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# MDT

  

## Questions

*and*

## Answers



*Leprosy Control Programme*  
**World Health Organization**



## FOREWARD

*During the last decade, leprosy control has greatly benefited from technological developments in the chemotherapy of the disease. The introduction of the multidrug therapy (MDT) following the recommendations of the Study Group on Chemotherapy of Leprosy for control programmes (TRS 675, 1983) has created a new awareness and enthusiasm in many endemic countries to the extent that elimination of the disease as a public health problem through MDT is seen as a clear possibility. As of the end of 1990, over 3 million patients have already benefited or are benefiting from MDT.*

*In spite of the progress made so far, much remains to be done. One of the impediments often observed in the field with regard to MDT is the inadequate understanding of the rationale behind MDT and its real potential for curing the disease. Questions continue to be raised on MDT for which answers exist but probably not in a clear format in the existing literature. It is because of this felt need that the WHO Leprosy Unit has published this booklet with information in a reasonably clear question and answer format. It is earnestly hoped that this document meets the needs of the field personnel in leprosy control and that this would be read in conjunction with the WHO Guide to Leprosy Control (1988) which provides more detailed information on all aspects of control, including MDT.*

*The WHO Leprosy Unit would appreciate receiving relevant feedback on this document so that comments/suggestions can be taken into account during its next revision.*

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### Q.1

**Is WHO-recommended multidrug therapy (MDT) the best combination available for treatment of multibacillary (MB) and paucibacillary (PB) leprosy in leprosy control today?**

*A: Yes, it is the best combination available today, as proved by its successful application in leprosy control under varying conditions. The combination not only cures leprosy but is also quite cost effective.*

### Q.2

**What is the evidence that WHO/MDT is effective in MB and PB leprosy?**

*A: The most important indicator for the effectiveness of cure of a chemotherapeutic regimen is the rate of occurrence of relapse following successful completion of the scheduled course of treatment. The information available with the Leprosy Unit, WHO, from a number of control programmes shows that the relapse rate is very low (0.1% per year for PB and 0.06% per year for MB on the average). In addition, the low frequency of side effects has made it highly acceptable to patients in a variety of settings.*

### Q.3

Can MDT prevent the resistance of M. leprae to anti-leprosy drugs?

*A: Yes it can, as explained below: It is estimated that an advanced, untreated lepromatous leprosy patient harbours about  $10^{11}$  or 11 logs live organisms. Out of these, the proportion of naturally occurring drug-resistant mutants is estimated to be 1 in 7 logs for rifampicin; 1 in 6 logs each for dapson and clofazimine. The organisms resistant to one drug will be susceptible to other drugs in MDT as their mechanisms of action are different. For example, in a population of 11 logs M. leprae, 4 logs or 10 000 M. leprae will be naturally resistant to rifampicin. These organisms will not be killed by rifampicin, but will be killed by dapson and/or clofazimine. Therefore it is of vital importance that patients on MDT take their daily dose of dapson and clofazimine regularly, in addition to the supervised monthly dose of rifampicin.*

Q.4

**What is the rationale for using a three-drug combination for MB leprosy and a two-drug combination for PB leprosy?**

*A: As mentioned earlier, the frequency of naturally-occurring drug-resistant mutants of M. leprae to rifampicin is estimated to be 1 in 7 logs, and for dapsone and clofazimine, this frequency is about 1 in 6 logs each. This means that the frequency of mutants resistant to two drugs will be about 1 in 12 logs or 13 logs, and the frequency for mutants resistant to three drugs will be 1 in 19 logs. As the maximum bacillary load in an advanced, untreated multibacillary patient is estimated to be only 11 logs, and in a paucibacillary patient 6 logs, the chances of having naturally occurring drug resistant mutants resistant to two or three drugs is extremely remote. Therefore, the three drug combination for MB leprosy and the two drug combination for PB leprosy should be able to kill all the live organisms in a patient.*

Q.5

**Why is rifampicin given only once a month?**

*A: Rifampicin is an exceptionally potent bactericidal agent against M. leprae. A single dose of 600 mg is capable of killing 99.9% or more of viable organisms. However, the rate of killing is not proportionately enhanced by subsequent doses. It is also possible that rifampicin exerts a delayed antibiotic effect for several days, during which the organism is incapable of multiplying. The high bactericidal activity of rifampicin makes once a month application of the drug feasible and cost-effective for leprosy control programmes.*

Q.6

**Why is 300 mg clofazimine given once a month in addition to 50 mg daily?**

*A: It is of vital importance that clofazimine and dapsone be taken regularly by the patient, in order to prevent the emergence of rifampicin-resistant M. leprae. Clofazimine being a repository drug, ie., it is stored in the body after administration and is then slowly excreted, it can be given as a loading dose. This will ensure that the optimal amount of clofazimine is present in the body tissue, even if the patient occasionally misses his/her daily dose.*

Q.7

**What is the rationale behind continuing dapsone, even in patients known to be or suspected of being infected with dapsone-resistant M. leprae?**

*A: A patient who is known to be or suspected of being infected with dapsone-resistant M. leprae harbours several sub-categories of dapsone-resistant organisms, some having a high level of resistance to dapsone i.e. impossible to be killed even with a full dose of dapsone, and others having a low or a moderate level of resistance to dapsone i.e. which can be killed with a full dose of dapsone. Therefore, when patients are treated with a full dose of dapsone, although the high degree dapsone-resistant M. leprae will not be killed by dapsone, it is likely that the low or moderately dapsone-resistant M. leprae will be killed. In addition, the low cost, safety and ease of dapsone administration makes inclusion of dapsone into MDT regimens attractive.*

Q.8

**What are the chances of developing multiple drug resistance with MDT?**

*A: As mentioned earlier, the frequency of naturally occurring mutants, resistant to two drugs is about 1 in 12 logs to 1 in 13 logs, and for three drugs is about 1 in 19 logs. As even an advanced untreated lepromatous patient harbours only 11 logs of organisms, the probability of developing multidrug resistant mutant *M. leprae* is extremely low. However, the widespread prevalence of dapsone resistance, if coupled with poor compliance to the self-administered, (dapsone and clofazimine), components of the MDT may lead to development of mutants resistant to more than one drug. The present WHO-recommended MDT will, in all probability, be able to prevent occurrence of multiple drug resistance through its strong supervised component of monthly administration of rifampicin and clofazimine.*

Q.9

Some programmes are using modified MDT regimens, are these acceptable?

*A: The WHO-recommended regimens are minimal regimens, and any modification which apparently strengthens these regimens is acceptable, as long as the additional costs are affordable. However, three main considerations should be taken into account:*

- a) rifampicin should be one of the components of MDT;*
- b) rifampicin 600 mg should be given at least once a month for all patients; and*
- c) at least two anti-leprosy drugs should be used in the MB regimen, and one anti-leprosy drug should be used in the PB regimen, in addition to rifampicin, in order to prevent the selection of rifampicin-resistant M. leprae.*

Q.10

**Can MDT eliminate persisting *M. leprae*?**

- A: The persisting M. leprae are by definition those viable organisms which are fully susceptible to the drugs but are surviving despite adequate treatment by anti-leprosy drugs, probably because they are in a low or dormant metabolic state. So far we do not have a drug which can kill these persisting organisms, although rifampicin is known to be capable of killing persisting organisms in another mycobacterial disease, tuberculosis. The evidence so far accumulated, shows that persisters, even if they exist, do not play an important role in the occurrence of relapse in leprosy among patients treated with MDT.*

Q.11

**Is there any evidence that the drugs included in MDT can antagonize each other's antibacterial activity?**

- A: All experimental and clinical evidence indicate that there is no antagonism among the drugs included in MDT. The experience with MDT so far has shown the combination to be the most effective.*

Q.12

What is the reason for giving MDT to MB patients for two years and to PB patients for six months?

- A: *The most important component of the MDT regimens is rifampicin. The frequency of naturally-occurring mutants, resistant to rifampicin is 1 in 7 logs. The majority of rifampicin-susceptible M. leprae are killed by the monthly doses of rifampicin, but it probably takes two years in MB for daily doses of dapsone and/or clofazimine to eliminate all rifampicin-resistant mutants, these being weakly bactericidal agents. This is a very conservative estimate and in reality it may take less time. In PB patients six months of rifampicin by itself should be satisfactory, theoretically, to kill all the organisms. However, dapsone has been added in order to avoid rifampicin resistance in patients who are wrongly classified as PB.*

Q.13

**Is it necessary to give MDT to MB patients until skin smear negativity?**

*A: The bacteriological index (BI) is one of the tools for assessing the efficacy of a treatment regimen in leprosy. However, the BI cannot differentiate between dead and viable organisms. The evidence accumulated from THELEP-supported field trials of Fixed Duration MDT in some parts of the world suggests that it is probably not necessary to continue MDT beyond two years in MB patients. The clearance of dead bacilli from skin tissue is continued at about 0.6 to 1.0 unit of BI per year, even after MDT is discontinued. So far no relapse or clinical deterioration is reported from these trials. However, in view of the limited information available so far, the original recommendation that treatment should be continued for at least two years and, wherever possible, up to smear negativity, still stands.*

Q.14

**Is it necessary to give MDT to PB patients until clinical inactivity is achieved?**

- A: *It should be recognized that clinical activity in PB leprosy does not necessarily provide direct correlation with bacterial multiplication. In a large proportion of patients it is not possible to achieve clinical inactivity by six months even though all the organisms are killed. The evidence from the follow-up of PB patients in THELEP-supported field trials of MDT shows that the lesions become inactive gradually over a period of one to two years after the treatment is discontinued. The occurrence of relapses in PB patients is very low and as yet there is no established relationship between disease activity status at the time of completion of treatment and subsequent relapse. However, it is important that the initial classification of patients designated as paucibacillary leprosy is accurate.*

Q.15

**Is it necessary to give MDT to MB and PB patients who were on dapsons monotherapy and are now bacteriologically and clinically inactive?**

- A: *The reports available from routine control programmes suggest that a small proportion of patients who had several years of dapsons monotherapy are relapsing, especially MB leprosy patients. Wherever resources permit, MB patients who were treated with dapsons monotherapy and are clinically and bacteriologically inactive should be treated with WHO/MDT for two years.*

#### Q.16

**Does MDT help in achieving skin smear negativity earlier than with dapsone monotherapy?**

*A: The main function of the MDT is to kill all viable organisms, which can be achieved in a relatively short period. The clearance of dead bacilli depends largely on the individual's host response which, especially in individuals suffering from MB leprosy, is defective. The results of several large-scale, long term field trials show that the rate of clearance of dead bacilli is about 0.6 to 1.0 logs per year and is not enhanced by MDT.*

#### Q.17

**Is the threat of rifampicin-resistant leprosy a serious problem?**

*A: There are a few isolated reports of rifampicin-resistant leprosy, these are mainly from areas where rifampicin was given as monotherapy, either alone or in combination with dapsone to dapsone-resistant patients. At the moment, the problem of rifampicin-resistant leprosy is not a serious one, however, selective non-compliance to dapsone and/or clofazimine by patients may facilitate selection of rifampicin-resistant strains.*

Q.18

**Does MDT expose patients to a higher risk of serious side effects?**

- A: When more than one drug is used, naturally there is a risk of side effects from each of the drugs used in the combination. However, in practice, the side effects reported from the use of MDT in several hundreds of thousands of patients around the world, show that these side effects are mild and easily controllable in the field.*

Q.19

**Does MDT increase the frequency and severity of lepra reactions?**

- A: The evidence available shows that there is a significant reduction in the frequency and severity of ENL (Type 2) reactions in MB leprosy patients on MDT. It is possible that this is attributable to the anti-inflammatory effect of clofazimine. On the other hand, there seems to be a higher reporting of reversal reactions (Type 1) in PB leprosy patients. However, it is not clear whether this is because of more stringent follow-up of patients which detects mild reactions that would otherwise have been missed, or whether there is a real increase in the incidence of reversal reactions.*

Q.20

**What kind of damage can occur if patients are irregular in taking MDT?**

*A: If patients do not take MDT regularly, the disease activity will progress and the patient may develop serious disabilities and deformities. These patients will become a source of infection to the community, in addition to perpetuating stigma generated by unsightly deformities. More seriously, if the irregularity is selective to one or the other drug in MDT then there is a possibility of drug resistance to multiple drugs.*

Q.21

**What treatment can be given to patients who do not tolerate MDT due to adverse reactions or contra-indications?**

*A: It is very important to establish conclusively that the adverse reactions seen are due to the anti-leprosy drugs. Once this is established, other anti-leprosy drugs can be tried, but the choice is very limited. For example, ethionamide/protionamide may be used in the place of clofazimine or dapsone, provided the drug is administered under strict medical supervision. Newer anti-leprosy drugs, like ofloxacin, minocycline and clarithromycin may become available in the near future as alternative or additional drugs.*

## Q.22

**What is to be done if leprosy programmes run short of one or more drugs used in MDT?**

- A: Hopefully such a situation would be exceptional and one that should be avoided at all costs. There are practically no alternatives available in such situations. It is important that project managers at all levels keep a close watch on their drug supply position and take timely action. The principle of using three drugs in MB leprosy and two drugs in PB leprosy should be adhered to under all circumstances.*

## Q.23

**How should patients who refuse to take clofazimine be managed?**

- A: The experience gained so far shows that the number of patients who refuse to take clofazimine is not very large. However, in certain populations, this can be a serious problem. It may be worthwhile spending some time in educating the patient about the advantage of taking clofazimine, in particular the reversible nature of the discolouration produced by the drug. In most cases this approach should be sufficient to encourage the patient to continue with clofazimine. In exceptional cases, ethionamide/prothionamide 350-500 mg per day may be used in place of clofazimine, although the risk of possible serious side effects when this drug is used in combination with rifampicin should be clearly borne in mind and also explained to the patient.*

**Q.24**

**How serious are the side effects of clofazimine, such as discolouration and ichthyosis and how can they be managed?**

*A: The discolouration caused by clofazimine usually does not cause any serious problem, except for the fact that it may be cosmetically unacceptable to some patients. The accompanying ichthyosis may predispose certain dermatitis, especially in dry climatic conditions. This can be reduced by moistening the skin, followed by regular application of vaseline or vegetable oils and avoidance of unnecessary exposure to bright sunlight.*

**Q.25**

**How long does it take to reverse the discolouration caused by clofazimine?**

*A: The discolouration caused by clofazimine is completely reversible. It starts to appear by the third month of MDT and reaches its maximum intensity by the end of the first year. After discontinuation of MDT, the discolouration starts to diminish noticeably by six months and returns to its normal colour by the end of one year after stopping MDT.*

Q.26

**Will the wide-spread use of rifampicin for treating tuberculosis (TB) and sexually transmitted diseases (STD) have any effect on the use of MDT in leprosy patients?**

- A: It is possible that if a leprosy patient with tuberculosis is treated for tuberculosis with a rifampicin containing anti-tubercular regimen, he may run the risk of developing rifampicin resistant leprosy. Hence, the need to treat both diseases simultaneously. Use of rifampicin for STD for very short periods may have no significant effect on the emergence of rifampicin-resistant M. leprae.*

Q.27

**Is MDT contra-indicated in patients suffering from tuberculosis?**

- A: MDT is not contra-indicated in patients suffering from tuberculosis. It must be remembered that tuberculosis is a more serious disease and must be treated promptly. WHO/MDT for leprosy is not adequate for the treatment of tuberculosis and therefore an appropriate anti-tubercular regimen should be given, in addition to the antileprosy MDT, to patients who are diagnosed to have both leprosy and tuberculosis - except if daily rifampicin is part of the anti-tuberculosis treatment, then there is no need to administer monthly rifampicin as part of the leprosy MDT.*

Q.28

**A small number of patients do not show any clinical or bacteriological improvement with MDT. How should these patients be managed?**

*A: There may be several reasons for such occurrences in a small number of patients. The two most important reasons may be poor drug compliance and other concomitant, debilitating, intercurrent infection. The problem of poor compliance may be solved by supervised drug administration and health education. The problem of concomitant intercurrent infection needs thorough investigation (including, where indicated, tests for HIV infection) and appropriate management. If these measures fail, it may be necessary to seek expert opinion.*

Q.29

**Is it necessary to give MDT cover to patients who have to receive steroids (e.g. for late reversal reaction or other medical conditions) even after successful completion of the scheduled course of MDT?**

*A: The risk of possible endogenous reactivation is probably higher during the initial few years (during the surveillance period) after completion of chemotherapy. Immunosuppressive drugs, like corticosteroids, are known to accelerate the multiplication of organisms located in dormant foci and cause disseminated reactivation; for example, in TB. The evidence for such occurrence in leprosy is inconclusive.*

*It is probably safer, in the interests of the patient, to reintroduce MDT if the patient is likely to be on a higher dose of corticosteroids or any other immunosuppressant drugs for more than 12 weeks. MDT may be reintroduced in such cases after 12 weeks and continued until corticosteroids are completely withdrawn.*

### Q.30

**Is MDT safe during pregnancy and lactation?**

- A: Since leprosy is exacerbated during pregnancy it is important that MDT be continued. All evidence so far indicates that MDT is safe during pregnancy. A small quantity of anti-leprosy drugs are excreted through breast milk but there is no report of adverse reaction due to this except for mild discolouration of the infant due to clofazimine.*

### Q.31

**After patients have stopped treatment, how does one recognize relapse? How can relapse be distinguished from the various types of reactions?**

- A: Relapse, in MB leprosy, is defined as the re-multiplication of M. leprae, suspected by the marked (at least 2+ over the previous value) increase in the BI at any single site, usually with evidence of clinical deterioration. This can be confirmed in most cases by growth of M. leprae in mouse footpad system. Recognition of relapse in paucibacillary leprosy is somewhat difficult as it is hard to distinguish it from reversal reaction. In theory, a therapeutic test with corticosteroids may be able to distinguish between these two phenomena: definite improvement within four weeks of corticosteroid therapy, denoting reversal reaction and non-response to corticosteroids during the same period favouring the diagnosis of clinical relapse.*

### Q.32

**In some control programmes, after completion of MDT, patients continue with a single drug, usually dapsone, for various lengths of time. Is it necessary?**

*A: The continuation of dapsone monotherapy after a course of MDT is quite unnecessary. Some control programmes may be using this to ensure regular follow-up; to satisfy patients who are not willing to discontinue treatment; or, in situations where the physician may not be convinced of the efficacy of MDT.*

*Whatever the reason, this approach puts an unnecessary burden on the patient and on the field workers and cannot be recommended.*

### Q.33

**How often should skin smears be taken during and after the completion of MDT?**

*A: As changes in the BI are generally quite slow, it is sufficient to take skin smears at the beginning, at the end of two years and once a year thereafter before stopping MDT. During surveillance it is probably sufficient to repeat skin smears once a year for five years in MB cases and once a year for two years in PB cases. In addition, whenever clinical deterioration/relapse is suspected, skin smears should be taken from the most active sites.*

Q.34

**Is post-MDT surveillance of patients essential?**

*A: Post-MDT surveillance of patients is necessary mainly for two reasons:*

- a) to detect late reversal reactions promptly, and*
- b) to detect relapse*

*This may be done by actively contacting the patient at his/her home or at the clinic at regular intervals or by giving the patient clear instructions about early signs/symptoms of reaction/relapse and requesting him/her to report immediately to the health centre.*

Q.35

**It is said that almost all the bacilli seen in skin smears after MDT are dead bacilli. Is there any way to accelerate their removal?**

*A: There are some reports that immunotherapy using M. leprae or other mycobacteria derived vaccines may be useful in accelerating the clearance of dead bacilli from the tissues. However, more research is needed before this approach can be recommended for use in routine leprosy control programmes.*

Q.36

**Does the presence of dead bacilli in the skin and other tissues cause the patient any problems?**

*A: In most patients the presence of dead bacilli in the skin and other tissues do not cause any problem and the dead organisms are gradually cleared by the phagocytic system of the body. However, in a proportion of patients, the antigens from dead bacilli can provoke immunological reactions, such as reversal reaction, causing serious nerve damage and subsequent disabilities.*

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