Treatment of Leprosy

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Background and Goals of Treatment

This chapter discusses the antibacterial treatment of leprosy infections. Antibiotic treatment is a key component of leprosy treatment, as it is vital to prevent the progression of the infection. Treatment with rifampin and other antibiotics is highly effective and cures 98% of patients with the leprosy infection. Furthermore, the relapse rate is very low, at about 1% over 5–10 years. There is little *M. leprae* drug resistance in leprosy and few reports of multi-drug resistance (1, 2, 3, 4, 5, 6, 7, 8). An antibiotic treatment may take months or years to produce clinical improvement, especially in patients with an initial high bacterial index (BI). Because inflammation is such an important part of the disease process, treating patients with steroids is often required for clinical improvement. Patients may also experience immune-mediated reactions after effective antibiotic treatment.

This chapter focuses on the current chemotherapeutic regimens for leprosy and their clinical use (see Chapter 5.2 for a detailed pharmacology of these agents). Chemotherapy is only part of the treatment of leprosy, which must also include

1. Assessing nerve damage severity and duration (see Chapter 2.5; Chapter 4.3)
2. Treating Type 1 and Type 2 reactions
3. Managing neuropathic hands and feet (see Chapter 4.3)
4. Discussing the adverse effects of medication
5. Educating the patient about the leprosy disease and their individual prognosis

6. Explaining the psychological issues that accompany leprosy
7. Addressing the stigma of leprosy (see Chapter 4.5)

WHO Regimen

In 1982, a WHO expert committee recommended that all leprosy patients should be treated with a combination of either two or three drugs (rifampin, dapsone, and clofazimine) (9). All patients receive rifampin and dapsone, and multibacillary (MB) patients also receive clofazimine. Concerns had been raised that if the drugs were used as single agents, *M. leprae* would develop resistance to them. Therefore, the WHO committee recommended multi-drug therapy (MDT) to mitigate the development of drug resistance to any single anti-leprosy drug.

The effectiveness of dapsone against *M. leprae* was discovered in the late 1940s, after which it was widely used as a single agent for the treatment of leprosy patients. This usage led to the development of dapsone resistance, presenting initially as disease relapse 15 years after dapsone monotherapy, but eventually as primary dapsone resistance in untreated patients (10). Clofazimine was subsequently discovered to be an effective anti-leprosy drug. In addition, studies on rifampin showed that it had excellent antibacterial activity against *M. leprae*. A single monthly dose of 1.200 mg of rifampin was found to be as effective as a daily dose in treating patients with an initial high bacterial load (11). These discoveries were important because they facilitated the development of the WHO regimen (12).

For MB patients, the keystone of the WHO regimen is rifampin in conjunction with daily doses of dapsone and clofazimine. Paucibacillary (PB) patients are treated with monthly doses of rifampin and daily doses of dapsone. The treatment duration was initially 24 months for MB patients, later reduced to 12 months in 1998 (13). The treatment duration for PB patients has always been six months. Several countries, such as the USA, treat patients daily with rifampin. However, the relapse rates are very low for monthly rifampin regimens, so this amendment to the WHO regimen is unnecessary and puts patients at risk of developing rifampin adverse effects. Drug taking by leprosy patients was supervised initially, an approach that was probably critical for the good results that were obtained. Now, supervision is only recommended and practice varies between national programs. The WHO regimen was introduced without formal trials, so a rigorous assessment of the outcomes has never been done. This lack of assessment has created an evidence gap in our knowledge about this regimen (14). Table 1 provides details concerning drug dosage and duration of treatment.

The WHO provides treatments as blister packs to all countries reporting patients with leprosy. The packs are then disbursed to individual treatment centers by the national program. Blister packs are also provided for 10–14 year-olds, while smaller children are given weight-based doses (see Table 1). The blister packs are a robust means of delivering MDT. The WHO works closely with do-

nors and manufacturers to plan the manufacture, procurement, and shipment of the MDT drugs with the maximum available shelf life, at a time most appropriate for each national program. The WHO also arranges independent laboratory testing of the drugs at the manufacturer's own expense to ensure that the finished WHO product is the best available for the national programs. Such testing is considered essential to maintain the confidence of national programs in the donated product.

TABLE 1 WHO recommendations for multi-drug treatment of Hansen's disease

		WHO[a]	
Drugs		**PB**	**MB**
Dapsone	Adult	100 mg daily	100 mg daily
	Child (10–14 yrs)	50 mg	50 mg
	Child under 10	25 mg	25 mg
Rifampin	Adult	600 mg once/month	600 mg once/month
	Child (10–14 yrs)	450 mg once/month	450 mg once/month
	Child under 10	300 mg once/month	300 mg once/month
Clofazimine	Adult	–	50 mg daily plus 300 mg once/month
	Child (10–14 yrs)	–	50 mg daily plus 150 mg once/month
	Child under 10	–	50 mg twice a week and 100 mg once a month
Duration (months)		6 doses (6 blisters) that can be taken until 9 months	12 doses (12 blisters) that can be taken until 9 months

[a] The WHO classification (7) defines only two types based primarily on the number of lesions: paucibacillary (PB) and multibacillary (MB).

In the Ridley-Jopling classification, clinical and histological features define five types: polar tuberculoid (TT), borderline tuberculoid (BT), mid-borderline (BB), borderline lepromatous (BL), and polar lepromatous (LL). The two classification systems over lap as follows: PB = TT, BT; MB = BB, BL, LL.

In the USA, PB patients are treated with rifampin 600 mg and dapsone 100 mg daily for 12 months. MB patients are treated with rifampin 600 mg, clofazimine 50 mg daily, and dapsone 100 mg for 24 months.

The classification of patients for treatment with the WHO regimen has changed several times (see Chapter 2.1; Chapter 2.4). The changing classification means that it is difficult to compare treatment studies because the patient population may have changed. Currently, patients, including children, are assigned to treatment regimens based on the number of skin lesions only. PB patients have up to five skin lesions; MB patients have six or more lesions. However, this classification does not take into account the neurological involvement that many patients have at presentation. For research purposes, slit-skin smears should be done for all patients to assess their bacterial load. In research centers, most patients will have a skin biopsy performed, which helps with their classification. In hospital-based settings, patients with tuberculoid (TT) and borderline tuberculoid (BT) leprosy can be treated with a six-month PB regimen. Patients with mid-borderline (BB), borderline lepromatous (BL), and lepromatous (LL) leprosy can be treated with the MB regimen. Any patient who is slit-skin smear positive should be treated with 12 months of MB MDT. If a slit-skin smear is not done before starting treatment, however, smear-negative patients are classified as MB, which results in them being both over- and under-treated in the WHO regimen. Table 2 lists the messages that should be relayed to patients when treatment starts.

TABLE 2 Points for new patients starting treatment

1. The cure rate is 99%.
2. There is no multi-drug resistance in leprosy.
3. Over 20 million patients have been treated with MDT since 1988.
4. Your lesions will start to improve after a couple of months. Some MB patients' lesions take years to improve, but they will eventually resolve.
5. You might become anemic while taking MDT.
6. Fifty percent (50%) of MB patients will develop immune-mediated reactions. These reactions are due to changes in immunity and do not mean that the MDT is not working.
7. If you have a high BI at the start of treatment, you will need to be monitored for 15 years.

Rifampin is a potent bactericidal for *M. leprae* (see Chapter 5.2), and the only bactericidal drug included in MDT regimens. Four days after a single 600 mg dose, bacilli from a previously untreated MB patient are no longer viable (15). Rifampin acts by inhibiting DNA-dependent RNA polymerase, thereby interfering with bacterial RNA synthesis. Rifampin is well-absorbed orally. Hepatotoxicity may occur with a mild transient elevation of hepatic transaminases, but this reaction is rare at the dosage and intervals recommended for leprosy and is not an indication for stopping treatment. Because rifampin is only given as a monthly dose in WHO MDT regimens, the adverse effects recognized from its use in tuberculosis (TB) are probably not seen. A monthly dose of rifampin probably does not cause induction of hepatic cytochrome p450, but this outcome has never been formally measured. Because *M. leprae* resistance to rifampin can develop in a one-step process, rifampin should always be given in combination with other antileprotics (16).

Dapsone (4, 4-diaminodiphenylsulphone [DDS]) acts by blocking folic acid synthesis (see Chapter 5.2). It is only weakly bactericidal. Oral absorption is good and it has a long half-life, averaging 28 h.

Dapsone, in the doses recommended for leprosy, causes mild hemolysis and, rarely, anemia or psychosis. Glucose-6-phosphate dehydrogenase deficiency seldom causes a problem and enzyme levels are not routinely tested before starting MDT. The 'DDS syndrome' (also dapsone hypersensitivity syndrome [DHS]) usually starts six weeks after commencing DDS and manifests as exfoliative dermatitis associated with lymphadenopathy, hepatosplenomegaly, fever, and hepatitis, and may be fatal (17, 18). New data suggest that dapsone is significantly associated with adverse effects. A recent systematic review of published studies on dapsone hypersensitivity reactions found a prevalence rate of 1.4% in 114 studies; 71% of the cases were patients being treated for leprosy (19). The symptom range was 6 hours–21 weeks. Eighty-two percent (82%) of patients required treatment with systemic steroids. In all cases, dapsone was stopped. The fatality rate was 9.9%, with death occurring from liver failure, sepsis, and bone marrow failure. Agranulocytosis (20) , hepatitis, and cholestatic jaundice occur rarely with DDS therapy. A retrospective hospital study from Nepal on Dapsone AE reported four deaths and patients with jaundice (77.7%), exfoliative dermatitis (44.4%), and hemolytic anemia (27.7%) (21). Shen has reported that deaths occurred after starting MDT in China, most commonly in the second month after starting MDT (22). Deps looked retrospectively at Brazilian patients and found that 48–56% had hemolytic anemia and 6–7% had a skin reaction (23). Other reports from Sri Lanka document agranulocytosis and one death in leprosy patients associated with starting dapsone (24). The safety of dapsone should be reappraised, as it can no longer be described as a safe drug. Hospital-based studies are likely to overestimate adverse effects. Instead, prospective assessments of adverse effects are needed in the community settings where dapsone is used. Zhang has shown that Chinese leprosy patients having HLA-B*13:01 genes were at a higher risk of developing DHS (25).

Clofazimine is a brick red, fat-soluble crystalline dye (see Chapter 5.2). The mechanism of its weakly bactericidal action against *M. leprae* is not known. High drug concentrations are found in the intestinal mucosa, mesenteric lymph nodes, and body fat. The most noticeable side effect is skin discoloration, ranging from red to purple-black, with the degree of discoloration depending on the dosage. It can accumulate in active leprosy skin lesions, thus making them more prominent. The pigmentation usually fades within 6–12 months of stopping clofazimine, although traces of discoloration may remain for up to four years. Urine, sputum, and sweat may become pink. Clofazimine also produces a characteristic ichthyosis on the shins and forearms. Gastrointestinal side effects, ranging from mild cramps to diarrhea and weight loss, may occur as a result of clofazimine crystal deposition in the wall of the small bowel.

The skin discoloration associated with clofazimine is psychologically distressing for many people. In India and Southeast Asia, patients often stop taking clofazimine because of the adverse effects. The discoloration is socially difficult for them, advertising to their friends that they are taking anti-leprosy medication and breaking confidentiality about treatment. In London, many patients, including Africans, prefer not to take clofazimine because of the visible stigmata it causes. The only data on this stigma comes from Kumar et al., who compared compliance in Indian patients taking MDT or a ROM (rifampin, ofloxacin, minocycline)-based regimen (26). They found that skin pigmentation was a significant problem and caused patients to stop taking their treatments.

Adverse Effects of MDT

As stated above, there has been no systematic collection of data on the adverse effects associated with MDT. This significant gap means that we cannot give patients evidence-based assessments of the frequency of adverse effects. It also means that comparing regimens is difficult. Since MDT is so effective bacteriologically, the adverse effect profile is very important when assessing new treatments. The above data on the high rate of adverse effects with dapsone suggests that patients should be forewarned. In the Brazilian uniform MDT (U-MDT) study, 90% of the patients had a fall in their hemoglobin levels, 15% had abnormal liver function tests (LFTs), and 10% had epigastric pain and nausea (27). Patients being treated with MDT should have their hemoglobin checked at the start of treatment and again after two months of treatment. DHS was not reported in the initial report of adverse effects. Furthermore, no data was collected on the frequency of clofazimine pigmentation. Although PB patients receiving the MB regimen had a significantly higher frequency of hemolytic anemia, which could be due to an interaction between clofazimine and dapsone, in all cases the anemia was mild (27). The adverse effects rates in regular MDT (R-MDT) and U-MDT treated groups were not significantly different, but anemia was more severe in patients in the R-MDT/MB group (28).

Outcomes of MDT Treatment

The response to MDT treatment is measured by three main outcomes:

1. Clinical improvement of the skin lesions
2. Fall in the BI of smear-positive patients
3. Relapse rate

The BI of smear-positive patients falls by about 1 log per year and continues after treatment with MDT has stopped. Presumably, the mycobacteria are dead and the macrophages continue to slowly remove the dead mycobacteria (see Chapter 2.4). Studies from Brazil (29, 27) and Bangladesh (30) show that the BI also falls with shorter regimens. Additionally, relapse rates are similar in both studies, using 12 or 6 doses of MDT/MB (19, 27) . Published clinical outcomes for patients treated with the PB regimen show that 2–44% of patients had clinically active skin lesions at the end of treatment. Nerve impairment occurred “de novo” in 2.5% of patients, and visible disabilities increased from 4% at enrollment to 7% at 8–10 years of follow-up. Relapse rates are low, ranging from 0% in Ethiopia (31) to 2.5% over four years in Malawi (32). For patients treated with the MB regime for 24 months, one study in Thailand found that 29% of lesions were still active after three years and that visible disabilities increased from 5% at enrollment to 13% at 8–10 years of follow-up (33). Relapse rates have been reported in six observational studies, varying from zero in China and Ethiopia to 2.04/100 person years in India. Data from West Africa (34) and India (34,

35) show that patients with a high initial BI (>4+) treated with two years of rifampin, clofazimine, and dapsone had a relapse rate of 8/100 person years, whereas patients with smear negativity had a relapse rate of 2/100 person years.

Duration of Treatment

The current recommended length of treatment for MB patients, originally 24 months, is 12 months. No controlled trial data guided this decision, but the classification of MB patients had been widened, so some patients who would previously have received PB treatment for six months now receive MB treatment for 12 months. New evidence supports this decision on the duration of treatment. A study from Bangladesh has followed 1612 patients in two separate cohorts, treated with either six or 12 months of WHO-recommended MDT (monthly doses [supervised] of rifampin 600 mg and clofazimine 300 mg, daily dapsone, and daily clofazimine), for over seven years (30). No patients have yet presented with a leprosy relapse. The rate of decline of the BI was similar in the two groups, and the loss to follow-up was 16.8% in both groups. The study continues to follow the patients. This study's findings were supported by data from a randomized and controlled clinical trial (RCT) on U-MDT in Brazil.

These studies show that it would be safe to reduce the treatment length to six months. In the Bangladesh study, the patients had supervised treatment every 28 days, which suggests that clinical leprosy can be cured with intermittent doses of rifampin spread out over several months. The relapse rate in other studies that have attempted to use a more intensive treatment regimen, such as longer than a month, have not been successful and have had much higher relapse rates. However, a relapse may occur over a very long period of time. Balagon et al. found that patients given a two-year treatment regimen in the Philippines relapsed 6–16 years after MDT. The peak time for relapse was 10 years. This finding emphasizes the importance of a long period of follow up, especially when patients have an initial high BI (36). An RCT has demonstrated that most relapses occur in the first few years after treatment (27).

Relapse

Relapse, in MB leprosy, is defined as the multiplication of *M. leprae*, with an increase of at least 2+ over the previous value in the BI at any single site, usually with evidence of clinical deterioration (new skin patches or nodules and/or new nerve damage) (37). Recognizing a relapse in PB leprosy is occasionally difficult, as symptoms may be similar to a Type 1 reaction. However, Type 1 reactions frequently occur and PB relapse is very rare. Administering a therapeutic test with corticosteroids to patients with new lesions may help distinguish between these two phenomena: a defi-

nite improvement within four weeks of corticosteroid therapy denotes a reversal reaction, and non-response to corticosteroids over the same period favors the diagnosis of a clinical relapse.

MB patients presenting with a relapse are re-treated with triple therapy regardless of any change in classification. PB patients require two years, and MB patients at least five years, of monitoring after treatment. Studies in Bangladesh showed a very low rate of events in treated patients (9), whereas 40% of MB patients had an immune-mediated post-treatment event (38). Patients can be discharged if there is no evidence of activity or reaction, but they should be advised to return if new symptoms develop, especially in the hands, feet, or eyes. Patients with reactions or physical or psychological complications may need much longer care. In both the Bangladesh and the Brazilian studies, the U-MDT relapse rate was acceptable for use.

Recently, it was shown that the same patient can be infected and re-infected years after the first treatment by different strains of *M. leprae* (39). So, what we used to call relapse may be re-infection, demonstrating that susceptible patients can get ill again, independent of time of treatment.

Uniform MDT (U-MDT)

A new uniform six-month regimen of dapsone, clofazimine, and rifampin for all patients has been tested in an RCT in Brazil (40). The hypothesis was that all leprosy patients could be treated with a single triple-drug MB regimen for six months (41). The concern was that patients with a high BI would have a higher relapse rate. Six-hundred and thirteen (613) new untreated patients with a high BI were randomized to receive treatment with either the standard 12-month R-MDT (12 months rifampin, dapsone, and clofazimine) or 6-month U-MDT (6 months rifampin, dapsone, and clofazimine).

The results of the U-MDT/CT-BR study demonstrated that the hypothesis was correct, namely, that U-MDT (six months of treatment) offers patients the same benefits as R-MDT (12 months of treatment). Among the groups who received the standard treatment of MDT and those who received the treatment for only six months, the study found

1. No statistically significant difference between the groups regarding the fall of the BI of the MB patients;
2. No statistically significant difference between the groups regarding the frequency of leprosy reactions;
3. No negative impact on the satisfaction of the patients when clofazimine was introduced in the treatment of PB patients;
4. No statistically significant difference between the groups regarding the disability progression;

5. Similar and acceptable relapse rates among the groups.

No less important was the fact that the study broke a paradigm concerning leprosy re-infection, confirmed by the sequencing of the complete genome of *M. leprae.* Specifically, the study confirmed that a treated patient can be re-infected. This finding establishes that not all cases of apparent recurrence mean that the treatment was insufficient.

Regarding relapse/re-infection, the relapse rate of 2.6 per 1000 patients per year of follow up (95% CI [0.81, 6.2] per 1000) during the active follow-up period means that 0.26% of patients relapsed every year on average. Regarding passive follow up, the authors performed a sensitivity analysis, i.e., they estimated the rate using follow-up person-years, which results in an overestimation of relapses. The patients' BIs fell at the same rate for both groups. During the active follow-up, four patients in the U-MDT group relapsed and none in the R-MDT group. However, during the passive follow up, three patients in the U-MDT and one in the R-MDT relapsed. These findings reflect a relapse rate of 4.46 per 1000 for U-MDT and 0.44 per 1000 people for R-MDT. The low rate of relapse is very encouraging. However, it is vital that follow up continues for 10–12 years in research studies so that we know what the late relapse rate is.

The work of Balagon, who treated a high BI patient with a fixed dose regimen, shows that a patient's BI continues to fall without further antibacterial treatment, a very important finding (25). In the RCT in Brazil, the adverse effects were more frequent among patients who had taken 12 doses than among those who had taken six doses, and one case of DHS was documented. While there are considerable programmatic advantages in giving all patients the same anti-leprosy treatment, there are ethical concerns about using clofazimine when patients do not need it, especially when it has adverse effects. The main finding of the trial—that six doses of rifampin is sufficient to treat all patients with a low relapse rate—represents major progress. Another critical finding from the study was that 70% of the patients with a high BI had immune-mediated reactions (Type 1 and ENL) and neuritis. This finding emphasizes the importance of recognizing and treating these complications.

A large study has also been conducted on U-MDT in India and China (42) in which 2091 PB and 1298 MB patients were given U-MDT (43). Patients have been followed up for five years. The clinical improvement rates for the PB patients were as follows: Forty-two percent (42%) had inactive lesions, 55.4% had improved, and 2.6% were static. By three years, the percentages were 0.2%, 12.1%, and 87.7%, respectively, and, by five years, 0.5%, 8.4%, and 91.2%. For the MB patients, the inactive, improved, and static rates were 10.4%. 84.9%, and 4.7% at treatment completion; 72.4%, 26.8%, and 0.8% at three years; and 80.7%, 18.2%, and 1.1% at five years. The reported adverse effects rate was 0.79 for PB patients and 2.64 for the MB patients. Patients' hemoglobin levels do not appear to have been measured, so some adverse effects might have been missed. Finally, the fall in BI for the MB patients was not reported. These studies show that U-MDT is associated with short-term clinical effectiveness and a low relapse rate. This approach should also be used to test regimens that are less toxic, such as ROM.

Second-Line Drugs

Several new drugs that are bactericidal for *M. leprae* have been identified: fluoroquinolones, minocycline, and clarithromycin (see Chapter 5.2). The fluoroquinolones perfloxacin and ofloxacin have a remarkable degree of bactericidal activity, with 22 daily doses killing 99.99% of viable *M. leprae* present in MB cases at the start of treatment (44). Daily minocycline (100 mg) treatments of MB patients for three months killed all viable *M. leprae* organisms (45). Clarithromycin, given in 500 mg daily doses to MB patients, has a similar bactericidal effect (46). Antagonism between these new drugs has not been demonstrated (47). Ofloxacin, minocycline, and clarithromycin are established second-line drugs. Minocycline may also cause hyperpigmentation of skin lesions, so it may not be an appropriate substitute for clofazimine if pigmentation is to be avoided (48).

Rifampin, Ofloxacin, and Minocycline (ROM) Regimen

The high rates of adverse effects seen with patients treated with the WHO MDT regimen has led to the development of a triple-drug combination of rifampin, ofloxacin, and minocycline (ROM) which can be given as a single monthly dose for six or 12 months. A systematic review has assessed 14 studies comparing ROM with MDT (49). Only two studies have been conducted using multiple doses of ROM for LL. Villahermosa et al. (50) have conducted a study in the Philippines that compared 21 patients with BL and LL. These patients were given either monthly ROM (n=10) or the standard MDT (n=11), which consisted of monthly doses of rifampin (600 mg) and clofazimine (300 mg), with daily doses of dapsone (100 mg) and clofazimine (50 mg) for 24 months. These patients had a mean BI of 4 (range 2.7–5.1) at entry to the study, which fell to 1.18 (range 0–3.5). The patients assigned to the WHO MB-MDT had similar falls in their BIs. Patients' skin lesions improved (measured by a score), as did the histological appearance of their skin biopsies during treatment. A study done in Brazil (51) had a similar design, allocating patients to either monthly ROM or MB-MDT. These patients mostly had LL. Both groups had a similar fall in BI (3.5 to 2.5) after 24 months of treatment, as well as similar clinical and histological improvements. In the Philippines study, the BI continued to fall after the completion of antibiotic treatment and no relapses were recorded during the subsequent 64 months. No toxicities were recorded in patients receiving ROM, whereas all patients who were on the WHO-MDT developed clofazimine-induced pigmentation.

In a 2001 study, Kumar randomly allocated 268 patients to either ROM or MDT, with cure rates of 99% for the ROM-6 and 97% for the PB-MDT group (52). Ten patients relapsed over the 5–8 year follow up, which shows that ROM and PB-MDT have similar cure and relapse rates. However, the rate of adverse effects was much lower in the patients receiving ROM, which is a benefit of that

treatment. Only a small study has been conducted on patients with MB leprosy (26). In this study, 19 patients who were started on ROM treatment were observed after treatment. Their skin lesions continued to improve even though they were not receiving active treatment.

These promising results confirm that an alternative regimen to MDT needs to be tested soon (53). Large trials could compare six-month U-MDT and six-month monthly ROM treatments. I anticipate that the cure rate would be the same for the two groups. This trial would provide important data on the clinical efficacy of ROM. Additionally, the cost-effectiveness of a ROM regimen would have to be assessed.

There are concerns that many patients do not complete their MDT, which partly explains the failure to recognize a high level of adverse effects. Furthermore, there have been very few systematic studies of compliance in leprosy. One study in North India registered a default rate of 28.8%, with a rate 34.0% for MB patients in particular (54). One study in Hyderabad, India, found that only 50% of patients who were attending clinics had dapsone metabolites in their urine or indicated their compliance with leprosy treatment on a questionnaire (55, 56). This finding highlights the potential problems with compliance.

The work done to shorten the MDT regimen is very encouraging. However, it is vital that new regimens with lower toxicity profiles be tested soon. The challenge of leprosy studies is that, on one hand, more care must be taken for patient safety but, on the other hand, the studies take place in low resource settings.

Summary

Following the rationale of TB treatment, if we want to control leprosy, we must reduce the treatment time by implementing a U-MDT. The four studies in China, India, Bangladesh, and Brazil have demonstrated that U-MDT is an acceptable option and can be adopted in endemic countries to treat leprosy patients. On the other hand, we need a new uniform regimen that does not include dapsone or clofazimine.

- If a shorter regimen is to be introduced, then more attention needs to be paid to the diagnosis of leprosy. Counting lesions will no longer be needed for classification; however, health workers will need to be better trained to recognize leprosy. In particular, they will need training to perform slit-skin smears so that patients' bacterial loads can be assessed.
- More effort needs to be made to ensure that patients taking a shorter regimen adhere to that regimen.
- The detection of nerve damage, which has been overlooked in the current WHO pauci/multibacillary classification, must be improved.

- The importance of reactions in the long-term outcomes for leprosy patients is being forgotten in the discussions about U-MDT. It is vital that patients are adequately assessed and warned about complications that will occur after a six-month treatment period. This stipulation applies to both reactions and nerve damage.
- It is vital that national leprosy programs be able to detect and treat patients who develop complications post-treatment.
- Too little attention has been paid to the accumulating evidence that dapsone causes significant toxicity. There are multiple case reports and a systematic review that relate deaths associated with dapsone. We therefore need a less toxic regimen urgently. The ROM-based monthly regimen would be less toxic and needs to be assessed.

The treatment of leprosy with MDT, in which effective drugs are being delivered free of charge to the poorest populations, has been a huge success story for the WHO. This effort needs to be maintained and improved over the next decade.

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