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LTBI: New Options for Short Course Treatment

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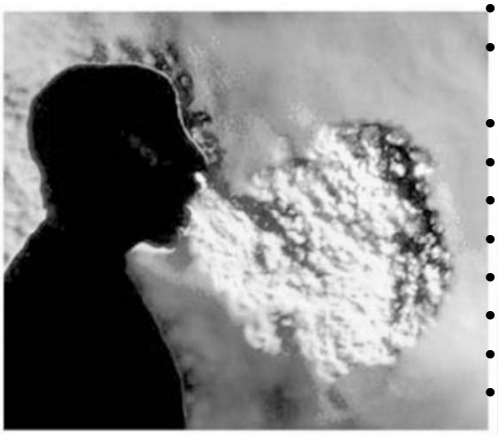
Conflicts of Interest

- Financial: None
- Scientific: Member of TB Trials Consortium and protocol team member, PREVENT TB "Study 26"

Latent TB Infection (LTBI): Basics

- Exposure to pulmonary TB leads to infection (LTBI) in some proportion of individuals, depending on:
  - Intensity of exposure
  - Vulnerability of host
- LTBI progresses to active TB disease in 5-10% of healthy US/European adults

Conditions Putting Individuals at Greatest RISK



- HIV/AIDS
- Immuno-modulating agents (TNF-inhibitors)
- Children < 5 years
- Silicosis
- Recent infection
- Diabetes
- Malnutrition/low BMI
- Smoking
- Cancer/chemotherapy
- Abnormal gut/absorption

New Engl J Med; vol ***359:e19, Oct 2008***

Intervening: Treating LTBI (TLTBI)

- A pillar of the US public health approach to TB control since mid-1960's
- Isoniazid (INH) reduced the likelihood of progression to active TB disease by 70-90%
- Changing a 5-10% risk to a 1-3% risk for healthy population
  - Much greater impact on high risk

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Infection proceeds to active TB disease in 5-10% of healthy adults

Table 4. Efficacy of various durations of isoniazid preventive therapy for persons with fibrotic lesions, by length of treatment—International Union Against Tuberculosis (IUAT) Trial, 1969–1977

Group	5-yr Tuberculosis incidence* (% reduction)			
	Placebo	12 wk	24 wk	52 wk
All participants (n = 27,830)†	14.3	11.3 (21)	5.0 (65)	3.6 (75)
Adherent participants‡ (n = 21,635)§	15	9.4 (31)	4.7 (69)	1.1 (93)
Fibrotic lesions <2 cm² (n = 18,663)†	11.6	9.2 (20)	4.0 (66)	4.2 (64)¶
Fibrotic lesions >2 cm² (n = 8,428)§	21.3	16.2 (24)	7.0 (67)	2.4 (89)

* Per 1000 person-years.
† Comparing placebo to 24 and 52 wk, $p < 0.05$; differences between placebo and 12 wk and between 24 and 52 wk not significant.
‡ Collected pill calendars for "almost all" of the months assigned for their regimen and had taken at least 80% of the pills from the calendar by the time of the next monthly visit.
§ For all interregimen comparisons ($p < 0.05$).
¶ Persons who developed tuberculosis on 52-wk regimen and had small fibrotic lesions were less likely to have collected pill calendars (47%) than all other groups (≥80%) ($p < 0.001$).
Source: International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of vaious durations of isoniazid thereapy for tuberculosis: five years of follow-up in the IUAT trial. *Bull. WHO* 1982;60:555-64.

Excerpt from LTBI Guidelines, 2000, MMWR

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Adherence: It's Important!

- Multiple studies across the world, involving >100,000 participants, showed the efficacy of INH
- Lessons learned
  - Impact of adherence on efficacy of INH
  - Impact of taking INH over a longer time period
    - Led to idea of intermittency
- Extrapolation of available data looking at length of treatment from 6-12 months in 2000 led to a recommendation for 9 months of INH as the optimal treatment length for both HIV and HIV negatives

Shorter Treatment for LTBI: Why?

- Assumed to increase uptake of treatment LTBI
- Assumed to increase completion of TLTBI
- Hope for decreased toxicity

Evidence for Shorter Regimens

Trial	Population	Regimen	Length	Intermittency	Result
Hong Kong, RCT	Silicosis, TST+	H	6 months	Daily, SA	TB in 7% placebo, ~4% all interventions
		RIF	3 months	Daily, SA	
		H/RIF	3 months	Daily, SA	
Blackburn, England, prospective observational, programmatic, 1981-1996, reduced length of therapy to 3 months	Children at high risk	H/RIF	9 months reduced to 3 months	Daily, SA	Reduction of childhood TB from 25% to 4% of all reported cases. Current regimen used in UK, adults & children

INH = H; Rifapentine = RPT; Rifampin = RIF, SA = self-administered; DOT = directly observed

Treatment of LTBI in HIV/AIDS

- Mostly low income countries with high burden of both TB and HIV (e.g., Haiti, Uganda, Kenya, Botswana)
- Haiti: compared twice-weekly INH for 6 months to RIF-PZA for 2 months, showed similar levels of protection.
- Subsequent multi-national study comparing 2 months of daily RIF-PZA to 12 months of daily INH among over 1500 patients followed for 3 years.
  - No difference between the regimens in terms of TB cases
  - 2-month RIF-PZA regimens was recommended in 2000 LTBI guidelines for use in both HIV infected and uninfected populations.
  - Once used programmatically, the toxicity associated with the RIF-PZA regimen came to the fore, and was quickly abandoned.

Evidence for Shorter Regimens: HIV+

Trial	Population	Regimen	Length	Intermittency	Result
Soweto	HIV +	H	6 months	Daily, SA	**All better than expected TB in pop; No difference between regimens**
		H/RPT	3 months	Once-weekly DOT	
		H/RIF	3 months	Twice-weekly DOT	
		H continuous	>2 years	Daily, SA	
Botswana	HIV +	H	6 months then placebo	Daily, SA	**Longer therapy HR .57 (.33-.99); Benefit seen almost entirely in TST+**
		H	36 months	Daily, SA	

INH = H; Rifapentine = RPT; Rifampin = RIF, SA = self-administered; DOT = directly observed

The PREVENT TB Study [aka TB Trials Consortium "Study 26"]

3 months of once-weekly rifapentine plus INH
vs. 9 months of daily INH for treatment of latent TB infection

Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, Hackman J, Hamilton CD, Menzies D, Kerrigan A, Weis SE, Weiner M, Wing D, Conde MB, Bozeman L, Horsburgh Jr. CR, Chaisson RE, and the TB Trials Consortium of the Centers for Disease Control and Prevention

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PREVENT TB Study

- Funded by CDC with support by sanofi aventis who supplied rifapentine
- Manuscript has been submitted and is pending publication
- Presenting on behalf of the CDC-funded TB Trials Consortium and protocol team, including co-chairs Tim Sterling and Elsa Villarino

Background

- Treatment of latent *M. tuberculosis* infection is a key component of TB prevention and elimination
- 9 months of isoniazid (INH) is highly efficacious, but effectiveness is diminished by low completion rates (30-60%)
- A shorter regimen is needed

Study Design

Randomized clinical trial of high-risk clients

Not placebo controlled

All subjects were followed for 33 months from date of enrollment

9H Arm	INH Self-administered Daily, 9 months, 270 doses
3HP Arm	INH + RPT DOT Weekly, 12 doses

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Study Design

- Non-inferiority study design, margin (delta) 0.75%
- Needed 3200 evaluable persons per arm to have > 80% power to show that 3HP not inferior to 9H
- 3HP
  - Rifapentine 900 mg max
    - Graduated dosing for persons ≤ 50 kg
  - INH 15-25 mg/kg; 900 mg max
- 9H
  - INH 5-15 mg/kg; 300 mg max.

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Inclusion Criteria

- Persons > 2 years old who were:
  - Tuberculin skin-test (TST)-positive close contacts of a culture-confirmed TB case
  - TST-converters
    - Documented negative → positive within 2 years
  - HIV-infected with
    - Positive TST
    - Close contact to TB case regardless of TST
  - TST-positive, fibrosis on chest radiograph consistent with prior untreated TB
  - Children 2-4 years old with + TST or close contact with a culture-confirmed TB case

Primary Aim

- Evaluate the effectiveness of weekly 3HP by DOT vs. daily 9H self-administered (SA)
- Primary endpoint:
  - Culture-confirmed TB in persons ≥ 18 y.o and culture-confirmed or clinical TB in persons < 18 y.o.

Exclusion Criteria

- Confirmed or suspected TB
- TB resistant to INH or rifampin in source case
- History of treatment with
  - > 14 consecutive days with a rifamycin
  - > 30 days with INH
- Prior treatment of TB or *M. tuberculosis* infection in HIV-uninfected persons
- Intolerance to INH or rifamycins
- Aspartate aminotransferase (AST) > 5x upper limit if AST determined
- Pregnant or lactating females
- HIV-1 antiretroviral therapy within 90 days of enrollment
- Weight < 10 kg

Enrollment and Follow-up

- Enrollment began June 2001
- Enrollment ended February 15, 2008
- Follow-up ended September 30, 2010
- Proportion of subjects completing 33 months of follow-up
  - 86% (H) and 88% (HP)

Analysis Populations

- Intention-to-treat (ITT)
  - All persons enrolled in the study
- Modified intention-to-treat (MITT) ← ***EFFECTIVENESS***
  - Enrolled in the study
  - Eligible
- Per protocol (PP) ← ***EFFICACY***
  - All persons enrolled in the study who were eligible
  - Completed study drug within targeted time period
  - Or developed TB or died but completed ≥ 75% of expected doses prior to event
  - All follow-up time counted; did not require reaching 33 months

Primary Endpoint: MITT Results for Adult, HIV sero-negative

Event rate estimates and the non-inferiority test for A33

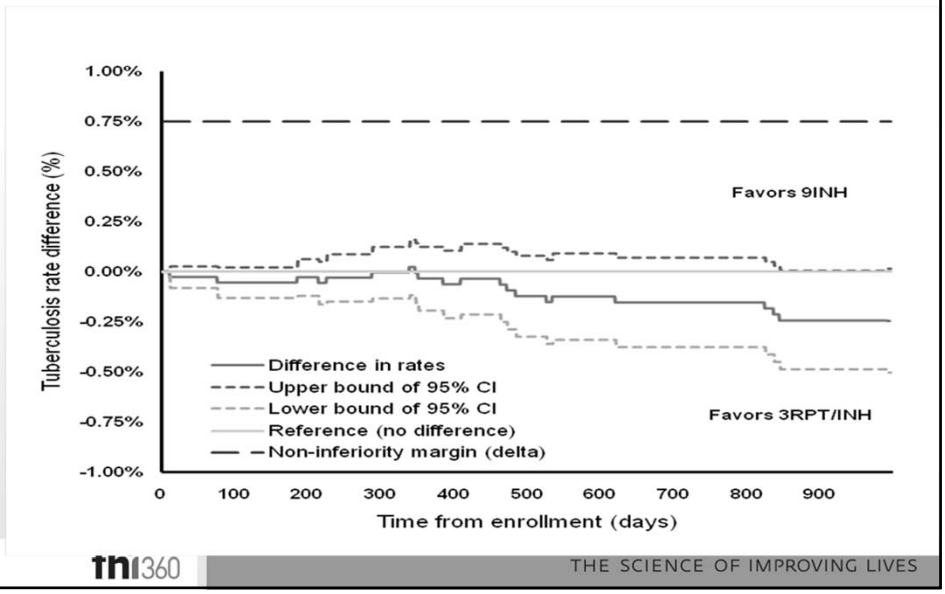
33 months of follow-up from time of randomization

Arm	N	# TB cases	TB per 100 p-y	Cumulative TB rate (%)	Difference in cumulative TB rate	Upper bound of 95% CI of difference in cumulative TB rates*
9H	3,745	15	0.16	0.43	-0.24	0.01
3HP	3,986	7	0.07	0.19		

* non-inferiority margin (delta) = 0.75%

Difference in TB rates between the 2 study arms, and non-inferiority "delta"

Modified Intention to Treat Population; A33 analysis



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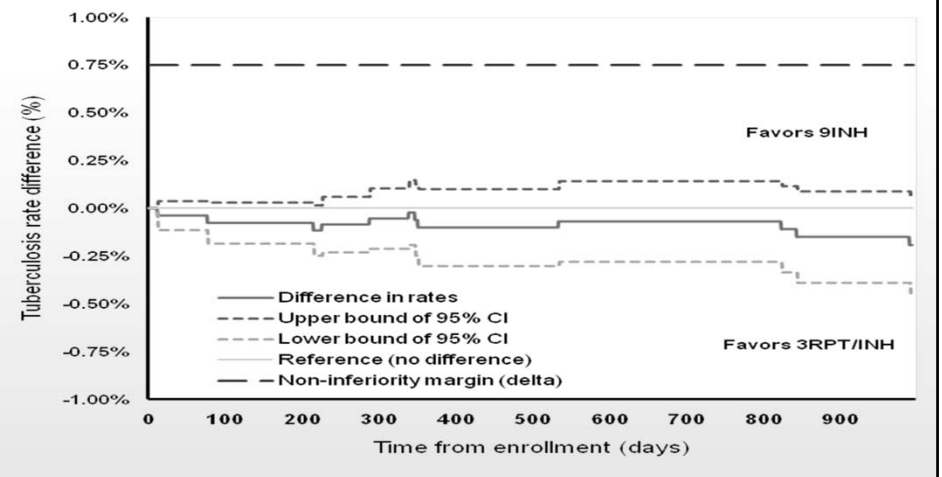
Difference in TB rates between the 2 study arms, and non-inferiority "delta"

Per Protocol Population; A33 analysis



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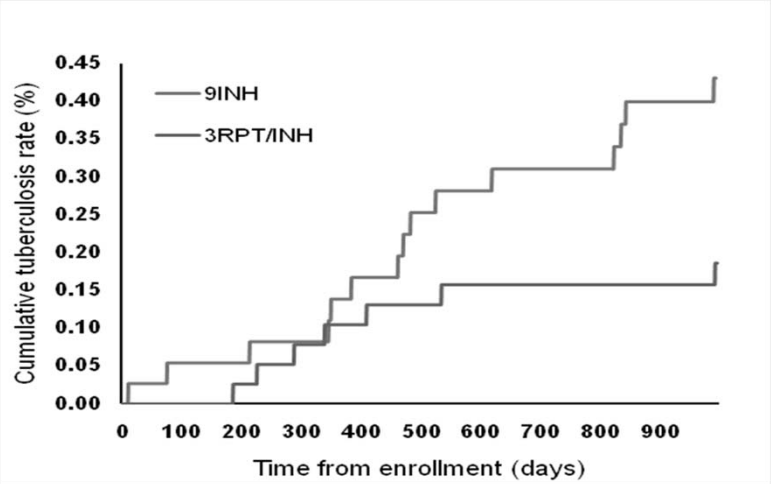
Cumulative TB Rate

33 months from enrollment—MITT



Log-rank P-value: 0.06

Tolerability: MITT population

Outcome	9H N=3,745	3HP N=3,986	P-value
Treatment completion	2,585 (69.0%)	3,362 (82.0%)	< 0.0001
Permanent drug d/c-any reason	1,160 (31.0%)	624 (18.0%)	< 0.0001
Permanent drug d/c-due to an adverse event	135 (3.6%)	188 (4.7%)	0.004
Death	39 (1.0%)	31 (0.8%)	0.22

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Reported Adverse Events

Among persons receiving ≥ 1 dose
During treatment or within 60 days of the last dose
Regardless of attribution to study drug

Toxicity	9H N=3,759	3HP N=4,040	P-value
Grade 1-2	364 (9.7%)	325 (8.0%)	0.01
Grade 3	194 (5.2%)	181 (4.5%)	0.16
Grade 4	39 (1.0%)	34 (0.8%)	0.37

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Reported Adverse Events

Among persons receiving ≥ 1 dose
During treatment or within 60 days of the last dose
Accounting for attribution to study drug

Toxicity	9H N=3,759	3HP N=4,040	P-value
Related to drug	206 (5.5)	328 (8.1)	<0.0001
Rash only	17 (0.5)	35 (0.9)	0.02
Possible HS	15 (0.4)	158 (3.9)	<0.0001
Other	71 (2.0)	122 (3.0)	0.001
Not related	399 (10.3)	220 (5.5)	<0.0001

HS: hypersensitivity reaction

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Hepatotoxicity

Among persons receiving ≥ 1 dose
During treatment or within 60 days of the last dose

Toxicity	9H N=3,759	3HP N=4,040	P-value
All hepatotoxicity	113 (3.0)	24 (0.6)	<0.0001
Related to drug	103 (2.7)	18 (0.5)	<0.0001
Not related	13 (0.4)	6 (0.2)	0.08

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Limitations

- Few HIV-infected participants
  - Enrollment of this population was extended to December 2010
  - Tolerability and effectiveness data pending
- Complete tolerability assessment in young children also pending
  - Enrollment of children 2-11 years old extended to December 2010

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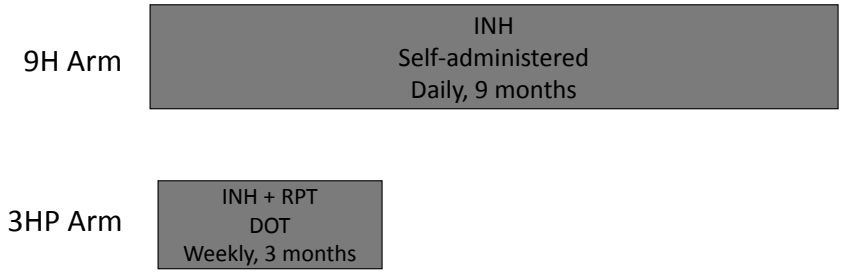
Conclusions: PREVENT TB



- **3HP by DOT was at least as effective as 9H by self-administration**
- **The 3HP TB rate was approximately half that of 9H**
- **The 3HP completion rate was significantly higher than 9H**
  - **82% vs. 69%**
- **3HP was safe relative to 9H**
  - **Lower rates of any adverse event, and less hepatotoxicity attributable to study drug**

Remaining Questions

- Effectiveness and safety when given on large scale in program settings
- DOT versus self-administered effectiveness
  - Studies to evaluate starting later 2011

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Pending Studies

- PREVENT TB
  - Children and HIV +
  - Results 2012
- INH x 9 months (daily SA) compared to RIF 600 mg x 4 months (daily SA)
  - Adults
  - Multinational
  - Results 2016

Conclusions

- High-quality evidence that 3 months, once-weekly, DOT INH + RPT is as effective as 9 months, daily, self-administered INH alone in adults without HIV
  - ATS/CDC/IDSA LTBI treatment guideline update in progress
  - Data in children and PLWHA pending
- Other studies corroborate findings: 3-month rifampin-based regimens have evidence that they are equivalent to longer INH-only Rx
- Anticipated that offering 12 weeks of therapy may increase uptake and completion of an effective regimen

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