TB preventive therapy for adults with HIV

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How Soon after Infection with HIV Does the Risk of Tuberculosis Start to Increase? A Retrospective Cohort Study in South African Gold Miners

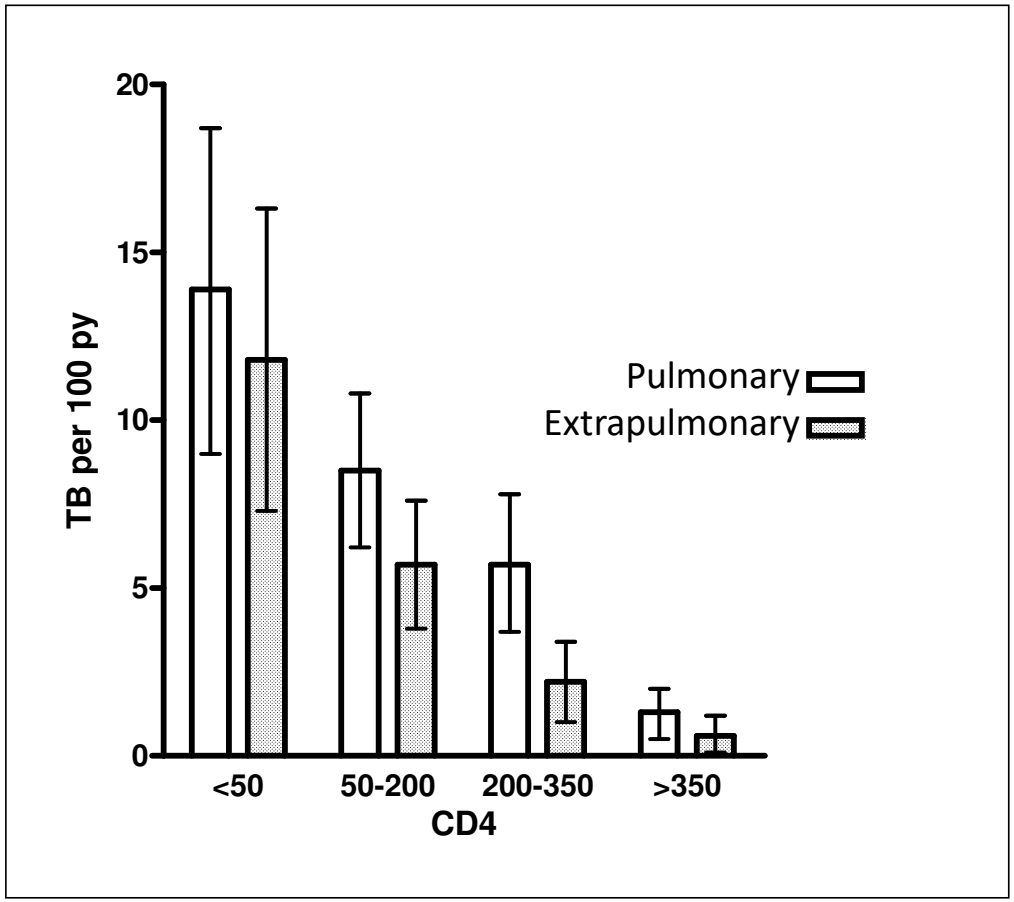
Pam Sonnenberg,[1] Judith R. Glynn,[1] Katherine Fielding,[1] Jill Murray,[2] Peter Godfrey-Faussett,[1] and Stuart Shearer[3]

TB incidence doubled within the first year of HIV infection

(adjusted RR 2.1 [95% CI, 1.4–3.1])

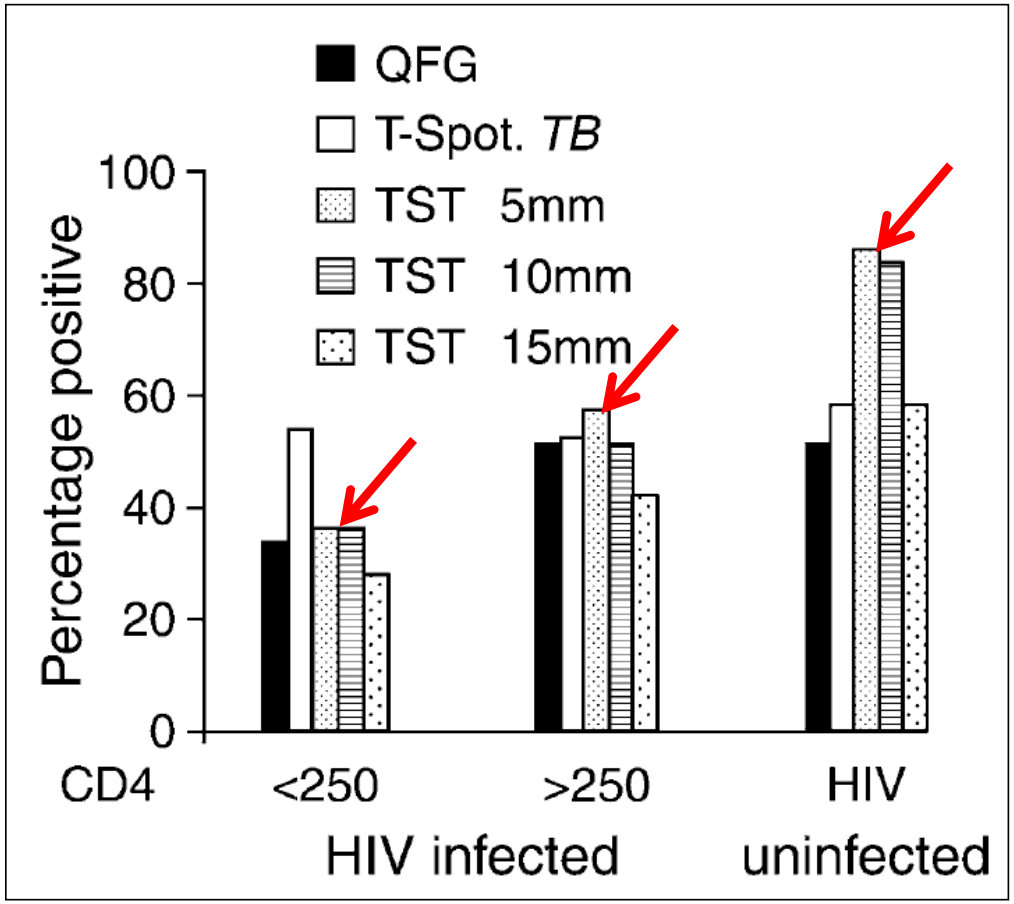
JID 2005;191:150

Incidence of TB in HIV+ by CD4 count: Cape Town pre-ART era



Holmes JAIDS 2006;42:464-9

Tests for diagnosing latent TB infection: IFN-γ release assays vs Mantoux



Rangaka, Am J Respir Crit Care Med 2007;175:514

- TB risk increases exponentially as CD4 declines
- Tuberculin skin test more likely to be negative in HIV, especially with lower CD4
- Therefore TST should not be useful in deciding which HIV+ patients need preventive therapy

Preventive Rx & TST status: pre-ART studies

TST status	Relative risk (95%CI)
Positive	0.38 (0.25, 0.57)
Negative	0.89 (0.64, 1.24)
Unknown	0.81 (0.49, 1.34)
Combined	0.68 (0.54, 0.85)

Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD000171

Essential to exclude active TB before starting preventive therapy to prevent selection of resistance

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Development of a Standardized Screening Rule for Tuberculosis in People Living with HIV in Resource-Constrained Settings: Individual Participant Data Meta-analysis of Observational Studies

Haileyesus Getahun[1]*, Wanitchaya Kittikraisak[2], Charles M. Heilig[3], Elizabeth L. Corbett[4], Helen Ayles[4,5], Kevin P. Cain[3], Alison D. Grant[4], Gavin J. Churchyard[6], Michael Kimerling[7], Sarita Shah[8], Stephen D. Lawn[4,9], Robin Wood[9], Gary Maartens[10], Reuben Granich[1], Anand A. Date[3], Jay K. Varma[2,3]

Best symptom screen for TB – any one of:

- Cough – active (any duration)
- Fever >2 weeks
- Night sweats
- Weight loss

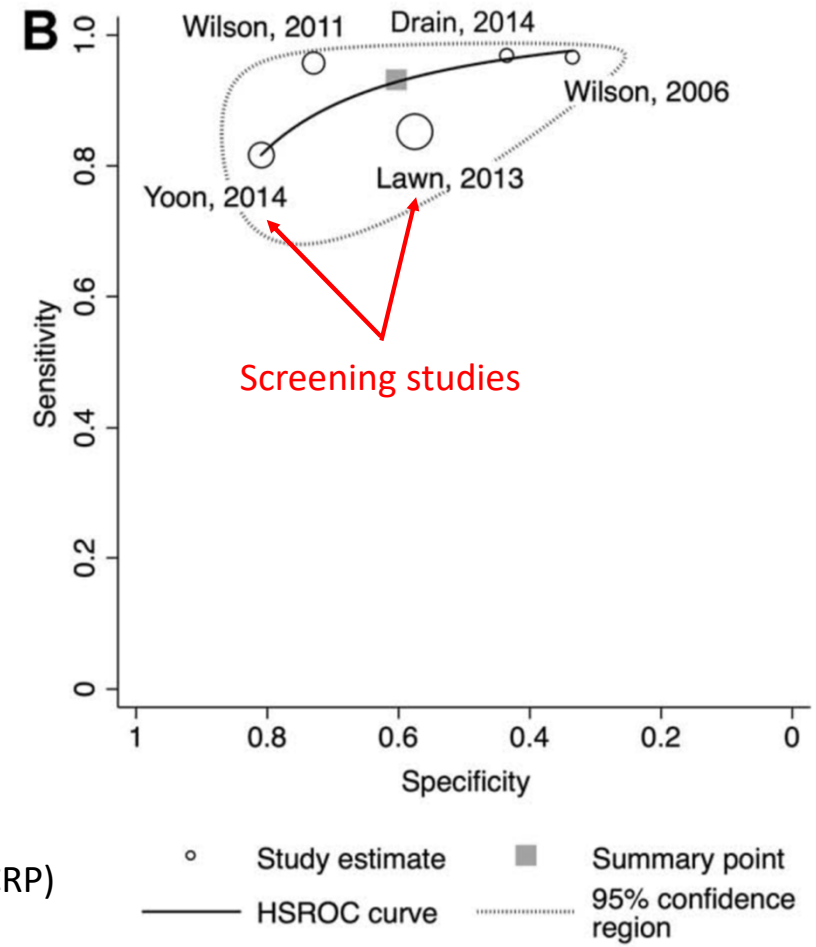
Sensitivity improved:

- Clinical vs community setting
- **Not previously screened for TB**
- Lower CD4 count

Negative predictive value ↓ with ↑ TB prevalence

NPV	TB prevalence
98.3%	5%
92.3%	20%

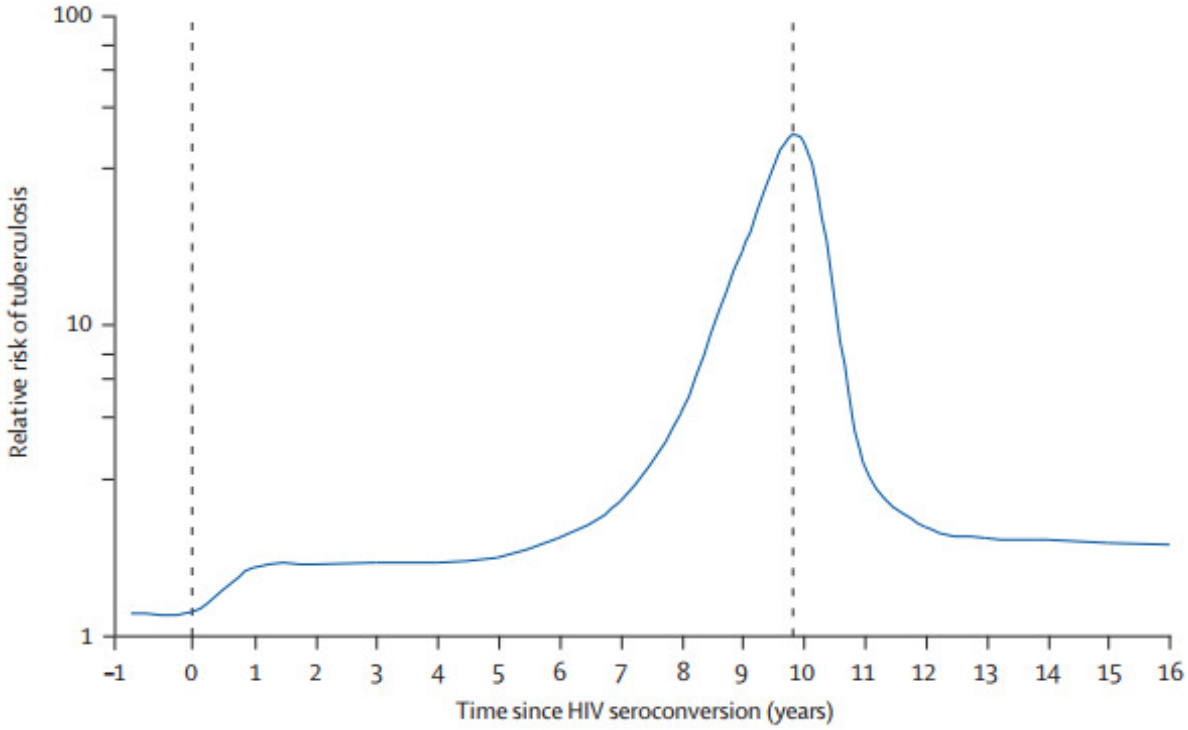
CRP for TB diagnosis in ambulatory PLWH



CRP in normal range makes TB unlikely
Not helpful in inpatients (as many other diseases increase CRP)

IJTLD 2017;21:1013

ART reduces TB incidence, but not to baseline



Lawn Lancet ID 2010;10:489

Effect of ART on WHO TB symptom screen: WHO meta-analysis

	On ART (n=4640)	Not on ART (n=8664)
Sensitivity	51.0% (28.4, 73.2)	89.4% (83.0, 93.5)
Specificity	70.7% (47.8, 86.4)	28.1% (18.6, 40.1)
Negative predictive value:		
TB prevalence 1%	99.3%	98.0%
TB prevalence 5%	96.5%	96.0%

Lancet HIV 2018; 5: e515–23

Effect of ART on chest x-ray (either abnormal or suggests TB): WHO meta-analysis

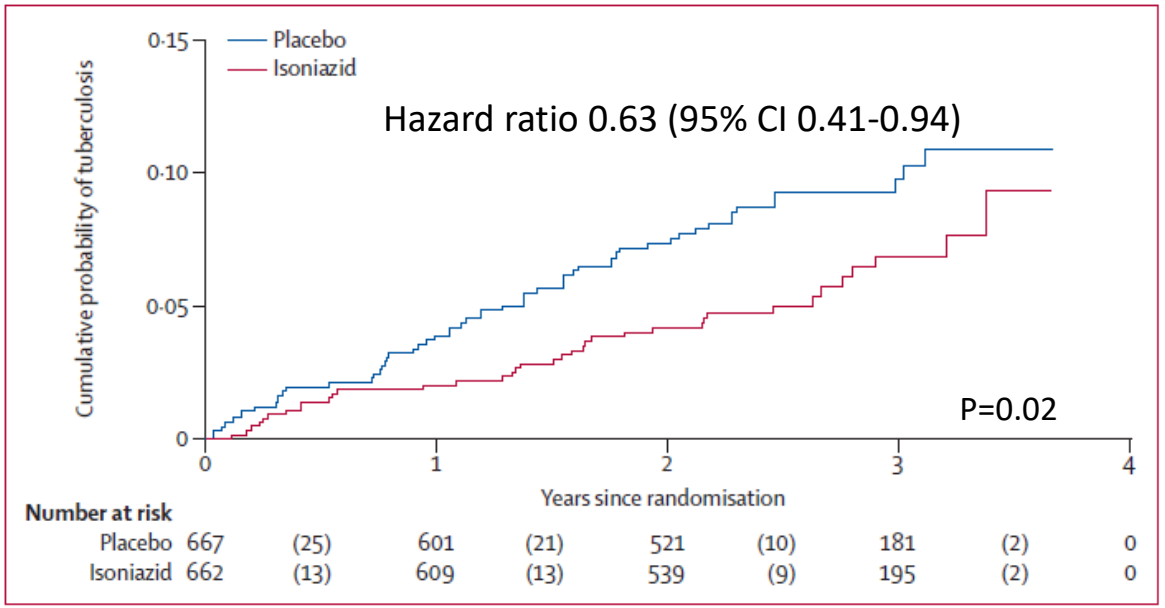
	On ART (n=646)	Not on ART (n=1801)
Sensitivity	↑↑84.6% (69.7, 92.9)	↑94.3% (76.2, 98.8)
Specificity	↓↓29.8% (26.3, 33.6)	↓20.1% (7.6, 43.8)
Negative predictive value:		
TB prevalence 1%	99.5%	99.7%
TB prevalence 5%	97.4%	98.5%

Lancet HIV 2018; 5: e515–23

Should we recommend CXR before TBPT?

- Most clinics have no on-site radiology
- Difficulty in interpreting CXR (computer algorithms show promise)
- Expensive
- Minimal change in negative predictive value
- Important to do CXR in goldminers, who need regular CXR anyway

12H vs placebo with ART, Khayelitsha



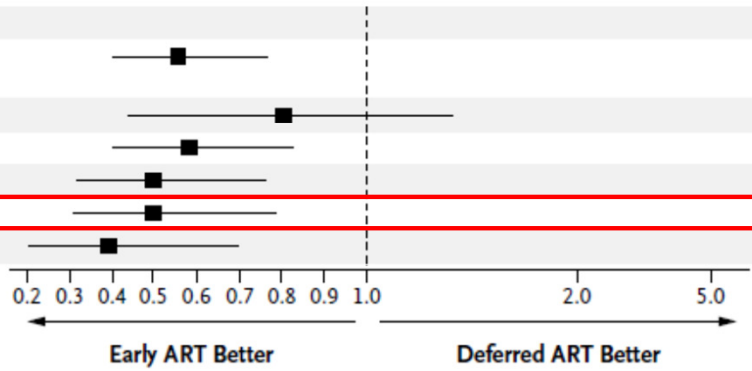
Number needed to treat (prevent 1 case TB) = 25

Number needed to harm (stop study drug due to toxicity) = 100

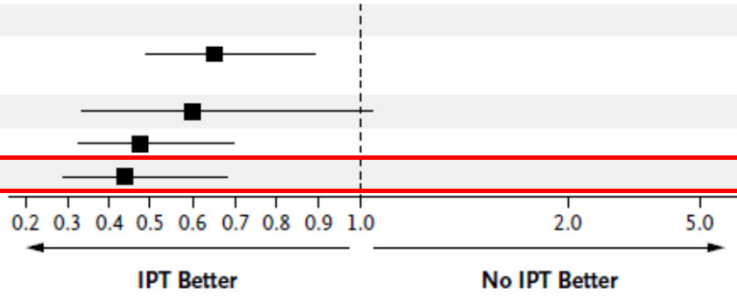
Rangaka Lancet 2014

6H plus early or deferred ART: Cote d'Ivoire

Subgroup	Early ART (groups 3 and 4)			Deferred ART (groups 1 and 2)			Adjusted Hazard Ratio (95% CI)
	no. of patients	*person-yr*	*rate*	*no. of patients*	*person-yr*	*rate*	
All patients							
Death or severe HIV-related illness (primary outcome)	64	2313	2.8	111	2248	4.9	0.56 (0.41–0.76)
Death	21	2520	0.8	26	2502	1.0	0.80 (0.45–1.40)
Death or AIDS	50	2333	2.1	84	2288	3.7	0.58 (0.41–0.83)
AIDS	33	2333	1.4	65	2288	2.8	0.50 (0.33–0.76)
Tuberculosis	28	2337	1.2	55	2298	2.4	0.50 (0.32–0.79)
Invasive bacterial diseases	14	2358	0.6	36	2332	1.5	0.39 (0.21–0.71)



Subgroup	IPT (groups 2 and 4)			No IPT (groups 1 and 3)			Adjusted Hazard Ratio (95% CI)
	no. of patients	*person-yr*	*rate*	*no. of patients*	*person-yr*	*rate*	
All patients							
Death or severe HIV-related illness (primary outcome)	71	2334	3.0	104	2227	4.7	0.65 (0.48–0.88)
Death	18	2538	0.7	29	2484	1.2	0.60 (0.34–1.09)
Death or tuberculosis	42	2372	1.8	83	2263	3.7	0.48 (0.33–0.70)
Tuberculosis	26	2372	1.1	57	2263	2.5	0.44 (0.28–0.69)



TEMPRANO NEJM 2015

Is TST needed with ART? Khayelitsha data

TST did not predict efficacy:

TST- aHR 0.43 (95%CI 0.21, 0.86)

TST+ aHR 0.86 (95%CI 0.37, 2.00)

IGRA did not predict efficacy:

IGRA- aHR 0.43 (95%CI 0.20, 0.96)

IGRA+ aHR 0.55 (95%CI 0.26, 1.24)

Rangaka Lancet 2014

Should IPT be started with ART or delayed?

REALITY trial of enhanced OI prophylaxis + ART with CD4 <100

- Intervention arm started INH day one, control arm week 12 (per country guidelines), duration 3-12 months
- TB incidence reduced 0.67 (95%CI 0.47-0.93)
- Well tolerated

IPT started with ART in Khayelitsha RCT (in those who were ART-naïve)

- Well tolerated

NEJM 2017;377:233
Rangaka Lancet 2014

IPT duration of benefit pre-ART

Zambia - benefit lost at 18 months

Uganda - benefit lost at 1 year

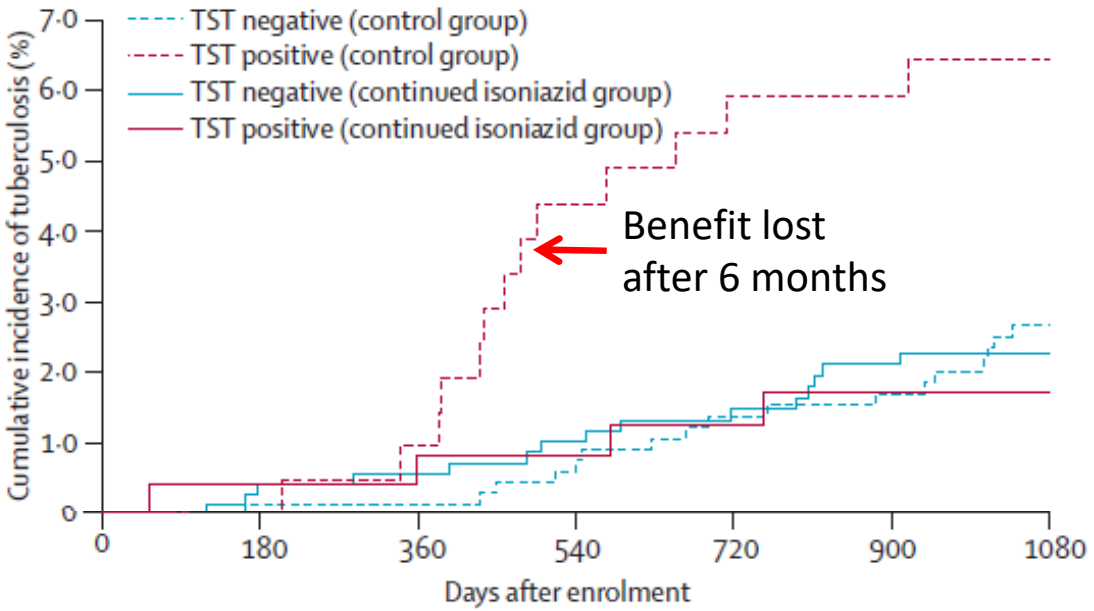
Botswana – benefit of 6H lost after 6 months

Thibela community cluster RCT gold mines SA

- High HIV prevalence
- Benefit lost immediately after 9 months INH

Quigley 2001
Johnson 2001
Samandari Lancet 2011
N Engl J Med 2014;370:301-10

BOTUSA – TB (pre-ART)



TST+ HR 0.08 (0.01–0.61)

TST- HR 0.86 (0.38–1.89)

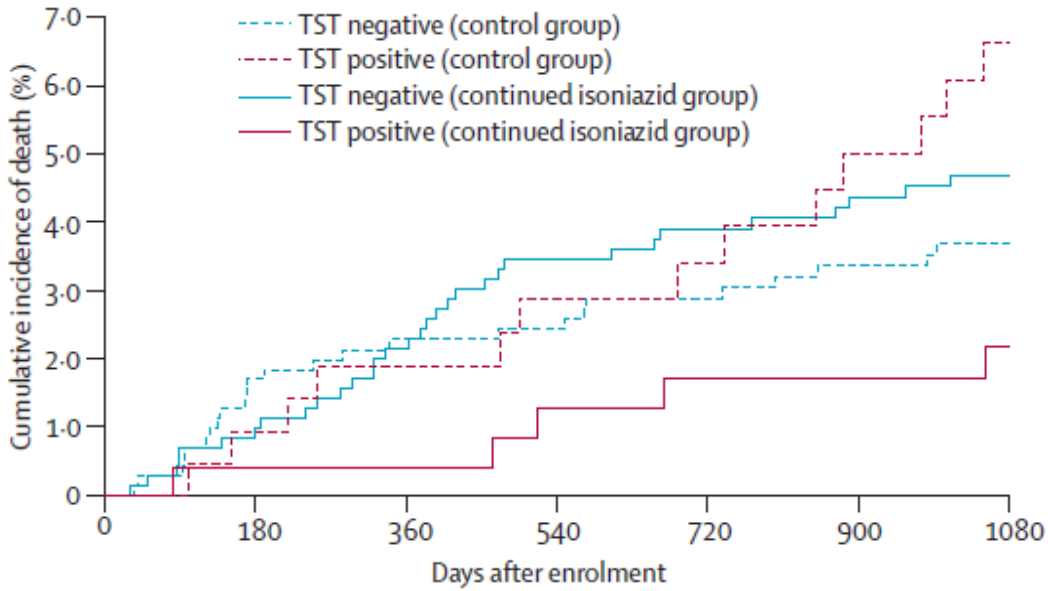
Severe AEs >6 months

1% placebo

1.3% INH

Samadari Lancet 2011

BOTUSA - mortality



TST+ HR 0.28 (0.08–1.03)

TST- HR 2.99 (1.27–7.04)

Longer duration IPT -Soweto trial (pre-ART)

HIV+ not needing ART, all TST+

No significant difference in TB incidence by H duration:

- IRR 0.74 (0.29-1.73; P=0.48) H continuous vs 6 months

On treatment analysis showed benefit for continuous INH for combined endpoint TB or death (P=0.02)

Continuous INH not well tolerated

- Grade 3/4 ALT/AST 5.5% vs 28% H 6 months vs continuous

NEJM 2011;365:11

Duration of benefit of preventive therapy

Mathematical model

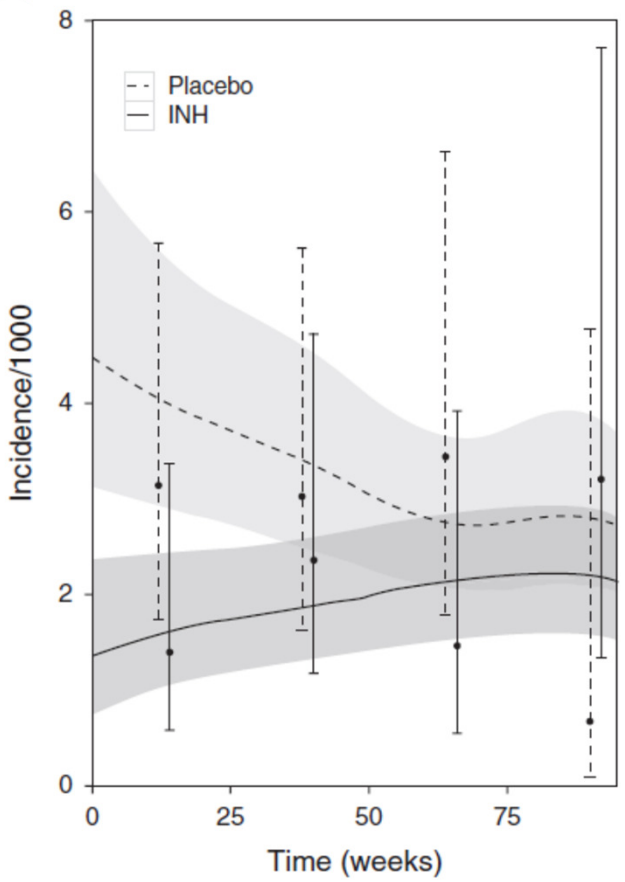
ART-naïve:

LTBI not cured by IPT (median 0%)

INH + rifampicin/rifapentine cures 19-100%

On ART (model based on Khayelitsha IPT ART study):

IPT cures LTBI (median 30%)



Houben, PNAS 2014
Sumner, AIDS 2016;30:1279

WHO 2018

In settings with high TB incidence and transmission, adults and adolescents living with HIV who have an unknown or a positive TST and are unlikely to have active TB disease should receive at least 36 months of IPT, regardless of whether they are receiving ART. IPT should also be given irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy. *(Conditional recommendation, low-quality evidence. Existing recommendation)*

TB preventive therapy in pregnancy

TB APPRISE study in 956 HIV+ pregnant women on ART

- Randomised to start IPT during pregnancy or 12 weeks postpartum
- Hepatotoxicity was similar in both arms
- Few TB events, no significant benefit of IPT during pregnancy
- Adverse pregnancy outcomes more common with IPT during pregnancy (excess 6.7 percentage points; 95%CI 0.8-11.9)

Western Cape observational cohort study

- 43,971 pregnant women; 16.6% received IPT during pregnancy
- Adverse pregnancy outcomes better with IPT (aHR 0.83; 95%CI 0.78-0.87)
- IPT reduced TB, but only with CD4 <350 (aHR 0.51; 95% CI 0.41–0.63)

N Engl J Med 2019;381:1333
Kalk CID 2020

Rifamycin + INH for preventive therapy

Three regimens:

- Rifampicin + INH for 3 months
- **Rifapentine + INH weekly for 3 months**
- Rifapentine + INH daily for 1 month (very few TB events)

All as effective as INH 6-12 months

Tolerability similar to INH (less hepatotoxic, more hypersensitivity)

Shorter regimens have higher completion rates

Important ARV-rifamycin drug-drug interactions

BMC ID 2017;17:265
Ann Intern Med 2017; 167:248
N Engl J Med 2011;365:2155
N Engl J Med 2011;365:11
Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD000171

Resistance and H-rifamycin regimens

H-rifamycin regimens theoretically should be less likely to select for resistance than H with good adherence

Fixed dose combination should reduce the risk of resistance (available for HR, not yet HRPT)

Widespread rifamycin use for prevention may result in rifamycin resistance – programs will likely only accept if administered by DOT, which will stretch resources. Weekly dosing HRPT an advantage

Current SA preventive therapy guidelines

Simplified 2018:

IPT for 12 months with ART, no TST

Pregnant women: start IPT during pregnancy if CD4 <350

Pilot studies underway in SA to inform guidelines:

Rifapentine + INH weekly for 12 doses

Conclusions

Symptom screening less sensitive in people on ART, but negative predictive value is high

RCTs show IPT for 6-12 months effective and well tolerated with ART & may be more durable than pre-ART studies

IPT should be started with ART

Longer duration IPT with ART not based on good evidence & may be harmful

TST does not predict response to IPT on ART

Rifapentine+INH for 12 wks has better completion rates than INH & similar efficacy