TB Prevention: Let's Move Beyond Only Using INH for Prevention

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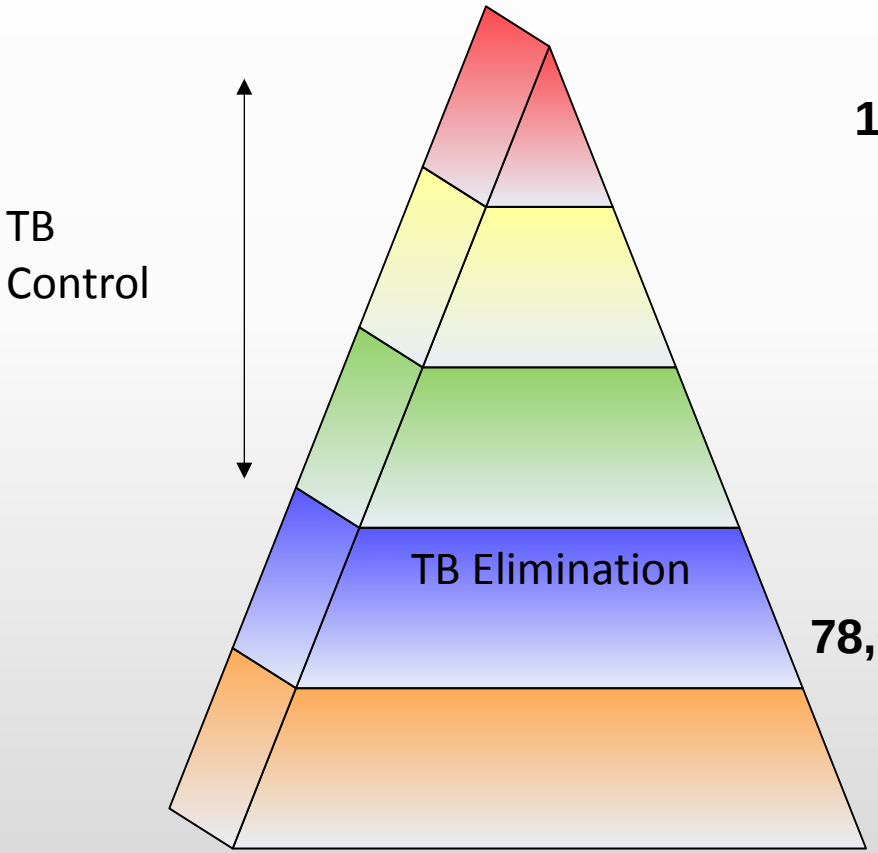
Disclosures

- I will be presenting on investigational or off-label use of rifabutin for LTBI treatment.

Objectives

- Identify three treatment regimens for tuberculosis infection.
- Identify common side effects and monitoring with rifampin in order to improve patient outcomes
- Identify common drug-drug interactions with rifampin in order to improve patient safety

Span of TB Control Activities in San Francisco 2014- update for PI or delete



114 San Franciscans with TB Disease

Over 400 TB suspect cases

1,100 Contacts to TB Cases

78,000 San Franciscans with TB Infection

850,000 San Franciscans

How far are we from elimination?- update for PI or delete

TB elimination: <1 case per million

United States, 2013

30 cases per million (all)

12 cases per million (U.S. born)

156 cases per million (foreign-born)

San Francisco, 2013

1360 cases per million (all)

23 cases per million (U.S. born)

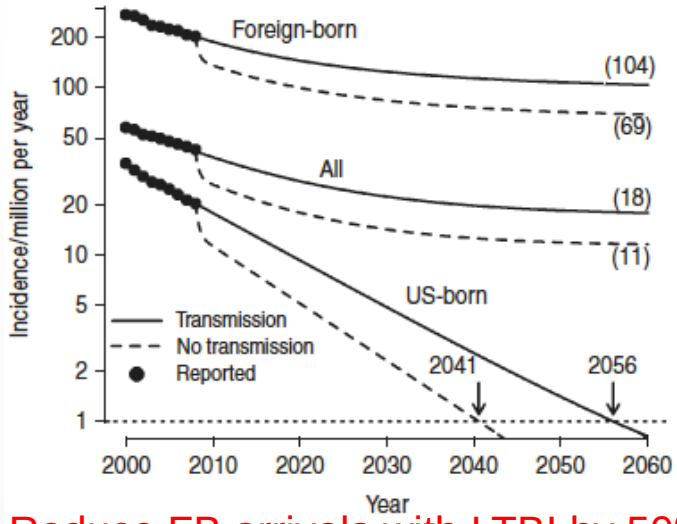
3510 cases per million (foreign-born)

www.cdc.gov, Reported Tuberculosis in the United States, 2013

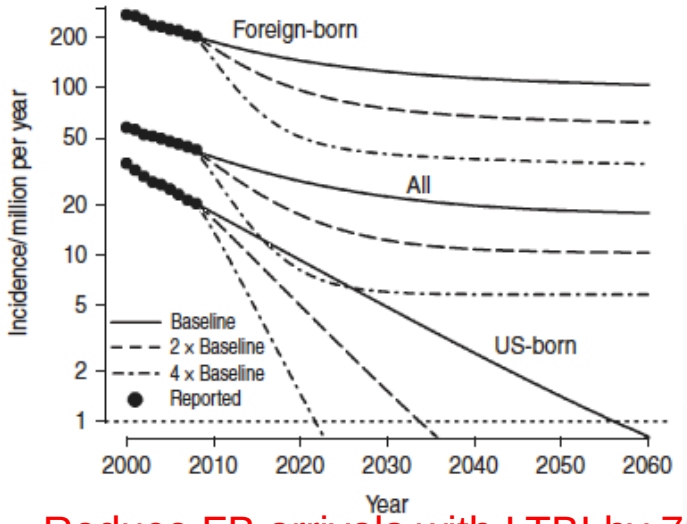
www.cdc.gov

Incidence Projections to 2060- simplify slide

(a) Cut in transmission

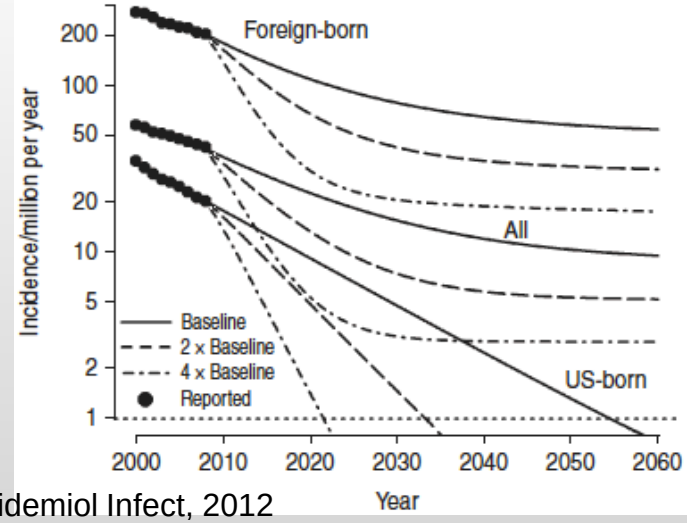


(b) Increase LTBI treatment, 2x or 4x more



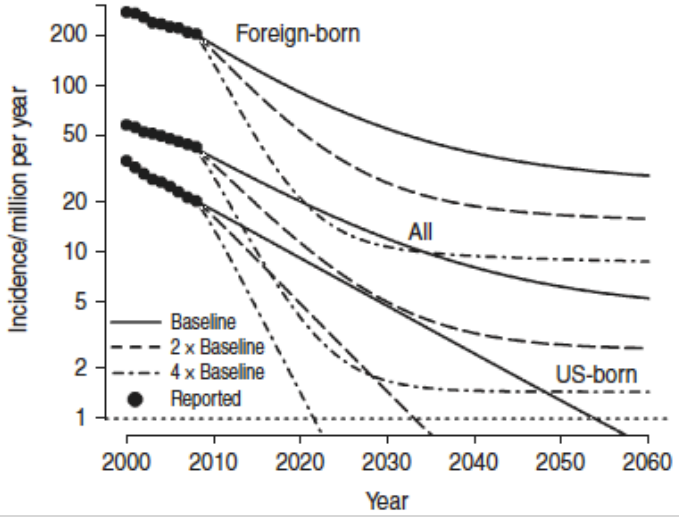
Reduce FB arrivals with LTBI by 50%

(c)



Reduce FB arrivals with LTBI by 75%

(d)



Hill et al., Epidemiol Infect, 2012

INH + Rifapentine (3HP)

- INH + Rifapentine, Qweek x 12 weeks
- Recommended as an equal alternative to INH x 9 mo in healthy patients ≥12 yo and HIV-infected patients not on ART.
- Not recommended in the following:
  - Children <2yo
  - HIV-infected patients on any ART
  - Pregnant or planning to become pregnant
  - Contact to INH/RIF resistant cases
  - Prior adverse events / hypersensitivity to INH/RIF

Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection. MMWR 2011;60:1650–1653

Dosing- 3HP

Drug	Dosage	Maximum dose
INH	15 mg/kg rounded to nearest 50/100 mg in patients ≥ 12 years	900 mg
	25 mg/kg rounded to the nearest 50/100 mg in patients 2-11 years	
Rifapentine	10.0 – 14.0 kg = 300 mg	900 mg
	14.1 – 25.0 kg = 450 mg	
	25.1 – 32.0 kg = 600 mg	
	32.1 – 49.9 kg = 750 mg	
Rifapentine tablets can be crushed and administered with semi-solid food for children unable to swallow pills		

https://www.cdph.ca.gov/programs/tb/Documents/TBCB-INH-RIF-LTBI-fact-sheet.pdf

DOT- 3HP

- Current CDC recommendations: DOT for 3HP

- Recent CDC-sponsored study (TBTC Study 33, data still to be published) suggests self-administered treatment (SAT) is non-inferior to DOT in the US
- Study design for SAT: some pts received SMS reminders, not all doses were SAT (first dose and monthly visits were witnessed when able), only 4 SAT doses were dispensed at a time

https://www.cdph.ca.gov/programs/tb/Documents/TBCB-INH-RIF-LTBI-fact-sheet.pdf

Side effects- 3HP

- Possible hypersensitivity (3.8%)
- Rash (0.8%)
- Hepatotoxicity (0.4%)
- Thrombocytopenia (rare)
- Other toxicities (3.2%)

- Monitoring- similar to INH or RIF
- RFP drug-drug interactions similar to RIF

https://www.cdph.ca.gov/programs/tb/Documents/TBCB-INH-RIF-LTBI-fact-sheet.pdf

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2011 VOL. 365 NO. 23

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

	INH-RPT	INH
No. of patients	3,986	3,745
Administration	Directly-observed therapy	Self-administered therapy
Frequency	Weekly	Daily
Duration	12 weeks	9 months

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 CR Jr, Chaisson RE; TB Trials Consortium PREVENT TB Study Team. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011 Dec 8;365(23):2155-66. Slide courtesy, Dr. Neha Shah

Prevent TB Study Results

	INH-RPT	INH	P-value
Effectiveness	**1.9 per 1,000**	**4.3 per 1,000**	**Non-inferior**
Completion rate	**82.1%**	**69.0%**	**P<0.001**
Hepatotoxicity	**0.4%**	**2.7%**	**P<0.001**

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 CR Jr, Chaisson RE; TB Trials Consortium PREVENT TB Study Team. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011 Dec 8;365(23):2155-66. Slide courtesy, Dr. Neha Shah

Which of the following are reasons to choose rifampin for LTBI treatment in a patient?

A. Exposure to INH-resistant TB
B. Allergy to INH
C. INH-induced hepatoxicity
D. RIF more effective than INH
E. All of the above
F. A, B, and C only

Current recommendations

- Consider 4 month regimen of RIF (4R) in*:
  - Patients with INH intolerance
  - Contacts to INH-resistant TB

  * 6 months for pediatrics

- Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. MMWR 2000; 49 (No. RR-6)

Monitoring

ATS/CDC LTBI guidelines, 2000

- Routine baseline / follow-up laboratory testing

  → Not needed

- Except for:
  - HIV infection
  - Pregnancy / Early postpartum (<3mo)
  - History of liver disease / hepatitis
  - Regular EtOH use

  Also consider for: Statin/other hepatotoxic meds, age >50

Which one of these is NOT a common side effect of Rifampin?

A. Orange discoloration of urine
B. Rash
C. Gout
D. Elevated bilirubin

Adverse Effects

- Hepatotoxicity
  - Rare severe hepatitis, more common when combined with other medications
- Asymptomatic hyperbilirubinemia (0.6%)
- Dermatologic: Pruritis, rash (up to 6%)
- Hypersensitivity reaction (0.07-0.3%)
- GI: nausea, anorexia, abdominal pain
- Immune-mediated: thrombocytopenia, TTP, hemolytic anemia (<0.1%)
- Orange discoloration of body fluids

Monitoring

Evaluate monthly for:

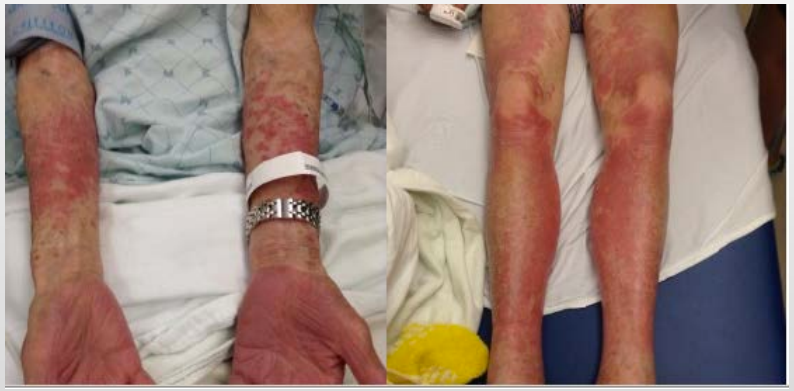
- Adherence
- Symptoms of hepatitis or other side effects
  - Anorexia, nausea, vomiting, or abdominal pain in right upper quadrant
  - Fatigue or weakness
  - Dark urine
  - Rash
  - Persistent numbness in hands or feet

Management of side effects: Drug-induced liver injury

- Review hepatotoxic meds (tylenol, statins, etc), ETOH use, prior hepatitis risk/screen
- HOLD Treatment if:
  - AST/ALT > 3 times the upper limit of normal + symptoms of hepatotoxicity
  - AST/ALT > 5 times the upper limit of normal + asymptomatic
- If less than parameters above, continue treatment with plan to repeat labs in 1-4 weeks.
- Depending on above, consider alternate therapy with close LFT monitoring.

Management of Side Effects: Derm

- Fixed drug eruption
- Rash, itching (1-5%, RIF)
- Pemphigoid reaction
- DRESS
- Anaphylaxis, urticaria



- Mild: anti-histamine, topical steroids, f/u visit
- Mild-moderate: hold meds and above, consider re-challenge once resolves
- Mod-severe: hold meds and above, emergency care / derm consult as needed. Consider alternate therapy once resolves

ARS: 65 yo HIV+ M with HTN, diabetes, hypothyroidism. Which of these diseases may have treatments with rifampin drug-drug interactions?

A. HTN
B. Diabetes
C. Hypothyroidism
D. HIV
E. All of the above

Drug-Drug Interactions

Requires re-dosing or alternate:

- Coumadin
- Opioids (e.g. Methadone)
- Antiretrovirals
- OCP's
- Proton-pump Inhibitor
- Chemotherapy
  - Cyclosporine
  - Tacrolimus
  - Tamoxifen

Monitor and titrate:

- Endo:
  - Levothyroxine
  - Corticosteroids
  - sulfonylureas
- CNS
  - Benzodiazepines
  - Phenytoin, lamotrigine
  - SSRI
- Cardiac
  - Statins
  - Anti-HTN: b-blocker, ACE-I, ARB, Ca-channel blockers

Rifamycin: Drug-drug Interaction

- Rifabutin is a less potent potent inducer of CYP3A4 than rifampin. Thus, can be considered in certain cases with close monitoring (methadone, anti-coagulation, anti-retrovirals)

Resources:

- Lexicomp / Micromedex Drug Interaction Look-up
- Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis. http://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/default.htm
- Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/367/overview

Do you use rifampin for LTBI treatment in your practice/program?

A. Yes
B. Yes, but we only use it in combo (RIF+INH) or in cases of INH resistance/intolerance
C. No
D. I don’t know

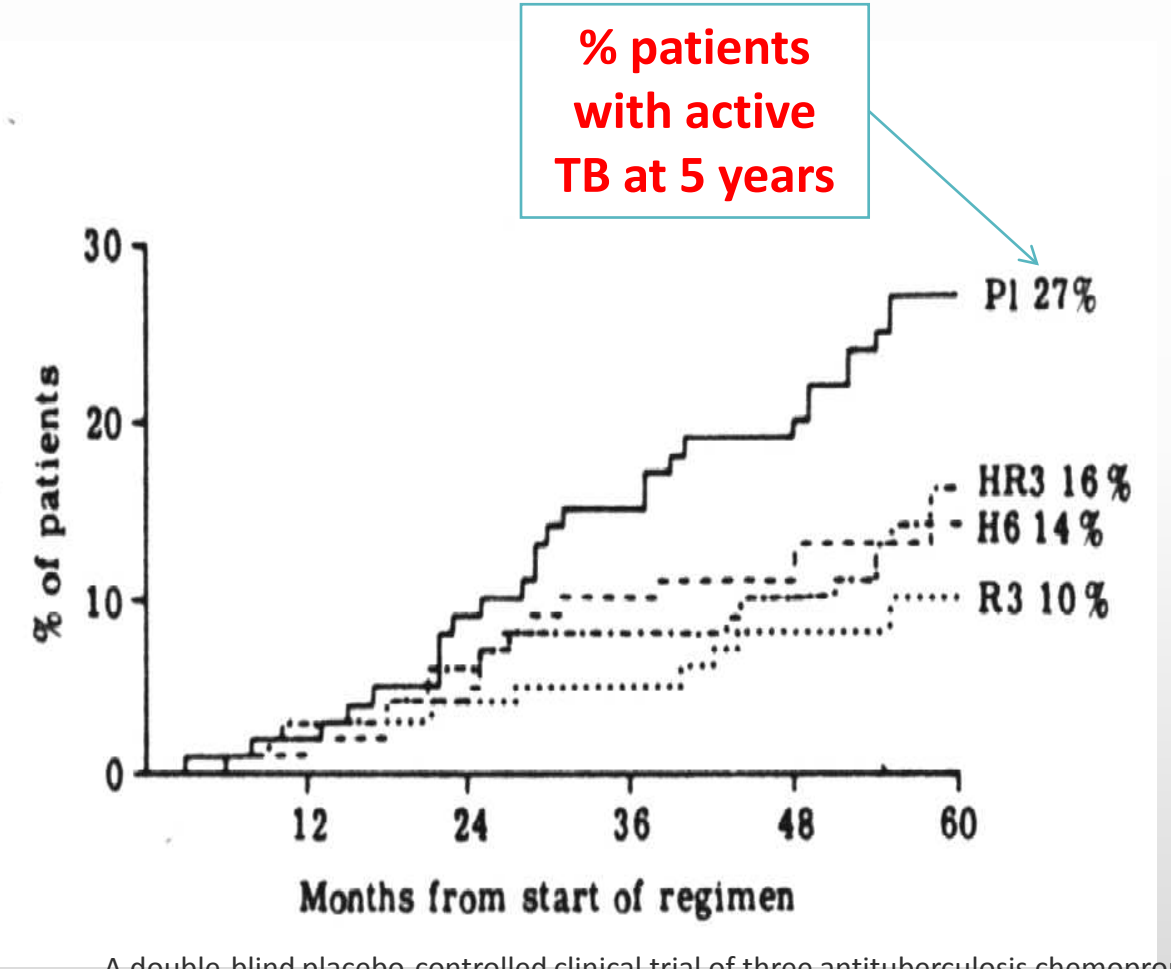
Pros / Cons Rifampin

Potential Benefit	Potential Risk
Shorter duration	Development of resistance
Decreased hepatotoxicity	Increased immune phenomenon (anemia, rash)
Cost	Cost
	Efficacy data limited

Need for more data

- Cost
- Efficacy
- Adherence
- Adverse events
- Development of resistance
- HIV
- Pediatrics

Efficacy of 3R in silicosis

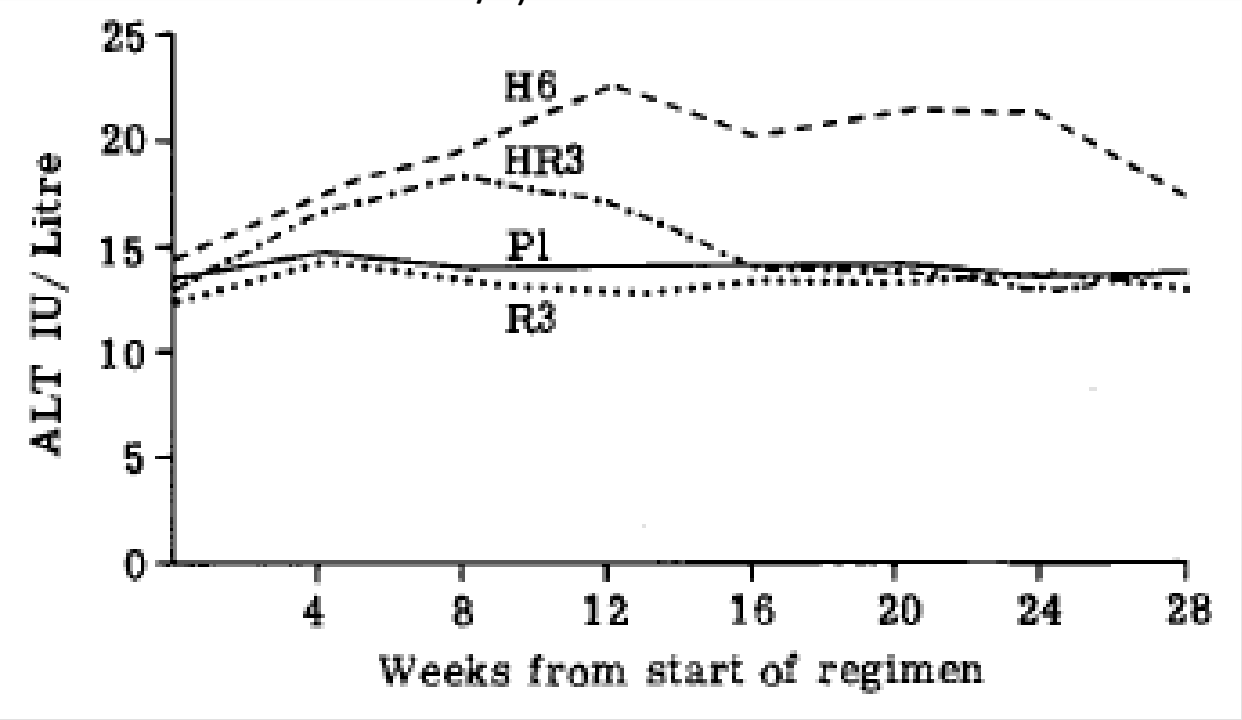


- RCT, n= 679
- Silicosis, PPD+
  - Pl- placebo
  - HR3- INH/RIF x 3 mo
  - H6- INH x 6 mo
  - R3- RIF x 3 mo
- Active pulmonary TB more frequent in placebo vs chemoprophylaxis groups ($p<0.01$)
- No significant difference between 3 chemoprophylaxis regimens

A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. Am Rev Respir Dis. 1992 Jan;145(1):36-41.

Efficacy of 3R in silicosis

Normal ALT <28 IU/L)



- Limitations- regimens self-administered
- Serum ALT significantly higher in H6 and HR3 compared to R3 ($p<0.001$)
- Similar freq adverse effects in all 4 groups
- No evidence of development of drug resistance

A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. Am Rev Respir Dis. 1992 Jan;145(1):36-41.

Rifampin in INH-resistant contacts

- Epidemic of INH/SM-resistance in Boston's homeless, 1984
- 204 TST converters eligible for LTBI treatment
- Mean follow-up periods ranged from 23.5-31.2 months for the 4 groups
- 3 cases of active in INH group were INH-resistant

	No treatment (n=71)	INH (n=38)	RIF (n=49)	RIF/INH (n=37)	RIF-containing treatment (n=86)
Number of active TB cases	6 (8.4%)	3 (7.9%)	0	0	0
P value (compared to "No treatment" group)		0.62	0.04	0.08	<0.01

Polesky A, et al. Rifampin preventive therapy for tuberculosis in Boston's homeless. Am J Respir Crit Care Med. 1996 Nov;154(5):1473-7.

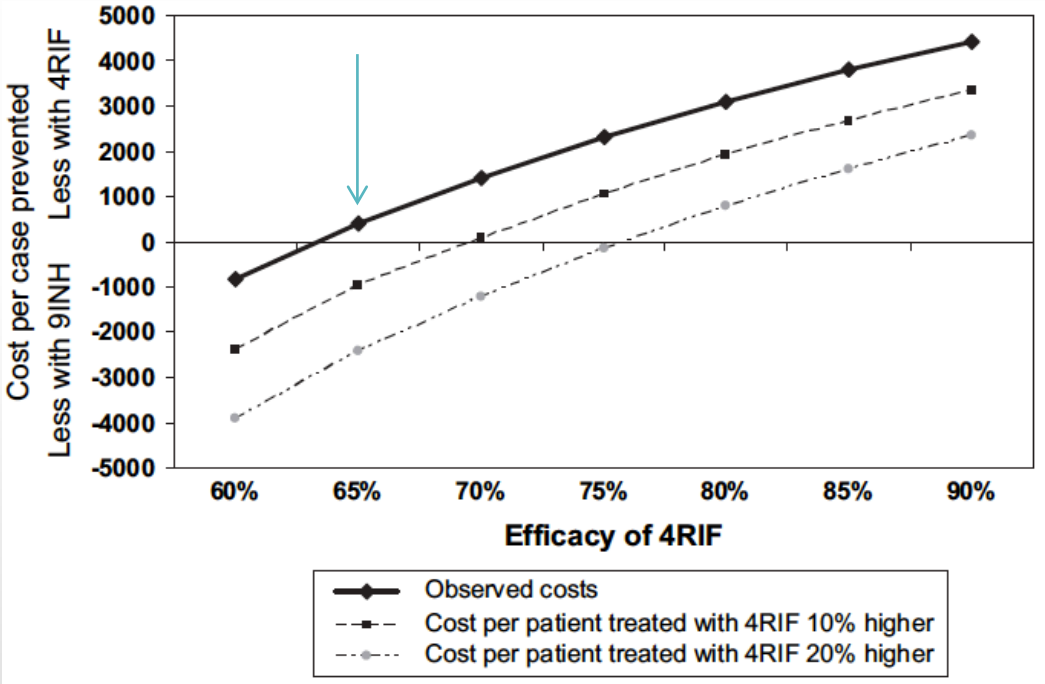
Efficacy: Phase 3 RCT

- Multi-center Phase 3 RCT: 4R vs 9H
- Results expected in 2017
- Study sites: Canada, Australia, Benin, Brazil, Ghana, Guinea, Indonesia, Korea, Saudi Arabia
- Objectives:
  - Effectiveness- incidence of confirmed active TB within 28 months post-randomization
  - Efficacy- incidence of confirmed active TB in those who took at least 80% of doses within allowed time
  - Serious adverse events

Menzies, D. 4 Months of Rifampin for the Treatment of LTBI. As presented at National TB Controller's Association Conference, Atlanta, GA, June 11, 2014

Cost-effectiveness

- Costs estimated based on open-label RCT (visits, labs, meds)
- If 4R efficacy >74%: 4R would be cheaper and would prevent more cases than INH
- If 4R efficacy > 65%: 4R would be cheaper than INH



Aspler A, et al. Impact of treatment completion, intolerance and adverse events on health system costs in a randomised trial of 4 months rifampin or 9 months isoniazid for latent TB. Thorax. 2010 Jul;65(7):582-7.

Cost-effectiveness

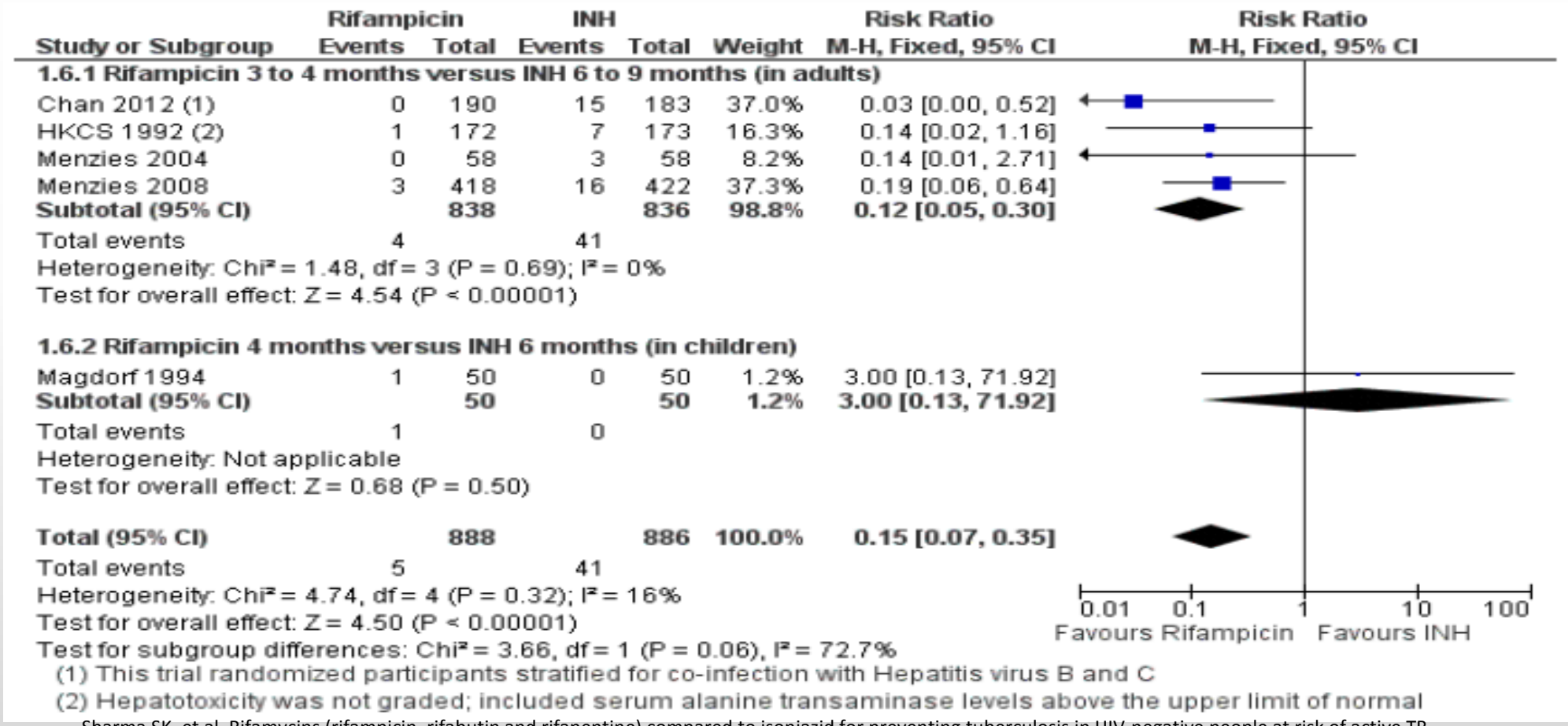
- Computerized model: 4R could be up to 17% less efficacious than INH and still be cost saving and more effective (Holland, et al)
- Decision-analysis model from multicenter RCT: if 4R efficacy ≥ 69%, then 4R is more cheap and effective compared to INH (Esfahani, et al)

* Holland DP, et al. Costs and cost-effectiveness of four treatment regimens for latent tuberculosis infection. Am J Respir Crit Care Med. 2009 Jun 1;179(11):1055-60.
* Esfahani K, et al. Potential cost-effectiveness of rifampin vs. isoniazid for latent tuberculosis: implications for future clinical trials. Int J Tuberc Lung Dis. 2011 Oct;15(10):1340-6.

Treatment Completion / Adverse Events

	Study design	Treatment Completion: RIF vs INH	Adverse events: RIF vs INH
Lardizabal, et al, 2006	Retrospective New Jersey N=474	80.5 vs 53.1 %(p<0.0001)	3.1% vs 5.8 % (p>0.05)
Page, et al, 2006	Retrospective Maryland N=2255	71.6 vs 52.6% (p<0.001)	Adverse events: 1.9 vs 4.6% (p<0.001) Hepatotoxicity: 0.08 vs 1.8% (p<0.001)
Menzies, et al, 2008	Randomized, open-label, multicenter (Canada, Saudi Arabia, Brazil) N=847	78 vs 60% (CI 12-24%, p<0.001)	Grade 3/4 hepatitis: 0.7 vs 3.8% (p=0.03) Decreased platelet/WBC: RIF>INH
Fresard, et al, 2011	Retrospective Switzerland N=624	83 vs 74% (p=0.02)	Hepatotoxicity: 2.0 vs 6.1% (p=0.03)

Hepatotoxicity: Favors RIF > INH



Study or Subgroup	Rifampicin Events	Rifampicin Total	INH Events	INH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Rifampicin 3 to 4 months versus INH 6 to 9 months (in adults)						
Chan 2012 (1)	0	190	15	183	37.0%	0.03 [0.00, 0.52]
HKCS 1992 (2)	1	172	7	173	16.3%	0.14 [0.02, 1.16]
Menzies 2004	0	58	3	58	8.2%	0.14 [0.01, 2.71]
Menzies 2008	3	418	16	422	37.3%	0.19 [0.06, 0.64]
Subtotal (95% CI)		**838**		**836**	**98.8%**	**0.12 [0.05, 0.30]**
Total events	4		41			
Heterogeneity: Chi² = 1.48, df = 3 (P = 0.69); I² = 0%						
Test for overall effect: Z = 4.54 (P < 0.00001)						
1.6.2 Rifampicin 4 months versus INH 6 months (in children)						
Magdorf 1994	1	50	0	50	1.2%	3.00 [0.13, 71.92]
Subtotal (95% CI)		**50**		**50**	**1.2%**	**3.00 [0.13, 71.92]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Total (95% CI)		**888**		**886**	**100.0%**	**0.15 [0.07, 0.35]**
Total events	5		41			
Heterogeneity: Chi² = 4.74, df = 4 (P = 0.32); I² = 16%						
Test for overall effect: Z = 4.50 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.66, df = 1 (P = 0.06), I² = 72.7%						

(1) This trial randomized participants stratified for co-infection with Hepatitis virus B and C

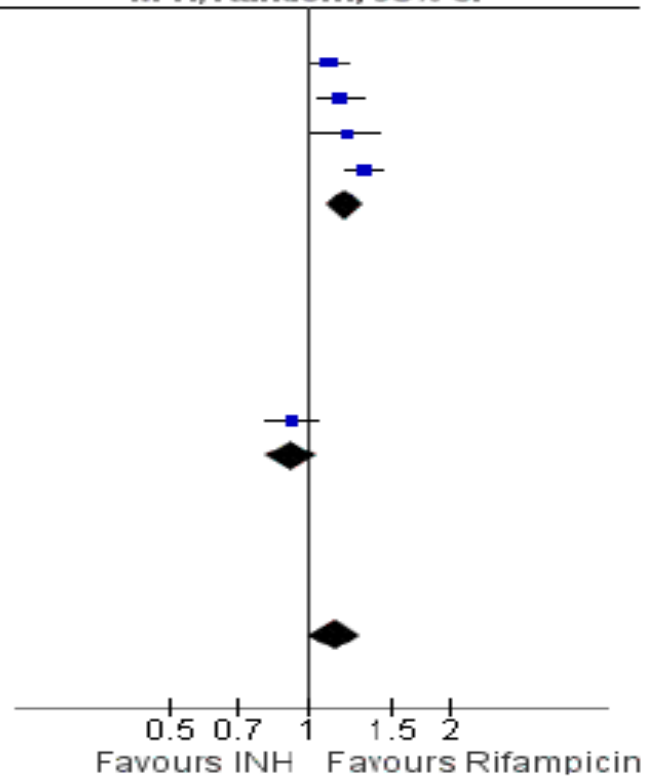
(2) Hepatotoxicity was not graded; included serum alanine transaminase levels above the upper limit of normal

Sharma SK, et al. Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. Cochrane Database Syst Rev. 2013 Jul5;7:CD007545.

Adherence: Favors RIF > INH

Study or Subgroup	Rifampicin Events	Rifampicin Total	INH Events	INH Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Rifampicin 3 to 4 months versus INH 6 to 9 months (in adults with silicosis or LTBI)						
Chan 2012 (1)	163	190	142	183	21.5%	1.11 [1.00, 1.22]
HKCS 1992	142	165	123	167	20.7%	1.17 [1.05, 1.30]
Menzies 2004	53	58	44	58	17.0%	1.20 [1.02, 1.42]
Menzies 2008	328	420	255	427	21.7%	1.31 [1.19, 1.44]
Subtotal (95% CI)		**833**		**835**	**80.8%**	**1.19 [1.10, 1.30]**
Total events	686		564			
Heterogeneity: Tau² = 0.00; Chi² = 6.63, df = 3 (P = 0.08); I² = 55%						
Test for overall effect: Z = 4.20 (P < 0.0001)						
1.3.2 Rifampicin 4 months versus INH 6 months (in children)						
Magdorf 1994	43	50	47	50	19.2%	0.91 [0.80, 1.04]
Subtotal (95% CI)		**50**		**50**	**19.2%**	**0.91 [0.80, 1.04]**
Total events	43		47			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.32 (P = 0.19)						
Total (95% CI)		**883**		**885**	**100.0%**	**1.13 [1.01, 1.28]**
Total events	729		611			
Heterogeneity: Tau² = 0.02; Chi² = 21.93, df = 4 (P = 0.0002); I² = 82%						
Test for overall effect: Z = 2.06 (P = 0.04)						
Test for subgroup differences: Chi² = 11.27, df = 1 (P = 0.0008), I² = 91.1%						

(1) Treatment of prisoners in this trial was by direct observation (except when on parole)



Sharma SK, et al. Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. Cochrane Database Syst Rev. 2013 Jul5;7:CD007545.

Summary

- Compared to INH, rifampin appears to:
  - Be cost-effective
  - Have higher rates of treatment completion
  - Reduced rates of hepatotoxicity / adverse events
- Additional data is needed on:
  - Efficacy
  - Development/risk of resistance
  - Use in special populations (pediatrics, HIV, immunocompromised, etc)
- Results of Phase 3 clinical trial is upcoming

Treatment Completion / Adverse Events References

- Lardizabal A, Passannante M, Kojakali F, Hayden C, Reichman LB. Enhancement of treatment completion for latent tuberculosis infection with 4 months of rifampin. Chest. 2006 Dec;130(6):1712-7.
- Page KR, Sifakis F, Montes de Oca R, Cronin WA, Doherty MC, Federline L, Bur S, Walsh T, Karney W, Milman J, Baruch N, Adelakun A, Dorman SE. Improved adherence and less toxicity with rifampin vs isoniazid for treatment of latent tuberculosis: a retrospective study. Arch Intern Med. 2006 Sep 25;166(17):1863-70.
- Menzies D, Long R, Trajman A, Dion MJ, Yang J, Al Jahdali H, Memish Z, Khan K, Gardam M, Hoeppner V, Benedetti A, Schwartzman K. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. Ann Intern Med. 2008 Nov 18;149(10):689-97.
- Fresard I, Bridevaux PO, Rochat T, Janssens JP. Adverse effects and adherence to treatment of rifampicin 4 months vs isoniazid 6 months for latent tuberculosis: a retrospective analysis. Swiss Med Wkly. 2011 Aug 15;141:w13240.