CURRENT CONCEPTS IN MANAGEMENT OF TUBERCULOSIS
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

<table>
<thead>
<tr>
<th></th>
<th>SM</th>
<th>Bed Rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Culture 3mths</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Neg 6 mths</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Xray improve</td>
<td>69%</td>
<td>33%</td>
</tr>
</tbody>
</table>

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)

163 Patients

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
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

12g PAS alone
Drug Resistance 33%

PAS + Str. Combined
No Resistance.

33% 73%

Str. 1g-2g daily alone

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
  \[\downarrow\]
  Resistant to one strain
  \[\therefore\]
  T/T with 3 drugs phase lasting 2-3 mths
  \[\downarrow\]
  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% 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 69%  31%  25%  8%
at 2 mo
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

700 Patients

6SHR  6 HR  2SHRZ/4HT  2 SHRZ /4 S₂H₂R₂

Relapse  2%  5%  6%  4%

Inference: ~ 100% Care Rate

≤ 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

6 HZS → 6 S₂H₂Z₂ → 6S₃H₃Z₃

Relapse 18-24% → Therapy ↑ 9 mths. → Relapse 5-6%

East African/MRC Trial
(Shortest Course CT) 1980s

430 Patients

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*
694 Patients (Drug Susceptible, Sp +ve)

- 3 SHRZ
  - Relapse: 22%
  - Culture Conversion at 2 mths: > 90%

- 3 SHRZ/2 H$_2$R$_2$Z$_2$
  - Relapse: 5%
  - Culture Conversion at 2 mths: > 90%

- 3 SHZ/2 H$_2$Z$_2$
  - Relapse: 16%
  - Culture Conversion at 2 mths: 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))

- 6 (SHRZE)$_3$
- 6 (SHRZ)$_3$
- 6 (EHRZ)$_3$
- 6 EHRZ
- 6 (SHRE)$_3$

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))

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)
• II\textsuperscript{nd} 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 spaced 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 → 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

- Cavitory disease
- c/s +ve at study entry (end 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 +

\[ \Rightarrow \]

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:  
\[ \uparrow \text{Doses} \]
\[ \Rightarrow \text{Extended t/t} \]
\[ \uparrow \text{Risk of Relapse} \]

\textit{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 H₂R₂ 2H₂R₂ 2H₂R₂

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

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 $\Theta$ 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 [CD₄ < 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 at least 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 $\uparrow P_{450} 3A$ (CYP3A): $\downarrow$ Conc. Of ART

  Rifampicin cannot be used with PI (except high dose ritonavir)

- Rifamycin can be used with NNRTI (Nevirapine/Efavirenz)

- PI $\uparrow$ levels of Rifabutin: $\uparrow$ toxicity

  Efavirenz $\downarrow$ Rifabutin levels
Immune Reconstitution

- ART: $\uparrow$ Immune Function $\downarrow$
  $\uparrow$ inflammation in TB lesions $\downarrow$
  Worsening Symp./Signs
- 11-35% Pts on ART
- C/F: Fever /Adenopathy/$\uparrow$Pul infiltrates
  Serositis
  Less Common: -Worsening Meningitis
  - $\uparrow$ 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. \( \text{CD}_4 > 200 \) :
   - Mx similar as HIV –ve Pts
   - Std. 6 mths intermittent ATT ↓ DOTS

2. \( \text{CD}_4 < 200 \) :
   - ↑ Risk of Acquired Rifamycin Resistance
   - ∴ Daily ATT Preferred.

3. One Intervention at a time
   - 1\(^{st}\) Priority : ATT
     ↓
   - Next : Pneumocystis Prophylaxis
     ↓
   - Next : ART (ensure adherence)