Treatment of LTBI – an update

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Disclosures

None

Learning objectives

- Understand the importance of latent tuberculosis infection treatment in **tuberculosis control and elimination**
- Recognize available **treatment regimens** for latent tuberculosis infection
- Discuss selected, **recent published reports** on treatment regimens for latent tuberculosis infection
- Review examples of **new agents and strategies** for tuberculosis prevention that are on evaluation

Global burden of *M. tuberculosis* infection

What is the estimated prevalence of latent tuberculosis infection (LTBI) worldwide?

a) <1%
b) ~10%
c) ~25%
d) ~50%
e) ~100%

Global burden of *M. tuberculosis* infection

WHO region	LTBI prevalence %	LTBI prevalence in children <15y %	Recent infection rate (within 2 years) %
AFR	22	13	1.5
AMR	11	2	0.2
SEA	31	7	1.2
EMR	16	8	0.7
WPR	28	2	0.5
EUR	14	2	0.3
GLOBAL	**23 (20 – 26)**	**6 (5 – 7)**	**0.8 (0.7 – 0.9)**

Houben RMG et al. PLoS Med 2016; 13(10): e1002152

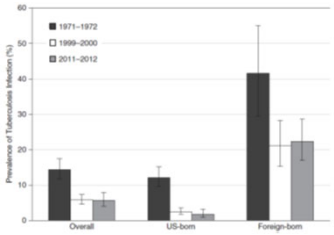
WHO End TB Strategy

VISION	**A world free of tuberculosis** – zero deaths, disease and suffering due to tuberculosis			
GOAL	**End the global tuberculosis epidemic**			
INDICATORS	**MILESTONES**		**TARGETS**	
	2020	**2025**	**SDG 2030**	**END TB 2035**
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20% (<85/100 000)	50% (<55/100 000)	80% (<20/100 000)	90% (<10/100 000)
TB-affected families facing catastrophic costs due to TB (%)	Zero	Zero	Zero	Zero

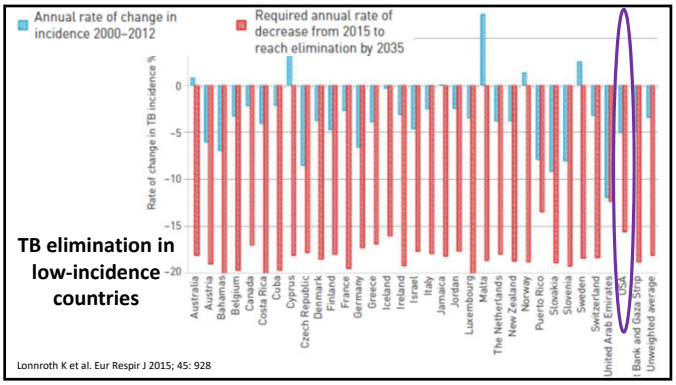
http://www.who.int/tb/strategy/end-tb/en

U.S. burden of *M. tuberculosis* infection

	LTBI by TST	LTBI by QFT
U.S. prevalence	4.4%	4.8%



Mancuso JD et al. AJRCCM 2016; 194(4)



TB elimination in low-incidence countries

Lonnroth K et al. Eur Respir J 2015; 45: 928

LTBI: Primary driver of TB disease in the US

- During 2011-2014, only 3,827 (14%) of 26,586 genotyped TB cases were attributed to recent transmission
- Reactivation of LTBI, rather than recent transmission, is the primary driver of TB disease in the US, accounting for >80% of all TB cases
- Modelling analyses suggest that LTBI treatment rates need to improve significantly to achieve TB elimination

Steward JR et al MMWR 2018; 67(11):317
Yuen CM et al Plos One 2016; 11(4):e0153728
Hill AN et al Epidemiol Infect 2012; 140:1862

LTBI Cascade of Care

LTBI diagnosed
↓
Offered LTBI treatment
↓
Accepted LTBI treatment
↓
Completed LTBI treatment

LTBI Cascade of Care - Contacts

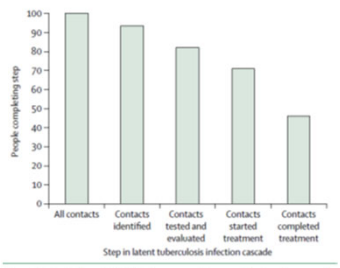


Figure 3: Latent tuberculosis infection prevention cascade using the example of contact investigation

- In this example, 93% of contacts have been identified
- 82% of those have completed evaluation
- Of the contacts with LTBI (21%), 71% start treatment
- 46% of those who start treatment complete it
- Thus, only 33% of contacts with LTBI complete treatment

LoBue PA et al. Lancet Infect Dis 2017; 17:e327

Clinical definition of LTBI

- Evidence of exposure/infection with Mtb
  - Tuberculin skin test (TST) with purified protein derivative (PPD), or
  - Interferon gamma release assay (IGRA); i.e., QuantiFERON®-TB or T-SPOT®.TB
- AND no sigs or symptoms of active TB
- AND negative CXR
- AND negative AFB culture if specimen collected

Treatment regimens for LTBI

Drugs	Duration	Dose	Frequency	Total doses
Isoniazid and rifapentine	3 months	INH 900 mg max dose Rifapentine 750 mg if 32-50 kg; 900 mg if ≥ 50 kg	Once weekly*	12
Rifampin	4 months	600 mg (10 mg/kg)	Daily	120
Isoniazid	6-9 months	300 mg (5 mg/kg) 900 mg (15 mg/kg)	Daily Twice weekly*	180 – 270 52 – 76

Intermittent regimens must be provided by directly observed therapy (DOT) in which a health care worker observes the ingestion of medication

https://www.cdc.gov/tb/topic/treatment/ltbi.htm

What is new in LTBI treatment within the past year?

Morbidity and Mortality Weekly Report

Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to Treat Latent *Mycobacterium tuberculosis* Infection

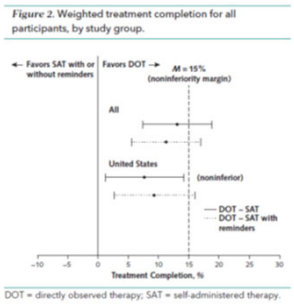
Andrey S. Borisov, MD[1]; Sapna Bamrah Morris, MD[1]; Gibril J. Njie, MPH[1]; Carla A. Winston, PhD[1]; Deron Burton, MD[1]; Stefan Goldberg, MD[1]; Rachel Yelk Woodruff, MPH[1]; Leeanna Allen, MPH[1]; Philip LoBue, MD[1]; Andrew Vernon, MD[1]

CDC continues to recommend 3HP for treatment of LTBI in adults and now recommends use of 3HP:

1) in persons with LTBI aged 2–17 years
2) in persons with LTBI who have HIV infection, including AIDS, and are taking ART with acceptable drug-drug interactions with rifapentine
3) by DOT or self-administered therapy (SAT) in persons aged ≥2 years

MMWR / June 29, 2018 / Vol. 67 / No. 25

I-Adhere (TBTC Study 33)



Belknap R et al. Ann Intern Med 2017; 167(10):689

Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults

- RCT in multiple sites: Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, Saudi Arabia, South Africa
- 6,063 high-risk LTBI participants (70% close contact, 12% casual contact, 4% HIV, 3% other immunosuppression)
- Mean age 38 y/o; 40% males; 28 months of follow-up
- LTBI treatment completion rate: 79% rifampin vs. 63% isoniazid
- Rate of grade 3-5 adverse events: 0.8% rifampin vs. 2.1% isoniazid
- Grade 3-4 hepatotoxicity: 0.3% rifampin vs. 1.5% isoniazid
- 8 TB cases in rifampin group vs. 9 cases in isoniazid group
- "The 4-month regimen of rifampin was not inferior to the 9-month regimen of isoniazid for the prevention of active tuberculosis and was associated with a higher rate of treatment completion and better safety"

Menzies D et al. NEJM 2018; 379:440-53

Safety and Side Effects of Rifampin versus Isoniazid in Children

- RCT in multiple sites: Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia
- 844 high-risk LTBI participants (99% household contact)
- Median age 10 y/o (15% 0-4 y/o); 50% males; 16 months of follow-up
- LTBI treatment completion rate: 85% rifampin vs. 76% isoniazid
- Rate of minor symptoms related to study drug 4% vs. 4%
- 0 TB cases in rifampin group vs. 2 cases in isoniazid group
- "Among children under the age of 18 years, treatment with 4 months of rifampin had similar rates of safety and efficacy but a better rate of adherence than 9 months of treatment with isoniazid"

Diallo T et al. NEJM 2018; 379:454-63

One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis

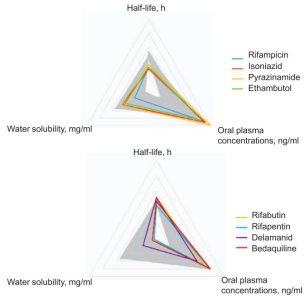
- RCT in multiple sites: Africa, Asia, South America, North America (3% US)
- 3,000 HIV+ participants were randomized. Median f/u 3.3 years
- Median age 35 y/o; 87% CD4 count >250; 50% on ART at entry
- TST/IGRA+ required in low endemic areas (US)
- Completion rate: 1HP 97% vs. 9H 90%
- Serious adverse events: 6% 1HP vs. 7% 9HP
- 32 (2%) TB cases in 1HP group vs. 33 (2%) TB cases in 9H
- "A 1-month regimen of rifapentine plus isoniazid was noninferior to 9 months of isoniazid alone for preventing tuberculosis in HIV-infected patients. The percentage of patients who completed treatment was significantly higher in the 1-month group"

Swindells S et al. NEJM 2019; 380:1001-11

What is coming?

Study	Regimen	Population	Sponsor
WHIPP TB	p3HP vs 3HP vs 6H	HIV+	KNCV, USAID
TBTC Study 37	6 weeks of rifapentine vs 3HP vs 3HR vs 4R	Household contacts, HIV+, recent conversions	TBTC, BMRC, University College London
A5300/PHOENIx	Delamanid vs. INH	Household contacts of MDR-TB	ACTG, IMPAACT
V-QUIN	6m levofloxacin	Household contacts of MDR-TB	NHMRC, VNTP
CORTIS	3HP vs no intervention	COR+ gene-based signature	U Cape Town, Gates Foundation

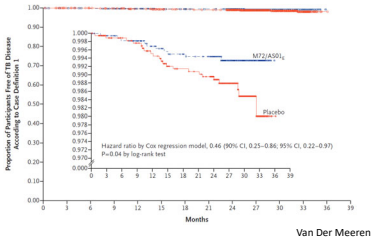
Long-acting formulations for LTBI?



Swindells S et al. IJTLD 2018; 22(2):125-32

TB vaccines… the future?

Phase 2b RCT in Kenya, South Africa, Zambia. 3,575 participants randomized to receive either M72/AS01E tuberculosis vaccine vs. placebo; LTBI by IGRA; HIV-negative; 18-50 y/o; 2.3 y median f/u. **Conclusion**: "M72/AS01E provided 54.0% protection for *M. tuberculosis*–infected adults against active pulmonary tuberculosis disease, without evident safety concerns"



Van Der Meeren O. NEJM 2018;379:1621-34

Conclusions

- Treatment of LTBI is an important component of TB control and elimination
- Treatment regimens for LTBI include once-weekly isoniazid plus rifapentine for 3 months, daily rifampin for 4 months, (daily isoniazid plus rifampin for 3–4 months), and daily isoniazid for 6–9 months
- Isoniazid monotherapy is efficacious in preventing TB, but the rifampin- and rifapentine-containing regimens are shorter, have similar efficacy, adequate safety, and higher completion rates
- Novel vaccine strategies, host immunity directed therapies and ultra-short antimicrobial regimens for TB prevention, such as daily isoniazid plus rifapentine for 1 month, are under evaluation

Thank you!

Questions?

TB and chronic diseases

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Disclosures

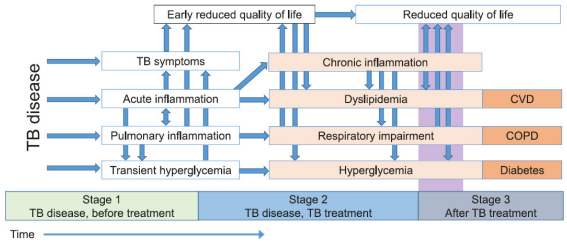
None

TB and chronic diseases

1. Can certain chronic diseases increase the risk of TB?
   a) Yes
   b) No
   c) We don't know

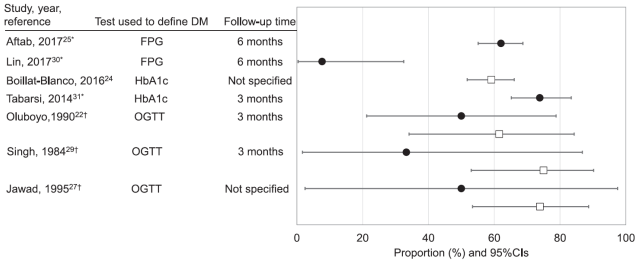
2. Can TB increase the risk of certain chronic diseases?
   a) Yes
   b) No
   c) We don't know

Conceptual framework for increased risk of non-communicable diseases after active TB



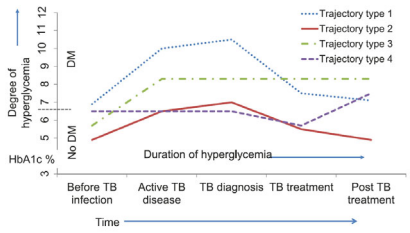
Magee MJ et al. IJTLD 2018; 22(11): 1258-68

TB patients with a new pre-DM or DM diagnosis who reverted to normal blood glucose with TB treatment



Magee MJ et al. IJTLD 2018; 22(11): 1258-68

Possible trajectories of blood glucose after TB



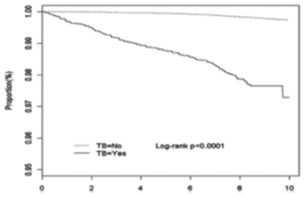
Magee MJ et al. IJTLD 2018; 22(11): 1258-68

Pulmonary impairment after TB recovery

Characteristics	Case Patients (n = 107)	Comparison Subjects (n = 210)	p Value
Male gender†	74 (69)	111 (53)	0.005‡
Ethnic group†			
White	25 (23)	47 (22)	0.889
Hispanic	29 (27)	53 (26)	0.943
African-American	23 (22)	55 (26)	0.407
AAIO†	30 (28)	53 (25)	0.523
Ever-smokers†	61 (57)	107 (51)	0.217
Ever used crack cocaine†	21 (20)	36 (17)	0.395
Occupational pulmonary risk†	6 (6)	14 (7)	0.834
Born in United States†	55 (51)	111 (53)	0.831
HIV-positive†	15 (14)	15 (7)	0.186
Not classed			
Pulmonary impairment†	63 (59)	41 (20)	< 0.001‖
Age,§ yr	47 (15)	41 (15)	0.003‖
BMI§	23.75 (4.98)	27.66 (5.78)	< 0.001‖
Height,§ inches	67 (4)	66 (4)	0.163
Smoking history,§ pack-yr	12.01 (16.24)	7.24 (14.36)	0.011‖
FVC,§ % predicted	82.77 (24.89)	95.51 (19.49)	< 0.001‖
FEV_1,§ % predicted	77.77 (27.37)	95.43 (19.48)	< 0.001‖
FEV_1/FVC ratio,§ % predicted	76.07 (13.34)	83.97 (7.85)	< 0.001‖
FEF_{25-75},§ % predicted	72.68 (41.45)	98.61 (31.79)	< 0.001‖

Pasipanodya JG *et al*. Chest 2007; 131:1817–1824

TB and subsequent risk of lung cancer

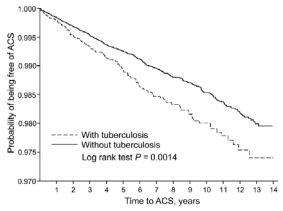


TB was associated with a 3-fold increased risk of lung cancer diagnosis (aHR 3.32; 95% CI: 2.70-4.09) after adjusting for potential confounders

Yu YH et al. J Thorac Oncol. 2011; 6(1):32-7

TB disease and atherosclerotic CVD

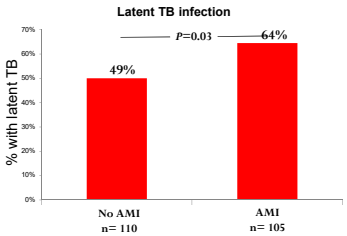
- Large retrospective cohort studies have shown that TB disease is associated with:
  - ↑ 1.4-fold risk of acute coronary synd
  - ↑ 1.9-fold risk of myocardial infarction
  - ↑ 1.5-fold risk of ischemic stroke
  - ↑ 3.9-fold risk of peripheral arterial dz



IJTLD 2014 18(1):79; Stroke 2010 41:244; Epidemiol Infect 2017; 145(7):1363-1367; Respirology 2017;22(8):1670-1676

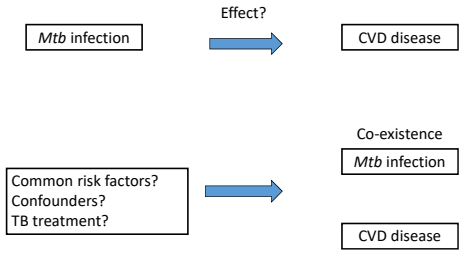
Latent TB and acute myocardial infarction

- **Case-control study**
- **Lima, Peru**
- **7/2015 – 3/2017**
- **Cases: first time type 1 AMI within 1 year**
- **Controls: no AMI**



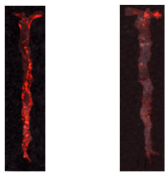
Latent TB adjusted OR = 1.9 (95% CI; 1.1 – 3.5) for acute myocardial infarction (AMI) after adjusting for age, sex, hypertension, dyslipidemia, diabetes mellitus, tobacco use, obesity and family history of CAD

Huaman et al. Clin Infect Dis 2018; 66(6): 886-92



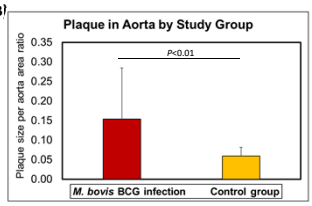
Mycobacterial infection aggravates atherosclerosis in a mouse model

A) Oil Red-O staining of *en face* aorta



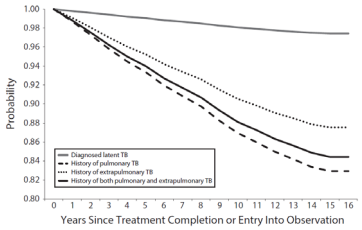
M bovis BCG infection Control group

B)



Huaman *et al.* Translational Science 2019

Mortality after TB treatment



WHY? WHAT ARE PATIENTS WHO HAVE RECOVERED FROM TB DYING FROM?

Miller TL *et al.* Am J Public Health 2015;105:930-37

Conference Dates and Location:
March 4–7, 2019 | Seattle, Washington

Abstract Number:
736

MORTALITY AFTER PRESUMED TB TREATMENT COMPLETION IN PERSONS WITH HIV IN LATIN AMERICA

Author(s):
Serena Koenig[1], Ahra Kim[2], Bryan E. Shepherd[3], Carina Cesar[3], Valdilea Veloso[4], Claudia P. Cortes[5], Denis Padgett[6], Brenda Crabtree-Ramírez[7], Eduardo Gotuzzo[8], Catherine McGowan[2], Timothy R. Sterling[2], Jean William Pape[9]

PLWH who present with baseline TB have an elevated risk of long-term mortality, even after TB treatment completion. Further study is necessary to understand the long-term clinical impact of TB disease in PLWH

WHY? WHAT ARE PLWH WHO HAVE RECOVERED FROM TB DYING FROM?

What to do with our TB patients?

- Screening for the development of certain diseases?
  - We don't know
  - More research is needed
- Encourage our TB patients to follow-up with primary care services?
  - Yes!
  - We can all to this!

Conclusions

- Studies indicate that TB is associated with an increased occurrence of certain chronic disease, including pulmonary and cardio-metabolic conditions
  - Whether TB contributes to pathogenesis or is a marker of other underlying risk factors to develop these conditions is not well understood
- Patients who recover from TB have higher mortality rates than the general population
  - Causes of death not well studied
- Encourage TB patients to establish care with primary care and preventive services!

Thank you!

Questions?