Treatment of Active Tuberculosis Montreal TB Course, November 26, 2010

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Overview

- TB drugs – what they do (good and bad)
- Goals of TB treatment
- Standard TB treatment
- Intermittent treatment and DOT
- Drug resistance – how it develops
  - How to treat (briefly)

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TB Drugs: Rifampin (RIF)

- Introduced in 1970
- The most effective and important TB drug
  - Allows shortening of therapy to half
- Bactericidal, and sterilizing
- Side effects: Drug interactions
  - Rash
  - Hepatitis
  - Hematologic

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Serious Adverse Events with INH or RIF (RCT of single drugs used for Latent TB)

	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**	-

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* severity, type + relationship to study drug by independent blinded 3-member panel

TB Drugs: Isoniazid (INH)

- One of the oldest TB drugs – introduced in 1950
- The second most important/effective drug
- Bactericidal
- Early activity important (first few days)
- Side effects: Hepatitis
  - Rash
  - Neuropathy, anemia, lupus-like

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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

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TB Drugs: Pyrazinamide (PZA)

- Introduced in 1980
- The 3rd most important TB drug
  - Allows shortening of therapy by 3 months
- Bactericidal, but only early effect
- Side effects: Hepatitis
  - Rash
  - Arthralgias (Pains but not arthritis)

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TB Drugs: Ethambutol (EMB)

- Introduced in 1960
- The least effective 1st line TB drug
  - ONLY to protect against resistance
- Bacteriostatic
- Side effects: Optic neuritis (blindness)
  - Rash

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Goals of TB Treatment

1. Reduce further morbidity and prevent mortality

   Get better as quickly as possible
2. Reduce contagiousness

   Reduce bacillary load quickly
3. Prevent emergence of drug resistance
4. Prevent relapse (long term cure)

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Building a TB regimen

1. Get better quickly:
   - INH - Most important – in first week
   - RIF – Bactericidal effect through-out therapy
   - PZA –if given for 1st 2 months – can shorten total therapy to 6 months
   - Add other drugs? – will not make patients better faster
- First two months are critical = initial intensive phase

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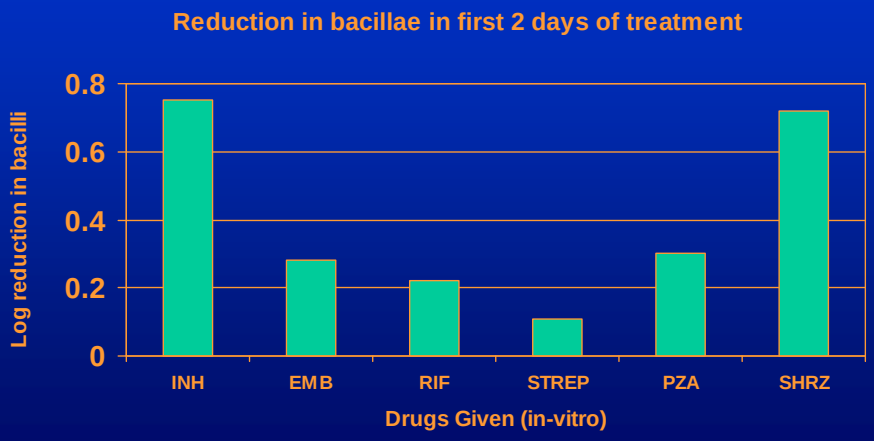
Initial intensive phase - early bactericidal activity



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Building a TB regimen

2. Prevent resistance:
   - Most important rule: Never give a single drug
     - If possible active TB
     - Or if side effects and drugs have to be stopped
     - Or if treatment is failing – do not a single drug
     - Or if recurrent TB – give at least two NEW drugs
- EMB – is important to prevent resistance,
  - PZA – does not prevent resistance
- More drugs reduces chance of failure, relapse and resistance

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Association of Number of drugs in regimen and Treatment outcomes (from multivariate meta-regression)

	Failure IRR (95% CI)	Relapse IRR (95% CI)	Acquired drug resistance† IRR (95% CI)
Initial phase ≤ 3	1.0 (reference)	1.0(reference)	1.0 (reference)
Initial phase ≥ 4	**0.4 (0.2 – 0.7)**	0.9 (0.6 – 1.3)	**0.4 (0.2 – 0.7)**
Continuation = 2	1.0 (reference)	1.0(reference)	1.0(reference)
Continuation ≥ 3	**0.5 (0.3 – 0.9)**	0.9 (0.7 – 1.2)	**0.5 (0.3 – 0.9)**

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Building a TB regimen

3. Long term cure = prevent relapse
   RIF – more RIF = less relapse
   After first 2 months – 2 drugs enough
   INH & RIF

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Duration of Rifampin and Relapse

Rifampin duration	Arms (N)	Pooled event rate	95% Conf Interval
No Rifampin	43	11.8%	8.8 – 15
1-2 months	66	**11.6%**	8.9 – 14
3-5 months	22	**6.2%**	4.2 – 8.2
6-7 months	131	**5.5%**	4.8 – 6.3
8+ months	25	1.1%	0.3 – 1.9

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Duration of Rifampin and Treatment outcomes
(from multivariate meta-regression)

Duration of RIF	Failure IRR (95% CI)	Relapse IRR (95% CI)	Acquired drug resistance IRR (95% CI)
2 Months	2.2 (0.7 – 7.2)	**18.6 (7.4 – 47)**	**7.9 (2.4 – 26)**
3 – 5 months	2.5 (0.7 – 8.4)	**9.4 (3.3 – 26)**	3.2 (0.7 – 14)
6 Months	0.6 (0.2 – 1.7)	**6.6 (2.7 – 16)**	2.0 (0.7 – 6.0)
≥ 8 Months	**1.0 (reference)**	**1.0 (reference)**	**1.0(reference)**

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Reducing relapse

- Longer therapy (8-9 months total) reduces relapse
  - But 2-3 months extra in all patients = risk,cost,work
- Who to choose = risk factors for relapse
  - More extensive disease at start (AFB+, Cavities)
  - Smear/culture positive at 2 months
  - Cavities at 2 months, or 5 months
  - HIV infected ?

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Summary points - current therapy

- Initial intensive phase
  - Two months duration is optimal
  - Minimum 3 drugs (4 is better)
  - INH - most potent bactericidal agent
  - RIF - second most potent, least resistance
  - PZA - allows total therapy to be 6 mos only
  - EMB - protects against resistance
- Continuation phase
  - Four months minimum, 6-7 months reduces relapse
  - 2 drugs minimum

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Intermittent therapy

- Possible because of long half life of drugs
- And slow growth of M TB
- Intermittent therapy does work
  - In-vitro (cultures only)
  - In animal studies
  - In humans – randomized trials
- What is the lowest frequency?
- How early can it start?

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Intermittent regimens and Failure

Administration of drugs	Arms (N)	Pooled event rate	95% Conf Interval
Daily – all	173	2.6%	1.8 – 3.4
Daily – then intermittent	76	2.0%	0.4 – 3.7
Intermittent all – thrice weekly	53	2.7%	0.1 - 4.4
Intermittent all – twice weekly	17	**8.8%**	1.5 – 16

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Intermittent regimens and Relapse

Administration of drugs	Arms (N)	Pooled event rate	95% Conf Interval
Daily – all	149	6.7%	5.4 – 8.0
Daily – then intermittent	65	7.0%	5.1 – 8.9
Intermittent all – thrice weekly	52	6.8%	5.6 – 8.1
Intermittent all – twice weekly	17	**10.7%**	7.2 – 14.3

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Intermittent therapy and outcomes – from Meta-regression

(RCT in New cases with RIF)

Intermittent schedule	Failure IRR (95% CI)	Relapse IRR (95% CI)	ADR IRR (95% CI)
Daily throughout	1.0 (reference)	1.0 (reference)	1.0(reference)
Daily then thrice weekly	0.8 (0.5, 1.3)	1.0 (0.7, 1.3)	0.9 (0.4, 1.8)
Daily then twice weekly	1.3 (0.9, 1.8)	0.8 (0.7, 1.1)	0.7 (0.4, 1.1)
Thrice weekly throughout	1.3 (0.97, 1.7)	1.1 (0.9, 1.3)	**4.9 (3.3, 7.4)**

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In patients with HIV-TB
Effect of Intermittent regimens on Relapse

Use of Intermittent therapy	Studies	Event/ Subjects (N)	Pooled event rate	(95% CI)
Daily Initially	23	156/1303	7.7%	(1.7, 13.6)
Intermittent through-out	**7**	**35/323**	**14.4%**	**(0, 32.8)**

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Intermittent therapy and Treatment outcomes - INH resistance
(from multivariate meta-regression)

	Failure IRR (95% CI)	Relapse IRR (95% CI)	Acquired drug resistance IRR (95% CI)
Daily Initially	1.0 (reference)	1.0(reference)	1.0(reference)
3X weekly thru-out	**3.0 (2.0, 4.5)**	1.5 (0.9, 2.5)	**2.4 (1.4, 4.2)**
2X weekly thru-out	**2.4 (1.6, 3.5)**	**4.5 (1.9, 10.7)**	1.5 (0.9, 2.5)

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Summary - Intermittent therapy

- Intermittent regimens facilitates DOT
  - Once weekly = totally unacceptable
  - Twice weekly = worse results
  - Thrice weekly = slightly worse
    - OK under ideal conditions
    - BUT – worse if HIV infected or drug resistant
- Best is daily therapy in first two months
  - Then can switch to intermittent
- If self-administered – give daily

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Drug resistance

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Emergence of resistance
Therapy with one drug (First ever TB trial)

- In 1950 first TB trial was conducted in Britain.
- 109 patients received Streptomycin only
  - Only drug available at the time
- Resistance developed rapidly in these patients
  - First detected after three weeks
  - 60% resistant after two months
  - 80% resistant after three months

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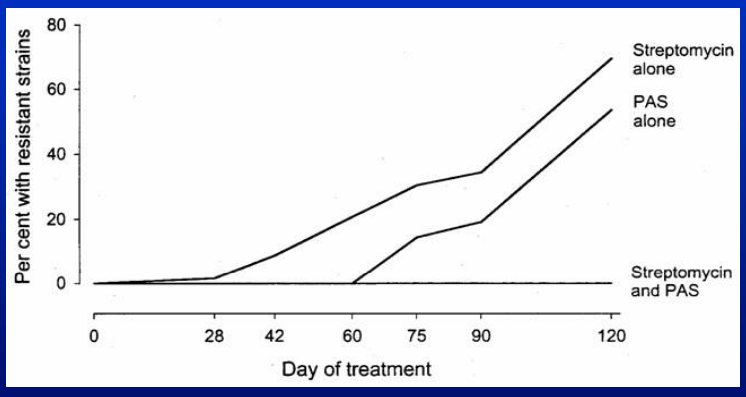
Emergence of resistance to streptomycin and/or PAS para-aminosalicylic acid given alone or in combination



. From Reider, Interventions for TB control, IUATLD.

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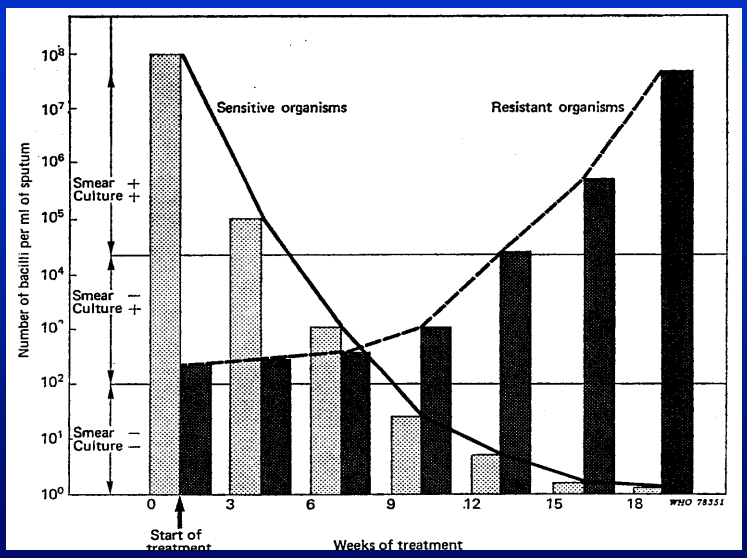
The "fall and rise" phenomenon – patients given INH alone



From Toman, Case Finding and Chemotherapy

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Rate of spontaneous mutations of M Tuberculosis to anti-TB drugs

Streptomycin	**10^{-6}**
Isoniazid	**10^{-6} - 10^{-7}**
Rifampin	**10^{-8} - 10^{-9}**
Ethambutol	**10^{-7} - 10^{-8}**
INH&Rif	**10^{-14}**

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Total number of bacilli – in different lesions

Latent TB	**10^3**
Infiltrates	**10^6 - 10^7**
Cavity (one)	**10^8 - 10^9**
Multi-cavities	**10^{10} - 10^{12}**
Death	**10^{13}**

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Probability of developing resistance during therapy

Number of Drugs	Total number of bacilli				
	10^4	10^6	10^8	10^{10}	10^{12}
One	1%	63%	100%	100%	100%
Two	0	0	.01%	1%	60%
Three	0	0	0	0	0

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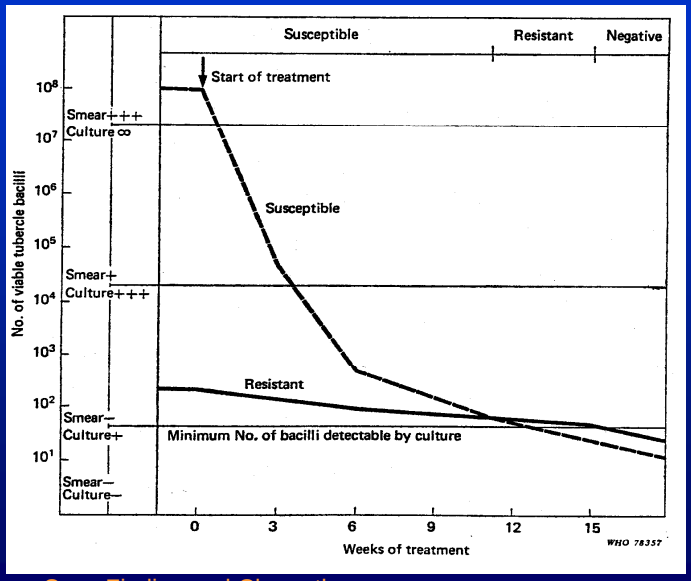
Transient drug resistance during therapy with two or more drugs (effect of default)



From Toman, Case Finding and Chemotherapy

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Drug resistance - prevention and therapy

- To prevent resistance:
  - Minimum two drugs
  - Give at least 3 when bacillary load is high
  - 4 drugs offer better protection
- Therapy if resistance known
  - Tailor to specific resistance pattern
- IF failure or relapse, while waiting…
  - Always give two new drugs
  - Usually Quinolone and injectable

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Association of Initial drug resistance with Treatment outcomes

(from multivariate meta-regression)

	Failure IRR (95% CI)	Relapse IRR (95% CI)	Acquired drug resistance IRR (95% CI)
Pan Sensitive	1.0 (reference)	1.0(reference)	1.0(reference)
Initially SDR	**12 (7 – 20)**	**2.3 (1.7 – 3.0)**	**7 (4.5 – 12)**
Initially PDR	**47 (22 – 103)**	**2.3 (1.3 – 4.2)**	**29 (15 – 58)**

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Drug resistance - therapy

- If mono-INH resistance:
  - RIF/PZA/EMB – 2 months, RIF/EMB - 10 mos
  - Or, Quinolone/RIF/PZA/EMB for 6-9 mos
  - Moxifloxacin = INH in one RCT
- If mono-RIF resistance:
  - INH/PZA/Quin/EMB/Injectable – 2-6 mos
    - Then INH/EMB ??Quin – total 18 mos
- If PZA resistance:
  - INH/RIF/EMB – 2 mos, INH/RIF – 7 mos

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Multi-Drug resistance - therapy

- MDR = Resistance to INH & RIF
- High rates of failure & relapse (20%)
- High mortality (10-20%)
- Success rates: average 60%

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Rational selection of MDR-TB regimen

Group 1	Isoniazid Rifampin Ethambutol Pyrazinamide
Group 2	Streptomycin Kanamycin Amikacin Capreomycin
Group 3	Ofloxacin Levofloxacin Moxifloxacin Gatifloxacin
Group 4	Ethionamide Prothionamide Cycloserine Terizidone Thioacetazone P-aminosalicylic acid
Group 5	Clofazimine Imipenem Amoxacillin/Clavulanate Macrolides Linezolid

TB drugs: Serious adverse effects

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TB drugs: Serious adverse effects

- INH – Hepatitis, Rash, Neuropathy (B6)
- RIF –Drug Interactions, Hematologic, Rash, Hepatitis
- PZA – Rash, Hepatitis, Arthralgias, Uric acid (gout)
- EMB – Optic neuritis, rash
- Injectables – Renal, oto-toxicity

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Serious adverse effects - management

- Step 1: Stop all possible drugs
- Step 2: Immediately start enough new drugs to ensure adequate therapy (minimum 2 drugs at all times) = Quinolone + EMB or Injectable
- Step 3: When effect resolves re-introduce in reverse order of probability of causation

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Serious adverse effects - management

- Cause of rash: PZA>RIF>INH>EMB
- So – start with most important drugs AND least likely = RIF or INH
  - If no rash add second, etc
  - Speed – one drug added back every 3-4 days
- Cause of hepatitis: PZA>INH>RIF
- So – start with RIF, then INH
  - Speed – one drug every 2 weeks (much slower)
  - If no hepatitis with INH/RIF do **not** give PZA

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LTBI treatment

- **INH - efficacy and risks**
- 4 months RIFampin

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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**

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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

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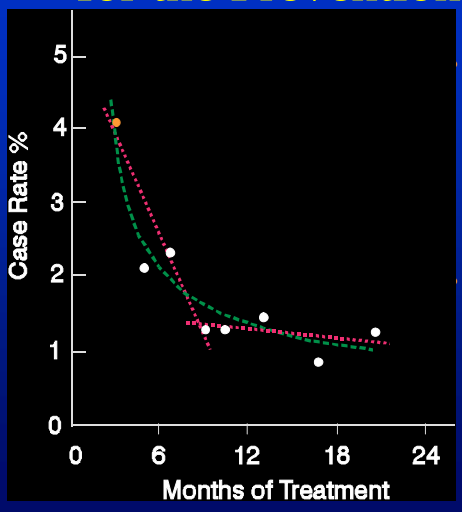
How Much Isoniazid Is Needed for the Prevention of TB?



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

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Problems with INH

1. Length - 9 months ideal
   - Results in poor compliance - less than 50% in most programs.
2. Drug induced hepatitis - rarely fatal.
   - Also rash, neuropathies
3. Costs - INH is cheap but close follow up is necessary and this is expensive

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LTBI treatment

- INH - efficacy and risks
- **4 months RIFampin**

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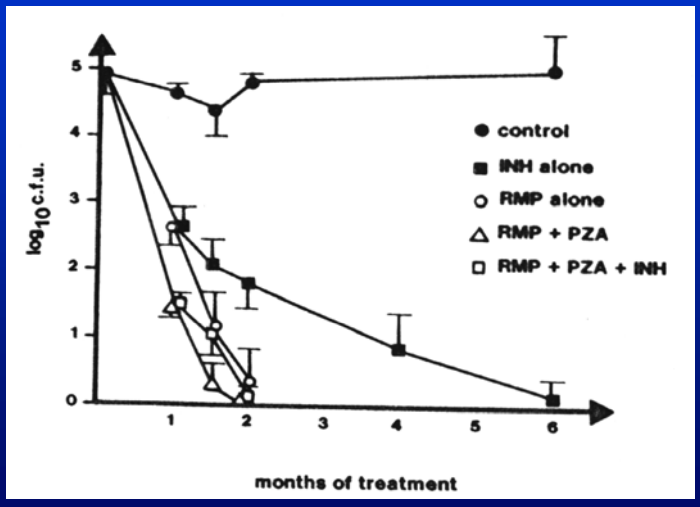
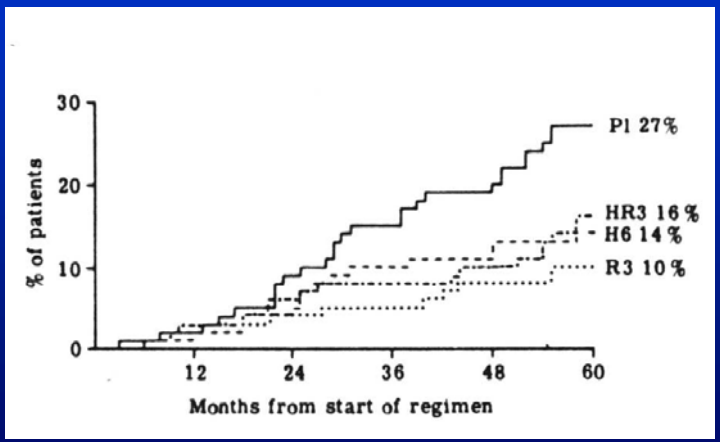
Experimental Study of Short-Course Preventive Therapy in Mice



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

- Homeless persons in Boston, screened in shelters
- **Extended Outbreak of INH resistant TB**
- 204 Exposed persons with documented TST conversion
- Therapy of LTBI was **not** randomized
- 71 no therapy – **8.6%** active TB
- 38 given INH – **7.9%** active TB (INH Resistant)
- 86 RIF or INH/RIF – **0** active TB
  - 49 Rifampin only – no hepatitis or increased LFT's

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

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

	9 INH	4 RIF	(Pvalue)
Patients taking therapy	770	1379	
Percent completing	**53%**	**72%**	(.001)
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)**

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RCT of 4RIF vs. 9INH for LTBI
Phase 1

	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

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

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

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Serious Adverse Events with INH or RIF (RCT of single drugs used for Latent TB)

	4 RIF (N=420)	9 INH (N=427)	P-value
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- 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**	-

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* severity, type + relationship to study drug by independent blinded 3-member panel

4RIF vs. 9INH for LTBI

Conclusions

4 months Rifampin appears promising!

- Serious adverse events significantly less
  - Particularly for grade 3 to 4 hepatitis
  - The most important/lethal complication
  - But hematologic effects will need monitoring.
- Completion significantly better with 4RIF
- Costs lower with 4RIF
  - Drug costs still excessive with 4RIF

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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

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Thanks/Merci

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