

NEWER DRUGS & POSSIBLE NEW MULTI-DRUG REGIMENS FOR LEPROSY

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CURRENT MDT REGIMEN FOR MB LEPROSY

- Among the three components, only **RIF** displays powerful bactericidal activity against *M.leprae*, **DDS & CLO** are modest bactericidal drugs.
- Consists of monthly and daily components. The role of daily component is to **eliminate RIF-resistant mutants**, but is **self-administered**.
- Duration of treatment has been progressively reduced, but **lacks of solid justifications**.

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THE NEEDS OF NEW MDT REGIMENS FOR MB LEPROSY

- The current MB regimen is **not RIF resistance-proof**.
- The duration of treatment remains too long, but it is highly unlikely to further shorten significantly the duration without **dramatically modifying the composition**.
- A **safe and effective alternative regimen** should be developed for patients with RIF-resistance or who cannot tolerate RIF treatment.

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Table 1. List of newer drugs with various bactericidal activities against *M. leprae*

Drug	Class	Bactericidal activity in mice*	Bactericidal activity in human*	Unit cost
Pefloxacin	Fluoroquinolone	++	++	Moderate
Ofloxacin		++	++	Moderate
Moxifloxacin		+++	+++	High
Clarithromycin	Macrolide	++	++	Moderate
Minocycline	Tetracycline	++	++	Moderate
Rifapentine	Rifamycin	+++	Not done	High
R207910	Diairyquinoline	+++	Not done	Not commercially available
Linezolid	Oxazolidinone	+	Not done	High

* Based on the activity of (+) for dapsona and (+++) for rifampicin.

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NEWER DRUGS

- Moxifloxacin (MXF) and R207910 are as bactericidal against *M.leprae* as RIF, and rifapentine (RFP) is even slightly superior than that of RIF. Unlike in TB, clarithromycin (CLR), a macrolide, is moderately active against *M.leprae*.
- It would be prohibitively expensive if the newer drugs are administered on daily basis, but the costs are manageable if they are administered once monthly.

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WE DON'T KNOW THE STERILIZING ACTIVITIES OF THESE NEW DRUGS !

- Progress of clinical trials in leprosy was extremely slow, only 5 of the 8 compounds listed in the Table had been tested in human trials, all were so-called « **short-term trials** (with duration ≤ 8 weeks) » and mostly in **monotherapy**.
- The **sterilizing** activity is the activity in killing the few, **slowly metabolizing organisms which survive the initial killing**, and is *the deciding factor* determining the **duration of treatment**.

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PRINCIPLES IN DESIGNING NEW GENERATION MDT REGIMENS

- To avoid potential risk caused by presence of unawared resistance to a given compound, the regimen must consist of **three components act by different mechanisms** .
- The pre-requisite of a compound to be a component of the **monthly administered regimen** is that a **single dose of monotherapy** displays definite **bactericidal** activity against *M.leprae* and is reasonably **tolerated** by the patients.

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A FULLY SUPERVISABLE, MONTHLY ADMINISTERED REGIMEN FOR RIF-SUSCEPTIBLE MB PATIENT

- **Rifapentine 900 mg (or, Rifampicin 600 mg) – Moxifloxacin 400 mg – Clarithromycin 1000 mg (or, minocycline 200 mg) once monthly (under supervision) for 12 months**

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AN INTENSIVE REGIMEN FOR PATIENT WITH RIFAMPICIN- RESISTANT LEPROSY

- **Intensive phase: Moxifloxacin 400 mg – Clofazimine 50 mg – Clarithromycin 500 mg – Minocycline 100 mg daily, supervised, for 6 months;**
- **Continuation phase: Moxifloxacin 400 mg – Clarithromycin 1000 mg – Minocycline 200 mg once monthly, supervised, for an additional 18 months**

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It is premature to apply either regimen in the routine programmes until its efficacy and safety are firmly established in carefully conducted clinical trials among patients with MB leprosy

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CLINICAL TRIALS

- As the first step, the clinical trials should begin with evaluation of the **side-effects** and **preliminary evidence of effectiveness** in a small number of patients with MB leprosy.
- If the **simplified regimen** is reasonably well tolerated and showing early evidence of effectiveness, then the second step should be **controlled clinical study**, aiming to confirm that the new regimen is **effective**, with **sterilizing activity** at least as effective as the current MDT regimen for MB leprosy.

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CONTROL CLINICAL STUDY

- Multiple arms.
- Each arm requires at least several hundreds of **well characterized MB leprosy patients** and will be followed-up at least 7 years after completion of treatment.
- **Long-term, multicentre and relatively expensive.**

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