CURRENT CONCEPTS IN MANAGEMENT OF TUBERCULOSIS

EVOLUTION OF DRUG THERAPY

Pre Streptomycin era:

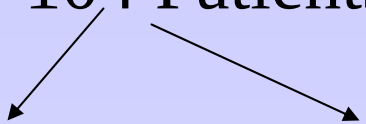
- Rest - Sanatorium/Affected portion of lung
  - Collapse therapy
- Use of Gold Salts/Sulphones/Vit D

50% Mortality - PTB

SM:

MRC Trial, 1946

104 Patients



	SM	Bed Rest
Death	4	14
Culture 3mths	10	1
Neg 6 mths	8	2
Xray improve	69%	33%

Inference: Immediate adv. in S arm

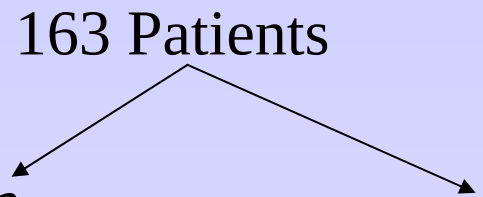
5 yr. FU: Most patients developed resistance

BMJ 1948; 2: 769-82

Domiciliary Treatment

Duly Effective means of t/t TB.

- 1950s: Primacy of chemotherapy over other forms established.
- TRC, Chennai; 1959 (land mark study)



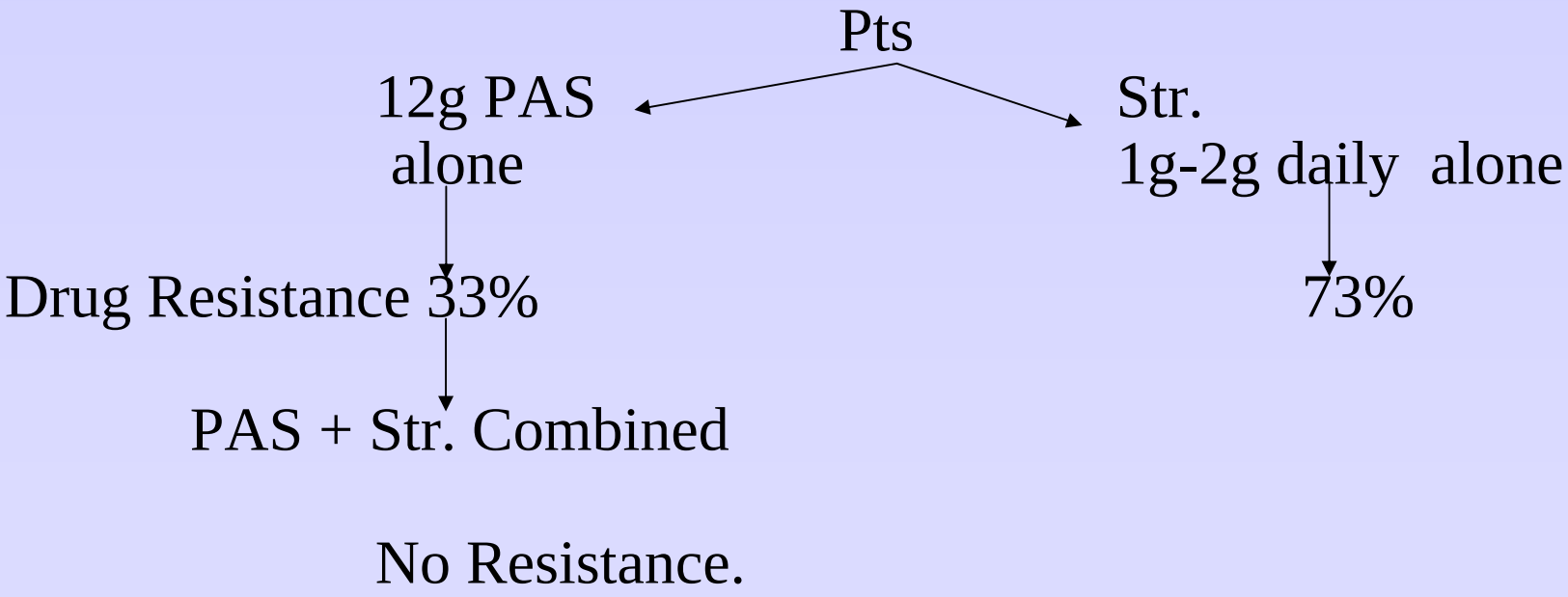
	Sanatorium (81)	Home (82)
	At 1 year	
- Cure Rate	92%	90%
Relapse Rate	10%	7%
- Family contacts no more liable to contract TB	11.5%	10.5%

Bull WHO. 1959 21:51-58

Multi Drug Theory

Cornerstone of effective t/t, prevents drug resistance.
Initial studies: S alone for active PTB
t/t failures/Relapse rates/R to S

Tempel et al



Am Rev. Tuberc 1951; 63: 295-311

Isoniazid & Effective Std t/t:

- 1952: INH introduced as ATT
- 1955: MRC– First national DR Survey with primary resistance

↓

Resistant to one strain

∴ T/T with 3 drugs phase lasting 2-3 mths

↓

2 drug phase explored.

T/T given for 12 mths : Failure Rate high because of failure to complete t/t

Two Phase Chemotherapy

1960s

MRC Trial

P + H + S – 6 wks

↓

P + H – 1 year

↓

t/t failure 3%

P + H – 1 year

↓

16%

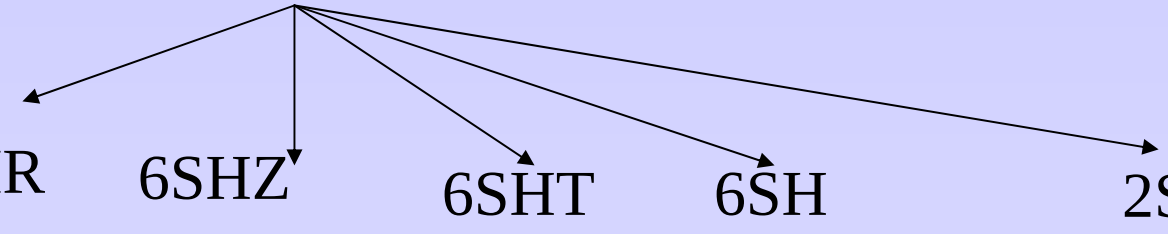
Tubercle 1962; 43: 201-219

Short Course Therapy

Mid 1970s

East African/MRC Trial (land mark study)

Pts: 540



	6SHR	6SHZ	6SHT	6SH	2SHT 16 HT
Relapse	2%	11%	22%	29%	4%
Culture Neg at 2 mo	69%	31%	25%	8%	

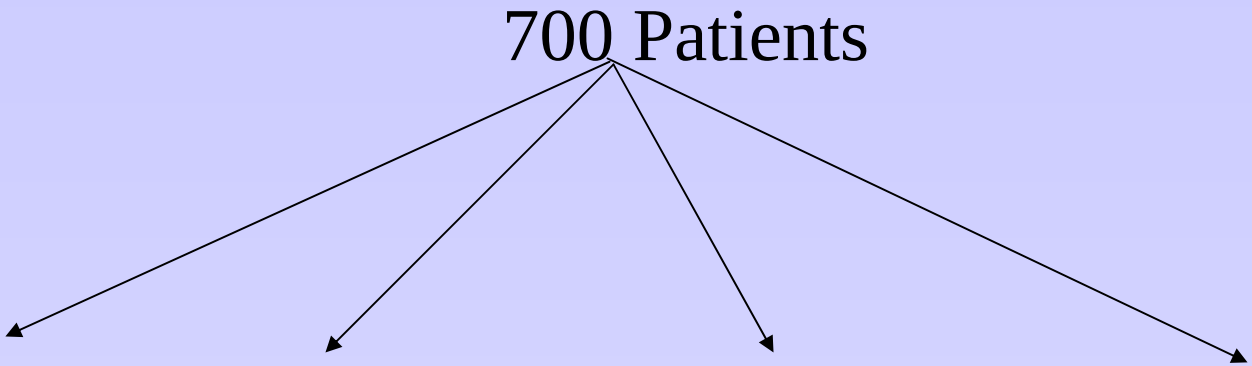
Inference:

- R containing regimen- Effective
- Relapses occurred within 1 year after ATT.
- Min- toxicity ass. With multidrug regimens.

  (2.5% : Drugs Stopped)
- Almost all relapse cases were with organisms (S) to S/H.

Lancet 1972; 1: 1079-85

East African/MRC Trial



	6SHR	6 HR	2SHRZ/4HT	2 SHRZ /4 $S_2H_2R_2$
Relapse	2%	5%	6%	4%

Inference: ~ 100% Care Rate

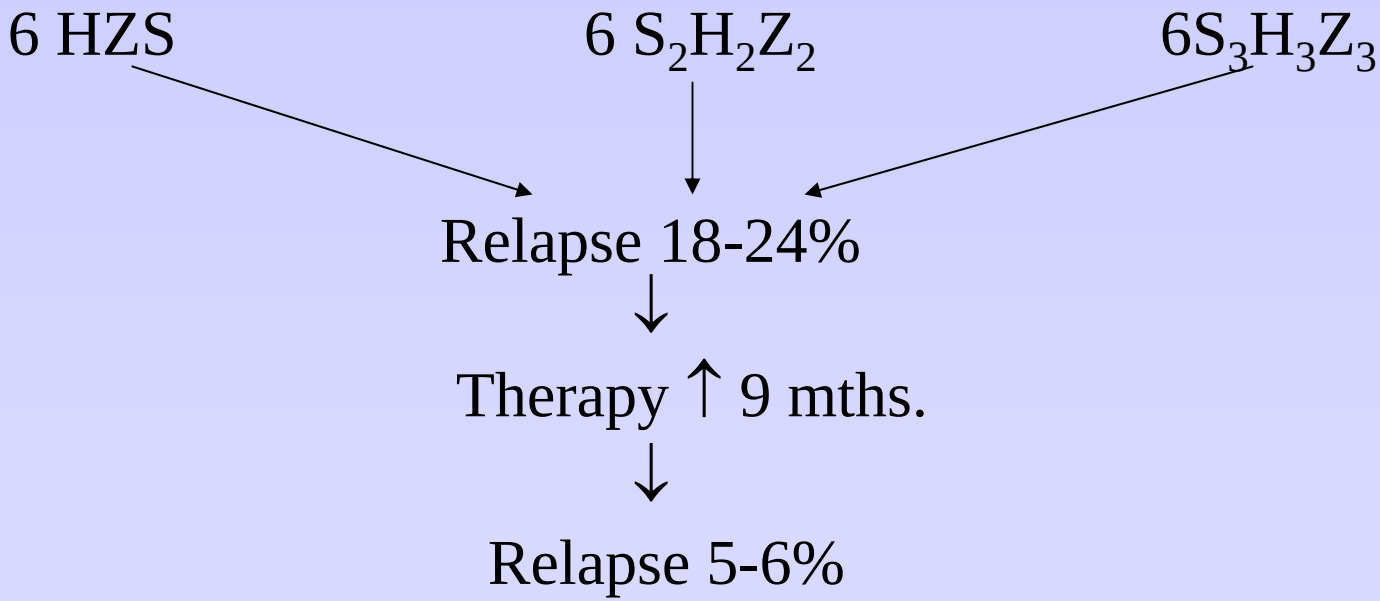
$\leq$ 6% Relapse Rates, Susceptible organisms

Intermittent therapy: Good Response

Acceptant Relapse Rates.

Am Rev Respir Dis 1977; 116: 3-8

Hong Kong Chest Service/MRC Trial

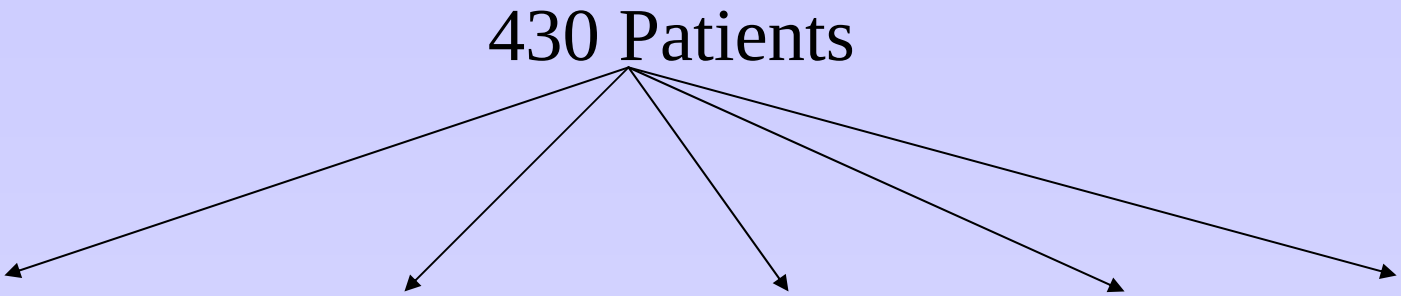


Am Rev Respir Dis 1977; 115: 727-33.

East African/MRC Trial

(Shortest Course CT)

1980s



2 SHRZ	2 SHRZ	2 SHRZ	2 SHRZ/2H	2 HRZ/2H
2 HRZ	2 HR	2 HZ		
Relapse 16%	11%	32%	30%	40%

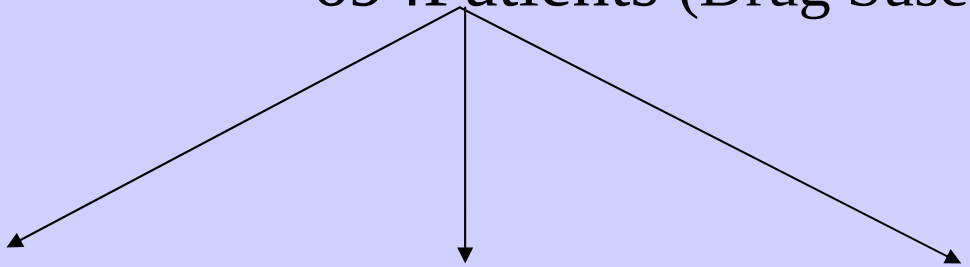
Inference: ↑ Relapse Rates with 4 mths course

Rifampicin essential

Am Rev Respir Dis 1981; 123: 165-70

TRC, Chennai; NTI, Bangalore

694Patients (Drug Susceptible, Sp +ve)



	3 SHRZ	3 SHRZ/2 $H_2R_2Z_2$	3 SHZ/2 H_2Z_2
Relapse	22%	5%	16%
Culture Conversion at 2 mths	> 90%	> 90%	74%

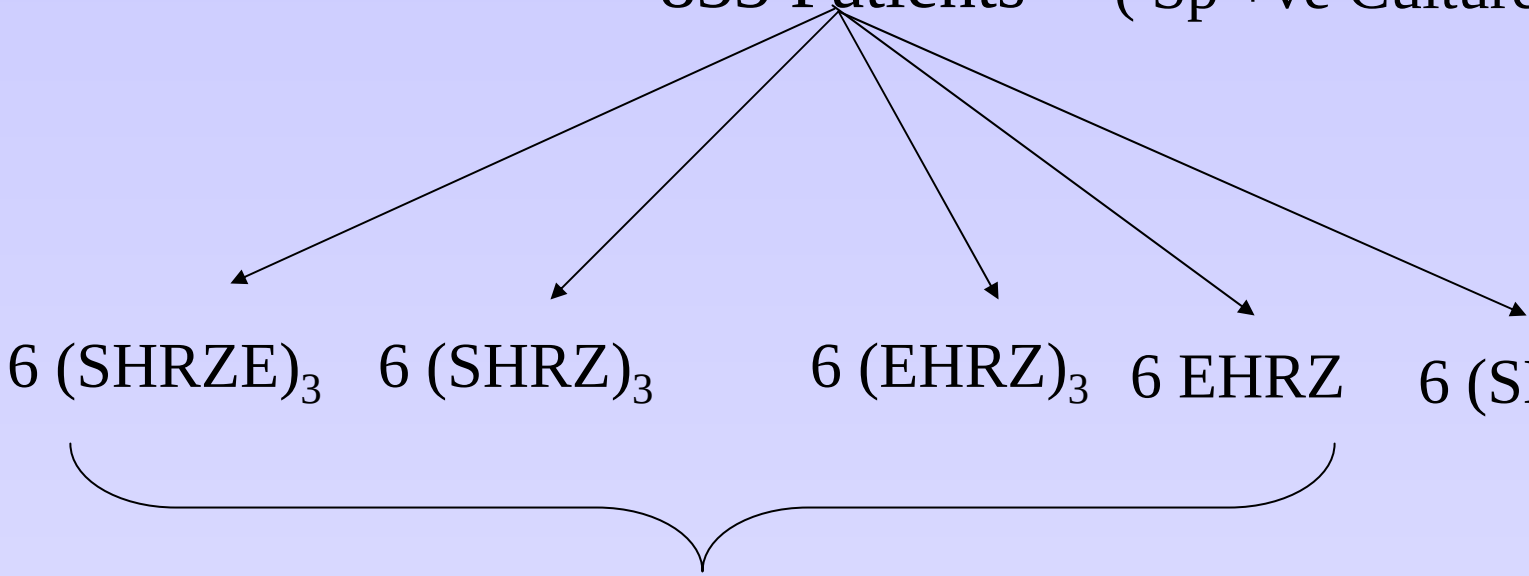
Inference: - 3 mth. therapy not effective for smear +ve PTB.

- 5 mth R containing regimen is effective.

Am Rev Respir Dis 1986; 134: 27-33

Hong Kong Chest Service/MRC Trial

833 Patients (Sp +ve Culture (S))



Relapse 18 mths	1.4%		7.8%
5 years	3.4%		10.3%

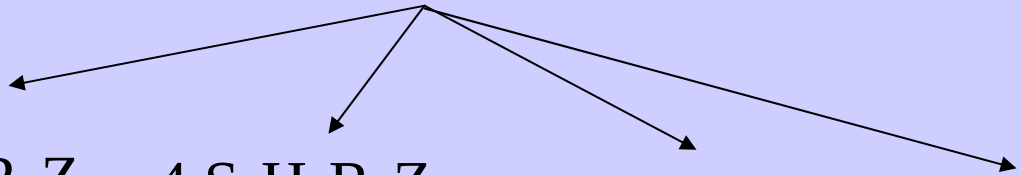
Inference: -PZA containing regimens: Relapse: 1-4%

Am Rev Resp. Dis 1987;136:1339-1342

- Early relapse in non-PZA series could be d/t large no. of residual drug susceptible organisms which started multiplying shortly after regimen was stored.

Hong Kong Chest Service/MRC Trial

892 Patients (Sp +ve culture (s))



$2S_3H_3R_3Z_3$	$4\ S_3H_3R_3Z_3$	$4\ S_3H_3R_3Z_3$	$6\ H_3R_3Z_3$
$2S_3H_3R_3$	$2H_3R_3$	$2\ H_3R_3Z_3$	
$2H_3R_3$			
Failure ---	---	----	2%
Relapse 2%	3%	6%	9%

-Inference: - S needs to be added in Intensive phase

- No significant diff. in relapse rates bet. diff. gr. of Z (2, 4, 6 mths.)

Am Rev Respir Dis 1991; 143: 700-706

Objectives of Treatment

- Rapid Reduction of No. of Bacilli
- Prevent Acquired Drug Resistance
- Sterilization to Prevent Relapses.

Drug Activity

- Bactericidal activity of drug
  assessed by
  - in vitro studies (culture medium)
  - animal studies
  - magnitude of full of bacterial content after starting Rx
- Sterilizing activity:
  assessed by
  - proportion of patients having bacteriological relapse after stopping Rx

Current SCC

Initial intensive phase: - Multiple drugs

- to reduce no. of organisms

Continuation phase: - Fewer drugs

- Kill the slowly growing organisms

- Rate of killing fastest in initial several days of Rx (Phase of BA)

Current SCC

- IInd Phase - Sterilization phase measured by Relapse Rates
- Sterilization Phase more imp. as it measures duration of treatment.

(Better the sterilization, lesser the duration)

- EBA less imp. : information about infectiousness of pt

Intermittent Treatment

- Based on lag phase effect of MTB in culture after exposure to bactericidal drugs.

- Adv: - Efficacy similar to Daily Rx
  - Few Ad. Effects.
  - Facilitates DOT
- Establishment of Intermittent Therapy

  ↓

  Major Breakthrough in TB Treatment

Newer Drugs For TB

- Required because

  1. Improve Current Rx: ↓Duration

     ↑ Spacing of intermittent t/t

  2. Improve Rx of MDR

  3. Provide more effective t/t of LTBI

- Current Drugs/Regimens:- ↓ duration a/w ↑ relapses

  - Pt non-adherence

  d/t ↑ duration

Rifamycins

- Rifampicin based regimen → 6 mths

- Widely space regimens with Rifampicin: Less effective

DR in HIV+

Rifamycins with longer half life: Rifabutin/Rifalazil

↓

Proved ineffective,

a/w ↑DR in widely spaced regimens.

Rifapentine

Half life $\rightarrow$14-18 hrs

TBTC study 22

1003 HIV –ve

↓

2HRZ

Rpn/H (600/900) O/W (4 mths)	R/H (600/900) T/W (4 mths)
Relapse Rate 9.2%	5.6% (P=0.04)

Rifapentine

Adverse outcome: Multivariate analysis

- Cavitatory disease
- c/s +ve at study entry (eand of intensive phase)
- White Race
- < 90% IBW at time of TB Dx.

Lancet 2002; 360: 528-34

- TBTC – 25

150 Pts

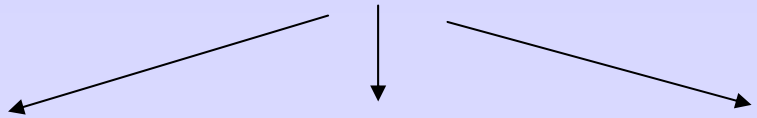
HIV –ve Drug susceptible TB

↓

Intensive phase

↓

Continuation phase O/W Rpn/H



600 mg 900 mg 1200 mg

1 Pt. Discontinued t/t: ad. effect.

Sp. Culture +ve, cavity +

↓

T/T Extended by 3 mths

of 20 Pts only 1 relapsed (600 mg gr.)

[∴ Relapse Rate 5% compared with 22% when Rpn/H given for 4mths.]

Inference: ↑ Doses Extended t/t } Effective in Pts with ↑ Risk of Relapse

AJRCCM 2002;165:1526-30

Moxifloxacin-Treatment Shortening Drug

↓

- FQ given in MDR-TB
- TRC, Chennai, 2002: FQ in Drug susceptible cases.

341 Patients (Sp culture (S), Smear +ve)

3 OHRZ	3 OHRZ	3 OHRZ	2 OHRZ
	1 H_2R_2	$2H_2R_2$	$2H_2R_2$
83 Pts	81 Pts	86 Pts	91 Pts
Cure Rate ~98%			
Relapse 8%	4%	2%	13%
(2 years)			

Inference:

- High cure rates
- Low Relapse Rate
- ↑ Relapse in 4th category: For ultra short Course regimen, atleast 3 mths intensive phase

Ind J Tub 2002; 41: 27-38

Moxifloxacin

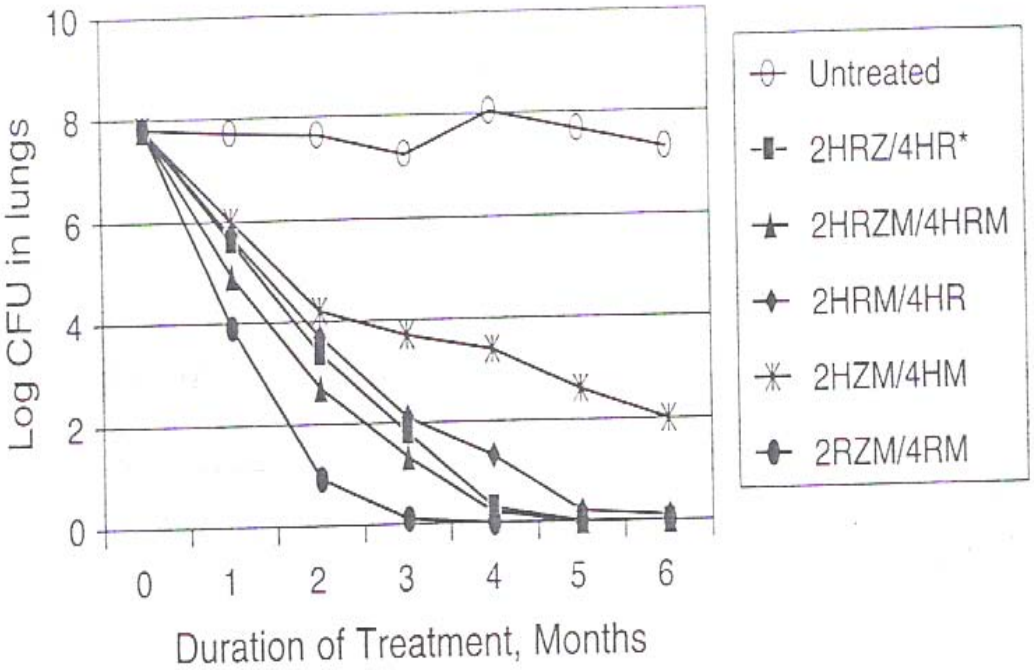
-Moxifloxacin/Gatifloxacin → Most potent FQ against MTB in vitro

(MIC 2-4 times less than for levofloxacin)

Moxifloxacin: - greatest sterilizing activity among FQ

- long $T_{1/2}$
- BA comparable to H, more than R

Moxifloxacin



*H=isoniazid, R=rifampin, Z=pyrazinamide, M=moxifloxacin

Experimental study of moxifloxacin-containing regimens in murine tuberculosis. (*Adapted from* Nuermberger EL, Yoshimatsu T, Tyagi S, et al. Moxifloxacin-containing regimen greatly reduces time to culture conversion in murine tuberculosis. Am J Respir Crit Care Med 2004;169:334–5; with permission.)

Emerging Drugs

Diarylquinolines (R207910)

- Potent in vitro activity in animal model
- Active against both sensitive/DR strains.
- In mouse models, combinations with any 2 of H/R/Z regimen.

  More superior than std. regimen of HRZ

Nitroimidazopyrans (PA-824)

- Effective against Drug Sensitive/DR strains
- MIC comparable to H
- MOA: ⊖ protein/lipid synthesis
- Good Lung/spleen/other tissue penetration

Emerging Drugs

Dihydroimidazo-oxazoles (OPC 67683)

- Currently, in Ph-I Study
- Potent in vitro activity against MTB.
- May ↓ duration of therapy in active TB/MDR-TB
- More effective than current drugs for ATT.

Pyrroles (LL 3858)

- Lupin Ltd (Mumbai)
- Sub micro molar MIC
- Active age in mouse models
- Combined with ATT drugs → Faster Sterilization

Oxazolidinones

- MOA : ⊖ protein synthesis.
- In vitro data: Linezolid active against MTB →used for MDRTB.
- Prolonged use of Linezolid : Peripheral optic Neuropathy.

SQ 109

- Active against MTB in vitro (MIC: 0.1-0.63 μg/ml)
- Bactericidal.
- Combined with HR: ↓ Mutagenicity ↑ activity
- MOA : ⊖ Cell Wall Synthesis
- OD dosage reqd.

HIV Related TB

Issues related to TB T/T

Optimal duration of therapy

- Published observational cohort studies of Std. 6 mth regimens by DOTS in HIV +ve & HIV –ve Pts.

↓

	HIV +ve	HIV –ve
Treatment failure	2-3%	3-7%
Relapse	5-8%	2-5%

- Pts with advanced HIV disease → ↑Risk of T/T failure & relapse

(Reason: Re-infection in endemic areas)

- Acquired Rifamycin resistance ⊕ in T/T failure & Relapse Cases
- Vermon A *et al*

HIV +ve

- Rifapentine (30 Pts) daily x 2 wks ↓ Daily/Intermittent till 2 mths	Rifampicin (30 Pts) daily x 2 wks ↓ Daily/Intermittent till 2 mths
- Continuation phase: 1 /wk	2 /wk
- Rx failure/ Relapse: 16%	10%
- Rifamycin Resistance: 13%	0%

Lancet 1999; 353: 1843-7

Associations for Resistance:-

- Advanced HIV [$CD_4 < 200$]
- use of highly intermittent therapy

  (1/2 per wk)

Recommendations:-

- use Std 6 mths regimen
- ↑ to 9 mths if delayed clinico-radiological response
- T/T failure related to advanced immune suppression
- Daily Rx preferred in advanced HIV atleast during intensive phase

CCM 26; 2005: 283-294

Challenges of using ART during ATT

- ↑ rates of HIV disease progression during ATT,

↓

ART improves outcome

- However, ART: Substantial risk of HIV disease progression

Clinical/Lab evidence of advanced HIV disease [$CD_4 < 200$]

Adherence to ART

-Adherence – Challenge because of long term T/T

-DOTS team for TB – ensure adherence with ART

Overlapping adverse events

-Drug related adverse events may be similar with ART/ATT

e.g. skin rash –	ATT:	HRZ
	ART:	Nevirapine/Efavirenz
	Others:	Co-trimoxazole

-Temporal Sequence of events – best clinical tool for determining the cause

Drug Interactions

- Rifamycins ↑ P_{450} 3A (CYP3A): ↓ Conc. Of ART

  Rifampicin cannot be used with PI (except high dose ritonavir)
- Rifamycin can be used with NNRTI (Nevirapine/Efavirenz)
- PI ↑ levels of Rifabutin: ↑ toxicity

  Efavirenz ↓ Rifabutin levels

Immune Reconstitution

- ART: ↑ Immune Function
  ↓
  ↑ inflammation in TB lesions
  ↓
  Worsening Symp./Signs
- 11-35% Pts on ART
- C/F: Fever /Adenopathy/↑Pul infiltrates
  Serositis
  Less Common: -Worsening Meningitis
  - ↑ CNS tuberculoma
  - Soft tissue/Bone abscesses
  - skin lesions.

Immune Reconstitution

- D/D: Inf. /S/E of drugs/T/T failure of TB.
- C/F of immune reconstitution: within days of ART

Median time – 11 days

Risk factors:

- Severity of illness (↑ risk with very low CD_4)
- Potency of ART

Timing of ART in TB

- Controversial
- Individualized

Recommendations

1. $CD_4 > 200$: Mx similar as HIV –ve Pts
   Std. 6 mths intermittent ATT ↓ DOTS
2. $CD_4 < 200$: ↑ Risk of Acquired Rifamycin Resistance
   ∴ Daily ATT Preferred.
3. One Intervention at a time

   1st Priority : ATT

   ↓

   Next : Pneumocystis Prophylaxis

   ↓

   Next : ART (ensure adherence)