Controversies in management of Latent Tuberculosis Infection in People Living with HIV infection in the Asia Pacific region

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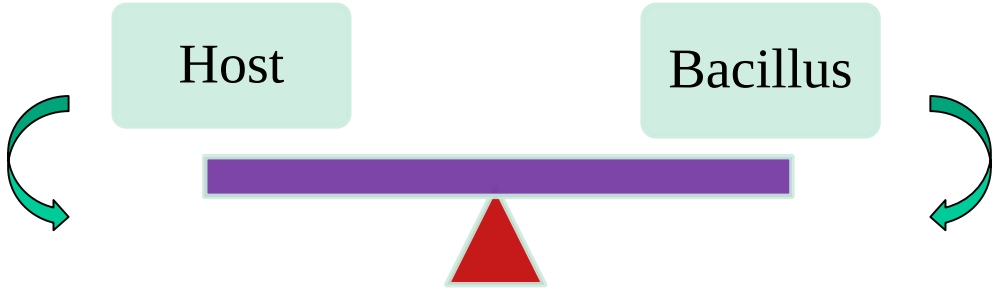
Conflict of Interest Statement

- I have NO conflict of interest to declare
- In this talk, I will revisited some of the basics of "latent tuberculosis infection" and their implications in the interpretation and generalization of available data related to current controversies
- Views to be expressed just represent my personal views.

What is Latent TB Infection?

- Direct identification of the latent bacillus is NOT possible currently.
- A state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens with no evidence of clinically manifest active TB. (WHO LTBI guidelines 2018)
- Immune response cannot differentiate immunity (BCG/NTM and/or exposure or resolved infection), infection or disease

Delicate Balance



- Possible Fluctuations in the Host-Pathogen Balance

- Substantial changes on either side may tip the balance:
  - Higher TB Risk for
    - Recent Infection: esp within first year
    - Soon (6 or 12 months) after Immunosuppression (e.g. TNF blockers, EULER. Ann Rheum Dis. 2010;69:976-86.)
    - Late intervention after infection or change in immune status may miss a substantial part of risk

Diagnostic tools for LTBI

- Measurement of host immune responses to *Mycobacterium tuberculosis* complex
  - Traditional standard: Tuberculin skin test
    - Use PPD (2 unit RT-23 in HK)
  - Interferon-γ release assay (IGRA)
    - Use more specific antigens: ESAT6, CFP10
    - T-Spot.*TB*® (Oxford Immunotec) (Separate monocyte layer from fresh blood)
    - QuantiFERON®-TB Gold in-tube / QuantiFERON®-TB Gold-plus (CD4 + CD8) (QIAGEN) (Fresh whole blood)
  - Skin tests utilizing ESAT-6 and CFP-10
    - C-Tb test (Statens Serum Institut) and Diaskintest (Generium)
  - (Serological tests: not useful so far)

Comparison between LTBI Tests

Leung CC et al. Eur Respir J. 2011;37:690-711

	Tuberculin Skin Test	QuantiFERON®TB-Gold / IT	T-Spot.TB
Antigens	Purified Protein Derivative	ESAT6, CFP10, (TB7.7)	ESAT6, CFP10
	(Complex mixture; Potential cross-reactions)	(Specific; Absent in BCG and most NTM)	(Specific, Absent in BCG and most NTM)
Test Method	Skin test: intradermal/multiple puncture;	Whole blood interferon assay;	Blood monocyte spot test;
	Two visits	Single visit	Single visit
Laboratory Support	No; Clinic / bedside procedure	High; Fresh blood delivery;	Highest; Fresh blood delivery;
		No cell separation	Cell separation required
Interference by BCG	Yes	No	No
Booster Effect	Yes; problem especially in serial testing	No; result by affected by serial testing	No; result by affected by serial testing
	(two tests > 1 week to exclude booster)	(may be affected by prior TST)	(may affected by prior TST)
Choice of cut-off	5, 10, 15 mm in different clinical scenarios	Single	Single
	Trade-off: sensitivity and specificity	Not fully clarified yet	Not fully clarified yet
	Higher disease risk with larger induration	Not fully clarified yet	Not fully clarified yet
Conversion	Criteria established for recent conversion	Not fully clarified yet	Not fully clarified yet
Infection or Disease	Does not distinguish	Does not distinguish	Does not distinguish
Recent vs Remote	Does not distinguish	Does not distinguish adequately	Does not distinguish adequately
Exposure correlation	Some degree, especially if not BCG-vaccinated	Higher	Higher / Highest
Immune compromise	Affected significantly	Less affected	? Least affected
Advance age	Significantly affected	Less affected	Less affected
Proxy sensitivity*	71-82%	QFT-Gold:73-82%;	86-93%
		QFT-Gold IT: 63–78%	
Proxy specificity†	No BCG:95-99%; BCG: low and heterogeneous	No BCG:98-100%; BCG: 94-98%	86-100%
Longitudinal data	Abundant	Scanty	Scanty

***** positive rate in culture-confirmed TB; † negative rate among low risk individuals

Key difference: IGRA not affected by BCG; other differences quantitative

Predicting TB: Meta-analysis

Rangaka MX, et al. Lancet Infect Dis. 2012 ;12:45-55

- All 15 studies (26 680 participants): IGRA+ve: 4-48 TB/1000 person-yrs.

- 7 studies (low/middle income areas, no potential bias):
  - TB Incidence Rate Ratio (test+ vs test-)
    - IGRA: 2·11 [95% CI 1·29-3·46]
    - TST (cutoff 10mm): 1·60 [95% CI 0·94-2·72]
  - proportion of test-positive:
    - IGRAs < TST (reduce number to treat)
  - Neither perform very well: ? because of reinfection ; IGRA marginally (not significantly) better

- Performance of IGRA could be better in high income areas but potential bias prevent firm conclusion.

Chest. 2012 Jul;142(1):63-75. doi: 10.1378/chest.11-3157.

Predictive value of interferon-γ release assays and tuberculin skin testing for progression from latent TB infection to disease state: a meta-analysis.

Diel R[1], Loddenkemper R[2], Nienhaus A[3].

Author information

Abstract

BACKGROUND: Given the current lack of effective vaccines against TB, the accuracy of screening tests for determining or excluding latent TB infection (LTBI) is decisive in effective TB control. This meta-analysis critically appraises studies investigating the positive and the negative predictive value (PPV and NPV, respectively) from a test-determined LTBI state for progression to active TB of interferon-γ release assays (IGRAs) and the tuberculin skin test (TST).

METHODS: We searched MEDLINE, EMBASE, and Cochrane bibliographies for relevant articles. After qualitative evaluation, the PPV and NPV for progression of commercial and "in-house" IGRAs and the TST for persons not receiving preventive treatment in the context of the respective IGRA studies were pooled using both a fixed and a random-effect model. Weighted rates were calculated for all study populations and for groups solely at high risk of TB development.

RESULTS: The pooled PPV for progression for all studies using commercial IGRAs was 2.7% (95% CI, 2.3%-3.2%) compared with 1.5% (95% CI, 1.2%-1.7%) for the TST (P < .0001). PPV increased to 6.8% (95% CI, 5.6%-8.3%) and 2.4% (95% CI, 1.9%-2.9%) for the IGRAs and the TST, respectively, when only high-risk groups were considered (P < .0001). Pooled values of NPV for progression for both IGRAs and the TST were very high, at 99.7% (95% CI, 99.5%-99.8%) and 99.4% (95% CI, 99.2%-99.5%), respectively, although they were significantly higher for IGRAs (P < .01).

CONCLUSIONS: Commercial IGRAs have a higher PPV and NPV for progression to active TB compared with those of the TST, especially when performed in high-risk persons.

Low positive predictive values because of low overall TB risk

Regimens for Latent TB Infection (LTBI)

- Source likely isoniazid and rifampicin-susceptible
  - Daily isoniazid for 6-9 (36) months (under DOT if intermittent)
  - Daily isoniazid and rifampicin for 3 months
  - Daily rifamipicin for 4 months
  - Weekly isoniazid and rifapentine for 12 weeks (DOT/SAT in US)
  - Daily isoniazid and rifapentine for 1 month (HIV)

- Source isoniazid-resistant but rifampicin-susceptible
  - Daily rifampicin for 4 months

- Source MDR-TB but fluoroquinolone-susceptible
  - Fluoroquinolone-based regimens

Why Bother to Treat?

- Latent TB infection:
  - No symptom and NOT infectious
  - No immediate personal or public health risk but increased risk in progression to disease
- Intervention aims to decrease future TB risk
  - Personal Protection: Risk vs Benefit
  - Public Health: Preventable Risk & Programme Coverage

Medical Intervention: Key Consideration

- Do NO Harm, or at least
- Do More Good than Harm

Preventive treatment in PLHIV

Akolo C et al. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD000171.

- 6-12m isoniazid vs Placebo (4316 HIV-infected subjects in 7 trials)
  - TB risk
    - Overall: RR: 0.67, 95% CI:0.51-0.87
    - TST + : RR: 0.36, 95% CI: 0.22 to 0.61
    - TST - : RR: 0.86, 95% CI: 0.59 - 1.26 (not significant)
  - Adverse events leading to stopping treatment
    - Overall: 2.8% vs 1.8% , RR: 1.66, 95%CI:1.09 - 2.51
  - Reduction in mortality
    - TST+ : RR: 0.74, 95% CI: 0.55 to 1.00 (just reach stat. sig.)

Isoniazid Monotherapy

- Acceptance / adherence often suboptimal
- Hepatotoxicity increases with age (Kopanoff DE, et al Am Rev Respir Dis 1978; 117: 991–1001.)
  - <20: 0%
  - 20-34:0.3%
  - 35-49: 1.2%
  - 50-64: 2.3%

Adverse Effects: 9 INH vs 3 HP

Sterling TR, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011;365:2155-66.

Adverse Drug Effects	**9INH N=3759** n (%)	**3HP N=4040** n (%)	P
Hepatotoxicity	103 (2.7)	18 (0.4)	<0.001
Rash	21 (0.6)	31 (0.8)	0.26
Possible Hypersensitivity	17 (0.5)	152 (3.8)	<0.001
Other drug reaction	65 (1.7)	131 (3.2)	<0.001
Overall	206 (5.5)	332 (8.2)	<0.001

Eur Respir J. 2018 Oct 25. pii: 1801470. doi: 10.1183/13993003.01470-2018. [Epub ahead of print]

Short-course Regimens of Rifapentine plus Isoniazid to Treat Latent Tuberculosis Infection in Older Chinese: a Randomised Controlled Study.

Gao L[1], Zhang H[1], Xin H[1], Liu J[2], Pan S[3], Li X[1], Guan L[2], Shen F[2], Liu Z[3], Wang D[3], Guan X[2], Yan J[3], Li H[1], Feng B[1], Cao X[1], Chen Y[2], Cui W[2], Zhang Z[4], Ma Y[4], Chen X[4], Zhou X[4], Jin Q[1]; LATENTTB-NSTM study team.

Author information

Abstract

Latent tuberculosis infection (LTBI) management is now a critical component of the End TB Strategy. In this randomised controlled trial (ChiCTR-IOR-15007202), two short-course regimens with rifapentine plus isoniazid, the 3-month once-weekly regimen and the 2-month twice-weekly regimen, were initially designed to be evaluated for 50-70 years aged rural residents with LTBI in China. Due to the fast-growing occurrence of adverse effects, the treatments were early terminated after 8 weeks for once-weekly regimen and after 6 weeks for twice-weekly regimen, respectively. In the modified intention-to-treat analysis on the completed doses, cumulative rate of active disease during 2 years follow-up was 1.21% (14/1155) in the untreated controls, 0.78% (10/1284) in the group of 8-week once-weekly regimen, and 0.46% (6/1299) in the group of 6-week twice-weekly regimen. The risk of active disease was decreased with adjusted hazard ratio of 0.63 (95% CI, 0.27-1.43) and 0.41 (95% CI, 0.15-1.09) for the treatments, respectively. No significant difference was found in the occurrence of hepatotoxicity, 1.02% (13/1279) *versus* 1.17% (15/1279) (p=0.704). The short regimens tested must be used with caution among elderly because of the high rates of adverse effects. Further work is necessary to test the ultra-short regimens in younger people with LTBI.

- Poorly tolerated in older Chinese aged 50-70
  - Early treatment termination because of fast-growing occurrence of adverse effects
  - Even for hepatotoxicity: ~1% c.f. 1.2% TB risk in untreated controls

Decreasing TB risk in LTBI trials

- TB program expansion: early treatment access
  - Decrease Styblo ratio / recent tranmission
- ART: from No to Set Criteria to All
  - Improve immune status & decrease TB risk

- Changing trial inclusion criteria
  - No LTBI test for PLHIV in “high TB prevalence” area
  - Interpretation confounded by healthy survivor effects

LTBI Treatment: TB Rates

Sterling TR, et al. N Engl J Med. 2011;365:2155-66.

Number of Subjects and TB cases up to 33 months

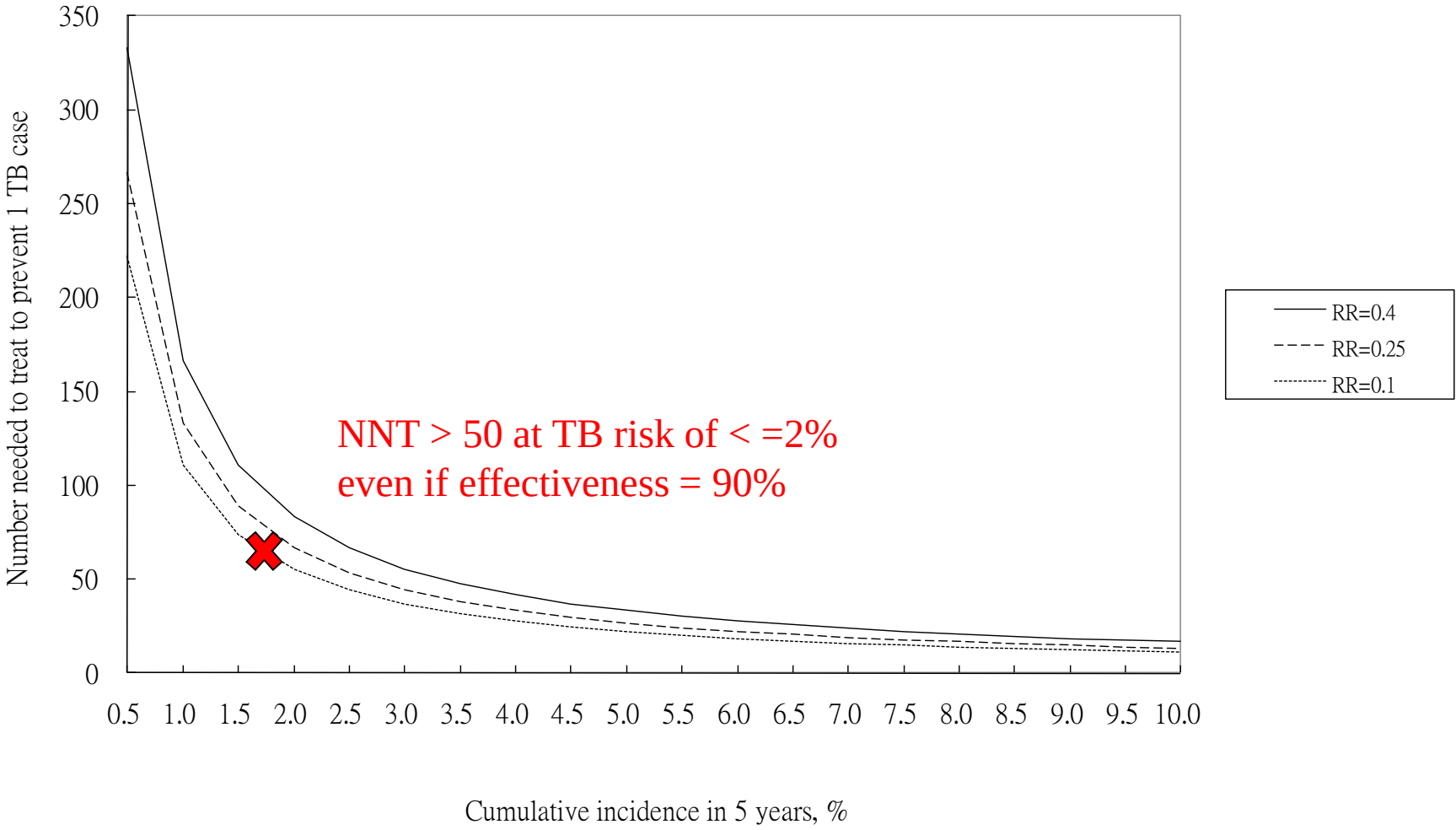
Modified ITT	No. of subjects	TB cases (%)
9 INH arm	3745	15 (0.43)
3HP arm	3986	7 (0.19)

Treatment completion rate in 9 INH (MITT) arm = 69%
Assuming overall effectiveness of 9 INH (MITT) = 75%:
TB risk if untreated = 0.43 / (1-0.75) = 1.7%

c.f. 4 TB cases (1.6%) among 384 subjects having received <= 2 doses of HP or < 30 days of INH

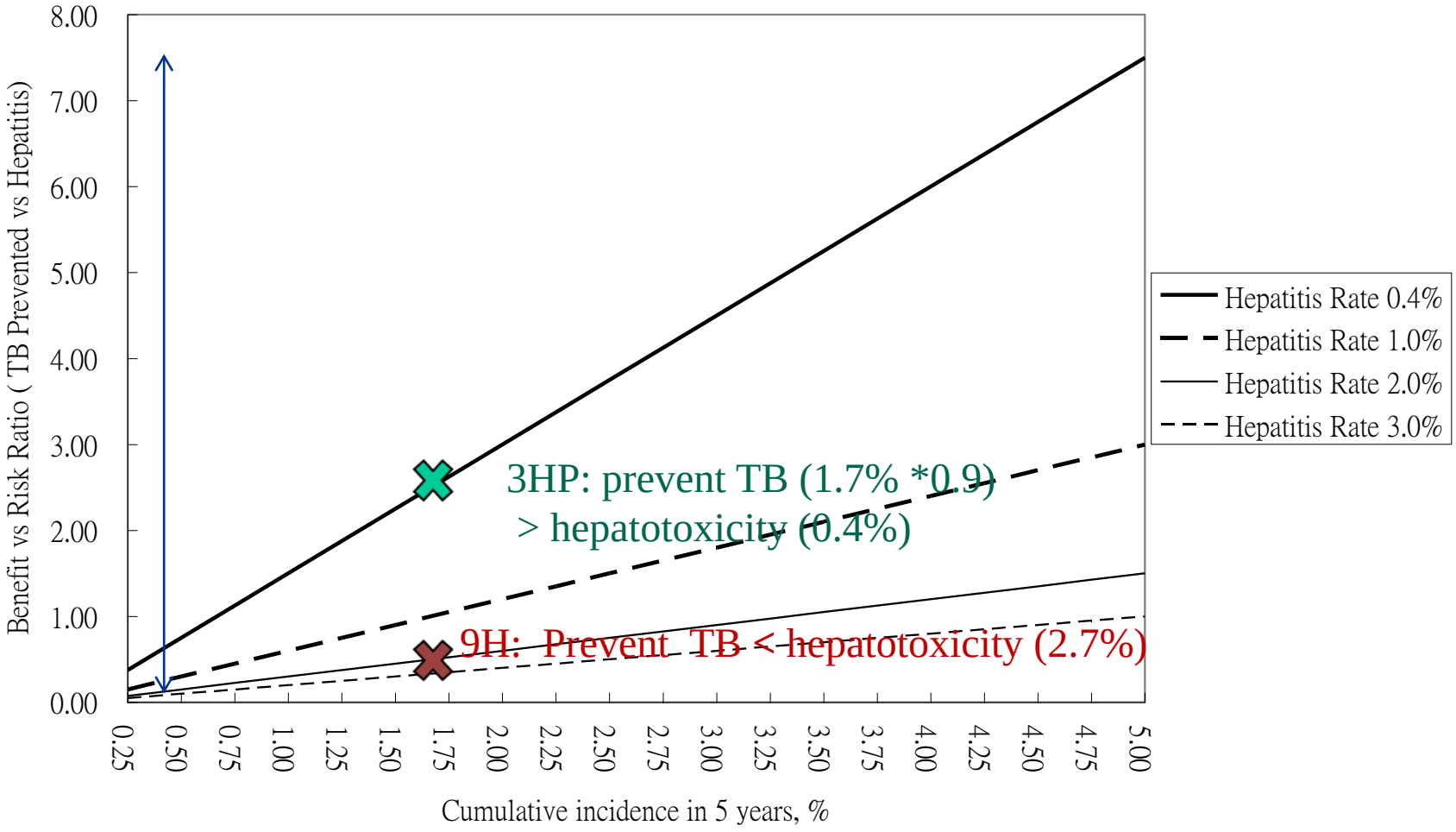
NNT to prevent 1 TB case in 5 years

Leung CC et al. Eur Respir J. 2011;37:690-711



Benefit versus Risk

Leung CC et al. Eur Respir J. 2011;37:690-711



LTBI guidelines (WHO 2018)

- LTBI testing not a requirement for initiating preventive treatment in PLHIV or child household contacts aged < 5 years. (Strong recommendation, moderate-quality evidence)
- Preventive treatment in PLHIV if NO active TB
  - Infant TB contact (Strong recommendation, moderate-quality evidence)
  - Children aged ≥ 12 months in a high TB prevalence setting (Strong recommendation, low-quality evidence)
  - Adults and adolescents with unknown or a positive TST irrespective of degree of immunosuppression, antiretroviral treatment (ART), previous treatment and pregnancy (Strong recommendation, high-quality evidence)
  - Children after completing TB treatment may receive 6 more months of isoniazid (Conditional recommendation, low-quality evidence

INH 12m vs Placebo

Rangaka MX et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. Lancet. 2014;384:682-90.

- Very high TB exposure
  - South Africa (TB incidence in 2014: 834/100000),
  - 39 (out of 1368)) culture+ prevalent TB excluded after randomisation
  - >40% previous TB
- High false negatives in LTBI tests
  - Low CD4 ~200,
  - Lower than expected TST or IGRA positive rates
    - TST+ (29.5%) vs TST- (41.5%) vs unknown (29.0%) ;
    - IGRA+ (29.3%) vs IGRA-(40.3%) vs unknown or indeterminate (30.4%)
  - High discrepency between TST/IGRA
    - TST+/IGRA+ (17.6%) vs TST−/IGRA−(29.2)% vs TST+/IGRA− (10.5%) vs TST−/IGRA+ (8.9%) vs unknown (33.9%)

INH 12m vs Placebo

Rangaka MX et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. Lancet. 2014;384:682-90.

Variable	Placebo		INH 12m		Adjusted HR(95% CI)
	TB /person-yr	Rate /100person-yr	TB /person-yr	Rate /100person-yr	
IGRA-	21/632	3.3	9/688	1.3	0.43(0.20-0.96)
IGRA+	19/482	3.9	13/427	3.0	0.55(0.26-1.24)
TST-	27/660	4.1	11/636	1.7	0.43(0.21-0.86)
TST+	14/496	2.8	12/461	2.6	0.86 (0.37-2.0)

Adjusted for CD4 and RT

IPT(6H) vs Placbo

TEMPRANO ANRS 12136 Study Group. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med. 2015;373:808-22.

Variable	IPT (6H) Deferred ART+Early ART		NO ITP Deferred ART+Early ART		Adjusted HR(95% CI)
	TB /person-yr	Rate /100person-yr	TB /person-yr	Rate /100person-yr	
All	26/2372	1.1	57/2263	2.5	0.44 (0.28–0.69)
CD4≥500/mm3	11/975	1.1	22/931	2.4	0.47 (0.23–0.97)
CD4<500/mm3	15/1396	1.1	35/1332	2.6	0.42 (0.23–0.76)
	TB cases/Study Subjects				
IGRA-	16/597 (2.7%)				0.58(0.21-1.61)
IGRA+	26/337 (7.7%)				0.43(0.19-0.99)

2008-2015: 2-by-2 factorial design: early ART, 6H or both in Ivory Coast (TB incidence 159/100 000 in 2014)
≥18 years, HIV infected, CD4<800/mm3, not meeting latest WHO criteria for ART
Adjusted HR for ART status (early vs. deferred), and trial center.

TB rate much higher in IGRA+ group; significantly reduced by 6H

Interpreting LTBI Trials

- Problem in generalization as the following are highly setting dependent:
  - Frequency of end-point affecting
  - Predictive value of diagnostic test affecting
  - Risk vs Benefit of treatment
- Meta-analysis designed originally for RCT on a biologically consistent effect (fixed or random effect) cannot resolve the problem

LTBI Prevalence

Houben RM, Dodd PJ. PLoS Med. 2016;13:e1002152

WHO Region	All LTBI		Recent Infection < 2yr	
	Prevalence,%	Proportion in Children<15,%	Prevalence,%	Proportion H resistant, %
AFR	22.4	13.3	1.5	7.4
AMR	11.0	2.3	0.2	7.0
SEA	30.8	7.4	1.2	9.5
EMR	16,3	7.9	0.7	13.1
WPR	27.9	2.4	0.5	14.7
EUR	13.7	2.0	0.3	29.5
Global	**23.0**	**5.9**	**0.8**	**10.9**

High burden of remote infection among the elderly in West Pacific

Poor agreement between diagnostic tests for LTBI among HIV-infected persons in Hong Kong

Leung CC et al. Respirology. 2016;21:1322-9.

Table 1 Baseline characteristics of the study sample with stratification by TST, T-Spot and QFT status

		TST			T-Spot			QFT		
		Negative	Positive		Negative	Positive		Negative	Positive	
	All *N* = 110	*N* = 104	*N* = 6	*P*	*N* = 101	*N* = 6	*P*	*N* = 105	*N* = 5	*P*
Male, %	86.4	85.6	100	1.000‡	87.1	100	1.000‡	86.7	80.0	0.527‡
Mean age, years (range)	42.7 (20–76)	42.5	45.7	0.480	42.6	45.3	0.551	43.2	36.4	0.167
Ethnic Chinese, %	90.9	90.4	100	1.000‡	92.1	100	1.000‡	92.4	60.0	0.064‡
Previous screening,%	84.5	83.7	100	0.588‡	84.2	83.3	1.000‡	84.8	80.0	0.575‡
ART, %	74.5	73.1	100	0.335‡	75.2	50.0	0.183	74.3	80.0	1.000‡
BCG scar, %	62.7	62.1	71.4	1.000‡	63.4	50.0	0.668‡	62.9	60.0	1.000‡
CXR scar, %	10.9	11.5	0.0	1.000‡	10.9	0.0	1.000‡	10.5	20.0	0.445‡
Median CD4 /μL (range)	414 (17–772)	396	368	0. 669§	390	389	0. 951§	387	560	0.049§
Median viral load†, copies/μL (range)	<75 (<75–399 880)	<75	<75	0. 382§	<75	<75	0.980§	<75	<75	1.000§

Previous screening: previous participation in the annual TST screening; ART: on anti-retroviral therapy; BCG scar: showing scar from previous vaccination with Bacillus-Calmette-Guerin; CXR scar: chest x-ray showing fibro-calcified lung scar.

†HIV viral load measured by Abbott Real Time HIV-1 assay.

‡Fisher's exact, two-sided P.

§Independent samples Mann–Whitney *U*.

ART, anti-retroviral therapy; BCG, Bacillus-Calmette-Guerin; CXR, chest x-ray; QFT, QuantiFERON-TB Gold in-Tube; T-Spot, T-SPOT.TB; TST, tuberculin skin test.

Majority: previously screened negative, on ART, CD4 not too low

TB risk in PLHIV in Hong Kong

Leung CC et al. Poor agreement between diagnostic tests for latent tuberculosis infection among HIV-infected persons in Hong Kong. Respirology. 2016;21:1322-9.

Table 4 95% confidence interval of disease risk by baseline test result and all serial testing

	Test	Result	Follow-up, years	TB cases	Rate (95%CI)[†]
Cohort	—	—	798	1	0.13 (0.00–0.70)
Baseline					
	TST	Negative	753	1	0.13 (0.00–0.74)
		Positive	45	0	0.00 (0.00–8.20)
	T-Spot	Negative	733	1	0.14 (0.00–0.76)
		Positive	45	0	0.00 (0.00–8.20)
	QFT	Negative	760	1	0.13 (0.00–0.73)
		Positive	38	0	0.00 (0.00–9.72)
	All test	Negative	687	1	0.15 (0.00–0.81)
	Any test	Positive	111	0	0.00 (0.00–3.32)
	Any test[‡]	Positive	66	0	0.00 (0.00–5.59)
All testing					
	TST	Positive	97	0	0.00 (0.00–3.80)
	T-Spot	Positive	75	0	0.00 (0.00–4.92)
	QFT	Positive	112	0	0.00 (0.00–3.30)
	Any test	Positive	222	0	0.00 (0.00–1.66)
	Any test[‡]	Positive	130	0	0.00 (0.00–2.84)

[†]Rate per 100 person-years.
[‡]Excluding all follow-up and TB cases after initiation of isoniazid preventive treatment.
QFT, QuantiFERON-TB Gold in-Tube; T-Spot, T-SPOT.TB; TST, tuberculin skin test.

Low TB risk in test-negative PLHIV on ART; Annual retest by any test(s): Not Predict

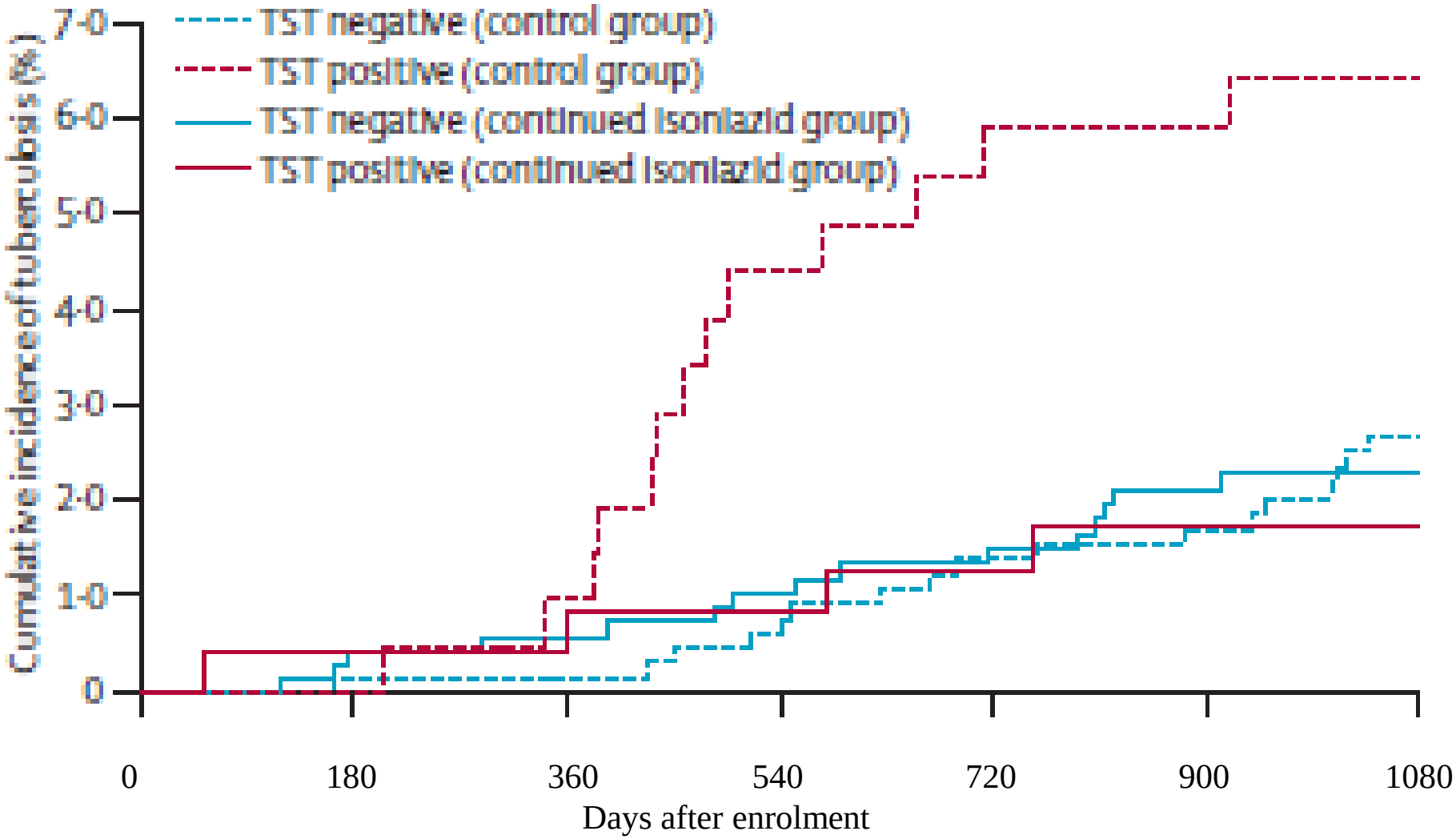
Duration of protection

- Non-HIV: long-lasting protective effect
  - Alaska study [Adv Tuberc Res 1970;17:28–106] : up to 19 yrs
  - 30-year children cohort [JAMA 1984;251:1283–5]

- PLHIV: follow-up data in high TB incidence areas (?Re-infection)
  - The protection of isoniazid treatment appears to be short-lasting (1 - 2.5 years). (Johnson JL, et al. AIDS 2001; 15: 2137-47, Quigley MA, et al. AIDS 2001; 15: 215-22.)
  - ? High risk of reinfection and / or HIV progression?

36 vs 6 months of isoniazid in PLHIV

Samandari et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet. 2011;377:1588-98



36 vs 6 months of isoniazid in PLHIV

Samandari et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet. 2011;377:1588-98

- Baseline:
  - BCG scar:78%; Median CD4:~300; TST+:22%;
  - Previous TB:4% (TB treatment within 3 years excluded);
  - ART: 2% (47% by month 36)
- Why 36H did not benefit those TST-?
  - Rise in TB rate 200 days after 6H among baseline TST+ but not TST- group
  - Direct interpretation: mainly reactivation in TST+ group but
    - High risk of reinfection expected (TB incidence 356 / 100 000 in 2014)
  - ? Healthy Survivor Effect
    - Less exposure or better immunity: No infection / disease despite exposure
    - TST- group < 50% TB rate of TST + group in 6H arm : anergy cases with recent TB excluded from study

N Engl J Med. 2011 Jul 7;365(1):11-20. doi: 10.1056/NEJMoa1005136.

New regimens to prevent tuberculosis in adults with HIV infection.

Martinson NA[1], Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, McIntyre JA, Gray GE, Chaisson RE.

Author information

Abstract

BACKGROUND: Treatment of latent tuberculosis in patients infected with the human immunodeficiency virus (HIV) is efficacious, but few patients around the world receive such treatment. We evaluated three new regimens for latent tuberculosis that may be more potent and durable than standard isoniazid treatment.

METHODS: We randomly assigned South African adults with HIV infection and a positive tuberculin skin test who were not taking antiretroviral therapy to receive rifapentine (900 mg) plus isoniazid (900 mg) weekly for 12 weeks, rifampin (600 mg) plus isoniazid (900 mg) twice weekly for 12 weeks, isoniazid (300 mg) daily for up to 6 years (continuous isoniazid), or isoniazid (300 mg) daily for 6 months (control group). The primary end point was tuberculosis-free survival.

RESULTS: The 1148 patients had a median age of 30 years and a median CD4 cell count of 484 per cubic millimeter. Incidence rates of active tuberculosis or death were 3.1 per 100 person-years in the rifapentine-isoniazid group, 2.9 per 100 person-years in the rifampin-isoniazid group, and 2.7 per 100 person-years in the continuous-isoniazid group, as compared with 3.6 per 100 person-years in the control group ($P>0.05$ for all comparisons). Serious adverse reactions were more common in the continuous-isoniazid group (18.4 per 100 person-years) than in the other treatment groups (8.7 to 15.4 per 100 person-years). Two of 58 isolates of Mycobacterium tuberculosis (3.4%) were found to have multidrug resistance.

CONCLUSIONS: On the basis of the expected rates of tuberculosis in this population of HIV-infected adults, all secondary prophylactic regimens were effective. Neither a 3-month course of intermittent rifapentine or rifampin with isoniazid nor continuous isoniazid was superior to 6 months of isoniazid. (Funded by the National Institute of Allergy and Infectious Diseases and others; ClinicalTrials.gov number, NCT00057122.).

?6 months of isoniazid after completing treatment

for children with HIV in high TB incidence areas

- No evidence that standard TB regimen does not work in children living with HIV
  - even if there is concern, better to prolong treatment to 9m like in Hong Kong (Chan CK, et al. Hong Kong Med J. 2013;19:474-83)
- To prevent reinfection in high TB incidence areas
  - Need prolonged treatment instead of 6 months (Botswana study)
- For previous TB, may consider preventive treatment
  - Recent re-exposure
  - Recent HIV infection or deterioration in immunity

? Both TST &IGRA in PLHIV

- No good data support:
  - Either test or their combination not reliable in low risk settings (Leung CC et al. Respirology. 2016;21:1322-9)
  - Positive predictive values (any combination of tests) necessarily capped by actual TB risk
  - In high risk situations, e.g. recent close contact with very low CD4 count, may consider treatment despite negative LTBI test

Annual LTBI testing in PLHIV

- No clear role
- Problem if annual risk of infection low c.f. within subject variability of test (Leung CC et al. Respirology. 2016;21:1322-9)
- LTBI test may be repeated
  - Immune recovery following ART
  - Recent exposure

Summary

- Issues of concerns:
  - Technical limitations: LTBI definition, diagnostic and treatment tools
  - LTBI trials: interpretation complicated by variable TB risks and concomitant variations in tool performance.
  - Balance risk vs benefit: problem with lowered TB risk and / or aging population

- Way forward:
  - Look at one's own TB epidemiology, healthcare infrastructure and socio-demographic situation to make an informed decision on what is best for one's community.