Update on the Treatment of Latent *M. tuberculosis* Infection

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VANDERBILT UNIVERSITY
MEDICAL CENTER

Objectives

- Discuss current options regarding the treatment of latent TB infection, including recent WHO and upcoming ATS/CDC/IDSA guidelines, to increase provider knowledge and awareness
- Illustrate the treatment effectiveness, tolerability, and safety of treatment modalities for LTBI to enrich provider and patient knowledge to increase treatment compliance.

Treatment of latent *M. tuberculosis* infection

- **Epidemiology of *M. tuberculosis* infection**
  - **Contribution of latent infection to TB disease burden**
- **TB elimination**
  - **Target and projections**
- **Current treatment regimens**
  - **World Health Organization guidelines**
  - **ATS/CDC/IDSA guidelines**
- ***M. tuberculosis* and HIV**
  - **Isoniazid, antiretroviral therapy**

Question 1

- Which will have the greatest effect on achieving TB elimination? Improved implementation of:

A. Current TB treatment

B. Current TB vaccines

C. Current treatment of latent *M tuberculosis* infection

D. Antiretroviral therapy for HIV + persons

Latent *M. tuberculosis* infection and contribution to TB burden

- The global burden of latent *M. tuberculosis* infection is enormous.
  - More than 2 billion people (33%) infected
    - Raviglione MD. JAMA 1995;273:220-6. Dye C et al. JAMA 1999;282:677-86

- From this reservoir, millions of people will develop active TB
  - 100-200 million cases

Prevalence of latent *M. tuberculosis* infection in the U.S.

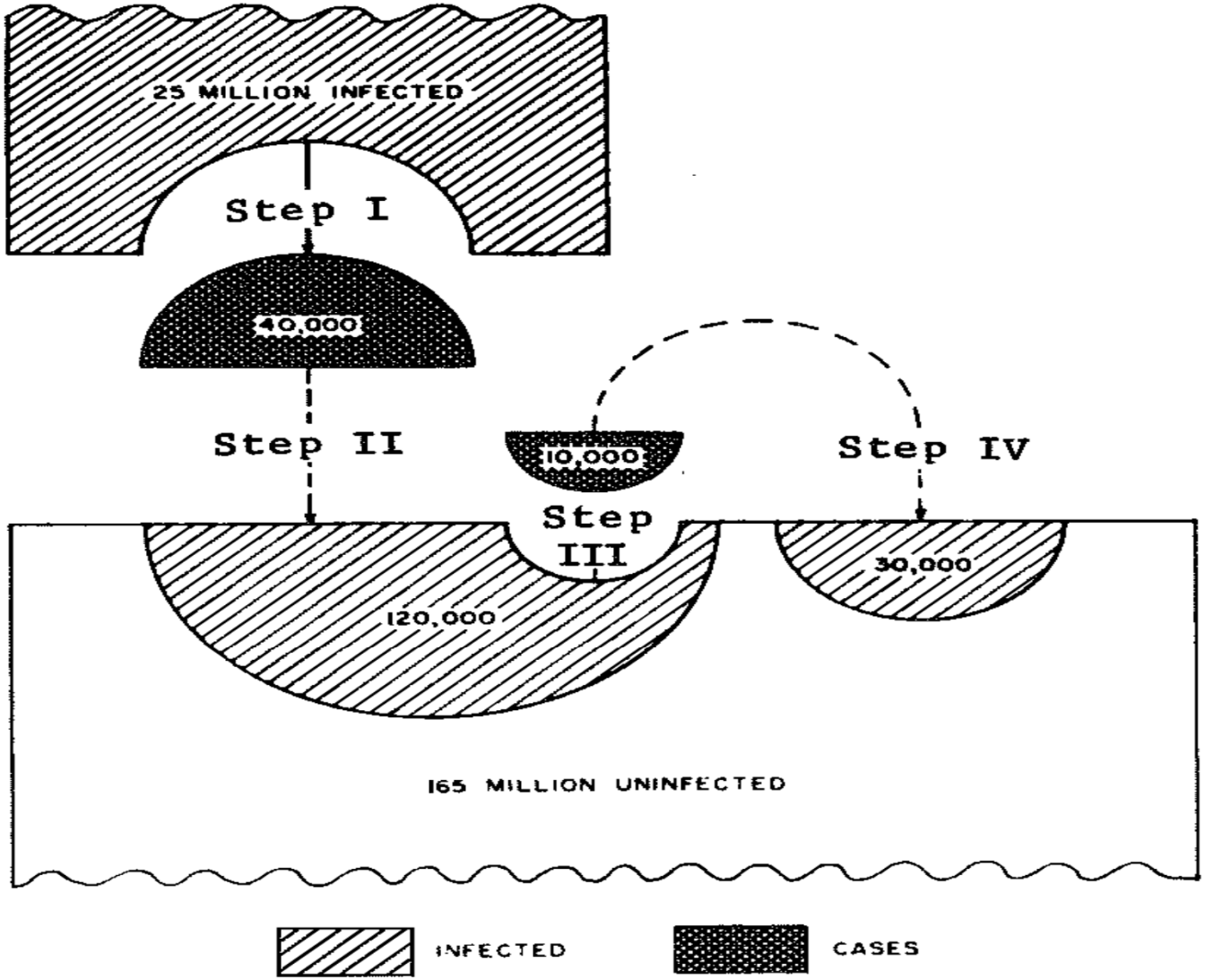
2011-2012

Method	Estimated Prevalence	Estimated # Persons Infected
TST	4.4 – 4.7%	12,398,000
QuantiFERON-Gold In-tube	4.8 – 5.0%	13,628,000

- **Based on the NHANES Survey**
- **Not significantly different than 1999 – 2000**
- **Prevalence in foreign-born: ~18%; U.S.-born: ~2%**

Miramontes R. PLoS ONE 2015:10 (11):e0140881
Mancuso JD. Am J Respir Crit Care Med 2016 Feb 11.
Ghassemieh BJ. Am J Respir Crit Care Med 2016 Feb 18.

Schematic: development of TB infection and disease, United States—1963



Ferebee SH. Bull Nat Tuberc Assoc 1967;53:4-7.

Rationale for treatment of latent *M. tuberculosis* infection

- Of the 39,920 TB cases reported in the U.S. during 2006-2008, 80% were attributed to reactivation
  - NHANES; CDC-universal genotyping
    - Shea KM. Am J Epidemiol 2014;179:216-25.

- As TB case rate declines, TB elimination will increasingly depend on treatment of the large pool of persons with latent TB infection—particularly those at increased risk of progression to active TB

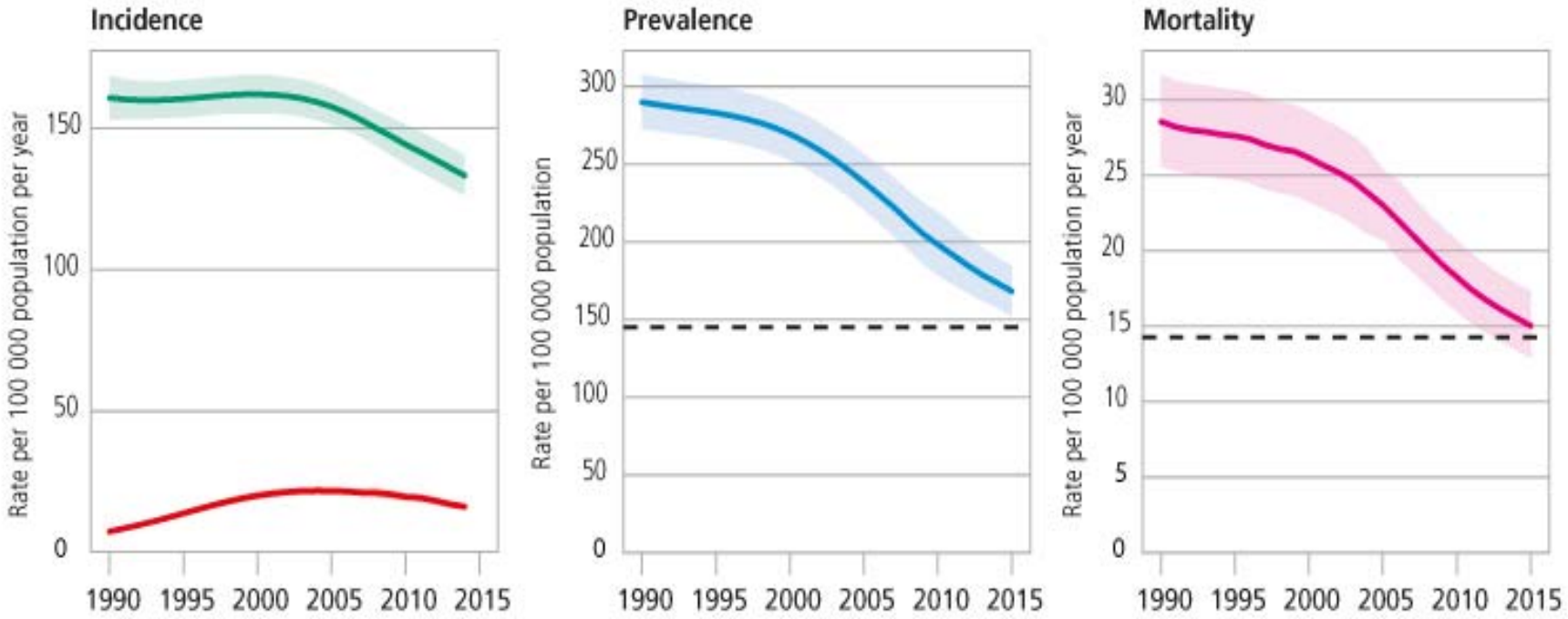
Targets for TB Control and Elimination
Global

- The Stop TB Strategy (2006 – 2015):
  - Halt and reverse TB incidence by 2015
  - By 2015: decrease the prevalence and deaths due to TB by 50% compared to 1990
    - Prevalence < 155 per 100,000 population
    - TB deaths < 14 per 100,000 population
  - By 2050: eliminate TB
    - < 1 case per million population

WHO-Stop TB Partnership. WHO/HTM/TB/2006.368

World Health Organization

Global trends in estimated rates of TB incidence (1990–2014) and prevalence and mortality rates (1990–2015)



Left: Estimated incidence rate including HIV-positive TB (green) and estimated incidence rate of HIV-positive TB (red).
Centre and right: The horizontal dashed lines represent the Stop TB Partnership targets of a 50% reduction in prevalence and mortality rates by 2015 compared with 1990. Shaded areas represent uncertainty bands.
Mortality excludes TB deaths among HIV-positive people.

Incidence: 9.6 million cases; 133/100,000 population
Prevalence: 42% lower than 1990 (13 million; 174/100,000)
Mortality: 47% lower than 1990 (1.5 million; 16/100,000)

Source: Global Tuberculosis Report 2015, WHO

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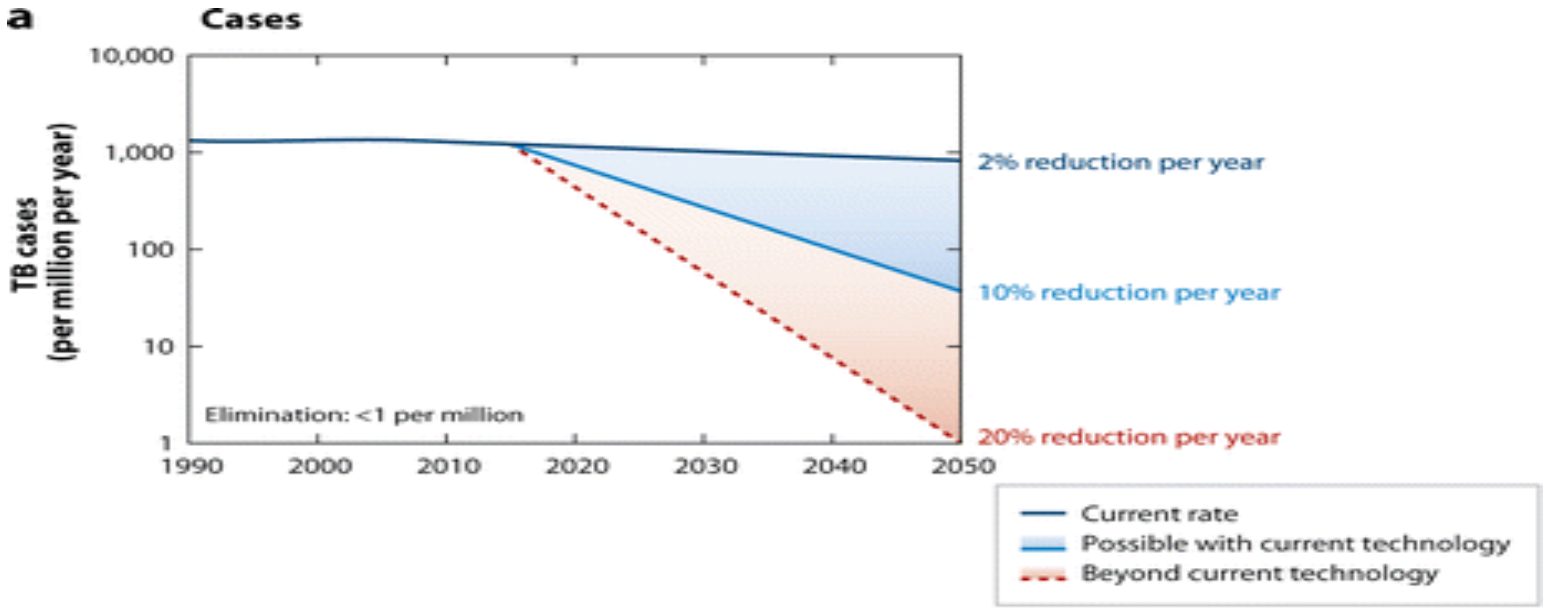
Targets for TB Control and Elimination
Global

- The End TB Strategy (2016 – 2035):

Indicator	Milestone		Target	
Year	2020	2025	2030	2035
Reduction in # TB deaths compared with 2015	35%	75%	90%	95%
Reduction in TB incidence compared with 2015	20% <85/100,000	50% <55/100,000	80% <20/100,000	90% <10/100,000

Global Tuberculosis Report 2015. WHO/HTM/TB/2015.22

Projected Trends in TB Incidence Rates, 2020 - 2050



Dye C, et al. 2013.
Annu. Rev. Public Health. 34:271–86

Screening for and Treating LTBI

Effect on TB incidence

- Identify persons with *M. tuberculosis* infection
  - TB risk if IGRA+ vs. IGRA-: pooled IRR: 2.11
  - TB risk if TST+ vs. TST-: pooled IRR: 1.60
    - Rangaka MX. Lancet Infect Dis 2012;12:44-55.
  - Implies 44-51% of TB patients would be IGRA or TST+
  - If treatment of LTBI is 65% effective, there would be 29-33% ↓ in TB incidence if complete coverage
    - Dowdy DW, Golub JE. Lancet Infect Dis 2012;12:827-8.
  - Similar to Bethel, Alaska (30% ↓)
    - Comstock GW. ARRD 1967;95:935-43.
- Household contact tracing
  - If performed contact tracing of all household contacts for 5 years and treated LTBI: 17-27% ↓ in TB incidence
    - Kassaue P. Am J Respir Crit Care Med 2014;189:845-52.

2015 WHO Guidelines

Treatment of latent tuberculosis

High or middle income countries; TB incidence < 100 / 100,000

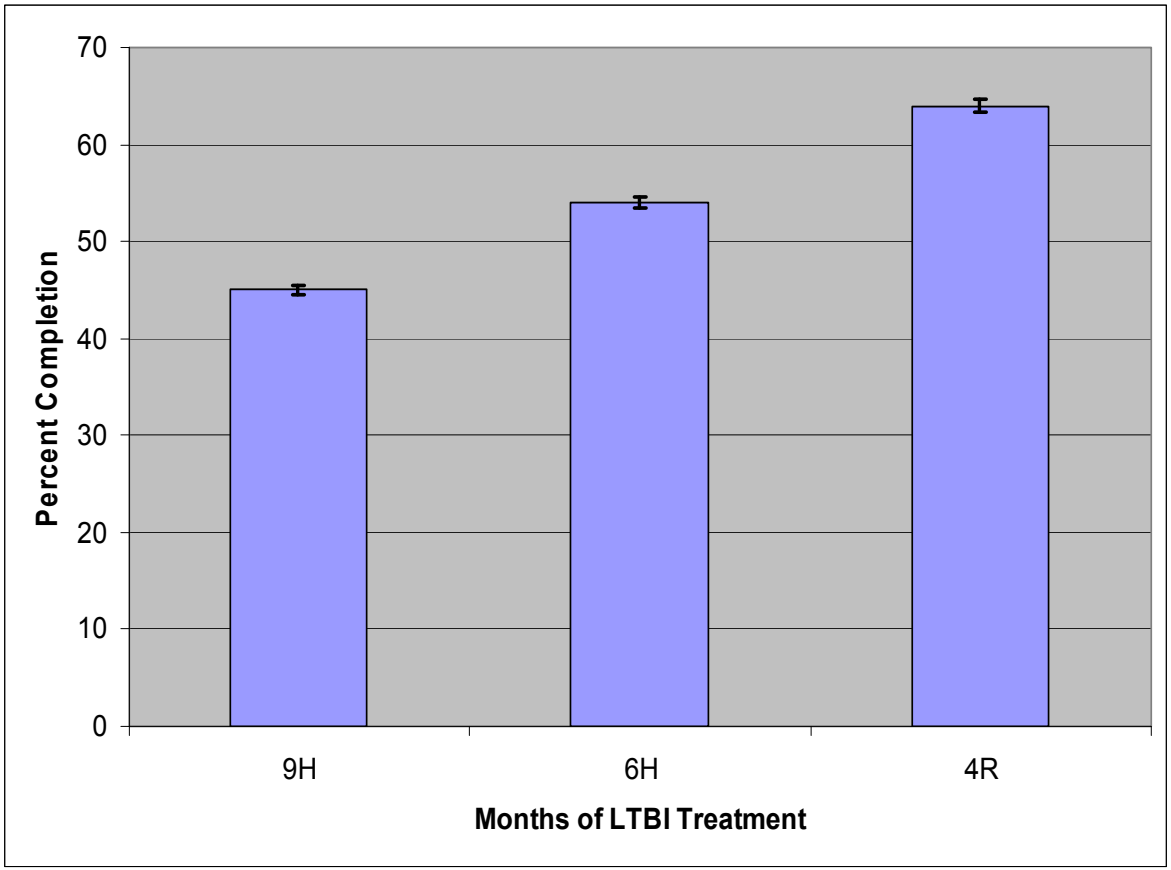
- Systematic testing and treatment of latent infection should be performed in:
  - Persons living with HIV
  - Adult and child contacts of pulmonary TB
  - Patients initiating TNF-alpha blockers
  - Persons on dialysis
  - Persons who will receive organ or hematologic transplantation
  - Persons with silicosis
- Test with either an IGRA or tuberculin skin test
- Treatment options:
  - 6-9 months of INH
  - 3 months of INH + RPT
  - 3-4 months of INH + RIF
  - 3-4 months of RIF

WHO/HTM/TB/2015.01. Getahun H. Eur Repir J 2015;46:1563-76.

Overall treatment completion rate: 47%

68 clinics in the U.S. and Canada in 2002

Completion rate increased as regimen duration decreased



Horsburgh CR Chest 2010;137:401-9.

Treatment of *M. tuberculosis* Infection

Current Regimens

Regimen	Efficacy Effectiveness	Tolerability Drug d/c AE Hepatotoxicity	Comments
9 INH (9H) daily	**90% 25-88% (median:60%)**	**0 - 31% 0.1 - 3.8%**	**6 and 12 months well-studied; 30-60% completion**
3 INH + rifapentine (3HP) once-weekly	90% (estimated) 90% (estimated)	4.9% 0.4%	82% completion Directly-observed
3 INH + rifampin Daily (3HR)	--- 41-59%	0 - 5.1% 0 - 5.1%	An alternative Hepatoxicity
4 rifampin Daily (4R)	--- 46-50% (3 months)	1.9 - 14% 0 - 0.7%	Not well-studied. Give when INH R, intolerance Not in HIV+

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3 months of weekly isoniazid + rifapentine 3HP

- **Several studies have recently been published in special populations or settings:**
  - **Children**
  - **HIV-infected persons**
  - **Possible flu syndrome**
  - **Hepatotoxicity and hepatitis C virus infection**
  - **Self-administered vs. directly-observed therapy**
  - **Health department clinics, jails**

Tolerability and Effectiveness in Children

TBTC S26 + IMPAACT

- Study 26 amended to enroll 352 additional children; 1,058 total There were 908 for efficacy evaluation
- Follow-up complete September 30, 2013
- No hepatotoxicity, grade 4 events, or deaths

Endpoint	3HP N=472	9H N=436	P-value
Treatment completion	88%	81%	0.003
D/C—adverse drug reaction	2%	0.5%	0.11
Grade 3 toxicity	0.6%	0.2%	0.49
TB	0 (0%)	3 (0.78%)	Upper bound of difference: 0.44%

Villarino ME et al. JAMA Pediatr 2015;169(3):1-9.

Tolerability and Safety in HIV + Persons

TBTC S26 + ACTG 5259

- Study 26 amended to enroll 191 additional HIV+ persons; 403 total. There were 399 for efficacy evaluation. Median CD4 ~500
- Follow-up complete September 30, 2013

Characteristic	3HP N=207	9H N=186	P-value
Treatment completion (MITT)	183/206 (89%)	123/193 (64%)	<0.001
Discontinue—adverse drug reaction	7 (3%)	8 (4%)	0.79
Grade 3 toxicity	14 (7%)	18 (10%)	0.36
Grade 4 toxicity	4 (2%)	10 (5%)	0.10
Grade 5 (death)	6 (3%)	5 (3%)	1.00
Hepatotoxicity → drug discontinuation	2 (1%)	8 (4%)	0.05
Possible flu syndrome	2 (1%)	0 (0%)	0.50

Effectiveness in HIV+ Persons

Modified Intention to Treat Population

Treatment Arm	N	#TB Cases	TB per 100 p-y	Cumulative TB Rate (%)	Difference in Cumulative TB Rate	Upper bound of 95% CI (%)
9H	193	6	1.25	3.50	-2.49	0.60
3HP	206	2	0.39	1.01		

Sterling TR, Scott N et al. AIDS 2016. In press.

3HP in HIV-infected Persons
Conclusions

- Among HIV-infected persons with median CD4 ~500 and not on antiretroviral therapy:
  - 3HP was as effective and safe for treatment of latent *M. tuberculosis* infection as 9H, and better tolerated.
- 3HP should be considered for the treatment of latent tuberculosis infection in HIV-infected persons

Sterling TR, Scott N et al. AIDS 2016. In press.

Question 2

- A 35 y.o. male with hepatitis C and EtOH abuse is a close contact of a smear-positive TB case. His interferon gamma release assay is positive. He is asymptomatic; CXR negative. SGOT = 100; SGPT = 115. The best treatment option:

A. 9 months of INH

B. 4 months of rifampin

C. 3 months of INH + rifampin

D. 3 months of once-weekly INH + rifapentine

Hepatotoxicity and hepatitis C virus infection

- Two study components:
  - Rates and risk factors for hepatotoxicity among all adults in Study 26, stratified by regimen
    - Of 6,862 adults who took ≥ 1 dose, 79 developed hepatotoxicity
      - 15/3545 (0.4%) on 3HP vs. 61/3317 (1.8%) on 9H (P < 0.001)
  - Case-control analysis for the role of viral hepatitis in hepatotoxicity associated with 9H, 3HP
    - 51 cases + 255 age-matched controls

Bliven-Sizemore EE et al. Int J Tuberc Lung Dis 2015;19(9):1039-44.

Hepatotoxicity and hepatitis C virus infection

Multivariate analyses

	PREVENT TB		Nested case-control study	
	Adjusted Risk Ratio (95%CI)	p-value	Adjusted Odds Ratio (95%CI)	**p-value**
Age, per year change	1.03 (1.02-1.05)	**<0.001**	---	**---**
Female sex	2.70 (1.65-4.42)	**<0.001**	2.75 (1.28-5.91)	**0.001**
White non-Hispanic race/ethnicity	2.22 (1.28-3.85)	**0.01**	2.97 (1.13-7.86)	**0.005**
BMI, per kg/m^2 increase	0.94 (0.90-0.99)	**0.008**	0.92 (0.86-0.99)	**0.02**
Elevated baseline AST	5.57 (3.31-9.37)	**<0.001**	---	**---**
9INH	4.55 (2.53-8.18)	**<0.0001**	9.20 (3.79-22.4)	**<0.001**
Chronic hepatitis C virus	**---**	**---**	**3.24 (1.12-9.3)**	**0.03**

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Bliven-Sizemore EE et al. Int J Tuberc Lung Dis 2015;19(9):1039-44.

Hepatotoxicity and hepatitis C virus infection

Conclusions

- The risk of hepatotoxicity was significantly lower in persons treated with 3HP than 9H.
- Underlying hepatitis C virus infection and elevated baseline AST were risk factors for hepatotoxicity.
- 3HP may be preferred in persons at increased risk of hepatotoxicity

Bliven-Sizemore EE et al. Int J Tuberc Lung Dis 2015;19(9):1039-44.

Self-administered once-weekly 3HP

TB Trials Consortium Study 33

- International, open-label, randomized controlled trial of 3HP for treatment of *M. tuberculosis* infection
- Non-inferiority trial; margin 15%
- MEMS caps to measure adherence

Regimen	N	Completion rate	Discontinuation due to AE
Directly observed	337	87%	3.6%
Self-administered	337	74%	5.4%
Self-admin with text message reminder	328	76%	4.3%

Belknap R. CROI 2015. Abstract 827LB.

I-Adhere: Completion

	Directly Observed Therapy	Self-Administered Therapy		
	Treatment completion % (N)	Treatment completion % (N)	Weighted difference compared to DOT (%)	Lower limit for 95% CI of weighted difference (%) [a]
All sites				
1st enrolled participants	86.9 (328)	74.4 (320)	-12.4	-18.2
All participants	87.2 (337)	74.0 (335)	-13.1	-18.8
United States				
1st enrolled participants	85.0 (254)	78.3 (249)	-6.8	-13.4 [b]
All participants	85.4 (261)	77.9 (262)	-7.7	-14.2 [b]

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I-Adhere: Completion

	Directly Observed Therapy	Self-Administered Therapy plus SMS		
	Treatment completion % (N)	Treatment completion % (N)	Weighted difference compared to DOT (%)	Lower limit for 95% CI of weighted difference (%) [a]
All sites				
1st enrolled participants	86.9 (328)	75.4 (313)	-11.8	-17.6
All participants	87.2 (337)	76.4 (326)	-11.2	-16.9
United States				
1st enrolled participants	85.0 (254)	76.0 (242)	-9.5	-16.4
All participants	85.4 (261)	76.7 (249)	-9.3	-16.0

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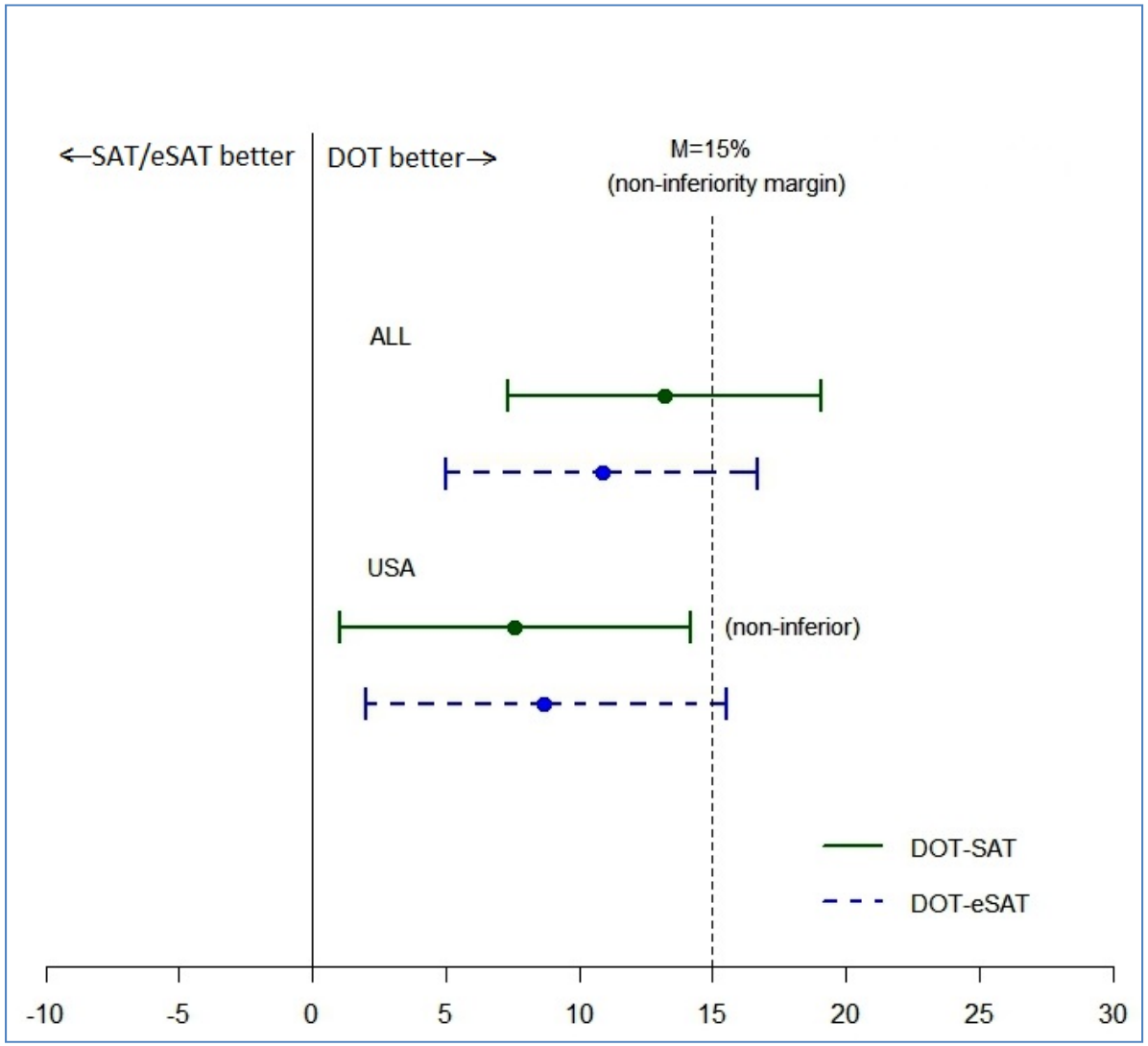
Overall, treatment completion with self-administered therapy was inferior to directly-observed therapy



Belknap R. CROI 2015. Abstract 827LB.

3HP in Operational Settings

- New York City Health Department TB Clinics
  - Among 631 persons eligible for treatment:
    - 503 (80%) offered 3HP
      - 302 (60%) accepted
      - 92 (18%) chose other treatment ; 81 because of clinic-based DOT
      - 109 (22%) refused treatment
    - Of the 302 who started 3HP, 196 (65%) completed
      - 46% treatment completion of other regimens ($P < 0.01$)
      - Historical estimates of treatment completion: 34%
        - » Stennis NL. Clin Infect Dis 2016;62;62(1):53-9.
- California: Urban County Jail
  - Among 91 persons who started 3HP, 77 (85%) completed
    - 11 were transferred out of jail
    - 2 stopped because of rash
    - 1 had an unrelated illness and declined further treatment
      - » Juarez-Reyes M. Open Forum Infect Dis 2016 Jan 6;3(1):ofv220

Question 3

- 25 y.o. male with HIV (CD4 = 450) and a positive interferon gamma release assay. He is asymptomatic and has a negative CXR. The best treatment option to prevent TB:

A. Isoniazid alone

B. Antiretroviral therapy alone

C. Isoniazid + antiretroviral therapy

D. No treatment necessary at this time

TB Prevention in HIV
ART and INH

- Observational study
- Rio de Janeiro, Brazil
- 11,026 HIV + persons receiving care at 29 public clinics, Sept 2003-Sept 2005

Intervention	TB per 100 p-y
No ART/no INH	4.01
ART	1.90
INH	1.27
ART and INH	0.80

- After adjusting for age, previous TB, and baseline CD4, 76% ↓ in TB risk if received ART and INH compared to no ART/no INH

Golub J. AIDS 2007;21:1441-8.

INH + ART to prevent TB

Randomized, double-blind placebo-controlled trial

- **Khayelitsha, South Africa**
- **Randomly assigned 12 months of INH (n=662) vs. placebo (n=667) to persons on ART**
- **Primary endpoint: time to incident TB**

	INH	Placebo	HR	95% CI
TB per 100 p-y	**2.3**	**3.6**	**0.63**	**0.41,0.94**

- **The beneficial effect of INH was not limited to those who were TST+ or IGRA+**
- **Without a more predictive test, authors suggest that INH should be recommended to all patients receiving ART in moderate or high TB incidence areas, regardless of TST or IGRA status.**

Rangaka MZ. Lancet 2014;384:682-90.

ART with or without INH

Cote d'Ivoire

- **ART started according to WHO guidelines**
  - **With or without INH (6 months) started within 1 month**
- **ART started immediately**
  - **With or without INH (6 months) started within 1 month**
- **Factorial design; no interaction between INH, early ART**
- **Follow-up: 30 months**
- **2,056 patients; 41% with baseline CD4 ≥ 500**
- **Primary outcome: death, any AIDS event, non-AIDS invasive bacterial disease, non-AIDS malignancy (combined)**
- **35% were QuantiFERON positive**
- **Early ART and INH independently ↓ severe illness**

Intervention	Adjusted HR	95% CI	P-value
Early ART	0.56	0.41, 0.76	< 0.001
INH	0.65	0.48, 0.88	0.005

Danel C—TEMPRANO Trial. N Engl J Med 2015;373:808-822.

Conclusions

- Most TB disease is due to reactivation of latent *M. tuberculosis* infection
- Preventing reactivation is critical for achieving TB elimination
- Treatment of latent *M. tuberculosis* infection can have a profound effect on decreasing TB incidence

Conclusions

- Several options for treatment of latent *M. tuberculosis* infection
- Short-course regimens favored due to higher treatment completion rates
- Antiretroviral therapy and treatment of latent *M. tuberculosis* infection both decrease TB risk in HIV-infected persons