

# An Overview of WHO Regimens for Treatment of Leprosy

**Dr. Bhushan Kumar**

Consultant Dermatologist  
Chandigarh, India

- Leprosy one of the major scourges of mankind will be (hopefully) eliminated despite seemingly un-surmountable odds, primarily due to the WHO MDT, political will, donor agencies, NGOs and committed health workers

- Development and implementation of MDT has transformed leprosy into a curable disease

- 1985 – 2005: > 15 million persons treated

- Registered cases

	2003	2004	2005	2006	2007
	513,793	407,791	295,816	265,661	231,361
India				139,252	82,801

- The seemingly great success of MDT prompted the World Health Assembly in 1991 to call for elimination of leprosy as a public health problem by the year 2000

### Some landmarks in the treatment of leprosy and the evolution of MDT

- Isolation/Segregation
  - Chaulmoogra oil - externally, internally and eternally (*Sushruta 600 BC*)
- 1941 - Guy Faget-Promin
- 1947 - Dapsone (Ambulatory treatment)
- 1960 - Ridley-Jopling classification  
Immunological basis-Mitsuda reaction, T-cells, humoral response, vaccination
- 1962- Clofazimine – confirmed to be effective in mouse foot pad
- 1964 - First confirmed dapsone resistance
- 1965 - Combined therapy to reduce drug resistance (Spickett)
- 1967 - Rifampicin - most potent bactericidal

- 1974 - Existence of persisters. Viable *M. leprae* in lepromatous patients treated with dapsone for 10-12 years. Portal of exit and entry of *M. leprae*. Survival of *M. leprae*
- Immunology of Leprosy Programme (IMMLEP), Special Programme for Research and Training in tropical Diseases (TDR)
  - Development of drugs, vaccines,diagnostics
- 1976 - Programme for Research for Chemotherapy of Leprosy (THELEP)
- 1981 - Study Group for Drug Regimens

## Study Group on Chemotherapy of Leprosy

- 1940 - Promin in Carville
- 1960 - Mouse foot pad- screening of drugs: *dapsone*, *thiambutosine*, *ethionamide*, *thiacetazone*, *clofazimine*
  - Clinical observation, bacteriological index
  - Efficacy of dapsone, clofazimine and rifampicin was established
- 1970 - Freerkson- Isoprodian, *Malta*
- 1972 - Relapse rather than growth in mouse foot pad as evidence of treatment failure

## THELEP (Programme for Research on Chemotherapy of Leprosy, 1976)

- To organise dapsone resistance surveys demonstrating the need for MDT regimens
  - 215 patients, 769 biopsies
  - More than 1/3 primary dapsone resistant bacilli
  - Persisting *M. leprae* in 9% of all specimens
- Establish the rationale for composition of MDT regimens for PB and MB
- Short term trials - biopsies from patients
- To organise controlled trials
- Screen drugs – animal models
- *Mali, Chingelput, London* – Persisters, Drug resistance
  - MB - *India*
  - PB – *Malawi and Indonesia*

## THELEP/ SWG

### Field Trials in *Karigiri/Polambakkam, Sungei Buloh & Malta*

- No relapses after 2 years of treatment in bacteriologically negative MB patients
    - Rifampicin - 1200mg / month in 2 doses
    - Clofazimine - 1200mg / month in 2 doses
    - Dapsone - 100mg daily
    - Acedapsone - 225mg I/M every 2 months
- 2200 patients -- no relapses
- Trials conducted in 1973 had shown that intermittent administration of rifampicin was as effective as daily rifampicin – 93 LL patients (*India*)

#### MDT for MB patients – some successive regimens

References	Regimens
12	<i>Rifampicin</i> , 1200 mg once a month <i>Dapsone</i> , 50 mg daily
11 <sup>a</sup>	<i>Rifampicin</i> , 600 mg daily on 2 consecutive days every 4 weeks <i>Thiambutosine</i> , 1 g/week intramuscularly
THELEP Protocol for field trials (1979) <sup>b</sup>	<i>Rifampicin</i> , 600 mg daily on 2 consecutive days once a month <i>Clofazimine</i> , 600 mg daily on 2 consecutive days once a month <i>Acedapsone</i> , 225 mg bimonthly (injections) <i>Dapsone</i> , 100 mg daily
10	<i>Rifampicin</i> , 600 mg daily on 2 consecutive days in every 4 weeks (or monthly) (first dose supervised, second dose preferably supervised) <i>Clofazimine</i> , 600 mg daily on 2 consecutive days every 4 weeks (or monthly) (first dose supervised, second dose preferably supervised) <i>Dapsone</i> , 100 mg daily
22	<i>Rifampicin</i> , 600 mg one monthly, supervised <i>Clofazimine</i> , 300 mg once monthly, supervised, and 50 mg daily, self-administered <i>Dapsone</i> , 100 mg daily, self-administered

<sup>a</sup> Trial started in 1973.

In: Draft report of the planning meeting for a protocol for field trials of chemotherapy of lepromatous leprosy, Geneva, 15 October 1979.

**(1981), THELEP/ SWG/ WHO/ILEP/ Study group on Chemotherapy of Leprosy**

- Dapsone resistance - Secondary and Primary
- Rifampicin anarchy
- Increasing number of patients – general demand for guidance
- Difficulties in implementation of Fifth Report
- To review the information collected since 1976 on drug regimens

**Classification** of patients into 2 categories. : PB: upto 2 BI, MB>2

Two **Drug Regimens**

**PB** - 6 months, **MB** - 24 months / upto smear negativity

- Drugs: *Rifampicin, Dapsone, Clofazmine*  
*Ethionamide, Prothionamide* to be considered
- Research needs
- Operational aspects - case detection, lab. facilities, drug delivery, records and follow up
- Health education

**Endorsed by WHO Executive Board, May 1982**

**Implementation : started on pilot basis**

	1982-85	1% coverage
	1991	42% “
	1992	50% “
	1997	100% “
1987/88	PB- only smear negative cases	
1991	World Health Assembly Elimination of Leprosy by 2000 as a Public Health problem	
1992	Calendar blister packs	

1993/1994

- Fixed duration therapy (FDT) for MB-24 doses
- Post MDT annual surveillance could be discontinued

1998

- Skin Slit Smear done away with
- PB (single lesion) - ROM
- PB (2-5 lesions) - same as before
- MB (more than 5 lesions) - reduced to 12 doses
- Leprosy Elimination Campaigns (LECs)
- Special Action Projects for Elimination of Leprosy (SAPEL)
- 1991- BLP 190 patients -12 months of MB MDT
- 1992- WHO started trials on 12 months of MB MDT

1997: *7th WHO Expert Committee on Leprosy*  
'possible to shorten duration of MDT (MB) to 12 months'

- Among newly detected MB cases
  - only 13% SSS +ve (>3)
- RMP kills >99.999% of viable organisms with 3 monthly doses
- DDS + CLF kill > 99.999% of viable *M. leprae* in 3 months
- RFM resistant mutants likely to be eliminated by 3-6 months with DDS+CLF
  
- Annual relapse rate 0.2% with standard MDT

- **Multicentric double blind trial (15 centres 1992)**  
(THEMYC 1997 Report)

1. 24 mo. WHO MDT
2. 12 mo. WHO MDT
3. 12 mo. WHO MDT+ OFLO 400 mg daily x 4 wks
4. Regimen 3 + RFM 600mg daily x4wks

- similar results in all regimens

- **Results of MB defaulted cases**

- A. 41 pts, retrieved after 1-6 yrs, average Tt. taken 7 months
  - Clinical improvement – all patients, SSS - 29 negative, 5 no change
- B. 139 pts, retrieved after 7.5 yrs, Tt. taken ≤ 12 months
  - Comparable to 24 months treated group

1999	Prevalence 4.5/10,000 Number of newly detected cases-static or even increased
2000	<ul style="list-style-type: none"><li>• Action Plan for Elimination of Leprosy</li><li>• Global Alliance for Elimination of Leprosy</li><li>• WHO Technical Advisory Group on Elimination of Leprosy (TAG)</li></ul> <b>THE FINAL PUSH</b> <ul style="list-style-type: none"><li>• Definition of 'Elimination' should be retained</li><li>• Need to improve Reporting System</li><li>• Raise Awareness and Political commitment</li><li>• Establish Task Force in Endemic Countries</li><li>• IEC activities to encourage self reporting</li></ul>

## Studies on:

- A-MDT
- Integration
- Relapses
- Impact of IEC & SAPEL
- Leprosy in Urban areas
- Use of Prednispacks
- MDT regimens of shortened duration
- Drug resistance
- Leprosy classification systems
- U-MDT to all (follow up for 7 years)

## WHO MDT- the reasons for success/ achievements

Was accepted in the absence of convincing field trials and data on adverse drug effects because -

- Core of Leprosy Elimination Strategy – > 25 years, >15 million cases treated, Only 4 countries have to achieve elimination
- Standardization of drug regimens
- Classification of patients into two main categories
- Fixed duration of treatment
- Prevention of development of drug resistance
- Renders patients non-infectious rather quickly
- Very few relapses - *MB* 0.77%, *PB* 0.66 -1.07%
- Robust – averages/redundancies built in to prevent treatment failure and overcome operational problems

## Relapses:

1980s

MB - 2241 (had prolonged monotherapy with dapsone)

22% skin smear positive

0.26 / 100 person years

PB 0.65 / 100 person years after 4 years - *Malawi*

0.12 /100 person years after 5 years -*Indonesia*

1990s

### Pilot survey by questionnaire -17 countries

100,000MB	600,000 person years	Below the acceptable limits of 1 per 100 person years
150,000 PB	of observation	

### 28 Programmes

20,000 MB	0.77%	9 years after stopping MDT
25,000 PB	1.07%	

## ROM & other single dose regimens

- Single skin lesion (SSL)- Single dose
- RCT (1483 patients) - single lesion- India
- ROM vs WHO MDT PB (follow up -18 months)
  - Improvement 51.8% vs 57.3%
  - Complete cure 46.9% vs 54.7%
  - 6 treatment failures in each group

*Indian J Lepr 1997; 69*

- ROM Vs ROM + *Convit vaccine, India*
  - Clinical outcome of test group better

*Int J Lepr 2000*

- RCT (622 patients) –Single dose vs WHO MDT PB, *Zaire*,  
Rifampicin (40mg/Kg)+Clofazimine (1200mg)  
Rifampicin (40mg/kg)+Clofazimine (100mg) + Dapsone (100mg)  
+Ethionamide (500mg)

Relapse rates 20.4/1000 person years in the test groups

### ROM single dose vs. WHO MDT PB (2-3 lesions)

1. 236 smear negative, 2-3 skin lesions, no nerve trunk involvement  
At 18 months FU (Marked improvement- >90% ↓ clinical score)

ROM	WHO MDT PB
46.2%	53.4%

- But, significant difference in favour of WHO MDT PB in patients with 3 lesions/ > one body part affected
- Reversal reactions & adverse drug reactions were minimal in both groups

*Indian J Lepr 2001;73:131-43*

2. 51 PB patients – FU 2 years

Clinical/ histopathological improvement similar in both groups

The operational convenience and drug compliance with ROM could make it an acceptable regimen when the disease is localized to 2 or 3 skin lesions

*Indian J Lepr 2005*

- **Long term follow up – ROM**

310 SSL PB cases treated in Bangladesh (1998-2000)

– 87% retrieved – average FU 6.3 years

Of these – 76% complete clearance of lesion

- 10 cases (3.6%) evidence of relapse (PB)

- None had NFI

Consideration should be given to possibility of relapse in patients received ROM for single lesion leprosy

*Lepr Rev 2007;78:160*

### Monthly ROM for PB & MB leprosy

#### WHO trial in *Myanmar & Guinea*

**Once a month ROM** 3 to 6 months- PB  
12 to 24 months - MB

- Final results expected by end 2007

#### 24 months ROM vs WHO MB MDT in MB leprosy

- 21 patients randomly allocated to the 2 groups
- ROM as safe & effective as MDT conferring similar bacteriological and histological improvements without increased rates of lepra reactions
- Follow up of 8 years showed similar long term efficacy and safety

### Newer Regimens

<b>U-MDT</b>	MB MDT	For all x 6 months
<b>ROM</b>	PB	Monthly x 3-6 months
	MB	Monthly x 12-24 months

- PMM (Rifapentine 600mg + Moxifloxacin 400mg +Mino100mg)
- MDT for 1 year + Ofloxacin 400mg daily for first 4 weeks
- Ofloxacin 400mg + Rifampicin 600mg daily- 4 weeks (PB)
- Rifampicin +Minocycline +Sparfloxacin +Clarithromycin daily X12 weeks

## Deficiencies / Difficulties

- Frequently changing – schedules, definitions  
microbiological rationale?
  - Nerve involvement not considered in classification (WHO)
  - Slow response in some patients
- MB** - 29% lesions still active after 3 years, *Thailand*
- PB**
- |          |                    |                    |
|----------|--------------------|--------------------|
| 6 months | resolution         | - 8%,              |
|          | regression         | - 44%              |
|          | increased activity | - 16% <i>India</i> |
- 1 year  
visible but not active – 59.6%, *Malawi*  
visible and active - 2.3%
  - Clinically active after treatment - 22% , *Thailand*

## Deficiencies / Difficulties contd...

- Slow fall of BI – especially in those with BI  $\geq 3+$
- Doing away with slit skin smear and even clinical response
- No effect/worsening of disability status
  - 2.5 -3.3% new /worsening of disability- PB, *Malawi*
  - 4% at recruitment, 7% at follow up, *Thailand*
  - Worsening of nerve function impairment  
MB: 8% -13%, PB:4 -7%, *Thailand*

**Side effects of drugs** - Variable percentages

- GIT side effects
- Pigmentation with clofazimine
- Rifampicin – daily dose – 8.5%  
monthly- hepatitis (0.8%), allergic reaction (0.2%)

**Relapses** MB- 20.4/1000 person years, *India*  
PB- 6.5/1000 person years, *Malawi*  
1.8% *Thailand*, 2.5% *Malawi*

**Vaccines** for Immunotherapy/ prophylaxis

**Definitions**

Adequacy & Regularity of Treatment  
Maximum period over which the drugs could be given

**Surveillance** - epidemiological and operational indicators

**The Global Strategy for Further Reducing the Leprosy Burden and Sustaining Leprosy Control Activities (2006-2010)**

- Eradication may take more time
- The operational guidelines are being widely implemented to sustain the gains achieved under elimination of leprosy as a public health problem
- Challenges remain in areas of :
  - Capacity building
  - Maintenance of expertise
  - Referral networks and their integration into GHS
  - Community awareness
  - Emergence of rifampicin resistant strains

(*Weekly Epidemiological Record*, June, 2007)

- Hence, a number of new more effective and less toxic drugs & regimens are going to be available and are likely to be useful in the future
- However, the development of more powerful regimens doesn't necessarily result in better disease control
- The key factor is to apply the effective regimens properly under routine field conditions

