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

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Goals of TB Treatment

- Reduce further morbidity and prevent mortality
  - Get better as quickly as possible
- Reduce contagiousness
  - Reduce bacillary load quickly
- Prevent emergence of drug resistance
- Prevent relapse (long term cure)

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Features of current standard therapy

- Initial intensive phase
  - Two months duration
  - Four drugs; HRZE
- Continuation phase
  - Four months duration
  - Two drugs: HR
- Fully ambulatory and intermittent

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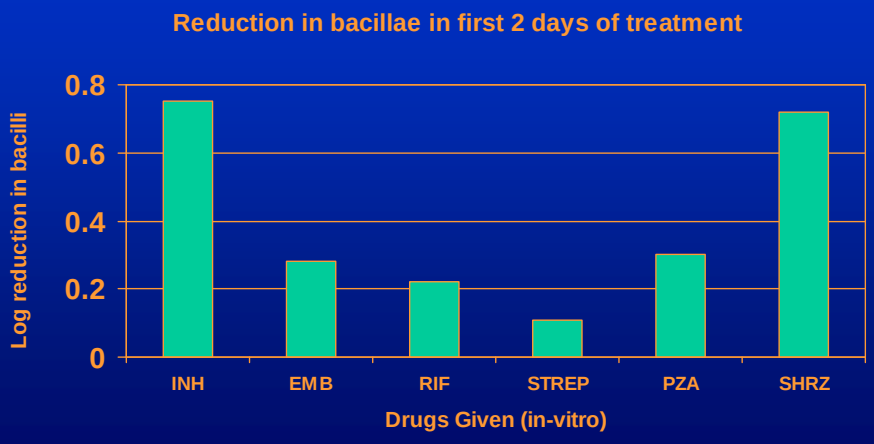
Initial intensive phase - early bactericidal activity



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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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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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Intermittent therapy

- Possible because of long half life of drugs
- And slow growth of M TB
- Intermittent therapy does work
- 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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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

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Summary points - current therapy

- Continuation phase - Four months duration is sufficient
  - If Drug-sensitive organisms
  - If HRZ given in first 2 months
  - If INH&RIF given, but PZA not needed
  - Some advantage to 3 drugs vs 2 drugs
- If No Rifampin (INH/EMB or INH/Thiac) then at least 6 months required

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Summary points - current therapy

- Intermittent regimens facilitates DOT
  - Once weekly unacceptable
  - Twice weekly is minimum
  - Thrice weekly - better
    - One advantage - when doses are missed
- If Intermittent within first month – worse outcomes if twice weekly from outset
  - Best is daily therapy in first two months
  - Then switch to intermittent

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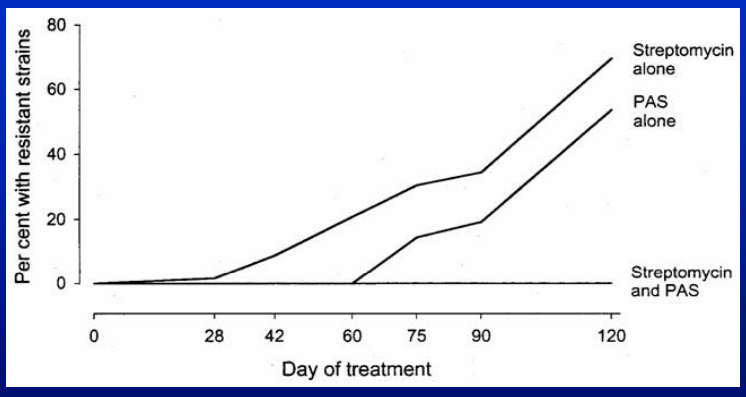
Emergence of resistance to streptomycin and/or PAS para-aminosalicylic acid given alone or in combination



. From Reider, Interventions for TB control, IUATLD.

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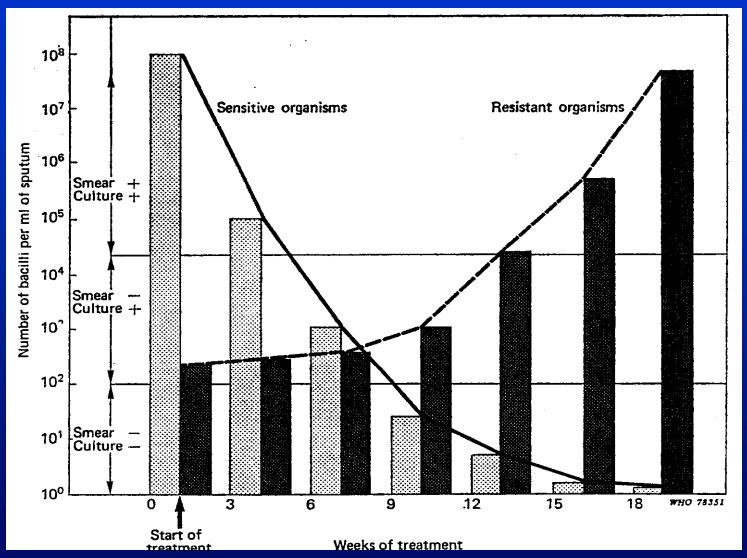
The "fall and rise" phenomenon – patients given INH alone



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From Toman, Case Finding and Chemotherapy

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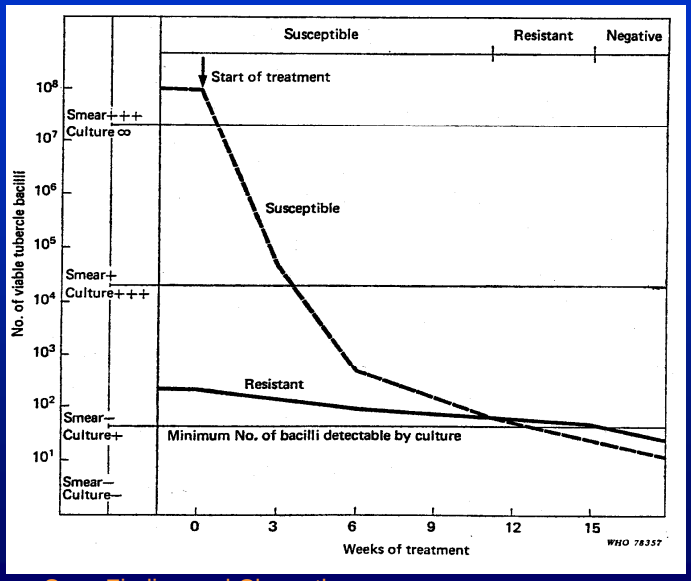
Transient drug resistance during therapy with two or more drugs (effect of default)



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 INH resistance:
  - RIF/PZA/EMB – 2 months, RIF/EMB - 10 mos
  - Or, RIF/PZA/EMB – 6-9 mos
- If 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 Protionamide 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 – Rash, Drug Interactions, Hematologic, 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)
- 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 INH or RIF
  - If no rash add second, etc
  - Speed – every 3-4 days
- Cause of hepatitis: PZA>INH>RIF
- So – start with RIF, then INH
  - Speed – every 2 weeks (much slower)
  - If no hepatitis with INH/RIF do **not** give PZA

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Thanks/Merci