Treatment of Latent Tuberculosis
Montreal TB Course,
October 30, 2009

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1

LTBI Treatment - Overview

- The INH story - efficacy and risks
- The 2RIF-PZA story
- 4 months RIFampin
- 2-3 months INH-RIF

LTBI Treatment - Overview

- The INH story - efficacy and risks
- The 2RIF-PZA story
- 4 months RIFampin
- 3-4 months INH-RIF
- Other regimens
- Treatment in HIV infected
- Drug resistant contacts

Placebo-Controlled Trials of Isoniazid for Treatment of Latent TB Infection, 1955-1965

19 controlled trials in 11 countries:

United States
Canada
Greenland
Mexico
Japan
Netherlands
France
Tunisia
Kenya
India
Philippines

Over 100,000 participants
Household contacts (6), entire communities (3), inactive pulmonary lesions (5), children with primary TB (2), school children (1) railway workers (1), mentally ill patients (1)

25%-92% protection

HEPATITIS NOT REPORTED OR NOT RECOGNIZED

The INH story

- In 1970 – given all this good news…
- The ATS STRONGLY recommended
  - 12 months INH for Tuberculin reactors
  - All ages, all types, all shapes….
  - (put it in the water)
- So, what happened next?

Outbreak of severe hepatitis on Capitol Hill - 1971

- There had been a highly infectious TB case, resulting in large contact investigation
  - Occurred in Washington, DC
  - Involved politicians, staff, journalists
  - Over 1000 started INH
- Within months, several cases of Hepatitis
  - Two died of liver failure
  - Both were journalists….

Age Specific Incidence of INH hepatitis

Age	Incidence of hepatitis
0-20	< 0.1%
21-34	0.3%
35-49	1.2%
49-64	2.3%
65 +	> 5%

From USPHS Surveillance Study - probable cases ONLY, and from Arkansas nursing home residents

Mortality from INH hepatitis

Study	Years	Age	Mortality (per 100,000)
USPHS surveillance	1971-72	< 35	0
		> 35	98
IUAT trial	1969-72	35-65	14
CDC surveillance	1972-3	All	54
	1974-83	All	14
	1984-8	All	6
Salpeter survey	1983-92	< 35	0.6
		> 35	2.4

Risk benefit studies of INH for low risk reactors

Author	Year	Age Group	Preferred	Margin
Rose	1986	10-80	INH	1-16 days
Tsevat	1988	20-80	No INH	4-17 days
Colice	1990	30	INH	3-19 days
Jordan	1991	20-35 50	INH No INH	3-19 days 2-33 days
Salpeter	1997	35-70	INH	3-5 days

Schematic of Risk Benefit Balance in Deciding RE: LTBI Therapy

Risks of therapy

- Older Age
- Liver Disease
- Alcohol Use

Benefits of therapy

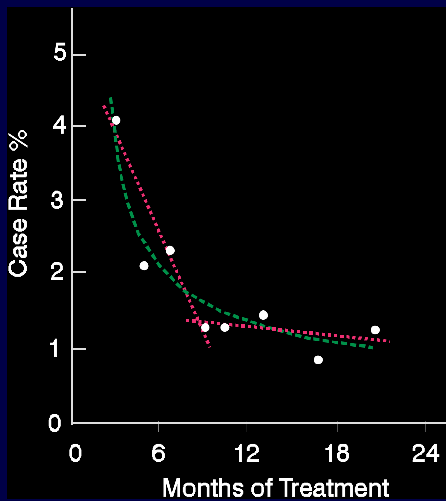
•Greater if greater risk of disease

Duration of INH Therapy and efficacy/effectiveness
Patients with Fibrotic Lesions

Population	Duration	Reduction in TB
All participants	INH 12 mo.	75%
	INH 6 mo.	65%
	INH 3 mo.	21%
Completer/compliers	INH 12 mo.	93%
	INH 6 mo.	69%
	INH 3 mo.	31%

Bull WHO 1982;555-64

How Much Isoniazid Is Needed for the Prevention of Tuberculosis?



- Longer durations of therapy up to 9 months, corresponded to lower TB rates
- No extra increase in protection among those who took >9 months

Comstock GW, 1998

INH - a short history

- 1950 - INH discovered to have anti-TB activity
- Early 1950's - INH found to prevent TB disease
- 1955-65 - large scale trials - 50,000 given INH
  - 60-90% reduction in disease
  - Hepatitis not noted
- 1970 - New ATS guidelines - Encouraging INH
- 1971-2- Hepatitis and deaths reported ➡
- 1973 - New guidelines, controversy, fear (loathing)
- 1974-2003 - Slow 'rehabilitation' of INH

Problems with INH

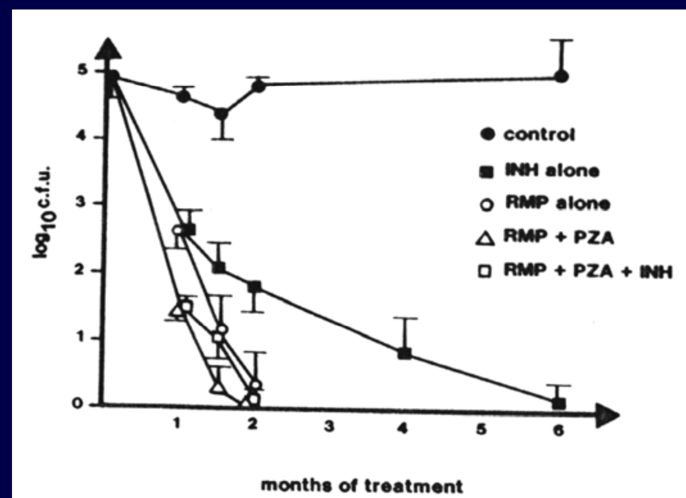
1. Length - 6 months minimum, 9 months better
   - Results in poor compliance - less than 50% in most programs, although can be 80%.
2. Drug induced hepatitis - can be fatal.
   - Although this is now rare
   - Also rash, neuropathies
3. Costs - INH is cheap but close follow up is necessary and this is expensive

Treatment of latent TB infection

Alternative regimens

- 2 months of Rifampin/ PZA
- 4 months of Rifampin alone
- 3-4 months of INH&RIF
- 6 months of Quinolone/ PZA
- 3 months of INH/ Rifapentine once weekly

Experimental Study of Short-Course Preventive Therapy in Mice



Lecour HF, et.al. Am Rev Respir Dis 1989:140:1189-93

International Study of 12INH vs 2RIF-PZA in HIV Infected patients - OUTCOMES

Regimen	2 RIF/PZA	12 INH	RR (CI)
No. enrolled	791	790	
Confirmed TB	19	26	0.7 (.4,1.2)
Conf/Probable TB	28	29	0.95 (.6,1.2)
Death	139	159	0.9 (.7,1.1)

International Study of 12INH vs 2RIF-PZA in HIV Infected patients - Adverse events

Regimen	2 RIF/PZA	12 INH	P value
No. enrolled	791	790	
Rash	1.4%	0.6%	0.14
Hepatitis	0.5%	0.3%	0.4
GI upset	0.5%	0.3%	0.4
Narcotic withdrawal	1.5%	0.0%	0.001
Total:Drugs D/C	9.5%	6.1%	0.01

Recommended regimens (and strength of supporting evidence) for treatment of LTBI - in 2000

Statements by: ATS/CDC, and CTS

Regimen	HIV (+)	HIV (-)
9INH	Strong (A)	Moderate (B)
6INH	Moderate (B)	Moderate (B)
2RIF-PZA	Strong (A)	Moderate (B)
4RIF	Weak (C)	Weak (C)

All regimens daily and self-administered

The 2RZ story unfolds

- Once the new recommendations were final
  - CDC and ATS promoted the 2RZ therapy
  - Use in pilot projects
  - Used in prisons, IVDU, other high risk
- So, what happened next?

Severe and Fatal Liver Injuries with 2RIF-PZA for LTBI

(MMWR, August 31st, 2001. Vol.50; No. 34)

- All from February 12th to August 24th 2001.
- 21 patients with severe liver injury
  - Median age 44 (28-73, 12 male/9 female)
- 5 deaths (plus 2 others reported earlier)
  - Age 32 –68, 3 male, 2 female
  - Onset in second month of therapy
- Onset at end, or even after therapy finished
- All patients HIV negative (?immune mediated hepatitis)

3 regimens in HIV negative patients: Treatment completion

Regimen	2 RIF/PZA	4 INH/RIF	6 INH
No. enrolled	139	131	132
Adherent at 2 mos	60%	58%	82%
Completed Rx	68%	62%	63%

L. Geiter, 1998

3 regimens in HIV negative patients: Serious Adverse Events

Regimen	2 RIF/PZA	4 INH/RIF	6 INH
No. enrolled	139	131	132
Hepatotoxic	9	0	1
Hyperbilirubemia	3	0	1
Gastrointestinal	2	0	0
Renal failure	1	0	0
Total	**15**	**0**	**2**
Drug D/C	8	0	2

L. Geiter, PhD thesis 1998 (never published)

Completion of therapy – 6 INH vs 2RZ

(From Gao et al, IJTLD; 2006:10:1080-1090)

Author	Location	6 INH	2 RZ
Halsey	Haiti	55%	74%
Mwinga	Zambia	66%	75%
Jasmer	USA	57%	61%
Leung	Hong Kong	89%	83%
Tortajada	Spain	77%	82%

Serious Adverse Events – 6INH vs 2RZ

(From Gao et al, IJTLD; 2006:10:1080-1090)

Author	Mean Age	6-12 INH	2 RZ
Halsey	31	0	0
Mwinga	31	3%	4%
Jasmer	37	3%	9%
Leung	60	6%	35%
Tortajada	nr	4%	12%

2 months Rifampin/PZA vs 6 months INH A randomized controlled trial in HIV Negative Persons

(Jasmer et al., Annals Int Med; 2002; 137: 640-643)

	2 RIF/PZA	6 INH	(Pvalue)
Participants	307	282	
% Completing	61%	57%	(NS)
Toxicity - Total	20%	16%	(NS)
- Rash	**6%**	**2%**	**(.01)**
- Nausea/Vomiting	6%	4%	(NS)
- Hepatitis – Grade 3/4	**7.7%**	**1%**	**(.001)**

A brief history of 2RIF-PZA does it sound familiar?

("Those who do not know history are condemned to repeat it")

- 1990: RIF-PZA eliminates TB infection in mice
- 1992-2000 several clinical trials in HIV infected
  - 60-90% reduction in disease
  - well tolerated and safe
- 2000: ATS recommended use of 2RIF-PZA
- 2000: more widespread use
- 2001-2: Hepatitis and deaths reported
- 2002: new guidelines, controversy, fear (loathing)

Treatment of latent TB infection

Alternative regimens

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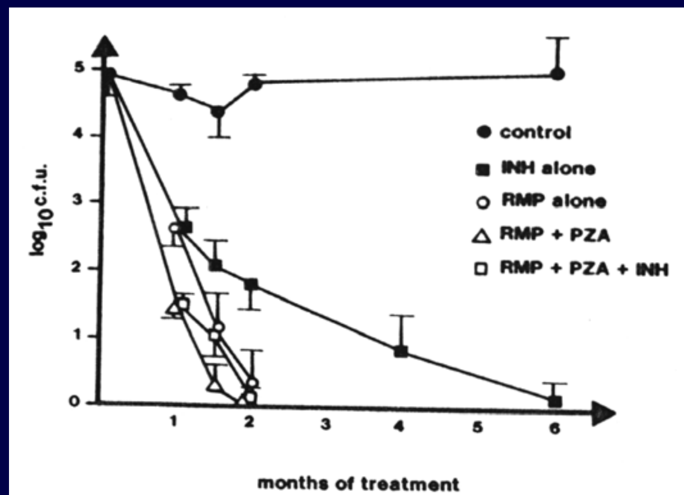
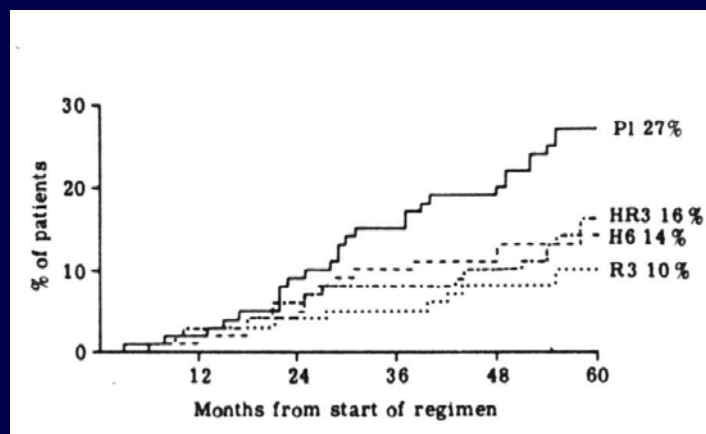


Lecour HF, et.al. Am Rev Respir Dis 1989:140:1189-93

Efficacy of 3 months of Rifampin for the Prevention of TB

Patients with Silicosis



Hong Kong Chest Service. Am Rev Respir Dis 1992;145:36-41

6 Months Rifampin Mono-Therapy
(For contacts of INH resistant cases)
(Polesky et al., AJRCCM; 1996: 155: 1735-38

- 204 Homeless persons in Boston,
- Documented TST conversions
- 71 no therapy – 8.6% active TB
- 38 given INH – 7.9% active TB (INH Resistant)
- 49 RIF only - no active TB, no increased LFT's

4 months Rifampin vs 9 months INH
A retrospective review (non-randomized)
Patient characteristics
(Page et al, Archives Int Med; 2006; 166: 1863-1870)

	9 INH	4 RIF	(Pvalue)
Patients starting therapy	770	1379	
Age	30.1	34.2	(.001)
Sex (% females)	59%	54%	(.03)
HIV positive	**1.8%**	**0.7%**	**(.01)**
Abnormal baseline LFT's	5.7%	4.3%	(NS)
Percent completing	**53%**	**72%**	**(.001)**

4 months Rifampin vs 9 months INH
A retrospective review (non-randomized)
Serious adverse events

(Page et al, Archives Int Med; 2006; 166: 1863-1870)

	9 INH	4 RIF	(Pvalue)
Patients taking therapy	670	1229	
Any adverse event	11.3%	8.3%	(.03)
Permanent D/C therapy	4.6%	1.9%	(.001)
Rash	**2.1%**	**1.6%**	**(NS)**
Nausea/Vomiting	2.8%	2.4%	(NS)
Hepatitis – Grade 3/4	**1.8%**	**.08%**	**(.001)**

RCT of 4RIF vs. 9INH for TB Prevention
Phase 1 Outcomes

	9 INH (N=58)	4 RIF (N=58)
Completed Rx good compliance, N(%)	36 (62%)[1]	50 (86)[1]
Completed Rx poor compliance, N(%)	8 (14%)	3 (5%)
Did not complete Rx, N(%)	14 (24%)[1]	4 (7%)[1]
MD stopped b/o Side effects N(%)	8 (14%)	2 (3%)
< 90% of doses correct at 1 month, N(%)	20 (34%)	12 (21)

[1] P-value = 0.01

Menzies et al, AJRCCM, 2004

RCT of 4RIF vs. 9INH for TB Prevention

Phase 1 Side effects

	9 INH	4 RIF
Major – hepatitis, N	3 (5%)	0
Major – other, N	5 (9%)	2 (3%)
Minor, %	14% [1]	27% [1]

[1] P-value = <0.001

RCT of 4RIF vs. 9INH for LTBI – Phase 2

Completion of Study

	4 RIF (N=420)	9 INH (N=427)	P-value
Completed Therapy	**328 (78%)**	**254 (60%)**	<.0001
Patient Non-compliant (Total)	**75 (18%)**	**144 (34%)**	
- Drop-out	**49 (12%)**	**77 (18%)**	
- Intolerance	**17 (4%)**	**51 (12%)**	
MD Non-compliant	**9 (2%)**	**16 (4%)**	

RCT of 4RIF vs. 9INH for LTBI – Phase 2
Therapy Stopped Permanently and Justifiably Because of Drug Related Adverse Events

	4 RIF (N=420)	9 INH (N=427)	P-value
All Grades – Total (%) *	16 (3.8%)	24 (5.6%)	NS
Grade 3 to 4 - Total	6 (1.5%)	17 (4.0%)	.02
- Hepato-toxicity	3 (0.7%)	16 (3.8%)	.003
- Hematologic	1	1	-
- Drug Interaction	1	0	-
- Rash	1	0	
Grade 1 to 2 - Total	11 (2.0%)	7 (1.6%)	NS
- Rash	8	4	NS
- GI intolerance	1	2	-
- Hematologic	2	0	-

* The severity, type and relationship to study drug judged by independent three-member panel blinded to patient allocation.

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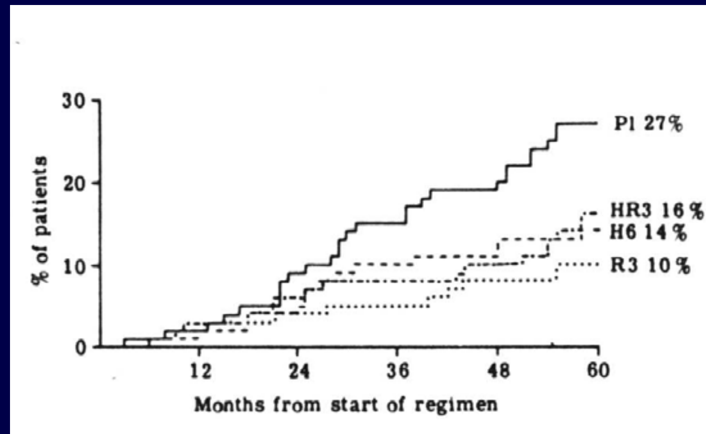

Hong Kong Chest Service. Am Rev Respir Dis 1992;145:36-41

Twice weekly INH – RIF for LTBI

(McNab et al., AJRCCM 2000; 162: 989-993)

Aboriginal Canadians with LTBI (non-randomized)

	$6INH_2RIF_2$	12 INH	P Value
Number	591	403	---
Completed Tx	487 (82%)	99 (25%)	<.001
Pregnancy	0	5 (1%)	---
Side effects	9 (2%)	39 (10%)	<.001
Active TB			
During Tx	1	9	
After Tx	1	6	
Total	2	15	<.001

3-4 Rifampin-INH vs 6-12 INH
A meta-analysis of 5 RCT's
Occurrence of active TB

(Ena & Valls, Clin Inf Dis; 2005; 40: 670-676)

	INH	INH/RIF	(Diff. %)
Hong Kong (silicotics)	25/173	26/167	(+1.1%)
Martinez (Spain – HIV)	0/98	1/98	(+1.0%)
Martinez (Spain - HIV)	4/64	2/69	(- 3.3%)
Rivero (Spain – HIV)	3/83	3/82	**(+0.1%)**
Whalen (Uganda – HIV)	7/536	9/556	(+0.3%)
Pooled estimates	39/954	41/972	**(+0.1%)**

3-4 mos Rifampin-INH vs 6-12 mos INH
A meta-analysis of 5 RCT's
Serious Adverse Events

(Ena & Valls, Clin Inf Dis; 2005; 40: 670-676)

	INH	INH/RIF	(Diff. %)
Hong Kong (silicotics)	13/173	8/167	**(- 2.7%)**
Martinez (Spain – HIV)	9/98	7/98	**(- 2.0%)**
Martinez (Spain - HIV)	15/64	5/69	**(- 16%)**
Rivero (Spain – HIV)	6/83	15/82	**(+11%)**
Whalen (Uganda – HIV)	3/536	13/556	**(+1.7%)**
Pooled estimates	46/954	48/972	**(+0.1%)**

Current status of LTBI treatment

- 9 months of INH - is still the preferred option
  - efficacy >90% if taken properly
  - safety record in past decade is good
- 2 months Rif-PZA - use with extreme caution
  - HIV positive persons may tolerate it better
  - special situations (eg prisons, short stay visitor)
- 4 months Rifampin - may be better alternative
  - toxicity, especially hepato-toxicity, appears low
  - efficacy still unclear

Thanks/Merci

Meta-Analysis: INH does not protect against TB – In HIV (+) who are TST (-)

(Pooled estimates: 0.84 (0.54-1.30))

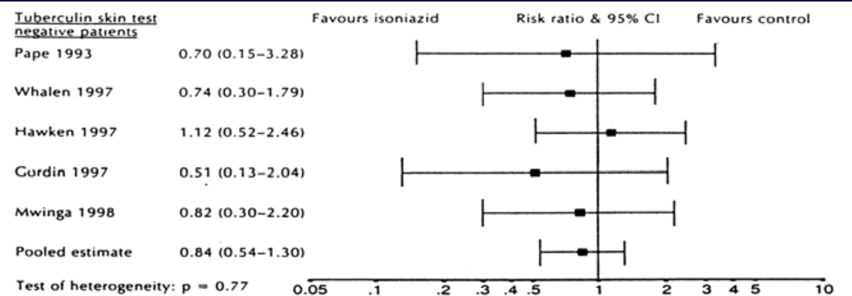

Fig. 1. RR and 95% CI of TB for INH versus placebo or control regimens in randomized controlled trials for prevention of TB in HIV infection. See Table 1 for study references.

Heiner BC, Lauren GE, Gordon GH, et al. Isoniazid prophylaxis for tuberculosis in HIV infection: a meta-analysis of randomized controlled trials. AIDS 1999;13:501-507.

AIDS 1999;13:501-7

Treatment of LTBI in persons at risk for MDR – a systematic review

(Fraser et al, IJTLD, 2006: 10: 19-23)

- Identified 907 titles, reviewed 32 papers, and found TWO observational studies:
- Schaaf, South Africa: Pediatric contacts of MDR
  - 3 drug regimen, tailored to DST
  - TB in 2/41 Treated vs 13/64 Not: 80% reduced
- Kritski, Brazil: Household contacts of MDR-TB
  - INH alone given
  - TB in 2/45 Treated vs 13/145 Not: 56% reduced

Levofloxacin & PZA for Contacts of MDR-TB

- Currently recommended by expert consensus
- 48 patients – transplant recipients
  - *(Pharmaco- therapy, 2002; 22: 701-704)*
  - 13 completed 12 months
  - 27 (57%) discontinued due to adverse events
- 17 patients - median age 36, 8 female 9 male
  - *(CMAJ; 2002: 167: 131-6)*
  - None completed therapy (average 1 month).
  - All developed side effects
    - Musculoskeletal and hepatitis

Current status of LTBI treatment Summary

- 9 months of INH - is still the preferred option
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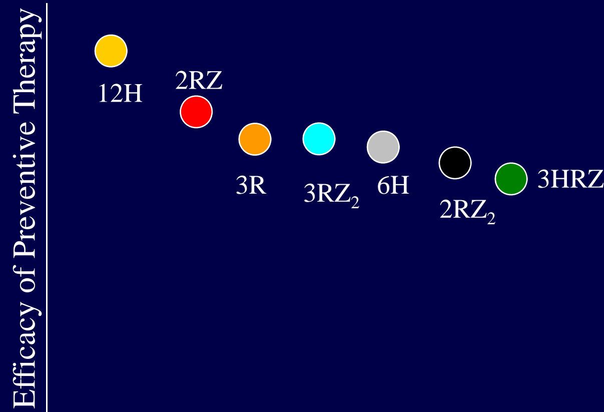
- 2 months Rif-PZA - use with extreme caution
  - HIV positive persons may tolerate it better
  - special situations (eg prisons, short stay)

Treatment of LTBI
Relative Efficacy of Regimens



From L. Geiter

Current status of LTBI treatment
Summary

- 4 months Rifampin - may be better alternative
  - Toxicity, especially hepato-toxicity, is low
    - Not assessed in large RCT
  - Efficacy untested - no RCT as yet
  - Although in one RCT 3RIF better than 9INH
- 3-4 months INH-RIF – Increasingly studied
  - Unclear if better than 4RIF alone
  - Less risk from mono-therapy
  - But, compliance and SAE may be worse