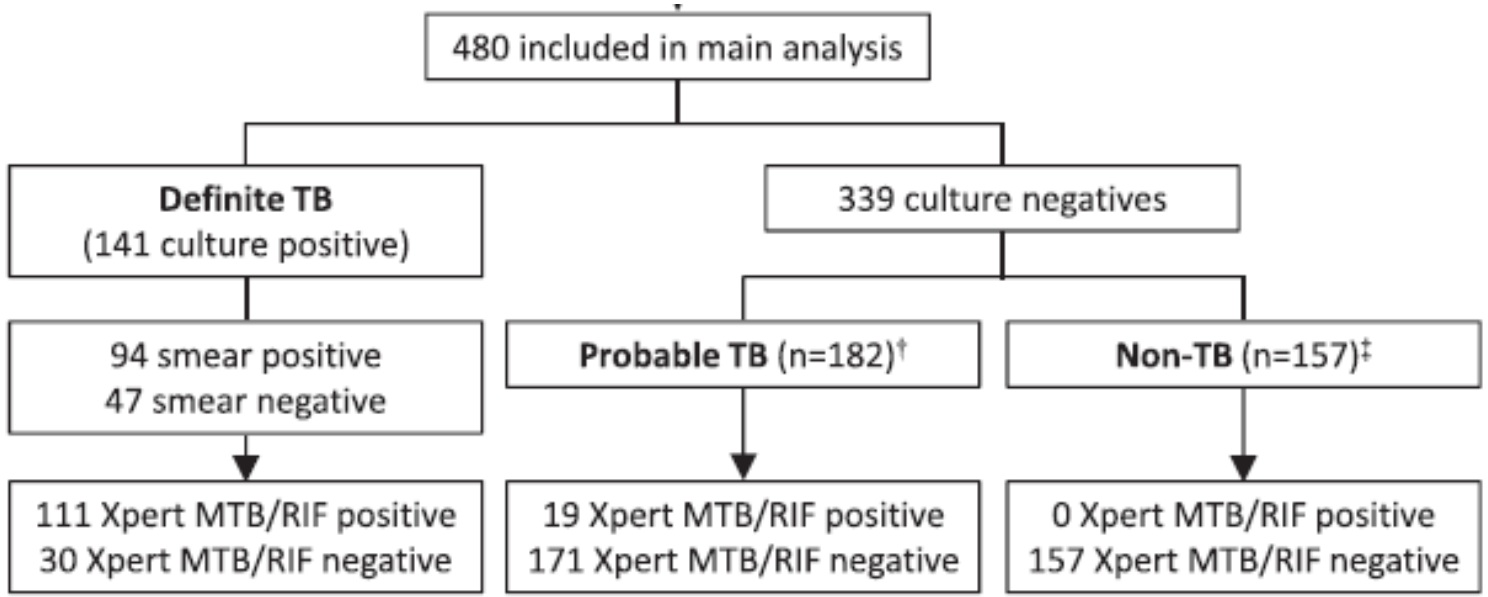


Bar graphs showing frequency of detected pathogens. (*n*=number of participants). Participants may have more than one pathogen detected.

Otoupalova, et al. Lancet Discovery series-
eClinical Medicine, 2025

Xpert MTB/RIF assay for TB diagnosis in HIV patients

Deda *AJRCCM* 2011



- **Smear microscopy was significantly less sensitive in subjects infected with HIV versus subjects uninfected with HIV (23 [50%] of 46 vs. 60 [73.2%] of 82; P <0.01).**

- **Xpert MTB/RIF detected 95% of smear-positive and culture-positive cases, but sensitivity in smear-negative cases was only 55%.**

What test is more sensitive for TB (can detect more tuberculosis) among people with HIV compared to those without HIV?

a. Sputum smear microscopy (AFB smear)

b. Urine lipoarabinomannan (LAM)

c. Sputum Xpert Ultra (PCR)

d. Sputum MGIT (liquid culture)

Urine LAM, a diagnostic *more* effective in PLWH- not available commercially in the U.S.

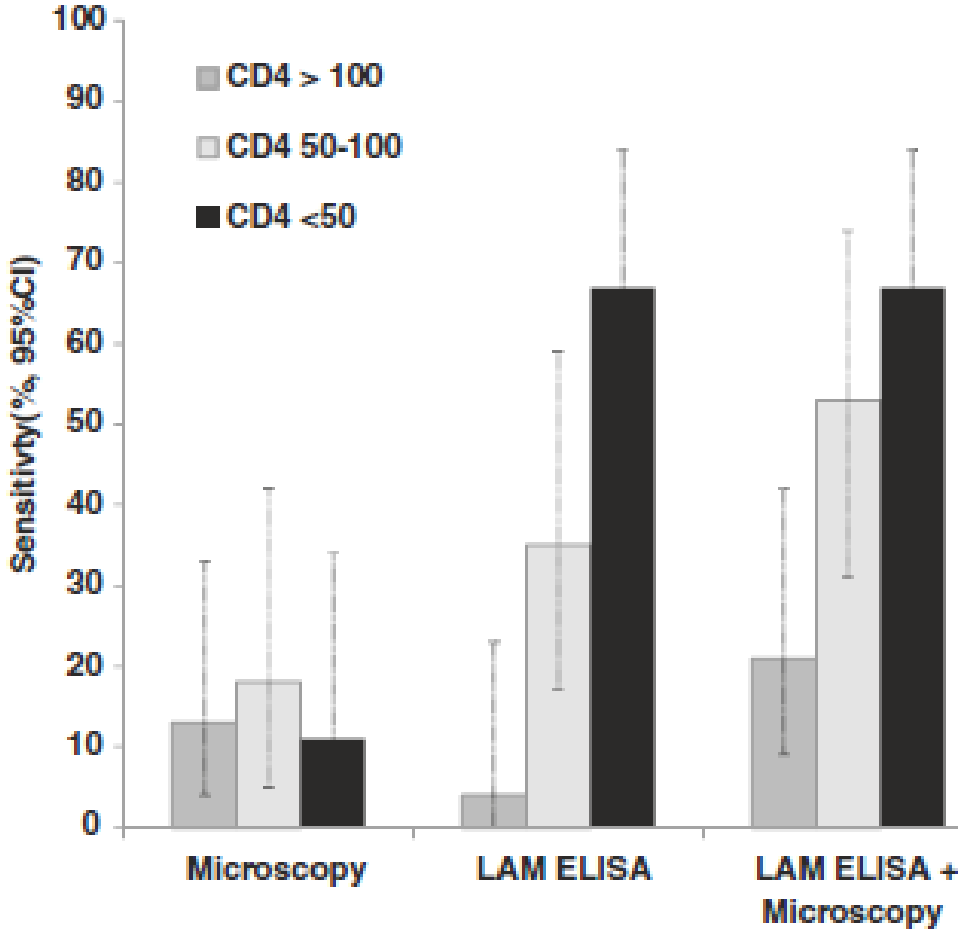


Figure 2 Graph showing the sensitivity of a commercially available enzyme-linked immunosorbent assay (ELISA) to detect lipoarabinomannan (LAM) within urine samples to diagnose tuberculosis (TB) in a cohort of patients accessing antiretroviral treatment (ART) in a South African township.

- Lipoarabinomannan (LAM) is a structurally important glycolipid found in the *M. tuberculosis* cell wall, accounting for up to 15% of the total bacterial weight.

- A point-of-care urine test has been developed.

Minion et al. *Eur Respir J* 2011
Lawn SD, *BMC Infect Dis* 2012

Case

34 year old man screened positive for HIV at community health fair→ referred to UVA HIV clinic

We performed history, physical examination, CD4 count and HIV viral load and other blood work:

-- Female partners, occasional unprotected sex. No injection drug use.

-- Asymptomatic. Physical exam normal.

-- Additional tests ordered:
Complete blood count, chemistries, liver function test
Hepatitis A, B and C serologies
Syphilis Ab
***Toxoplasma gondii* serology**
IGRA "Quantiferon"

Case continued

CD4 = 400, HIV viral load= 550,000
(if CD4<200 *Pneumocystis* and *Toxoplasmosis* prophylaxis)
Hgb 10, otherwise chemistries and liver function normal
Hepatitis A, B and C negative/ not-exposed
Toxoplasma negative
Syphilis negative

Quantiferon positive

What next?

Possible TB infection?

Starting antiretroviral therapy?

Case continued

Possible TB infection?

- A chest x-ray is performed and negative, given asymptomatic IGRA positive→ started on treatment of latent TB infection

3 mo isoniazid/ rifapentine once weekly (3HP)
3 mo isoniazid/ rifampin daily (3HR)

6-9 mo daily isoniazid (6-9H) (alternative)
4 mo rifampin (4R) (alternative)- no data for rifabutin
1 mo daily isoniazid/ rifapentine (1HP) (alternative)

Starting antiretroviral therapy?

- US: Any CD4, priorities in AIDS defining illness or acute seroconversion, nuance of ***when*** to start if active TB disease

US DHHS HIV/ Opportunistic Infections Guidelines 2024
clinicalinfo.hiv.gov

Rifamycin drug-drug interactions (use raltegravir and dolutegravir, happy to consult!)

TB Drug	ARV Drugs	Daily Dose
Rifampin[a,b]	• NRTIs (use TAF with caution[c]) • EFV 600 mg • DTG, RAL (twice daily), MVC without a strong CYP3A4 inhibitor (**note**: doses of these ARVs need to be adjusted when used with rifampin) • IBA, T-20	10 mg/kg (usual dose 600 mg)
	• DOR, ETR, EFV 400 mg, NVP, RPV (PO) • BIC, EVG/c, RAL (daily) • CAB/RPV (IM/PO) • HIV PIs • LEN (SC/PO), FTR, MVC with a strong CYP3A4 inhibitor	**Not recommended**
Rifapentine	• EFV • NRTIs (use TAF with caution[c])	1,200 mg/day for people weighing ≥40 kg
	• All other ARVs	**Not recommended**

TB Drug	ARV Drugs	Daily Dose
Rifabutin[a]	• NRTIs (use TAF with caution[c]) • ETR without boosted PIs • DOR and RPV (PO) (**note**: doses need to be adjusted when used with rifabutin) • DTG, RAL • MVC without a strong CYP3A4 inhibitor • IBA, T-20, FTR	5 mg/kg (usual dose 300 mg)
	• PIs with RTV MVC with a strong CYP3A4 inhibitor	150 mg daily[e]
	• EFV	450–600 mg
	• ETR with boosted PIs • BIC, EVG/c • CAB/RPV (IM/PO) • PIs with COBI • LEN (SC/PO)	**Not recommended**

Rifapentine behaves similarly to rifampin- evidence to use once daily dolutegravir with 3HP (TB infection), and trial evidence pending for twice daily dolutegravir with 4HPM-2Z (TB disease)

US DHHS HIV/ Opportunistic Infections Guidelines 2024
clinicalinfo.hiv.gov

What is the best choice of antiretroviral therapy (ART) regimens for a person living with HIV that has not taken ART previously to use while treated with daily rifampin?

a. Daily abacavir-lamivudine-dolutegravir (Triumeq) plus evening dolutegravir (twice daily dolutegravir)

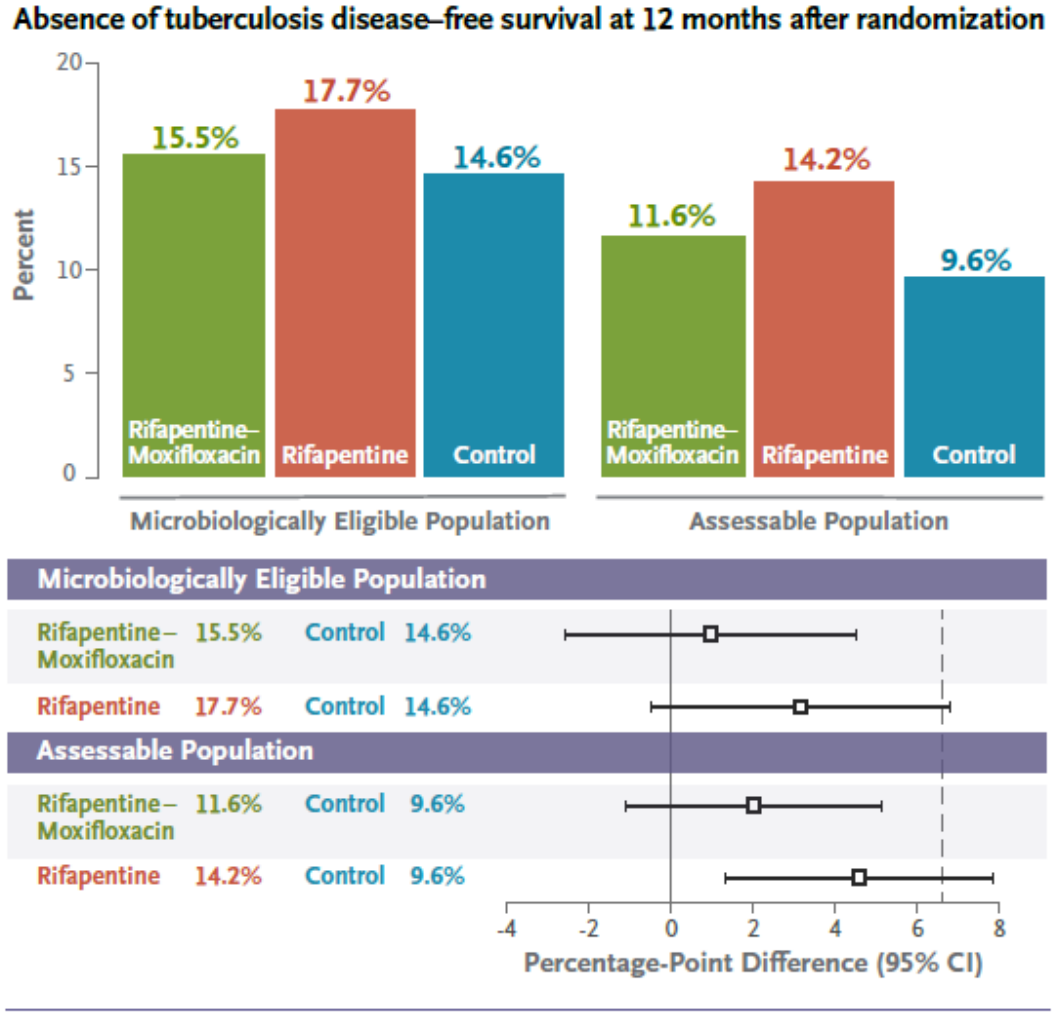
b. Tenofovir alafenamide (TAF)-emtricitabine (Descovy) plus twice daily dolutegravir

c. Tenofovir alafenamide-emtricitabine-bictegravir (Biktarvy)

d. Tenofovir alafenamide-emtricitabine-darunavir/cobicistat (Symtuza)

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

Dorman SE et al. DOI: 10.1056/NEJMoa2033400

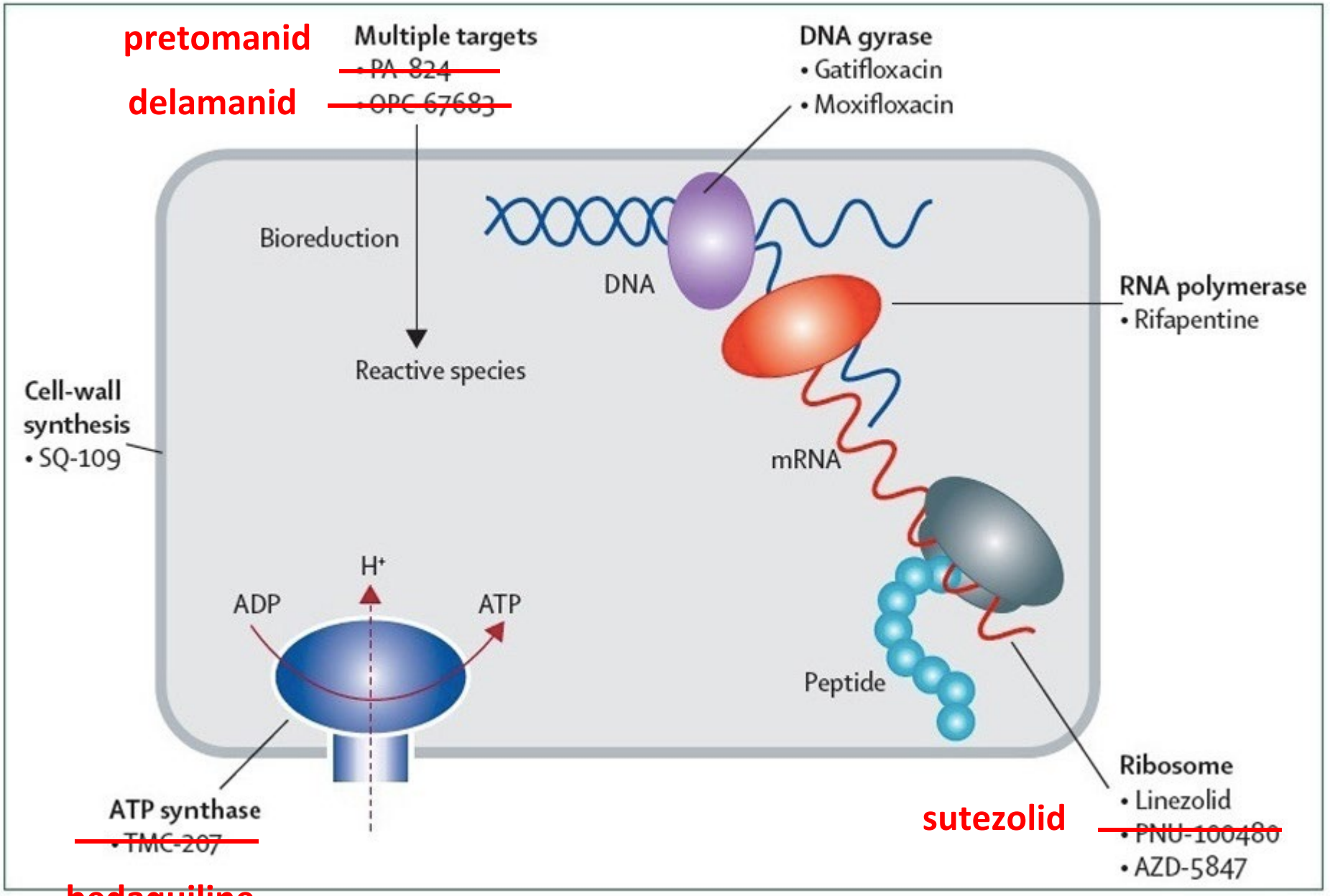


4 month Rifapentine/Moxifloxacin regimen was non-inferior:

Rifapentine 4 mo (17 weeks)
Isoniazid 4 mo (17 weeks)
Moxifloxacin 4 mo (17 weeks)
Pyrazinamide 2 mo (8 weeks)

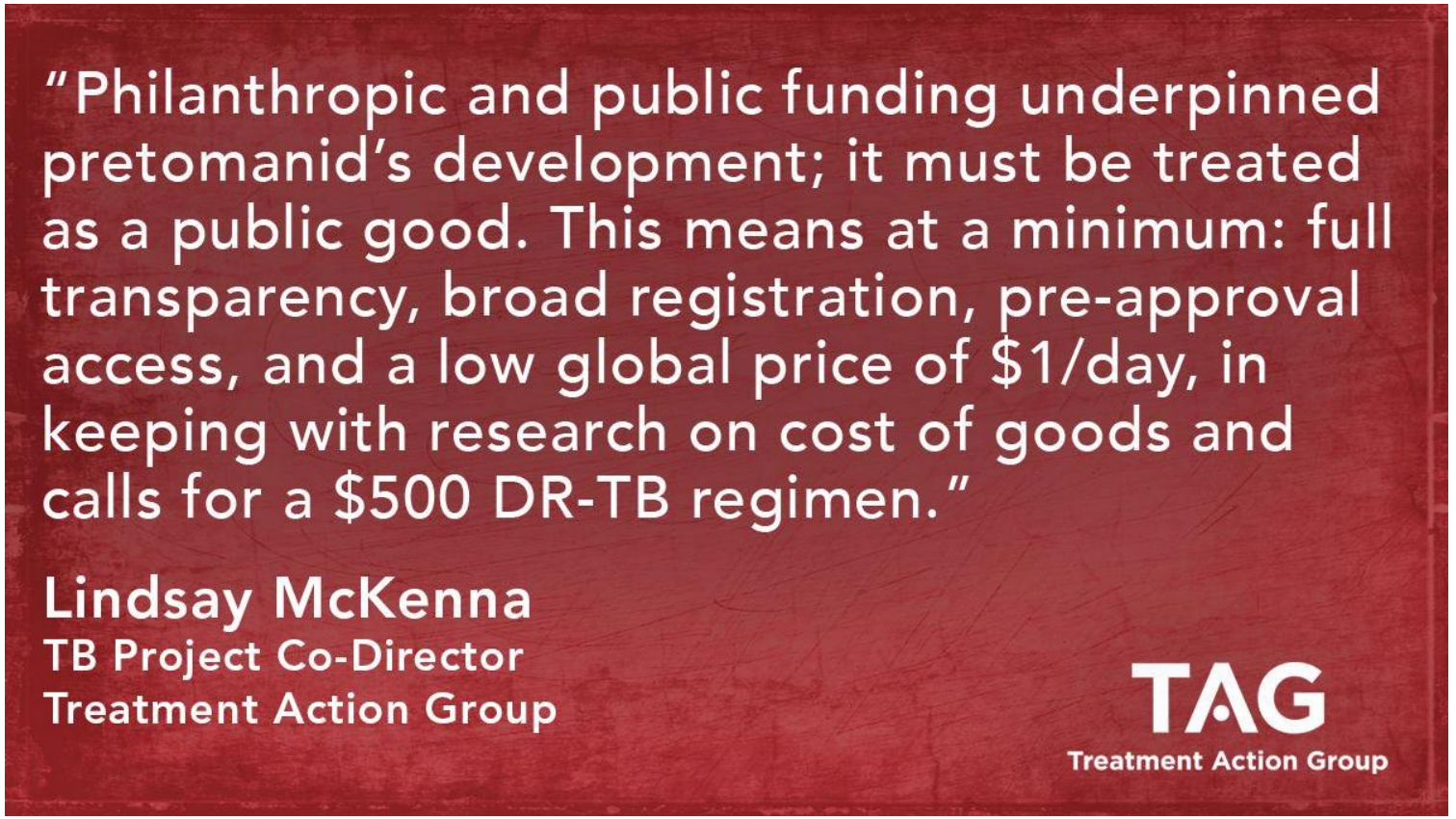
From an HIV/ART perspective, rifapentine is more similar to rifampin: initial CDC recs to have ART as efavirenz but rarely used anymore- now pending trial with twice daily dolutegravir ACTG A5406

Not yet recommended for extrapulmonary TB


pretomanid
delamanid
Multiple targets
• PA-824
• OPC-67683
DNA gyrase
• Gatifloxacin
• Moxifloxacin
Bioreduction
Reactive species
DNA
RNA polymerase
• Rifapentine
Cell-wall synthesis
• SQ-109
mRNA
H+
ADP
ATP
Peptide
ATP synthase
• TMC-207
bedaquiline
sutezolid
Ribosome
• Linezolid
• PNU-100480
• AZD-5847

Scientists Discover New Cure for the Deadliest Strain of Tuberculosis

The New York Times



Bedaquiline, Pretomanid and Linezolid (+/- Moxifloxacin) BPaL(M)- the new Standard of Care for RR/MDR-TB

Original Nix-TB trial: BPaL for 26 weeks for XDR-TB or non-responsive MDR-TB

→ ~Half were people living with HIV and results were similar to non-HIV, **but patients with CD4 counts <50 were excluded**. Adverse events included peripheral neuropathy (81%) and anemia (37%), as well as optic neuropathy, QTc prolongation, and hepatitis; the majority of adverse events were likely attributable to linezolid.

→ Still need more data to inform duration of therapy in people with HIV and low CD4 count (is regimen efficacy more important than duration?)

HIV/TB treatment nuances

Alterations in adherence due to increased pill burden

Overlapping toxicities that also impact adherence

Subtherapeutic concentrations of anti-TB drugs because of malabsorption or drug-interaction

Fragmentation of care between separate TB and HIV programs

Disease less amenable to surgery given lack of localized pulmonary focus

Differential stigma

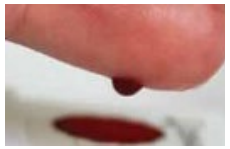


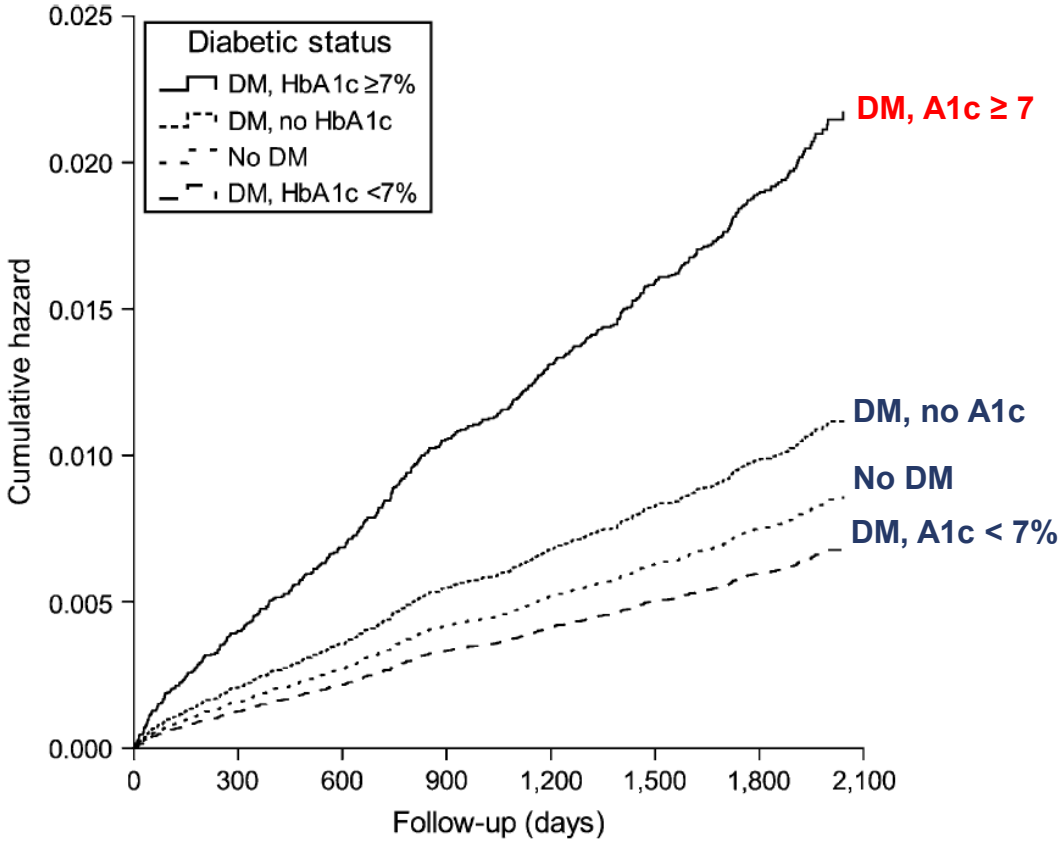
Table 9. Conditions or Situations in Which Therapeutic Drug Monitoring May Be Helpful

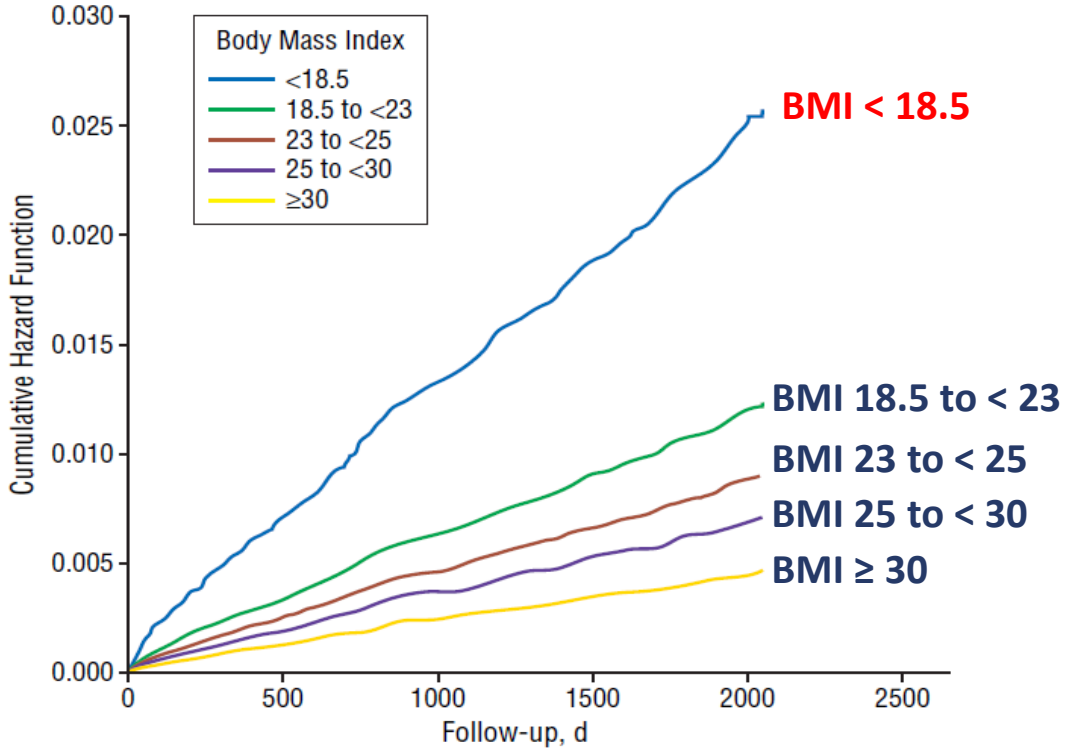
Poor response to tuberculosis treatment despite adherence and fully drug-susceptible *Mycobacterium tuberculosis* strain
Severe gastrointestinal abnormalities: severe gastroparesis, short bowel syndrome, chronic diarrhea with malabsorption
Drug–drug interactions
Impaired renal clearance: renal insufficiency,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

Abbreviation: HIV, human immunodeficiency virus.

ATS/IDSA/CDC guidelines,
Nahid et al, *Clin Infect Dis* 2016

Diabetes is associated with *increased* risk of developing TB, while increased BMI is associated with *decreased* risk

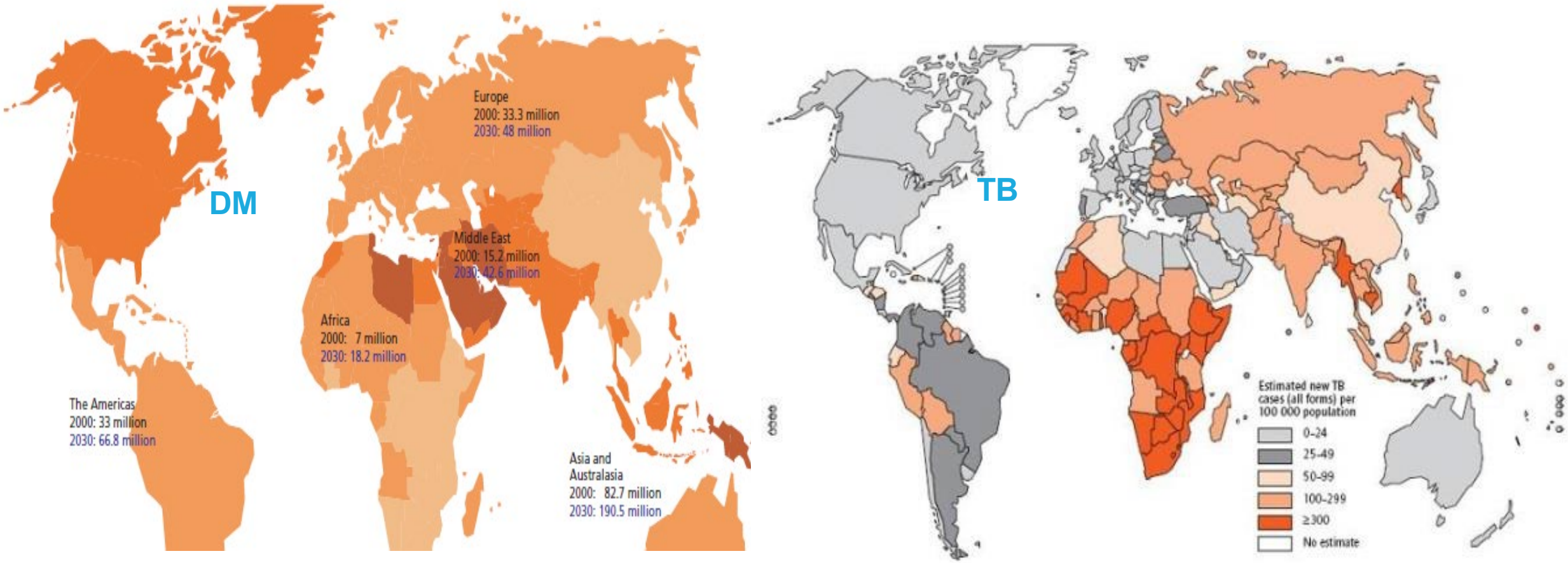




Hazard ratios:
0.36 (0.20 – 0.66) for BMI > 30,
0.55 (0.44-0.70) for BMI 25-30

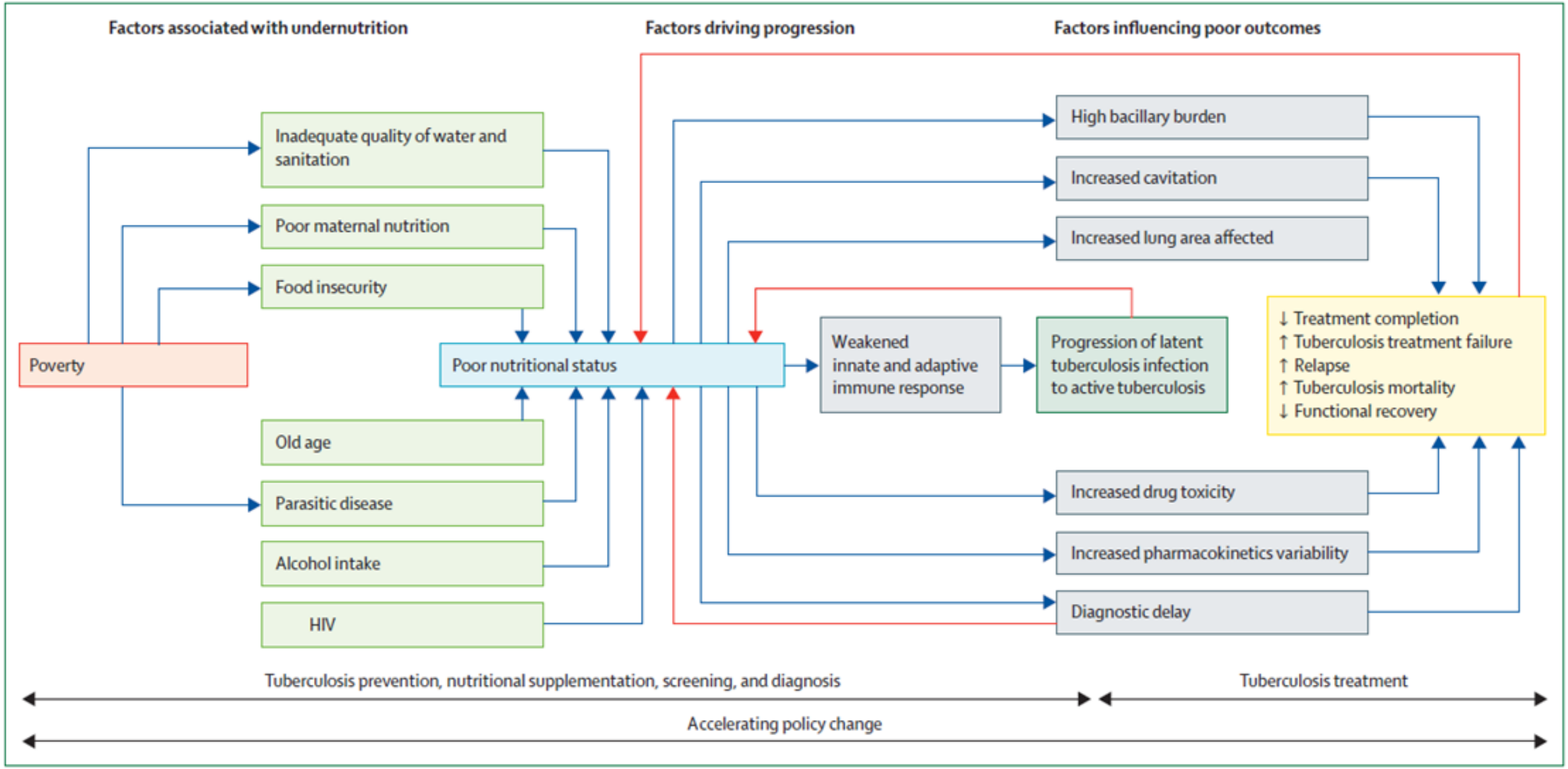
Leung et al. Am J Epi 2008

Leung et al. Arch Intern Med 2007



Diabetes and TB are converging, synergistic epidemics

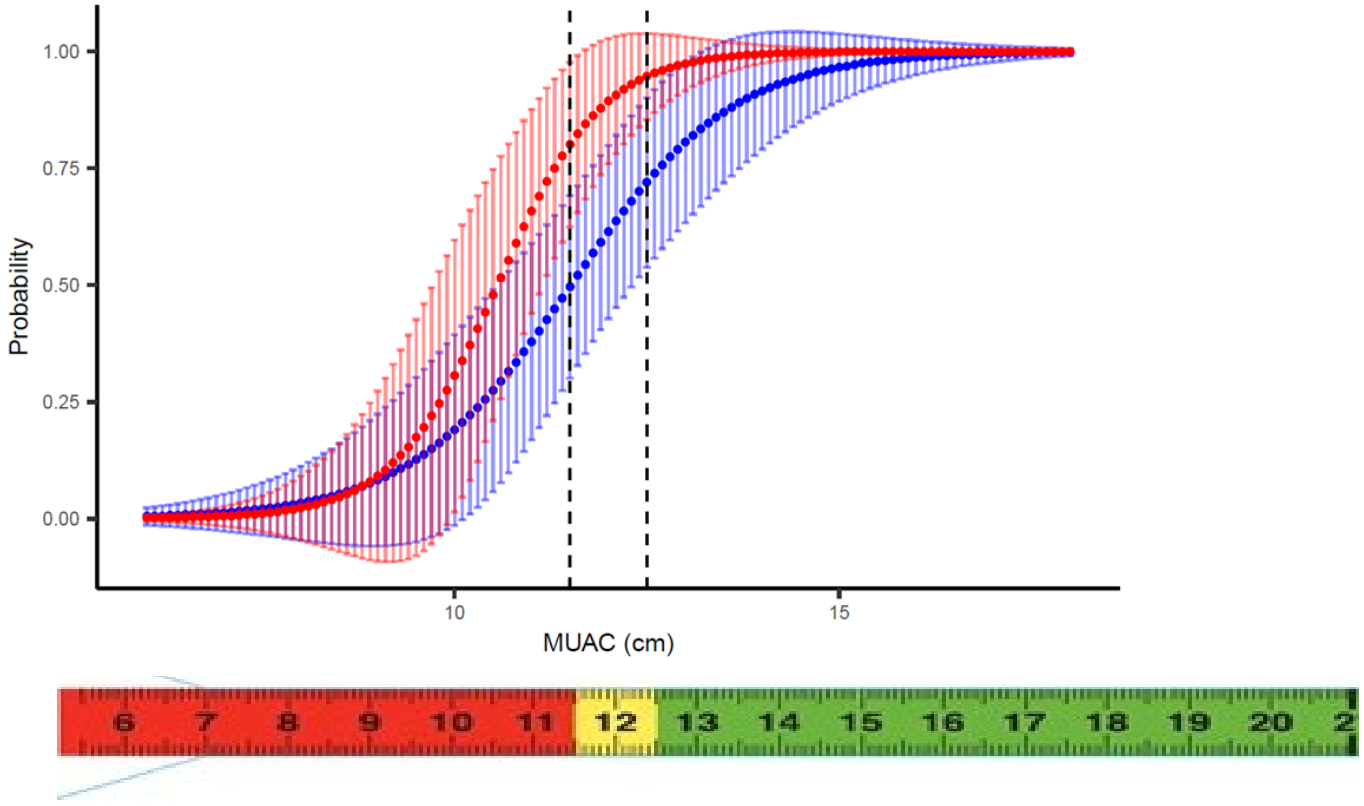
Malnutrition's multifactorial impact on tuberculosis treatment (downstream in the cascade)



Sinha et al, *Lancet Infect Dis* 2021

In multiple studies across populations, malnutrition at treatment initiation worsens outcomes, including children

Children with TB in rural Tanzania- probability and 95% CI interval of treatment success (blue) and survival (red)

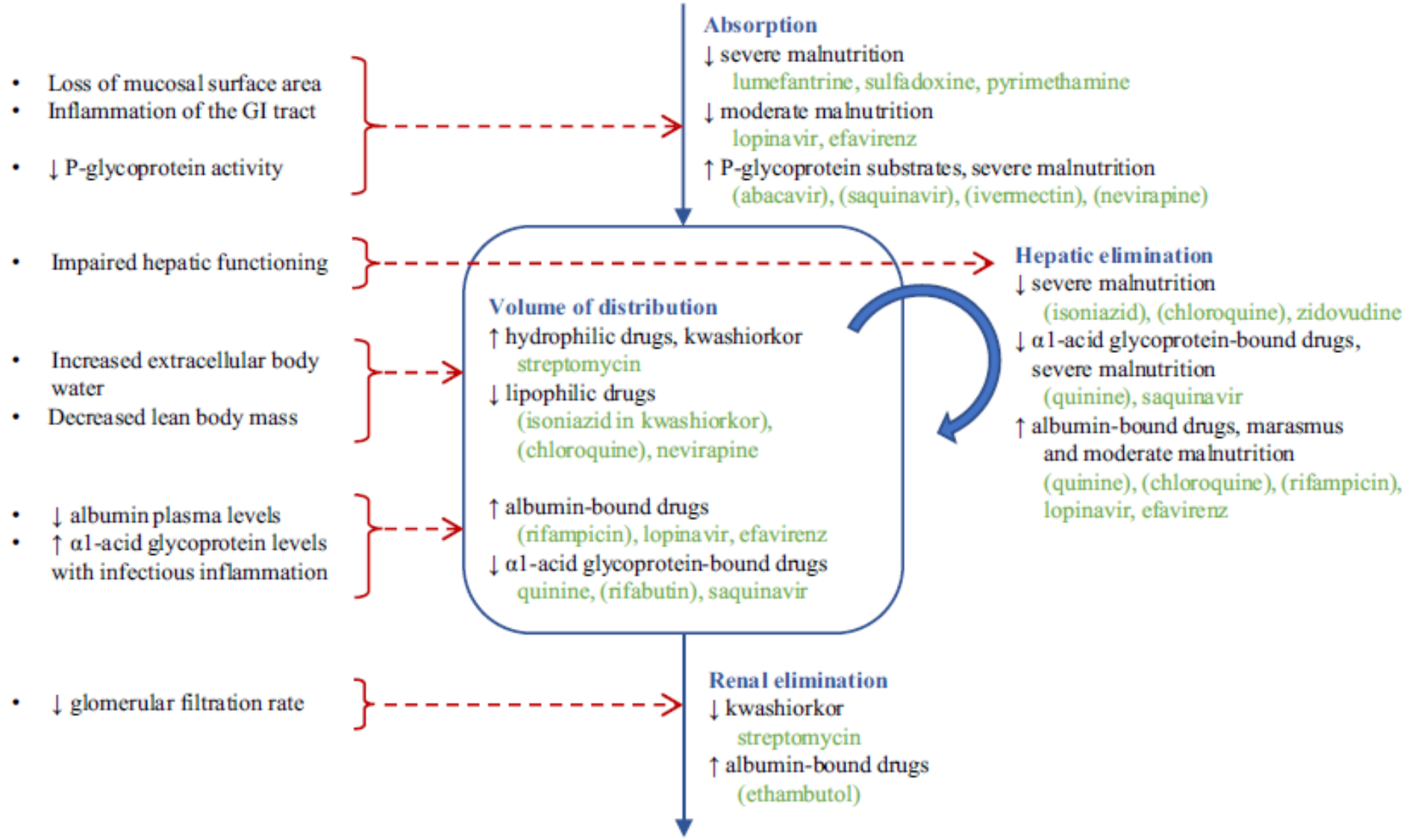


Van Aartsen, Union conf and Cintron et al, *in preparation*

Individual participant data meta-analysis of 5,148 adults with rifampin-resistant TB→ Low BMI at treatment initiation for RR-TB is associated with increased odds of unfavorable treatment outcome and mortality

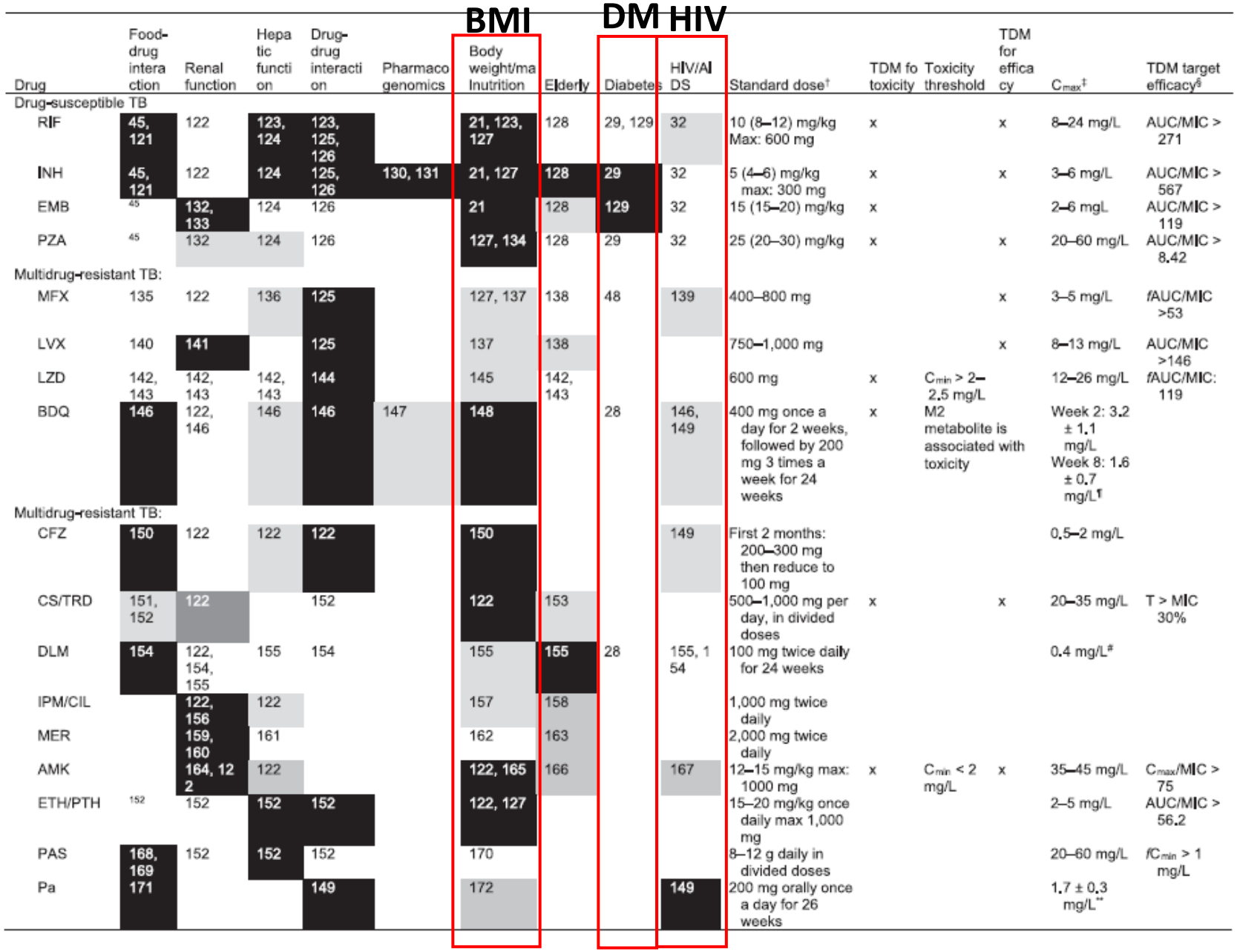
Campbell et al, *Clin Infect Dis* 2022

Malnutrition impacts multiple pathways of drug absorption, distribution and elimination



Verrest et al, *Clin Pharm* 2021

Factors that are likely, possibly and unlikely to impact TB drug efficacy or toxicity



Drug	Food-drug interaction	Renal function	Hepatic function	Drug-drug interaction	Pharmacogenomics	Body weight/malnutrition (BMI)	Elderly	Diabetes (DM)	HIV/AIDS (HIV)	Standard dose†	TDM for toxicity	Toxicity threshold	TDM for efficacy	C_{max}‡	TDM target efficacy§
Drug-susceptible TB															
RIF	45, 121	122	123, 124	123, 125, 126		21, 123, 127	128	29, 129	32	10 (8–12) mg/kg Max: 600 mg	x		x	8–24 mg/L	AUC/MIC > 271
INH	45, 121	122	124	125, 126	130, 131	21, 127	128	29	32	5 (4–6) mg/kg max: 300 mg	x		x	3–6 mg/L	AUC/MIC > 567
EMB	45	132, 133	124	126		21	128	129	32	15 (15–20) mg/kg	x			2–6 mgL	AUC/MIC > 119
PZA	45	132	124	126		127, 134	128	29	32	25 (20–30) mg/kg	x		x	20–60 mg/L	AUC/MIC > 8.42
Multidrug-resistant TB:															
MFX	135	122	136	125		127, 137	138	48	139	400–800 mg			x	3–5 mg/L	fAUC/MIC >53
LVX	140	141		125		137	138			750–1,000 mg			x	8–13 mg/L	AUC/MIC >146
LZD	142, 143	142, 143	142, 143	144		145	142, 143			600 mg	x	C_{min} > 2–2.5 mg/L		12–26 mg/L	fAUC/MIC: 119
BDQ	146	122, 146	146	146	147	148		28	146, 149	400 mg once a day for 2 weeks, followed by 200 mg 3 times a week for 24 weeks	x	M2 metabolite is associated with toxicity		Week 2: 3.2 ± 1.1 mg/L Week 8: 1.6 ± 0.7 mg/L¶	
Multidrug-resistant TB:															
CFZ	150	122	122	122		150			149	First 2 months: 200–300 mg then reduce to 100 mg				0.5–2 mg/L	
CS/TRD	151, 152	122		152		122	153			500–1,000 mg per day, in divided doses	x		x	20–35 mg/L	T > MIC 30%
DLM	154	122, 154, 155	155	154		155	155	28	155, 154	100 mg twice daily for 24 weeks				0.4 mg/L#	
IPM/CIL		122, 156	122			157	158			1,000 mg twice daily					
MER		159, 160	161			162	163			2,000 mg twice daily					
AMK		164, 122	122			122, 165	166		167	12–15 mg/kg max: 1000 mg	x	C_{min} < 2 mg/L	x	35–45 mg/L	C_{max}/MIC > 75
ETH/PTH	152	152	152	152		122, 127				15–20 mg/kg once daily max 1,000 mg				2–5 mg/L	AUC/MIC > 56.2
PAS	168, 169	152	152	152		170				8–12 g daily in divided doses				20–60 mg/L	fC_{min} > 1 mg/L
Pa	171			149		172			149	200 mg orally once a day for 26 weeks				1.7 ± 0.3 mg/L**	

Likely

Possibly

Unlikely

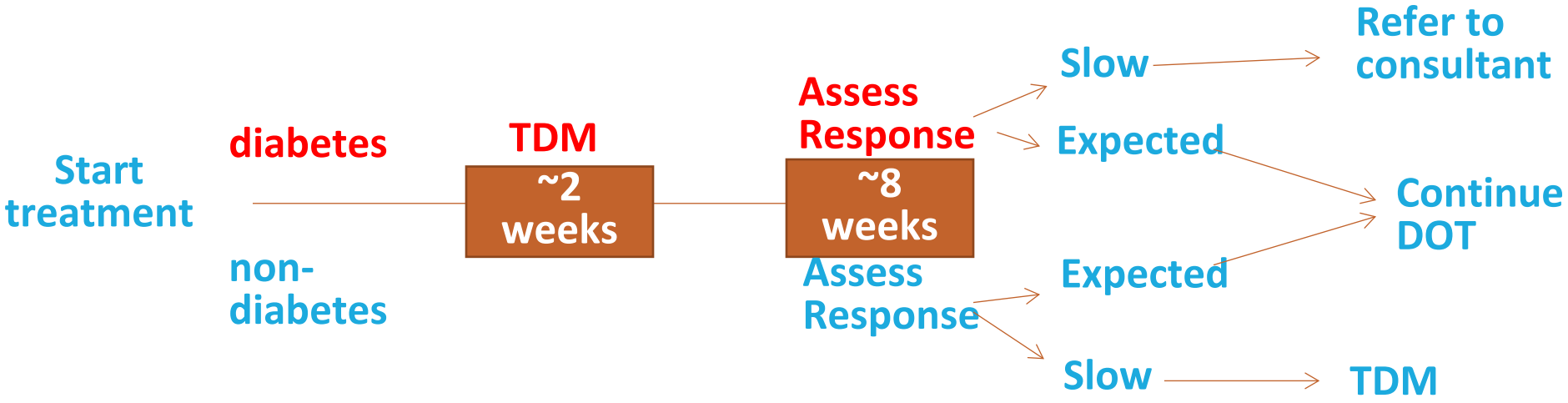
Alffenaar et al, *IJTLD* 2022. Clinical Standards for Dosing and Management of TB Drugs

Our approach in Virginia: the diabetes experience→ now undernutrition?, HIV, and RR-TB receive personalized dosing based on serum targets

- Diabetes/TB prolongs the time to sputum culture conversion and increases risk of death compared to non-diabetes/TB patients[1]

- Previously, in Virginia, diabetes/TB patients made up 40% of those with slow response to therapy, and were more likely to have serum concentrations of rifampin below expected peak range compared to non-diabetes TB.[2]

- 2013→ state recommendations for early therapeutic drug monitoring (TDM) and dose correction for isoniazid and rifampin for all diabetes/TB patients[3]. Effort to screen those without known diabetes by HgbA1c.



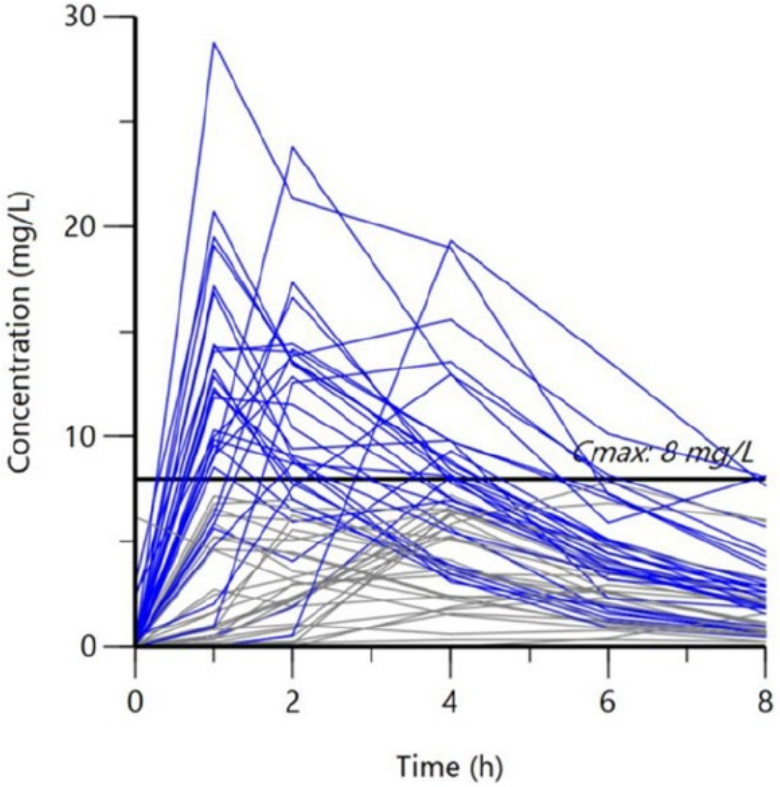
1. Dooley et al, *Am J Trop Med Hyg* 2009

2. Heysell et al, *Emerg Infect Dis* 2010

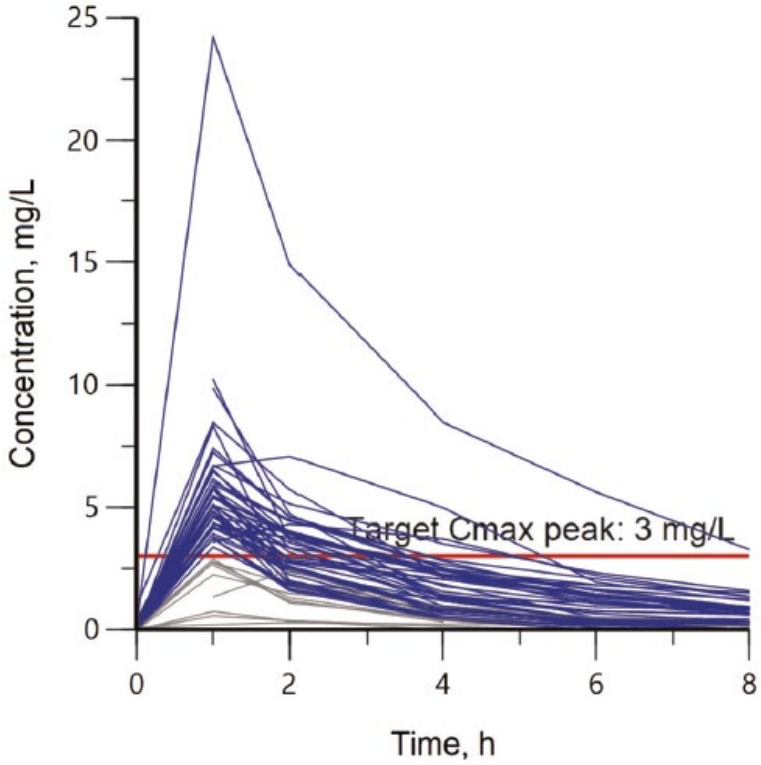
3. Heysell et al, *Tuberc Res Treat* 2013

Measuring serum concentrations at estimated Cmax (peak) can estimate total drug exposure (AUC)

Rifampin



Isoniazid



U.S. adults (Virginia and New Jersey) treated for TB with rifampin (N=58) and isoniazid (N=56)

Grey lines represent pharmacokinetic curves from people who had below target total serum exposure over the dosing interval (AUC)- isoniazid more reliable Cmax (peak) at 1 hour

Xie et al, *AAC* 2023 Rao et al, *IJTLD Open* 2023

Checking serum RIF an INH levels and dose adjusting to serum target (TDM) in people with diabetes hastens microbiological cure and shortens treatment in the U.S. in non-controlled studies

Table 3 Sputum culture conversion in adults with pulmonary tuberculosis matched 2:1 non-diabetes to diabetes for age, gender, sputum smear result and chest x-ray findings

Outcome	Matched non DM:DM 2009-2010			Matched non DM:DM 2014-15		
	non DM $N=60$	DM $N=30$	*p*-value	non DM $N=52$	DM $N=26$	*p*-value
Time to culture conversion (days, mean ± SD)	57 ± 35	61 ± 32	0.62	57 ± 37	42 ± 22	0.08
2 months culture conversion, No. (%)	34 (57)	15 (50)	0.55	31 (60)	21 (81)	0.12

TDM= therapeutic drug monitoring

Pre-intervention (no TDM) **Post-intervention (routine TDM)**

Alkabab, et al *BMC Infect Dis* 2017

Table 4 Treatment outcomes in groups with and without TDM

Outcomes	Non-TDM (n = 73) mean ± SD	TDM (n = 97) mean ± SD	*P* value
Days to sputum culture conversion	49 ± 27	34 ± 23	<0.001
Arizona	48 ± 27	—	
New Mexico	53 ± 29	—	
Tennessee	—	31 ± 23	
Virginia	—	38 ± 22	
Total weeks of treatment duration	36 ± 10	32 ± 9	0.04
Arizona	34 ± 10	—	
New Mexico	41 ± 6	—	
Tennessee	—	33 ± 12	
Virginia	—	32 ± 8	
2-month culture conversion, *n* (%)	51 (70)	84 (87)	0.01
Arizona	43	—	
New Mexico	8	—	
Tennessee	—	42	
Virginia	—	42	
Death, *n* (%)	3 (4)	3 (3)	1.00
Cured, *n* (%)	68 (93)	92 (95)	0.51
Loss of follow-up, *n* (%)	2 (3)	2 (2)	1.00

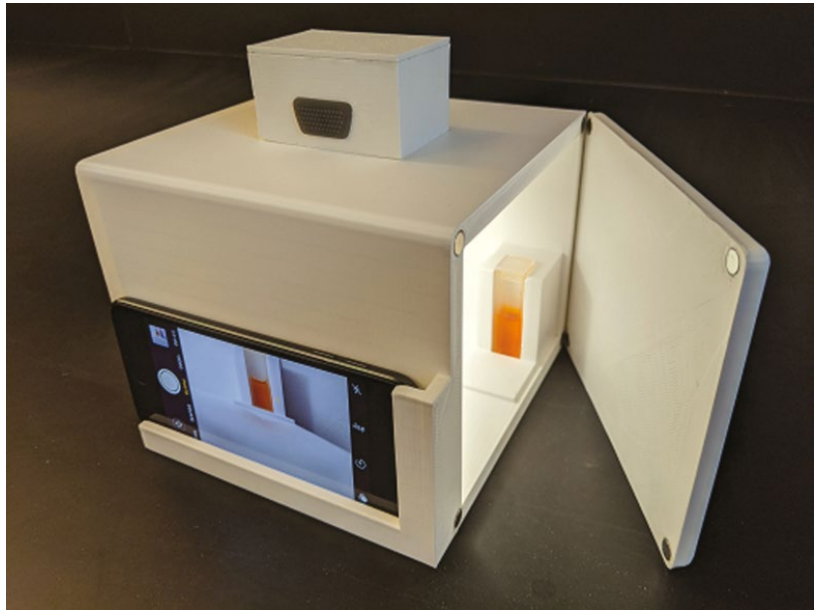
TDM = therapeutic drug monitoring; SD = standard deviation.

Alkabab, et al *IJTLD* 2022

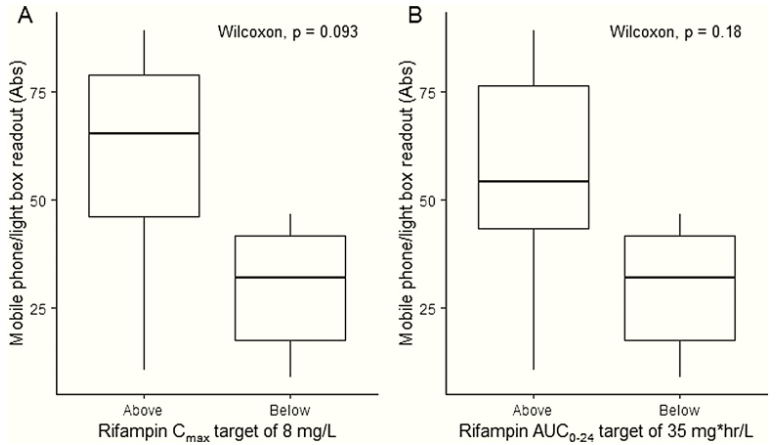
Personalized dosing can be performed in multiple settings and from different sample types

	Critically ill	Outpatients	Less resourced setting
Typical patient	Extreme changes in PK and PD, dialysis, and ECMO	Long-term conditions (HIV, TB, and fungal infections) Chronic disease	Both chronic and acute patients
Turnaround time	Hours	Days	Dependent on patient severity hours-days
Sampling	Blood and unbound concentrations	Blood DBS	Blood DBS Saliva Urine
Assays	LC-MS/MS Immunoassay HPLC-UV	LC-MS/MS Immunoassay HPLC-UV	Nanophotometer for saliva Immunoassay HPLC-UV
Dosing software	Licensed and network-based software	Licensed and network-based software	Freeware software Mobile applications

Kim et al, *Ther Drug Mon* 2022



In urine specimens from children collected following observed anti-TB dosing in rural Tanzania, urine spectrophotometry identified those with below target serum levels



Szipsky et al, *J Pediatric Infect Dis Soc* 2021

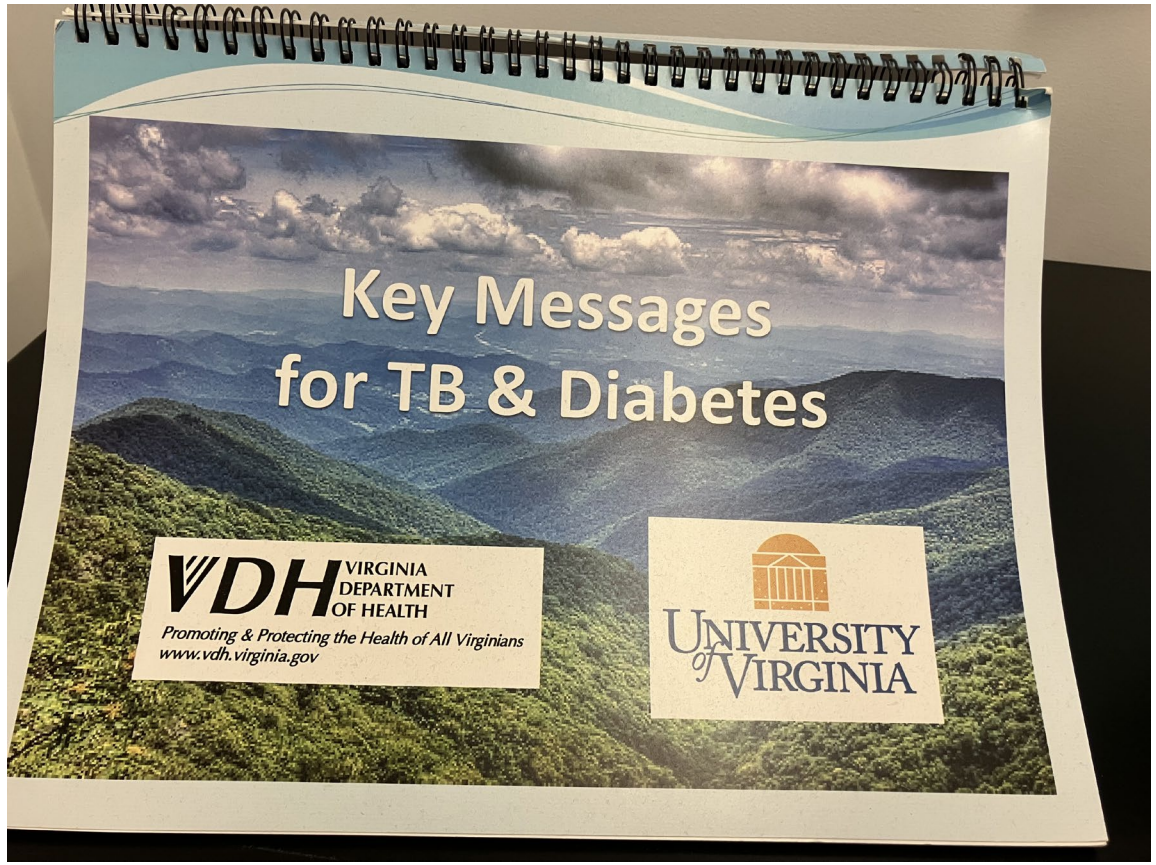
Even with personalized dosing adverse events are more common among malnourished people or those with gastroparesis and diabetes

Table 4 How to support people when continuing TB therapy in the context of mild–moderate AE*.

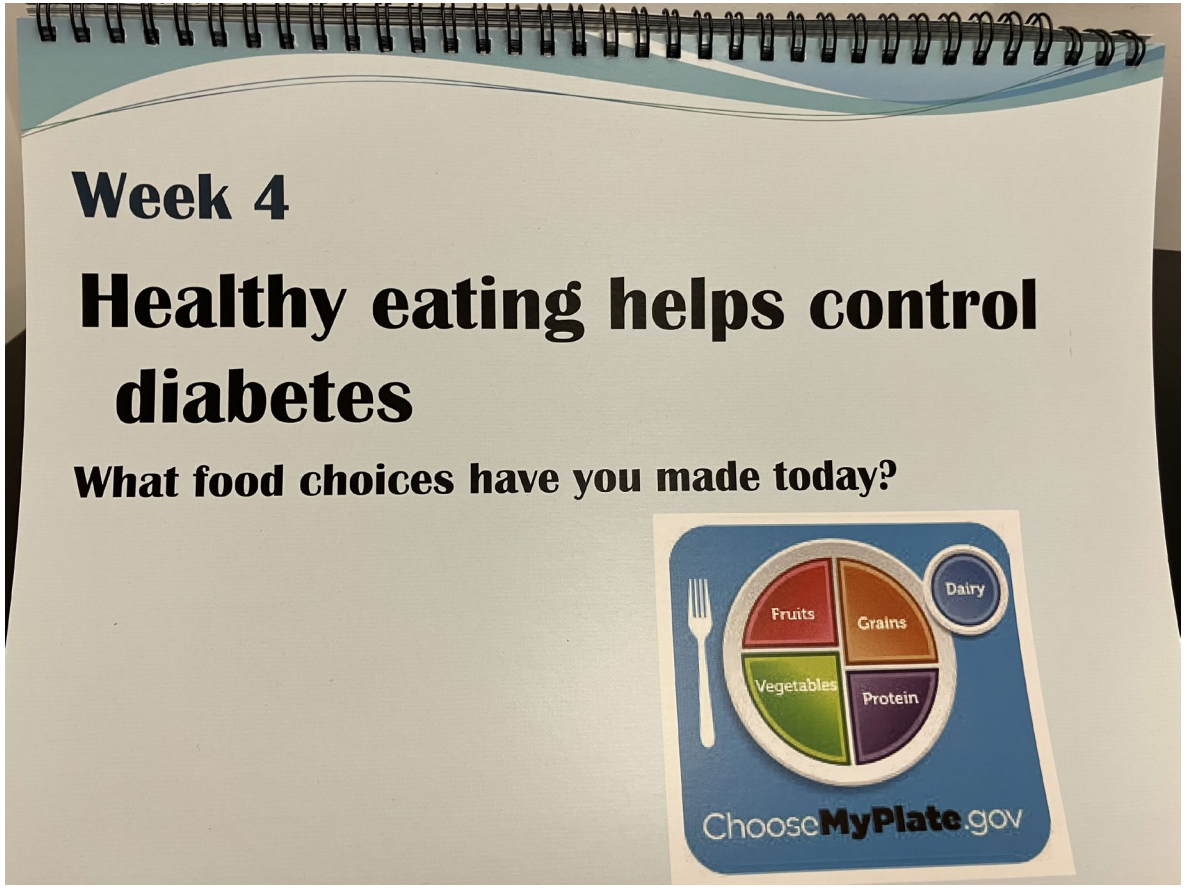
Modality	Examples
Structural and timing	• Change timing of doses (for sleep disturbance or daytime nausea) • Split doses of medication (for pill burden or nausea) • Positioning (e.g., sit upright after doses to avoid reflux)
Psychological	• Contextualisation o "Can you tolerate the joint discomfort knowing that pyrazinamide will stop in 2 weeks?" o "In case you stop this drug, the treatment duration of other drugs will have to be prolonged?") • Reassurance ("The urine colour change is from your rifampicin, and isn't harmful") • Education ("Your cough is likely caused by TB rather than your medication")
Pharmacological	• Analgesia (for joint pain) • Anti-emetics (for nausea/vomiting), confirm that this is not caused by hepatotoxicity (LFT) • Antihistamines (for itch, non-severe rash) • Change of drugs within a class (e.g., moxifloxacin for levofloxacin) • Supplemental levothyroxine if hypothyroidism due to TB drugs • Management of peripheral neuropathy with (increased) vitamin B6 supplementation with INH (limited data)
Topical therapies	• Moisturisers and/or sunscreen (for dry skin) • Makeup or coloured skin products (for clofazimine discoloration) • Anti-acne topical medication (for acne associated with INH use, especially the face)

Singh et al, *IJLTD*, 2023
Clinical Standards for the Management of Adverse Effects During Treatment for TB

Addressing overlapping comorbidities with gradual education for stage of TB treatment/recovery



Virginia Dept of Health- still in use?



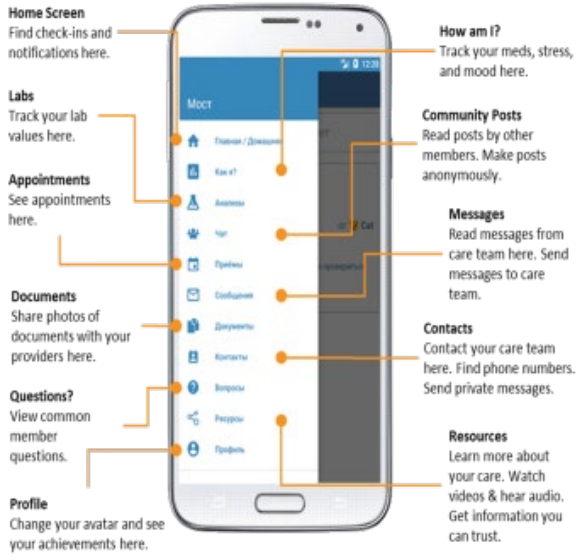
High quality drug susceptibility testing

pretomanid

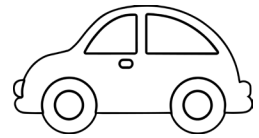
Regimen choice based on preference and host factors: 4 month DS-TB, 6 months RR-TB: many others in operational research

Community based

Peer support

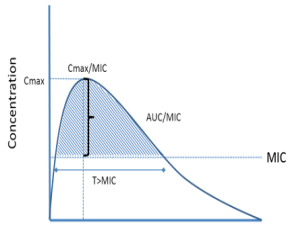


Person centered TB care



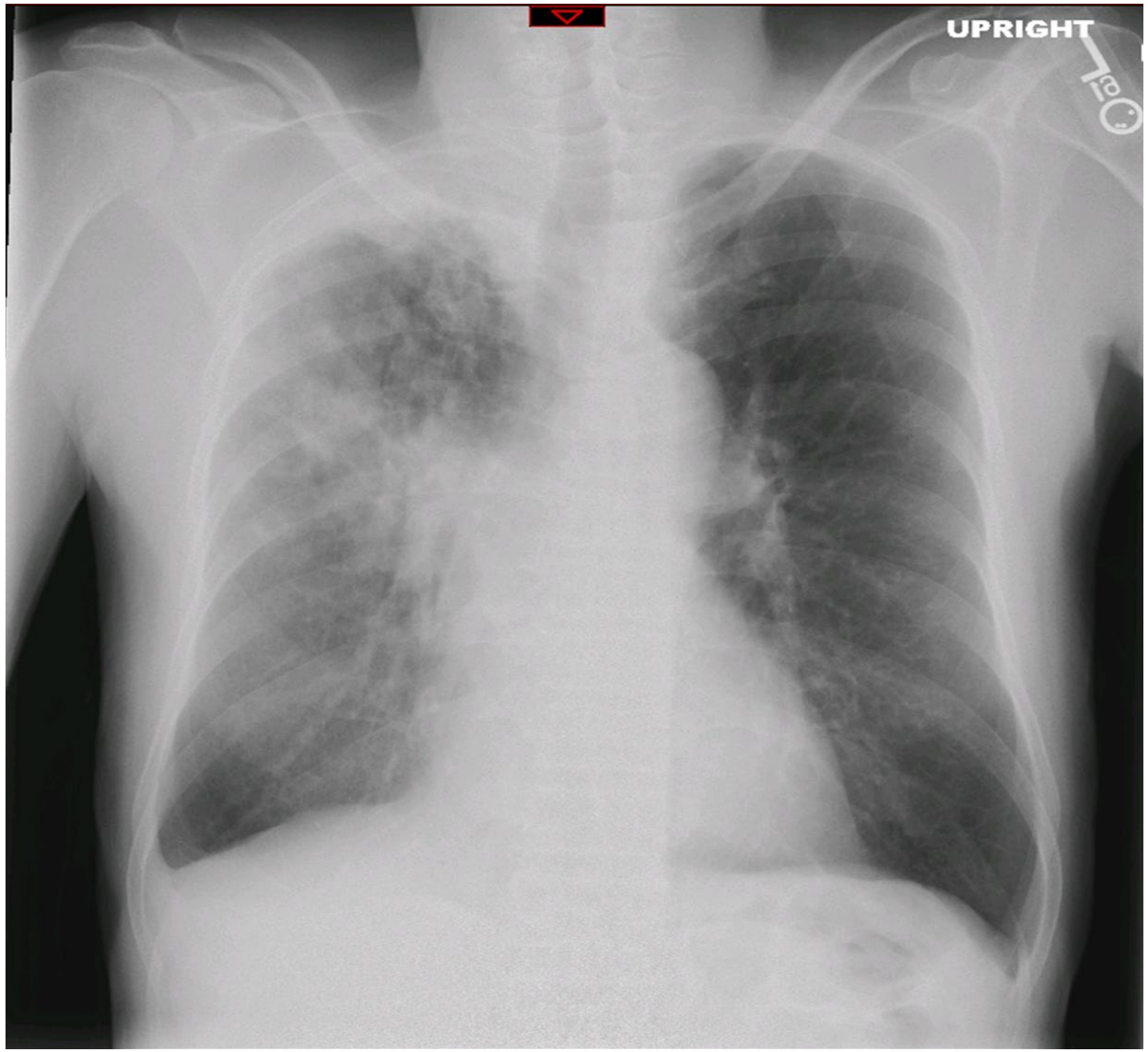
Mitigation of catastrophic and hidden costs

Provider access



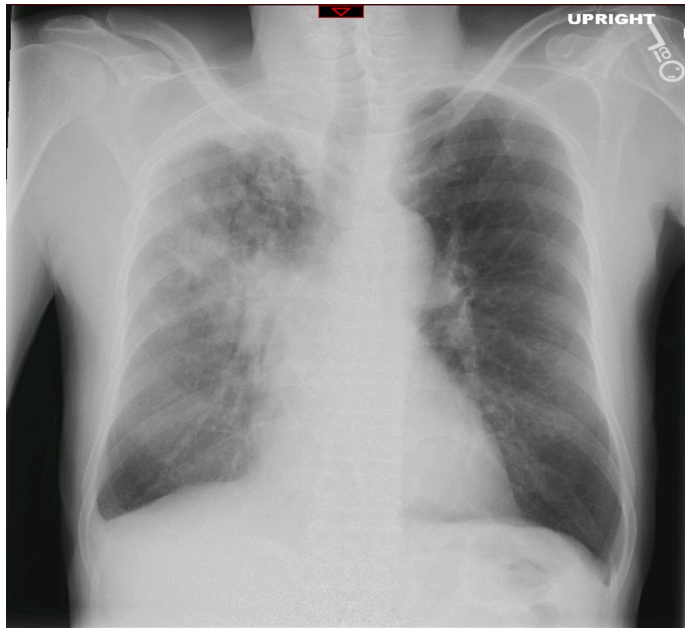
Optimized dosages

Let’s finish and synthesize with a representative person with new TB disease



A representative person with TB and DM/malnutrition

70 year-old man was admitted to the hospital with 2 weeks of fever



ROS also elicits a chronic cough

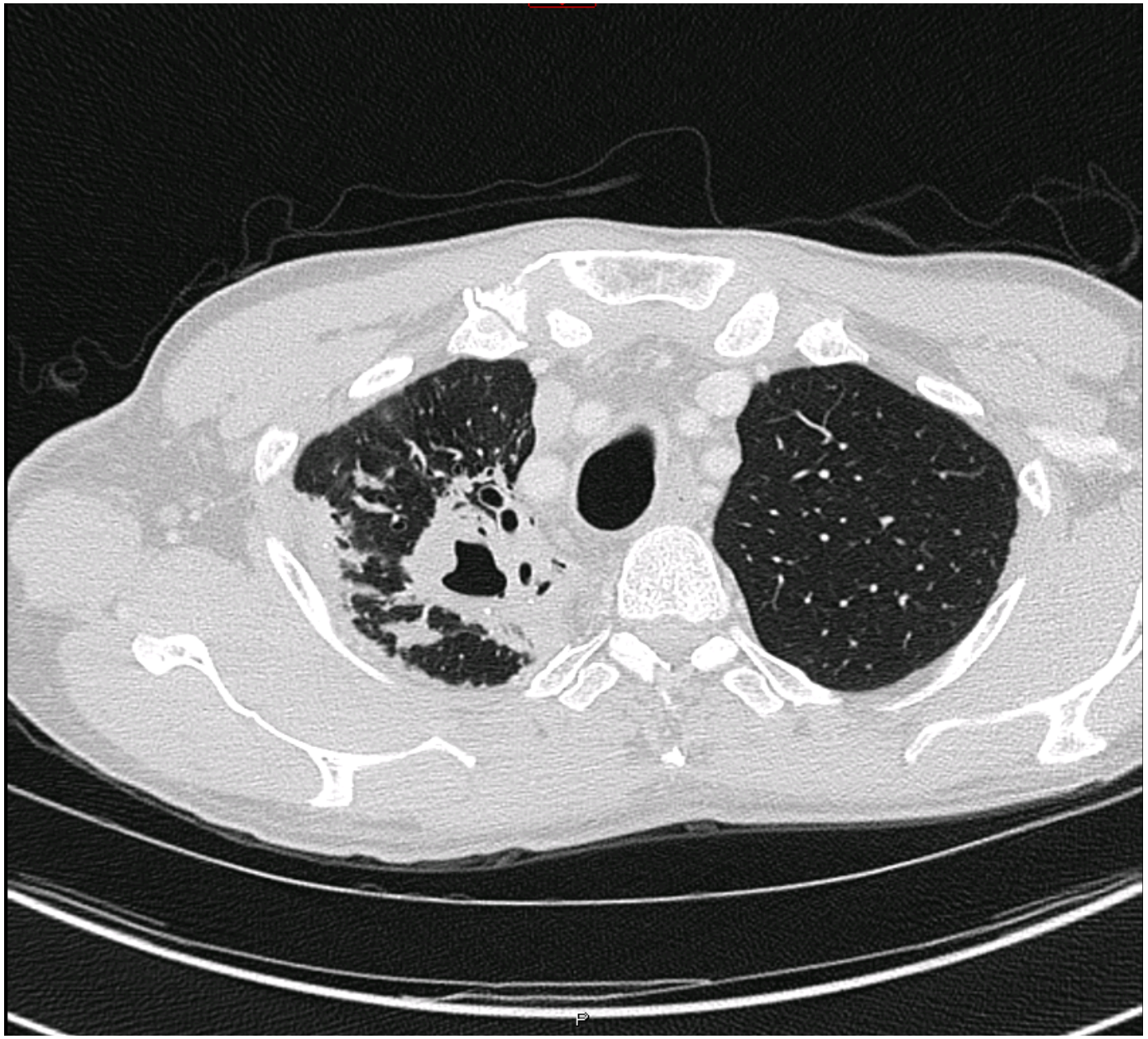
Fever wakes him at night, though does not soak the bed sheets, and accompanied by significant malaise. He notes 6-7 kg weight loss over the past 3 months but also taking a new medication for diabetes (pioglitazone)

He is originally from Ghana and returned recently following a 6 month visit. In Ghana he did not remember any TB contacts.

He is HIV negative, but has a known history of high blood pressure and Type II Diabetes (not regular fingerstick monitoring) and recent HgbA1c 9.5% prior to pioglitazone*

Weight 60 Kg BMI 18.8*

*Diabetes plus Undernutrition

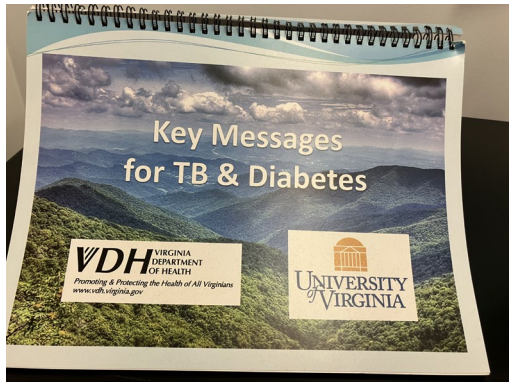


Multiple sputum specimens
2-3+ AFB smear pos

***M. tuberculosis* complex**

Xpert rifampin susceptible

Started on:
Isoniazid 300 mg daily
Vitamin B6 50 mg daily
Rifampin 600 mg daily
Pyrazinamide 1500 mg daily
Ethambutol 1200 mg daily

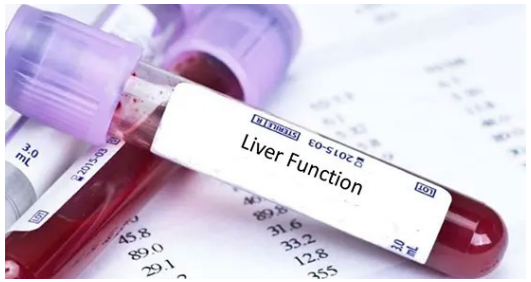


→ Food insecurity

Nutritional supplement (Boost)

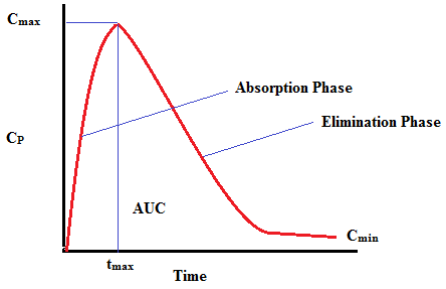
Grocery store vouchers

Adherence support for blood sugar monitoring



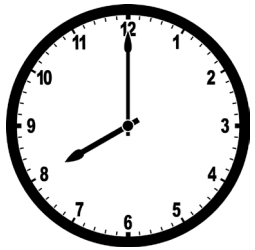
→ Mild nausea, at one week increase in ALT and AST ~ 3 x ULN

Medications held, sequentially added back rifampin + ethambutol, then isoniazid and *discontinued* pyrazinamide. Option for 4 month regimen?



→ Below Cmax target of RIF and INH

Dose increased **rifampin to 900 mg and isoniazid to 450 mg**



→ Poor appetite and malaise during day, lack of weight gain

Moved all medications to evening before bed to maximize daytime caloric intake

Thank you!

Scott Heysell

skh8r@uvahealth.org