

ISSUES RELATED TO CHEMOTHERAPY OF LEPROSY

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OVERALL GOALS FOR TREATMENT OF LEPROSY

1. To cure the individual patient and to prevent him/her to develop new nerve impairments.
2. To minimize the transmission of *M.leprae* to other persons.

Thus, successful treatment of leprosy has benefits both the individual patient and the community in which the patient resides.

NEW GENERATION MDT REGIMENS ARE NEEDED

- Duration of current regimens remains too long, particularly for MB leprosy
- Dapsone and clofazimine are weak bactericidal drugs against *M.leprae*
- Current regimen for MB leprosy is not **resistance-proof**
- Certain patients require safe and effective alternative regimen

NEW DRUGS WITH PROMISING BACTERICIDAL ACTIVITY AGAINST *MYCOBACTERIUM LEPRAE*

- **Fluoroquinolones:** pefloxacin, ofloxacin, levofloxacin, sparfloxacin, moxifloxacin.
- **Macrolide:** clarithromycin.
- **Tetracycline:** minocycline.
- **Rifamycin:** rifapentine.
- **Diarylquinoline:** R207910

FULLY SUPERVISABLE, MONTHLY ADMINISTERED REGIMENS

« ROM » combination:

- Rifampicin 600 mg
- Ofloxacin 400 mg
- Minocycline 100 mg

« PMM » combination:

- Rifapentin 600 mg
- Moxifloxacin 400 mg
- Minocycline 100 mg

A SINGLE DOSE OF « ROM » OR « PMM » FOR ALL PB CASES?

- More clinical trials are needed
- Post-treatment follow up should be longer

WHY PB AND MB LEPROSY ARE TREATED WITH DIFFERENT REGIMENS?

- Because the **size of the bacterial population** and the **underlying immunological response** of the hosts to *M.leprae* are so different between PB and MB leprosy, their requirements for chemotherapy, especially the **number of drugs** and **duration of treatment**, are bound to be very different.

A PROPOSED UNIFORM MDT (U-MDT) REGIMEN FOR ALL LEPROSY PATIENTS

- Rifampicin 600 mg once monthly
- Clofazimine 300 mg once monthly and 50 mg daily
- Dapsone 100 mg daily
- Duration: **6 months**

AN UNREASONABLE RECOMMENDATION

- **Over-treatment** of PB leprosy
- A **premature attempt** to shorten duration of MDT for MB leprosy to 6-months, when no information of long-term relapse rate after 12-month MDT is available among MB patients

FLAWS OF RESEARCH PROTOCOL ABOUT U-MDT

- Should not include PB cases in the trial
- Lacks of **control group** treated with either 12- or 24-month MDT for MB leprosy
- Definition of MB leprosy is too broad
- Definition of MB relapse is too vague; without **skin smear examination**, sensitivity and specificity of diagnosing MB relapse is poor
- Post-treatment **follow up** should be longer than five years

POOR ADHERENCE TO SELF-ADMINISTRATION OF TREATMENT

- A common behavioural problem among patients suffering from chronic diseases including leprosy, tuberculosis, AIDS, etc.
- Treatment behaviour of most patients is unpredictable
- Mere attendance at clinic or collecting drugs is not a reliable indicator of regular drug self-administration

HOW TO IMPROVE ADHERENCE OF PATIENTS TO TREATMENT?

- **Supervised or directly observed therapy (DOT)** is the only proven way to ensure that a patient receives treatment with the **right drug(s)**, in the **right dosage**, at the **right time**.

WHY MONTHLY RIFAMPICIN MUST BE ADMINISTERED UNDER SUPERVISION?

- Poor adherence of leprosy patients to self-administered therapy has been well documented
- Rifampicin is the key component of MDT regimens
- Supervised therapy is the only way to ensure *all* patients receive treatment regularly, which is in the best interest of patients and community

CONCLUSIONS & RECOMMENDATIONS BY THE 3RD MEETING OF WHO/TAG ON MONTHLY SUPERVISED THERAPY

- *Supervision of the monthly component of MDT regimen is no longer essential*
- *Large-scale implementation of accompanied MDT (AMDT)*

WHAT IS THE « ACCOMPANIED MDT » POLICY?

- *Patient is provided the entire supply of MDT drugs at the time of diagnosis, while asking someone close to or important to the patient assumes the responsibility of helping him or her complete a full course of treatment.*

FLAWS OF « AMDT POLICY »--A SIMPLE BUT WRONG SOLUTION OF IMPLEMENTING SUPERVISED THERAPY

- Confused operational difficulties with technical justifications
- Ignor completely the facts of poor adherence of leprosy patients to self-medication
- Lacks evidence based justification
- Neglect the importance of regular contacts between health workers and patients, crucial for prevention of impairment

UNANSWERED QUESTIONS ABOUT « AMDT » POLICY

- A routine exercise or only be applied in special situation?
- Who should be chosen to accompany patient: health worker, community volunteer or family member of patient?
- How an *accompagneur* 'helps' a patient to complete a full course of treatment? Is he/she expected to observe the patient swallow each monthly dose of treatment?
- How to train and supervise the *accompagneur* by the health worker?

LESSONS FROM « DOT- HAART » PROJECT IN HAITI

- Advanced AIDS patients have been successfully treated with directly observed therapy (DOT) with highly active antiretroviral therapy (HARRT), which is delivered by the community health promoters or *accompagneurs*, who are either farmers or market women usually living in the same neighborhoods or villages as their patients.

MAJOR TASKS OF *ACCOMPAGNEURS* IN « DOT-HARRT » PROJECT

- Observe directly the patients to ingest **at least one of the twice daily** HARRT treatment,
- Provide psychosocial support to the patients, and
- Link patients to clinical staff and available resources.

WHAT IS A COMMUNITY BASED « DOT-MDT » PROJECT?

- For those leprosy patients who are unable to visit the health centre once monthly, ingestion of the monthly component of the MDT regimen is directly observed by an *accompagneur*.

ADVANTAGES OF « DOT-MDT » OVER « DOT-HARRT » PROJECT

- Number of leprosy patients in most endemic countries are much less than that of AIDS patients in Haiti;
- MDT regimen for leprosy is simpler and better tolerated than the HARRT regimen for AIDS;
- Only monthly component of MDT regimen needs to be administered under supervision;and
- Duration of MDT regimens is fixed and shorter than that of HARRT regimen.

MAJOR TASKS OF *ACCOMPAGNATEURS* IN « DOT-MDT » PROJECT

- Directly observe patient to **swallow** the monthly component of MDT regimen,
- Provide patient adherence counseling about self-administration of daily component of MDT, and
- Accompany patient to health center whenever patient develops suspected signs or symptoms suggesting side-effects of MDT, leprosy reactions and neuritis, and for final examination by the end of MDT treatment.

FACTORS TO ENSURE BETTER PERFORMANCE OF *ACCOMPAGNATEURS*

- Carefully selection,
- Training with basic knowledge, and
- Regular supervision by health workers.

MONITORING THE ADHERENCE OF PATIENTS IN « DOT-MDT » PROJECT

- Monitored by in-direct method, *i.e.*, « **tablet count** », therefore patients are asked to keep empty MDT blister packs and bring them to health center at the end of treatment,
- Supplement with '**surprise**' **home visit** by *accompagneur* once monthly and by health worker at least once during the course of MDT treatment to check the remaining tablets in the blister packs.

DEFAULTER

- A defaulter has been defined as a patient who has not collected MDT treatment for 12 consecutive months.
- It has been recommended that defaulters who cannot be retrieved be removed from register.
- Removing defaulters from register has become one of the important approaches to reduce leprosy prevalence rate.

WHY DEFAULTERS SHOULD NOT BE INDISCRIMINATIVELY REMOVED FROM REGISTER?

- Because a significant proportion of the so-called « defaulters » are still living in the community.

HOW TO DEAL WITH THE ABSENTEES AND DEFAULTERS?

- Every efforts should be made to prevent an absentee to become a defaulter; a serious attempt should be made to trace an absentee beginning at the time of his/her first absence,
- Among the defaulters, only those who have died or permanently migrated from the country should be removed from register, others should be transferred or to be retrieved actively, with assistance of local community.

MDT TREATMENT FOR RETURNED OR RETRIEVED DEFAULTERS

- Current policy is that a new course of MDT will be given only to those who have active skin lesions, new nerve involvement or signs of leprosy reaction.
- It is difficult for general health workers to judge the signs of activity, particularly among MB patients close to lepromatous end. By definition, a defaulter has not completed MDT treatment, it seems more reasonable that a new course of MDT be given to every ex-defaulters after retrieve or return.

MAGNITUDE OF MB RELAPSE AFTER 24-MONTH MDT

Finding from **routine programs** by WHO:

- Very low relapse rate, about 0.1% per year.

Findings from **Institut Marchoux** and **JALMA**:

- 4-7 per 100 patients-year relapsed among patients with initial BI ≥ 4.0
- Relapse occurred late, mean incubation at least 5 ± 2 years

MAJOR DIFFICULTIES TO FOLLOW UP PATIENTS AFTER COMPLETION OF MDT

- Patients are removed from register, and essential records are lost
- General health workers lack of basic skills for detecting suspected relapse cases, and lack of manpower and resources to follow up patients after completion of MDT
- Lack of skin smear service in the field

RIFAMPICIN-RESISTANT LEPROSY IS AN IMPORTANT ISSUE

- Rifampicin is the key component of all MDT regimens
- Emergence of rifampicin-resistance would create tremendous difficulty for treatment of individual patients
- Its widespread dissemination would pose serious threat to leprosy control

MAJOR CONCLUSION FROM PREVIOUS STUDIES

- Rifampicin-resistance could emerge rather rapidly in a non-negligible proportion of MB patients whose treatment regimens were inappropriate

CAUTIOUS ABOUT STATEMENT OF NON-EXISTENCE OF RMP- RESISTANCE

- Post-MDT surveillance for relapse was discontinued in the field since 1994
- Rifampicin-susceptibility has rarely been tested, because great majority of mouse footpad laboratories have disappeared
- **'Absence of evidence' is not 'evidence of absence'.**

ALTERNATIVE TECHNIQUE FOR DIAGNOSING RIFAMPICIN- RESISTANT LEPROSY

PCR-based DNA sequence
analysis of *rpoB* gene of
M.leprae

MULTIDRUG RESISTANT *M.leprae*

A small number of strains
have already been detected!!

RESEARCH CAPACITY BUILDING FOR CHEMOTHERAPY OF LEPROSY

- Chemotherapy research is still needed and is highly relevant to the control activity.
- Currently, very few qualified investigators and institutes are involved in chemotherapy research; high-quality, long-term research projects are virtually non-existent.
- National and international organizations and NGOs should encourage and support chemotherapy research, particularly to support investigators and institutes from major leprosy endemic countries.