

# Latest Scientific Updates on HIV & TB co-infections, including TPT

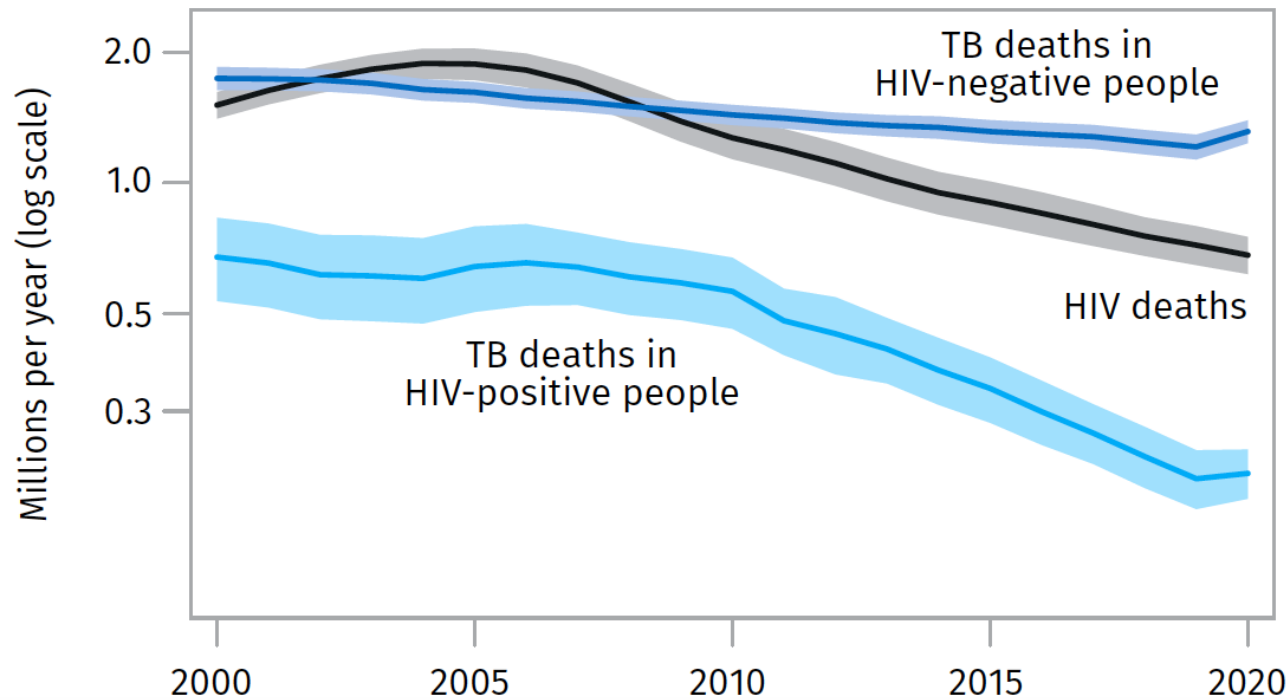
**Darma Imran**

Cipto Mangunkusumo Hospital - Jakarta  
Faculty of Medicine University of Indonesia

# Topic

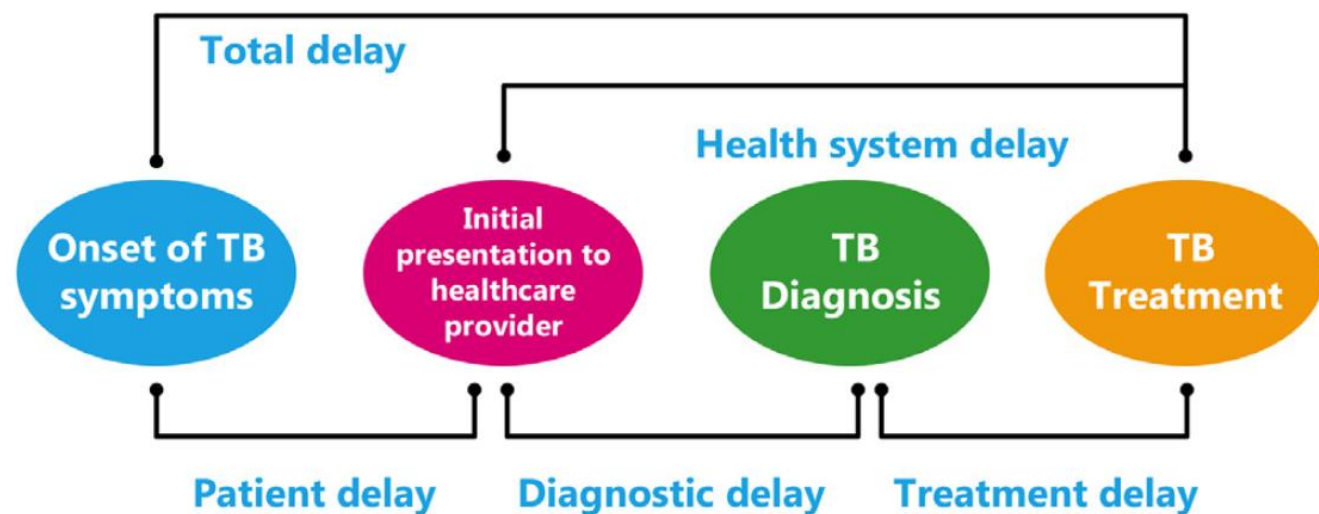
1. Impact of Covid-19 on HIV-TB Death in 2019-2020
2. Barriers to healthcare engagement in TB
3. TB Screening
4. TB diagnostic
5. TB Preventive Therapy (TPT)
6. Treatment of HIV-TB and TB Meningitis

# Impact of Covid-19 on HIV-TB Death in 2019-2020



- **2006 – 2019**
  - 68% decline in TB deaths among people living with HIV
- **2021 (Global Tuberculosis Report):**
  - TB deaths among PLHIV increased for the first time in 13 years
  - from 209.000 in 2019 to → 214.000 in 2020

# Barriers to healthcare engagement in TB



**50%**

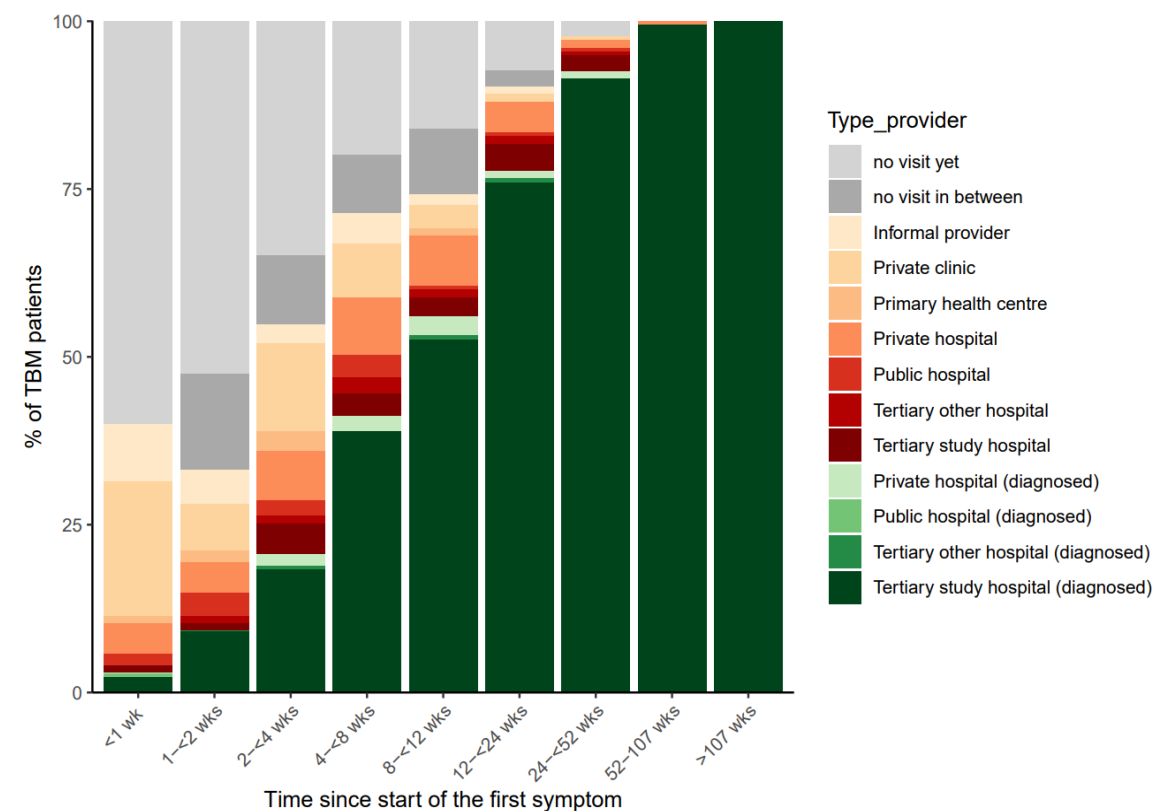
had one month delay in seeking care for their symptoms

Patient pathways and delays to diagnosis and treatment of tuberculosis in an urban setting in Indonesia

*B.W. Lestari, The Lancet Regional Health 2020*

# Tuberculous meningitis patient pathways and delays to diagnosis in Indonesia: a retrospective cohort analysis 2020

- RSHS (Bandung) & RSCM (Jakarta)
- Median total delay from onset of first symptoms to TBM diagnosis was 66 days (IQR 31-138).
  - Some patients were diagnosed with TBM around two years after onset of symptoms.
- Patients had a median 5 healthcare visits (IQR 3-8), up to a maximum of 24 visits for one patient



# Screening TB symptoms to initiate TPT

\*TPT = TB preventative therapy



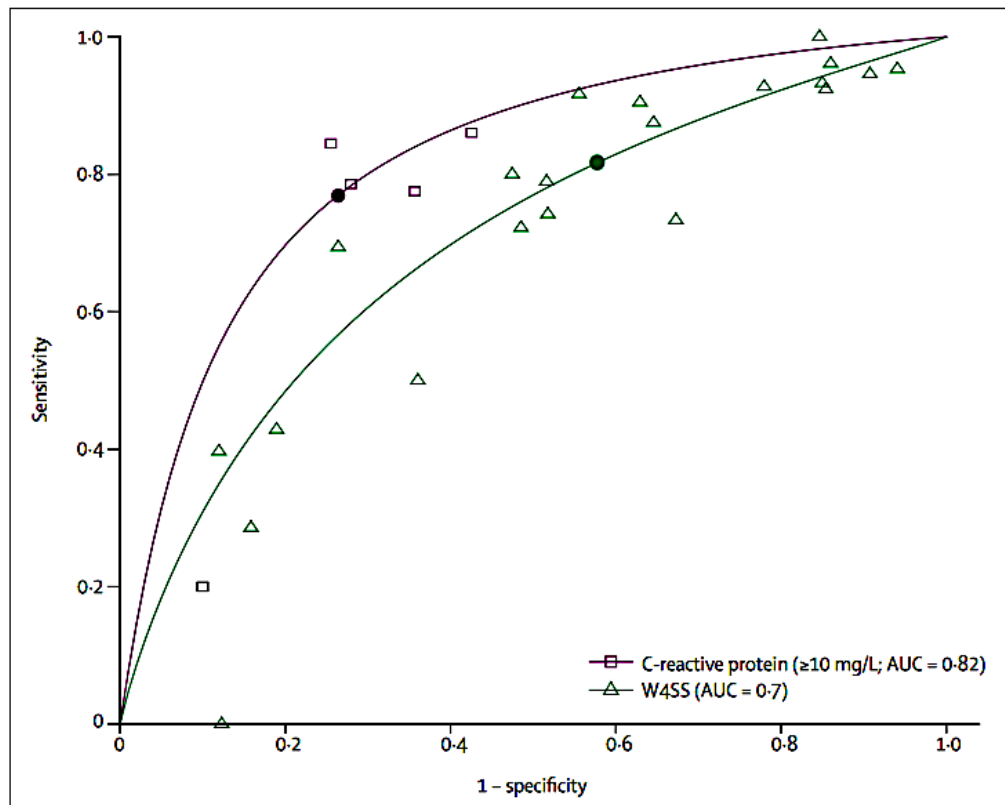
## WHO 4-symptoms screening:

1. Presence of cough
2. Fever
3. Night sweats
4. Weight loss

**Poor specificity**

Positive screening still require confirmatory testing before TPT could be initiated → **barrier to prompt initiation of TPT**

# C-reactive protein TB screening in HIV



**CRP-based screening had higher specificity compared with WHO 4-symptom screening**

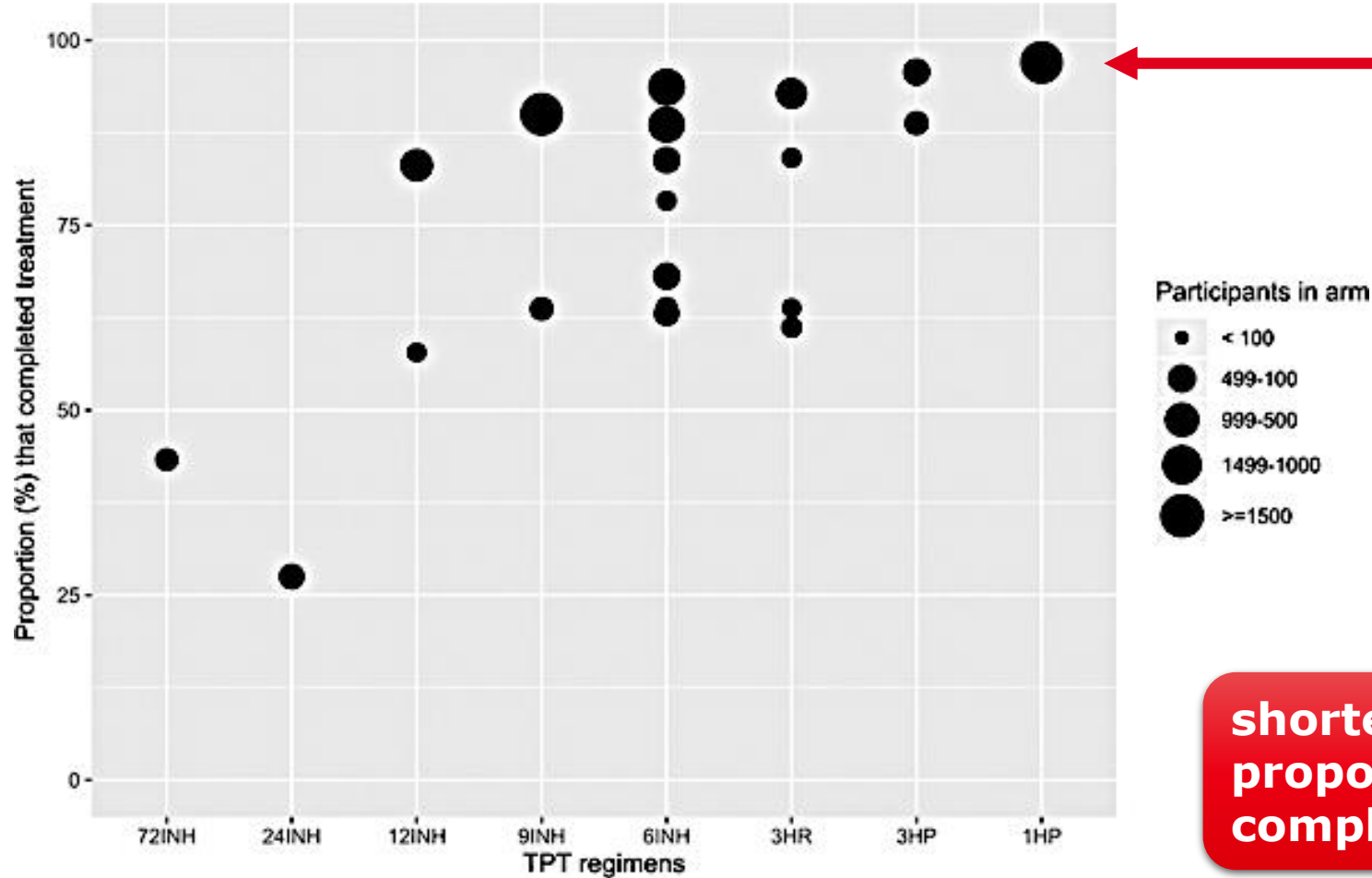
- **WHO 4-symptom screen**
  - Sensitivity 82%
  - Specificity 42%
- **CRP > 10 mg/L**
  - Sensitivity 77%
  - Specificity 74%

Dhana et al. Tuberculosis screening in HIV (meta-analysis). *Lancet Infect Dis* 2022

# TB Preventative Therapy (TPT)

- People living with HIV with latent TB infection are 20 times more likely to develop active TB. Initiation of ART not prevent reactivation of latent TB.
- The Temprano randomized controlled trial(RCT) found that 6 months of TPT reduced TB mortality by 39%.
- WHO Global tuberculosis report 2020: only 21% of eligible PLHIV initiated TPT globally.





One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis Swindells, NEJM 2019

**shorter regimens had the highest proportions of treatment completion**





Yanes-Lane et al. Tuberculosis preventive therapy for people living with HIV: A systematic review and network meta-analysis. PLOS Medicine. 2021

# Latent Tuberculosis Infection Treatment Regimens

Treatment regimens for latent TB infection (LTBI) use isoniazid (INH), rifapentine (RPT), or rifampin (RIF). CDC and the National Tuberculosis Controllers Association preferentially recommend short-course, rifamycin-based, 3- or 4-month latent TB infection treatment regimens over 6- or 9-month isoniazid monotherapy.

Clinicians should choose the appropriate treatment regimen based on drug susceptibility results of the presumed source case (if known), coexisting medical conditions (e.g., HIV\*), and potential for drug-drug interactions.

[https://www.cdc.gov/mmwr/volumes/69/rr/rr6901a1.htm?s\\_cid=rr6901a1\\_w](https://www.cdc.gov/mmwr/volumes/69/rr/rr6901a1.htm?s_cid=rr6901a1_w)

	DRUG	DURATION	FREQUENCY	TOTAL DOSES	DOSE AND AGE GROUP
Preferred	ISONIAZID <sup>†</sup> AND RIFAPENTINE <sup>††</sup> (3HP) 	3 months	Once weekly	12	<b>Adults and children aged ≥12 yrs</b> INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum RPT: 10–14.0 kg; 300 mg; 14.1–25.0 kg; 450 mg; 25.1–32.0 kg; 600 mg; 32.1–49.9 kg; 750 mg; ≥50.0 kg; 900 mg maximum <b>Children aged 2–11 yrs</b> INH <sup>†</sup> : 25 mg/kg; 900 mg maximum RPT <sup>††</sup> : See above
	RIFAMPIN <sup>§</sup> (4R) 	4 months	Daily	120	<b>Adults:</b> 10 mg/kg; 600 mg maximum <b>Children:</b> 15–20 mg/kg <sup>‡</sup> ; 600 mg maximum
	ISONIAZID <sup>†</sup> AND RIFAMPIN <sup>§</sup> (3HR) 	3 months	Daily	90	<b>Adults</b> INH <sup>†</sup> : 5 mg/kg; 300 mg maximum RIF <sup>§</sup> : 10 mg/kg; 600 mg maximum <b>Children</b> INH <sup>†</sup> : 10–20 mg/kg <sup>‡</sup> ; 300 mg maximum RIF <sup>§</sup> : 15–20 mg/kg; 600 mg maximum
Alternative	ISONIAZID <sup>†</sup> (6H/9H) 	6 months	Daily	180	<b>Adults</b> Daily: 5 mg/kg; 300 mg maximum Twice weekly: 15 mg/kg; 900 mg maximum <b>Children</b> Daily: 10–20 mg/kg <sup>‡</sup> ; 300 mg maximum Twice weekly: 20–40 mg/kg <sup>‡</sup> ; 900 mg maximum
		9 months	Twice weekly <sup>*</sup>	52	
			Daily	270	
			Twice weekly <sup>*</sup>	76	

Red box :  
adopted by our  
current guideline

\*For persons with HIV/AIDS, see Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV available at: <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-ary/367/overview>.

<sup>†</sup>Isoniazid is formulated as 100-mg and 300-mg tablets.





<sup>††</sup>Rifapentine is formulated as 150-mg tablets in blister packs that should be kept sealed until use.

<sup>\*</sup>Intermittent regimens must be provided via directly observed therapy (i.e., a health care worker observes the ingestion of medication).

<sup>§</sup>Rifampin (rifampicin) is formulated as 150-mg and 300-mg capsules.

<sup>‡</sup>The American Academy of Pediatrics acknowledges that some experts use rifampin at 20–30 mg/kg for the daily regimen when prescribing for infants and toddlers (Source: American Academy of Pediatrics).

# Status of the available AlereLAM and FujiLAM against Criteria of Rapid TB Diagnostic (WHO-TPP)

	WHO TPP Criteria	AlereLAM	FujiLAM	Xpert MTB/RIF Ultra Xpert MTB/RIF Smear Microscopy
Sensitivity in HIV positive (independent of CD4 count)	> 65% (not specifically defined for HIV-positives in the TPP)	<b>42%</b> [Bjerrum, S-2019] 	<b>70.7%</b> [Broger, T-2022] 	<b>90% (Xpert MTB/RIF Ultra)</b> [Dorman,S.E-2018] <b>77% (Xpert MTB/RIF)</b> [Dorman,S.E-2018] <b>47% (Microscopy)</b>
Specificity	98%	<b>96–98% against CRS</b> [Shah, M-2016] 	<b>95.7% against CRS</b> [Broger, T.-2019] 	<b>96% (Xpert MTB/RIF Ultra)</b> [Dorman,S.E-2018] <b>98% (Xpert MTB/RIF)</b> [Dorman,S.E-2018] <b>98% (Microscopy)</b>
Time-to-result	< 60 min	25 min	50 min	100 min (Xpert)

Modified from: Bulterys MA et al. Point-Of-Care Urine LAM Tests for Tuberculosis Diagnosis: J Clin Med. 2019

# Treatment of HIV-TB

- **Pulmonary TB**
  - ART should be started within 2 weeks regardless of CD4 cell count following initiation of antituberculosis treatment. [WHO 2021]
- **TB Meningitis:**
  - ART should be delayed at least 4 weeks (and initiated within 8 weeks) after treatment for TB meningitis is initiated.[WHO 2021]
  - **There is increasing evidence that we are underdosing RIF in many people with TB and that higher RIF doses are safe and well tolerated**

Dooley KE. Am J Respir Crit Care Med 2018

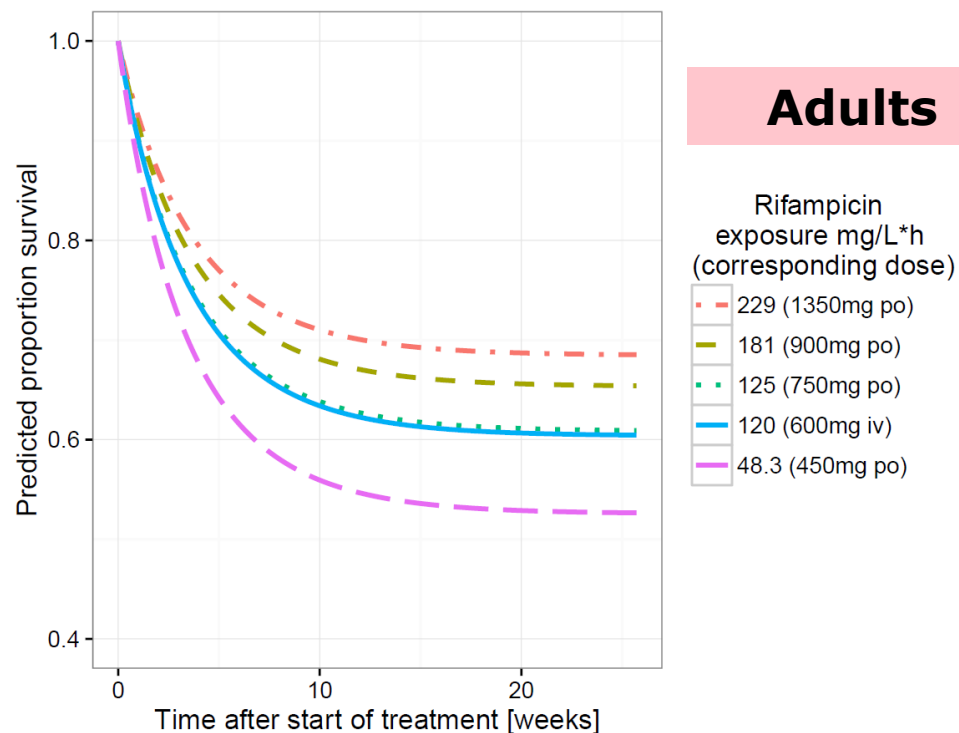
# Do TB Drugs get to the site of infection? And how do we measure this?

WHO recommends 2HRZE/10HR with R dose of 10-20 mg/kg for TBM

Drug	CSF:serum ratio*
Isoniazid	0.8-1.0
Rifampicin	0.04-0.11
Pyrazinamide	0.79-1.05
Ethambutol	Negligible (<MIC even with meningitis)
Ethionamide	Good
Fluoroquinolones	0.7-0.8
Streptomycin	Poor, decreases with restoration of blood-brain barrier on treatment

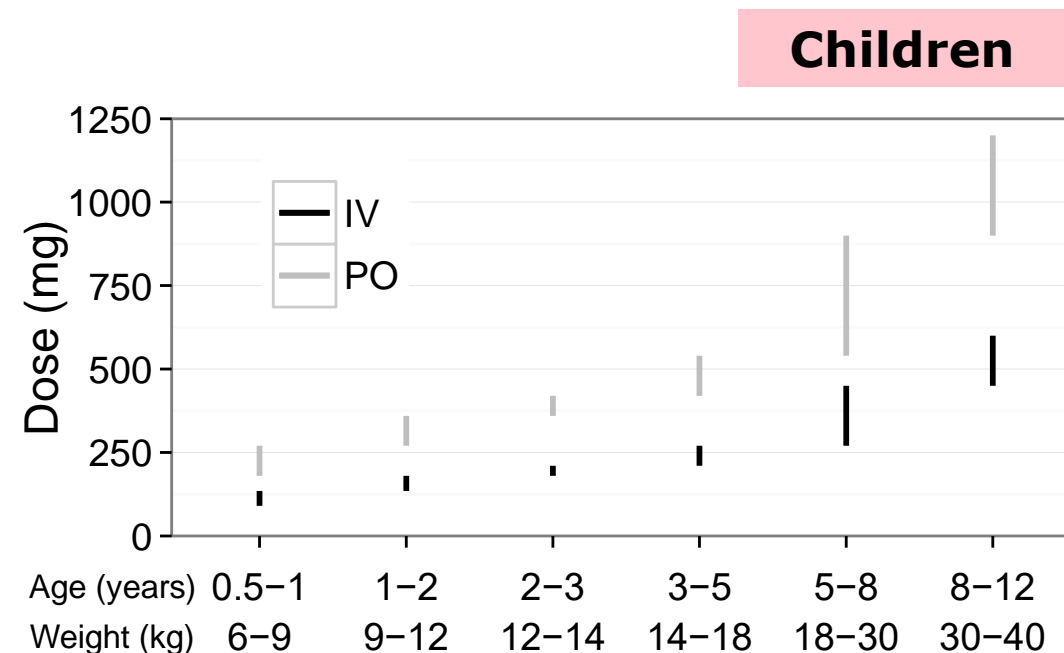
Slide from Kelly Dooley, MD, PhD - 3rd Tuberculous Meningitis International Consortium Meeting, Lucknow, India March 1<sup>st</sup> & 2nd, 2018  
Donald (2010) Tuberculosis 90: 279.

# Right dose of Rifampicin for TBM?



**Survival in adults with TBM dramatically increased as oral dose goes from 10 mg/kg (450 mg) to 30 mg/kg (1350 mg)**

Svensson et al Union Meeting, the Hague , 2018

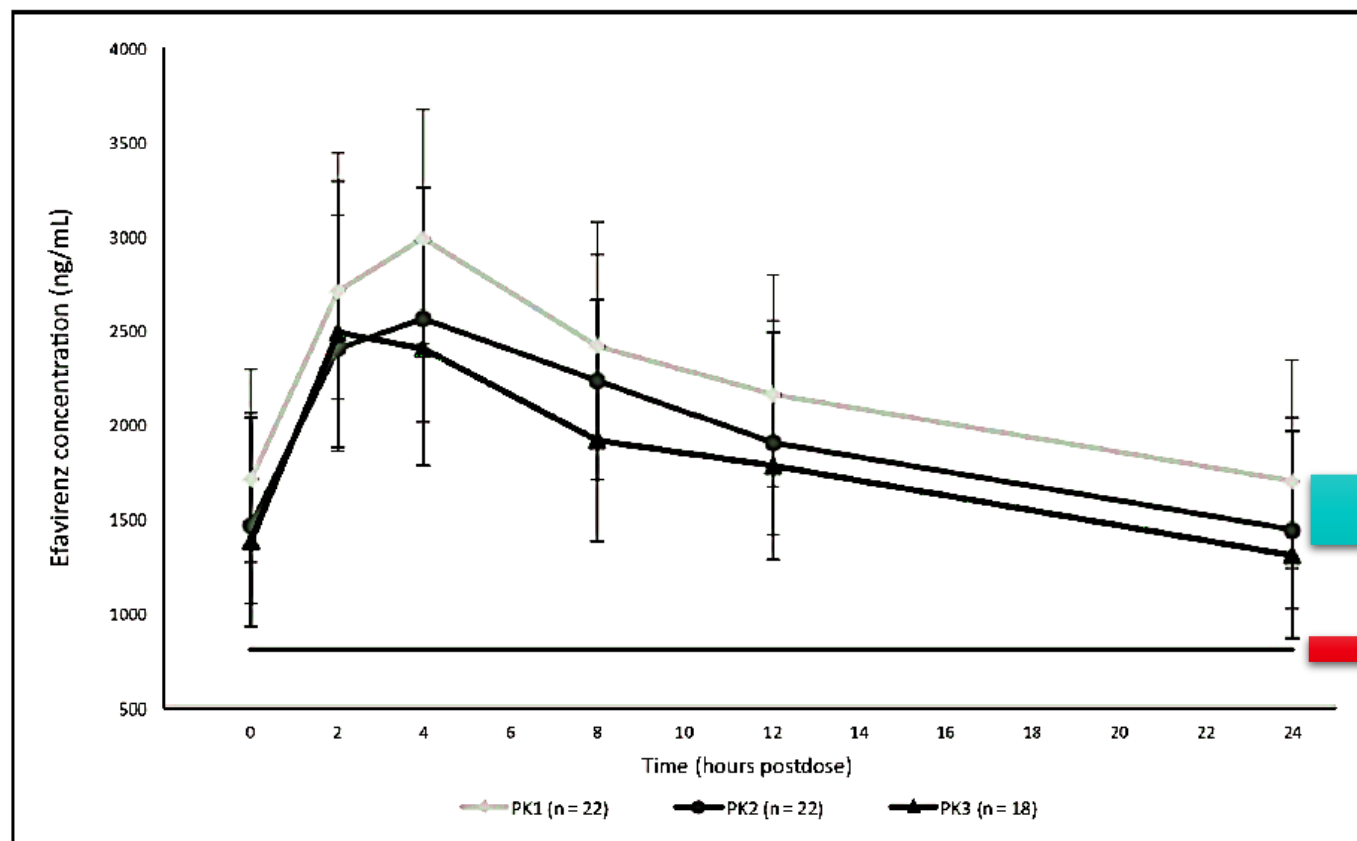


**To achieve the target exposure associated with reduced mortality in adults (Cmax of about 22), children would need at least 30 mg/kg of oral rifampicin daily**

Savic et al CPT 2015 98:622.

# Pharmacokinetics of Efavirenz 400 mg Once Daily Coadministered with Isoniazid and Rifampicin in Human Immunodeficiency Virus-Infected Individuals

Cerrone M et al. Clin Infect Dis. 2019



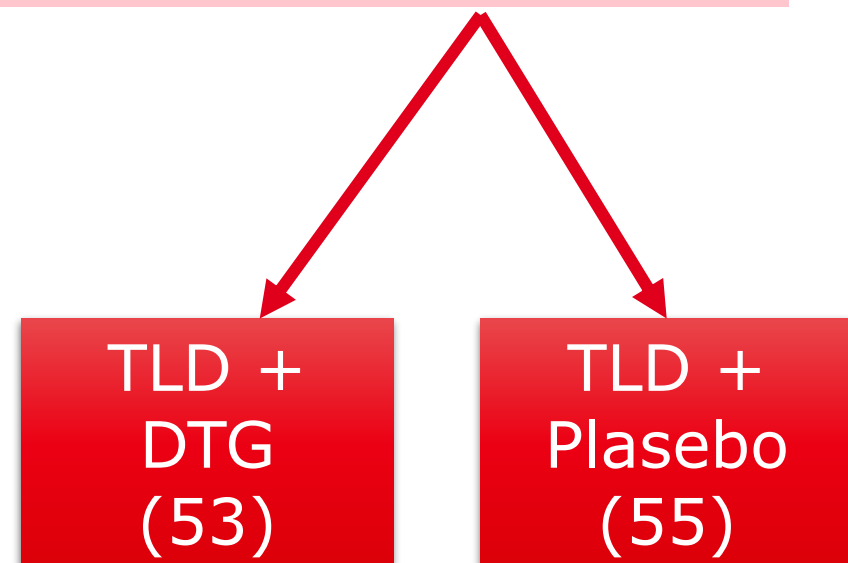
Although this findings are being confirmed by EFV PK determinations in PLWH coinfectd with TB, the result demonstrate for the first time that EFV400 can be coadministered with INH/RIF-containing anti-TB treatment

PK Study of Efavirenz 400

This line indicates the 800 ng/mL EFV concentration cutoff

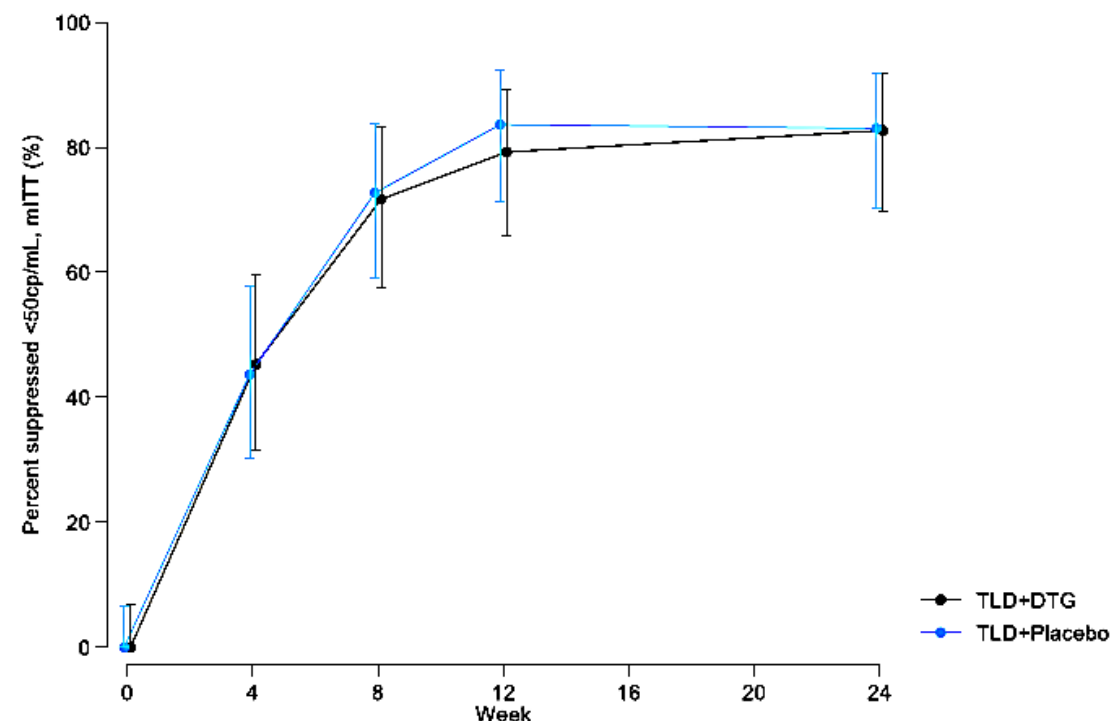
# Standard versus double dose dolutegravir in patients with HIV-associated tuberculosis: a phase 2 non-comparative randomised controlled (RADIANT-TB) trial

Griesel R, Hill A et al. Wellcome Open Res. 2021



Virological suppression at week 24  
in both arms were acceptable

Figure 2: Virological suppression over time (HIV-1 RNA <50 copies/mL) by mITT analysis





# Efficacy of high-dose RIF against EFV dan DTG?


STUDY PROTOCOL

Open Access

Pharmacokinetics, SAfety/tolerability, and EFficacy of high-dose RIFampicin in tuberculosis-HIV co-infected patients on efavirenz- or dolutegravir-based antiretroviral therapy: study protocol for an open-label, phase II clinical trial (SAEFRIF)



Ongoing study

Ruth Nabisere<sup>1</sup>, Joseph Musaaazi<sup>1</sup>, Paolo Denti<sup>2</sup>, Florence Aber<sup>1</sup>, Mohammed Lamorde<sup>1</sup>, Kelly E. Dooley<sup>3</sup>, Rob Aarnoutse<sup>4</sup>, Derek J. Sloan<sup>5</sup> and Christine Sekagya-Wiltshire<sup>1\*</sup> 

# Conclusions

1. The increase in TB deaths among people living with HIV is alarming and need urgent action.
2. Delays in detection and initiation of tuberculosis treatment can be barriers to effective disease control.
3. CRP is an attractive candidate as a triage test for TB-HIV.
4. TPT with shorter regimens had the highest proportions of treatment completion.
5. Based on current publication available Urine LAM meets WHO high priority TPP requirements.
6. There is increasing evidence that we are underdosing RIF in many people with TBM and that higher RIF doses are safe and well tolerated.



International AIDS Society

[iasociety.org](http://iasociety.org)



# Thank you

**Darma Imran**

Cipto Mangunkusumo Hospital - Jakarta  
Faculty of Medicine University of Indonesia  
Email: [darma\\_Imran@yahoo.com](mailto:darma_Imran@yahoo.com)

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