REPORT

MULTIDRUG RESISTANT TUBERCULOSIS

MDR TB

Basis for the Development of an Evidence-based Case-Management Strategy for MDR TB within the WHO’s DOTS Strategy

Proceedings of 1998 Meetings and Protocol Recommendations

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DOTS-Plus Executive Summary

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The World Health Organization (WHO) DOTS strategy for the management of tuberculosis (TB) cures the majority of TB patients and prevents new drug-resistant cases from arising. DOTS is a five-component policy package acknowledged by the World Bank as one of the most cost-effective interventions in human health. Patients with multidrug resistant tuberculosis (MDR TB) are generally not cured by standard 4-5 drug short-course chemotherapy, the cornerstone of DOTS. Thus, significant further transmission of MDR TB may still occur in DOTS-based countries. The potential spread of MDR TB could be a threat to the success of DOTS. In industrialized countries, management of MDR TB is based on the use of tailored treatment regimens with second-line drugs according to the patient’s drug susceptibility pattern. However, no conclusive evidence at programme level is yet available on how feasible the use of these regimens would be in low and middle income countries.

Following the release of the WHO/IUATLD Global Report on Drug Resistance Surveillance in 1997, two meetings were convened in 1998 to analyze the magnitude and impact of MDR TB on the control of TB and to discuss potential case-management strategies to address it. These meetings, held in Cambridge, United States, and in Geneva, Switzerland, were followed by the preparation of two protocols for the management of MDR TB. The conclusions of these meetings along with the protocols form the basis of what is now called “DOTS-Plus” for MDR TB management.

DOTS-Plus is a case-management initiative, in the testing phase, designed to manage MDR-TB within the DOTS strategy in low- and middle-income countries. The feasibility and cost-effectiveness of individualized and standardized treatment regimens of second-line anti-TB drugs will be tested. Pilot protocols will be introduced in specialized units of countries with strong DOTS programmes or countries with high levels of MDR TB that have successfully started a DOTS programme. The introduction of these protocols should be complemented, at the same time, with drug resistance surveillance within the WHO/IUATLD Global Project. Upon review of the feasibility and efficacy data generated by these protocols, a task force convened by WHO will draw appropriate policy guidelines and recommendations on the management of MDR TB.

Two studies have been implemented in Peru. One, at the district level, is funded by Partners in Health, an NGO associated with Harvard University, and uses individualized regimens based on second-line drugs. The other, countrywide, is led by the National TB Control Program and uses standardized regimens based on second-line drugs. Replication of these two studies in different settings is the next step in generating sound policy recommendations that could be inserted within the framework of the national TB control programmes of Member States.
Community-Based Approaches to the Treatment and control of Multidrug Resistant Tuberculosis

*Cambridge, MA, USA*
*4-5 April 1998*

*Proceedings*

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Executive Summary

On April 4th and 5th, 1998, Harvard Medical School’s Program in Infectious Disease and Social Change (PIDSC) convened 50 tuberculosis and public health experts to re-examine current TB-control policies in the light of new epidemiological and clinical research. The meeting, entitled “Community-Based Approaches to the Treatment and Control of Multidrug-Resistant Tuberculosis,” was co-sponsored by the World Health Organization’s Global Tuberculosis Programme, the American Academy of Arts and Sciences, and Partners In Health, a US-based and TB-focused non-governmental organization working predominantly in Latin America. Also present were representatives of the North American branch of the IUATLD, key foundations, multilateral aid agencies, and the pharmaceutical industry.

Rationale

TB remains the world’s leading infectious cause of adult deaths, the majority of which are due not to multidrug-resistant tuberculosis, but rather to lack of access to effective and rationally delivered therapy for drug-susceptible TB disease. New data suggest, however, that MDR-TB is emerging as an increasingly important cause of morbidity and death. In the United States, Europe, and Latin America, highly resistant strains of TB have caused numerous explosive institutional (hospital, prison, and shelter) outbreaks, with high case-fatality rates among the immunosuppressed and high rates of transmission to immunocompetent caregivers. Even more disturbingly, the WHO/IUATLD global survey of resistance to antituberculosis drugs now reveals that MDR-TB has already become established in almost all participating countries. Unfortunately, therapeutic options have been limited for most persons afflicted with MDR-TB, in large part because of the cost of the medications. But new clinical experience in Latin America—along with new surveillance data, the chief impetus for the meeting—suggests that MDR-TB can be treated even under adverse field conditions in resource-poor countries. With these developments in mind, the institutions organizing the April meeting sought to rethink existing global TB-control strategies, which had focused solely on the establishment of successful national TB programs based on DOTS. Although the majority of presentations cannot be adequately summarized here, highlights of the meeting are summarized below.

Agenda

The agenda for the two-day meeting was developed by the PIDSC and the WHO GTB over the course of the months prior to the meeting. Dr. Arata Kochi, director of the WHO GTB, opened the meeting by laying out the goals for the conference: to assess the scope and dynamics of the emerging MDR-TB problem, the strengths and limitations of existing control strategies, and the potential contribution of community-based treatment efforts. In the meeting’s first formal presentation, Dr. Paul Farmer (PIDSC, Partners In Health, [USA]) noted that, since the presence of MDR-TB signals TB-program failure, the key desideratum in global TB control remains the adoption of a successful DOTS program. In settings in which MDR-TB has already become established as a problem, however, Farmer signaled three reasons that DOTS alone would be insufficient: 1. those already ill with MDR-TB will not be cured with isoniazid- and rifampin-based short-course chemotherapy; 2. nosocomial transmission is likely when patients with
untreated MDRTB continue to seek care in clinics and hospitals; 3. patients with primary resistance to isoniazid and rifampin who receive standard, short-course chemotherapy are likely to develop resistance to pyrazinamide and ethambutol as well. Since empiric retreatment regimens are often based on the same four drugs plus a short course of streptomycin, patients initially resistant to two drugs may become resistant to as many as five. This was termed the “amplifier effect of short-course chemotherapy,” and mentioned its contribution to a large MDRTB outbreak in urban Peru, where the PIDSC-Partners in Health group has been working.

Dr. Mario Raviglione (WHO GTB) then reviewed the results of the WHO/IUATLD global survey of resistance to antituberculous drugs. The survey showed MDRTB to be present in 34 out of 35 countries assayed. In several of these countries—including Russia, Estonia, Latvia, Côte d’Ivoire, and the Dominican Republic—“hot zones” of ongoing MDRTB transmission have been identified. There was a clear association between failure to follow WHO guidelines and high rates of MDRTB; the survey was thus able to identify countries in which an increase in MDRTB was likely given current program conditions. Raviglione closed by underlining the importance of ongoing surveillance of drug resistance.

Dr. Sally Blower (University of California, San Francisco [USA]) used a mathematical model to project likely scenarios in the event non-eradicating TB control is pursued. In a scenario in which the relative efficacies of treatment of drug-susceptible disease is high, while that of treating drug-resistant disease is nil, a short-term (50-year) surge in MDRTB is projected as likely. She warned that the model did not incorporate HIV co-infection, which could accelerate the natural dynamics of TB epidemics. Blower also raised the specter of “perverse” outcomes, through which antituberculous therapy creates more cases of resistance than it does cures. Finally, Blower presented a preliminary model of the amplification of resistance through the administration of empiric short-course chemotherapy and inadequate retreatment regimens to patients with MDRTB.

In the afternoon session, “Responding to MDRTB,” Dr. Sergio Spinaci (WHO GTB) and Dr. Marcos Espinal (WHO GTB) reviewed WHO TB policy, which when adopted has improved outcomes in settings around the world. Furthermore, adoption of DOTS programs can clearly prevent the emergence of acquired drug resistance: a key finding of the WHO/IUATLD survey was the association between poor program performance and increased MDRTB risks.

The effects of DOTS on MDRTB—and the effects of MDRTB on DOTS—were the subject of brisk debate. Several participants challenged claims that MDRTB will disappear with only the global establishment of DOTS programs. In some of the examples previously invoked to support this claim (from Algeria and parts of China, including Beijing), resistance to rifampin was not yet known or exceedingly rare when better control programs were introduced. In other countries that saw the inauguration of DOTS programs, one of two things occurred: rates of MDRTB either remained steady or increased. In Korea, for example, overall drug resistance has declined since the initiation of a good program. But the very paper reporting this finding reveals that rates of MDRTB have increased between 1980 and 1995. It was argued by various participants that, based on a critical re-evaluation of several studies, MDRTB incidence falls only in settings like New York City, where patients with active MDRTB are treated effectively—that is, with longer courses of second-line drugs, selected in keeping with drug-susceptibility patterns. In no setting in the world with an already established MDRTB problem have case rates fallen when DOT with short-course chemotherapy was introduced.
The afternoon sessions included reports from Russia, Mexico, and Peru. Dr. Alex Goldfarb (Public Health Research Institute [USA]) sketched the Soros Foundation-funded TB initiative in Tomsk, Siberia. Noting that current plans focused on attempts to introduce DOTS, he underlined the difficulties inherent in treating Russian prisoners with MDRTB. Dr. Lourdes García (Instituto Nacional de Salud Pública de México), reporting from the district of Orizaba, Mexico, made it clear that ongoing transmission of drug-resistant strains of *M. tuberculosis* was to be expected when effective therapy could not be made available. RFLP studies illustrate that some 10 percent of all linked cases are due to MDR strains, suggesting that patients with MDRTB—fully 11 percent of all patients in this cohort—were efficient transmitters of their disease. Similar conclusions were drawn by Mercedes Becerra (PIDSC, Partners In Health [USA]), who, working in urban Peru, demonstrated that MDRTB can emerge even in a setting in which DOTS had been well established: of 258 patients who had failed DOTS or were close contacts of patients with drug-resistant disease, more than half (55%) were confirmed to have MDRTB. Becerra’s data, which draws on techniques in both conventional and molecular epidemiology, suggests high rates of intrahousehold MDRTB transmission within households and clinics. Furthermore, amplification of primary resistance through repeated courses of DOTS was demonstrated in two thirds of a smaller cohort of more than 50 patients with disease due to highly resistant strains.

Dr. Jaime Bayona, also representing PIDSC and Partners In Health, reported on a novel attempt to treat patients with MDRTB in northern Lima. This effort has been conducted in cooperation with Peru’s highly successful National Tuberculosis Programme (NTP). Working largely with poor families living in a slum, this community-based effort had initiated directly observed, individualized therapy for more than 50 patients with longstanding disease. Most of the cohort are resistant to all four of the drugs used in Peru’s NTP; most were also resistance to streptomycin, which is used in empiric re-treatment regimens. The majority of patients were *crónicos*, with significant parenchymal destruction when they entered treatment through the Partners In Health project. Using aggressive, individualized treatment regimens, however, 100 percent of patients smear-converted, and 85% percent remain smear- and culture-negative a year into treatment. With community-based therapy, noted Bayona, nosocomial transmission can be interrupted; the team estimated that after only 18 months of operation over 400 new infections had been prevented. The group has also drafted a handbook, *Responding to Multidrug-Resistant Tuberculosis*, offering detailed algorithms for the management of common complications of both the disease and the therapy.

Dr. Michael Iseman (National Jewish Medical and Research Center [USA]) responded to the presentations by noting that, of the various options, cohorting and isolation would seem to be the least defensible policy in an era in which our therapeutic armamentarium, though weak, contains drugs that can cure a majority of patients infected with MDRTB. Dr. Jennifer Leaning (Harvard Center for Population and Development Studies [USA]) expressed similar reservations, noting that her own experience in Russia led her to believe that many citizens saw the management of TB among Russian prisoners as a “test case” in the quest for more humane public-health policies.

Dr. Iseman added that he had ample reason to believe that patients with MDRTB would not respond to short-course chemotherapy based on the very drugs to which patients had demonstrated resistance. When empiric retreatment strategies based on short-course regimens of first-line drugs succeed, it is precisely because most relapsed patients do not, in fact, have MDRTB. He argued that policies directing patients with *documented* resistance to isoniazid and rifampin for treatment with these drugs were wasteful and ill-advised. He also pointed out that
the clinical outcomes in the community-based effort in Peru seemed to be at least as good as those registered in U.S. medical centers, where long-term hospitalization and surgery have been central to the cure of many patients with similar drug-resistance patterns.

In the lively discussion that followed, the high cost of drugs proved the sticking point and the chief criticism of the Peru project. The PIDSC-Partners In Health group countered by noting that most of their patients with primary MDRTB had received repeated rounds of short-course therapy, each directly observed. These had served solely to "pick off" other first-line drugs from the roster of usable therapies, leaving these patients more difficult, and more expensive, to cure. Identifying incident cases of MDRTB and triaging them into individualized regimens can dramatically decrease costs and increase cure rates. Dr. Howard Hiatt (American Academy of Arts and Science, PIDSC [USA]) argued that a zero-sum approach to the MDRTB problem was unwise; a far larger investment in global TB control is clearly warranted. Other major meeting sponsors, including the Rockefeller Foundation and Eli Lilly and Company, agreed that new resources needed to be devoted to the control of MDRTB.

By the end of the afternoon, most agreed that there were clearly settings in which DOTS alone was insufficient; complementary efforts to treat MDRTB would be desirable in MDRTB "hot zones" with the technical capacity and political will necessary for success. Kochi agreed, noting that what was called for in these instances might well be termed "DOTS-Plus."

The second day of the conference was dedicated to elaborating a "new social contract" that could build on the success of DOTS. Dr. Jim Yong Kim (PIDSC, Partners In Health [USA]) started the day by underlining the need for a new vision of TB control. Cost-efficacy analyses, he argued, do not capture the true strengths of community-based approaches to TB treatment and control, which have the beneficial effect of building local capacity for addressing the health and social problems that beset many communities in which TB is endemic. He detailed the experience of Partners In Health in urban Peru and rural Haiti, where the yield on health-care investments in poor communities is as evident in increased local capacity as in morbidity and mortality data. Community capacity-building should be a central part of TB-control strategies, he argued. Kim concluded by noting that, although treating MDRTB was costly, it was far less so than not treating it. He closed by echoing Kochi's call for "DOTS-Plus" as part of a more ambitious plan for social stewardship.

In a talk entitled "Bringing New Resources to New Problems," Dr. Helene Gayle (U.S. Centers for Disease Control and Prevention) underlined the importance to disease control of sustained and broad-based advocacy. The science on TB is good, she noted; the plan of action, sound. But because aggressive treatment of MDRTB would require a significant infusion of new resources, the endeavor needed advocates outside of the TB and public health communities. Gayle offered as example the efforts to eradicate guinea worm, which have garnered relatively greater resources than TB (given guinea worm's smaller global disease burden and a more focal area of endemicity) in large part because of the efforts of a small group of vocal advocates. Insufficient effort has been invested, Gayle argued, in making the TB pandemic the focus of public concern.

In one of the closing presentations, Dr. Margaret Hamburg (U.S. Department of Health and Human Services) echoed many of these themes by speaking of her own experience as Commissioner of Public Health during the New York City MDRTB epidemic. While it was clear from the outset that the decay of the TB care and control infrastructure had contributed to the gravity of the problem, it was not until the efforts of the public health community were backed by the clout of political figures and the support of other sectors, including organized labor, that
sufficient funds were made available for aggressive TB treatment and control. Thus, political pressure and broad-based support were central to the success of efforts to rein in the New York MDRTB epidemic. This positive outcome was also founded on an improved capacity to identify patients with MDRTB and alter therapy accordingly.
Conclusions

With a certain consensus reached, participants turned to the task of elaborating meeting conclusions. First, all patients with active TB, regardless of drug-susceptibility patterns, have a right to therapy. It was further underlined that "resistance to anti-tuberculous agents is an urgent problem demanding prompt attention. The present situation calls for a focused and concerted effort which, in tandem with the global implementation of DOTS, can bring the eradication of tuberculosis, thus far elusive, finally within our grasp." Those in attendance agreed that a "DOTS-Plus" approach to MDRTB would be most likely to succeed in a setting in which DOTS was already established or in the process of implementation. It was resolved that efforts to replicate the successful community-based program in Peru would be one prudent way to begin.

To help to initiate and oversee these pilot projects, it was further resolved that a new WHO Task Force on MDRTB was to be created. The goals of the Task Force are straightforward, if challenging: to bring new resources to TB; to identify sites in which to replicate the community-based approach to MDRTB control; to place the requisite technical assistance at the service of these and other pilot projects. The clinicians present, including Dr. Iseman, signaled their willingness to participate. The PIDSC/Partners In Health handbook on community-based treatment was identified as a document meriting further development as a tool for these endeavors. Sir John Crofton (University of Edinburgh [UK]) was asked to chair the Task Force; he, in turn, asked Hiatt to chair a "resources subcommittee." It was agreed that the new body should report to the WHO GTB, and that its members would meet in Geneva within three months.

Dr. Lee Reichman (National Tuberculosis Center [USA]) gave the final formal presentation, "The Unusual Suspects." He noted that one of the few heartening signs in TB control was the recent involvement of people without formal public health or clinical training, mentioning as an example the "Princeton 55" initiative headed by Ralph Nader and others new to the struggle against TB. As regards the importance of timing to an initiative designed to fight MDRTB, he cited a U.S. colloquialism: "You can pay now, or you can pay later." And the costs, Dr. Reichman noted, would only rise with delay.

Finally, Dr. Hiatt yielded the floor to Dr. Kochi, who underlined his satisfaction with the meeting, which represented a "sea change" in TB control. The WHO had previously used MDRTB in developing countries "chiefly as a scare tactic. We have to think about MDRTB in a new way. In the past, we have seen it as a virtual death sentence for the people in the developing countries, but now we can give people hope of a cure." Furthermore, Kochi agreed with the proposal that community-based disease control might also serve to strengthen the capacity of vulnerable communities to initiate projects ranging from family planning to micro-enterprise efforts.

In summary, the April meeting on community-based approaches to MDRTB treatment and control yielded the following conclusions:

DOTS is the central element of the Global TB Control Program:

- It is recognized by the World Bank as one of the most cost-effective of all health interventions and is a highly effective means of treating to cure;
• It substantially curtails the generation of acquired drug resistance, and—eventually—can
decrease primary drug resistance by curing over 90% of infectious, detected tuberculosis
cases as demonstrated in various settings including Peru and Beijing. In New York City the
extension of coverage with DOT (from 4.3% in 1990 to 33% in 1994), improved completion
rates (from 60% in 1991 to 89% in 1994), and individualized treatment of MDRTB led to a
reduction in drug-resistant tuberculosis; and
• It may lower the incidence and prevalence of TB.

DOTS, however, will not perform adequately among patients with MDRTB:

• It has been demonstrated to achieve only sub-optimal cure rates among those with resistance
to isoniazid and rifampin; and
• Although conclusive evidence has yet to be published, use of standard short-course
chemotherapy in high-MDRTB-prevalence settings may “amplify” resistance to ethambutol,
pyrazinamide, streptomycin, and other empirically deployed agents.

Surveillance must be an integral part of MDRTB control:

• Support should be garnered to enhance the ability of the supranational lab system to conduct
ongoing surveillance.
• Further laboratory collaboration between resource-rich regions (often low-prevalence
countries) and MDRTB “hot zones” should be fostered.
• Results from surveillance must guide MDRTB treatment strategies and must inform
approaches to prevention of further resistance.

Failure to manage/treat patients with MDRTB has multiple potentially damaging implications:

• Active MDRTB leads to the suffering and death of patients;
• Resistant strains are spreading to contacts in homes, schools, workplaces, and health-care
settings. This ongoing transmission sustains endemicity of drug-resistant TB;
• MDRTB epidemics may be dramatically potentiated by HIV; nosocomial outbreaks have
been explosive, lethal, and difficult to control; and
• Failure to control MDRTB demoralizes health-care workers and exposes them to
unacceptable occupational risks.

The clinical effectiveness of the current WHO guidelines for retreatment and treatment of MDR
has yet to be demonstrated:

• WHO is currently exploring the efficacy of standardized and individualized therapy for
MDRTB;
• WHO will continue to provide consultative support for national programs will to be involved
in such efforts;
• The success of the two approaches (standardized and individualized regimens) in lab-
confirmed cases of MDRTB must be demonstrated in several settings. In particular, it is
important to ensure that standardized therapy, if implemented in settings in which baseline
levels of resistance are elevated, will not further increase resistance.
Effective control of ongoing MDR-TB outbreaks requires new strategies. Since DOTS-based programs remain the key desideratum for global TB control, new and enhanced programs might well be termed “DOTS-Plus.” The features of such a program would be as follows:

- Would be best initiated in settings where DOTS has been adopted;
- Must bring substantial new resources to TB control; and,
- Should incorporate community-based approaches for three reasons: to decrease nosocomial transmission, reduce treatment costs, and enhance local community capacity.

A DOTS-Plus program based on individualized treatment of MDR-TB is a complex process. It will require:

- Linkage with a country’s NTP;
- Specialized clinical expertise;
- A surveillance component;
- High-quality laboratory support;
- An uninterrupted supply of all second- and third-line drugs; and
- Adequate personnel/resources to deliver care in home or other institutions/facilities.

To these ends, those present at the April meeting agreed that a new Task Force on MDR-TB should be convened within three months. Such a body should be composed of two central committees: a technical committee and a “resources” committee. Participants also agreed that the Task Force should report to the WHO GTB.
References


List of Participants

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Executive Summary

High levels of multidrug resistant tuberculosis (MDR TB) have been found in some developing countries/geographic areas. The current World Health Organization (WHO) DOTS strategy has been largely successful, with cure rates of over 90% in some countries. Nevertheless, full success in controlling TB will depend on controlling MDR TB. The trends in the extend of MDR are not yet available. Effective DOTS programmes should prevent the development of new cases of MDR and so reduce its prevalence. But where there are many infectious cases of MDR resulting from previous poor treatment or from treatment outside the national programme, these can continue to spread the most dangerous form of the disease.

Accordingly the WHO Global Tuberculosis Programme (GTB) convened this meeting to discuss and outline a management strategy to address MDR TB. Discussions focused on (i) the expansion of drug resistance surveillance (DRS) efforts by WHO/IUATLD, (ii) the presentation and review of two treatment protocols based on either a standardized regimen (WHO/IUATLD) of second-line drugs or an individualized regimen (Harvard Group), and (iii) on advocacy and fund-raising efforts. The meeting concluded that:

1. DOTS, the WHO strategy for TB control, which represents the organizational framework for the effective utilization of the available tools in identifying and curing patients, is the cornerstone of TB control and should be adopted by countries as the first step before launching a management initiative specific to MDR TB.

2. Since an increasing number of countries (96) are adopting DOTS now, WHO should explore innovative strategies to address MDR TB, as a public health threat to the control of TB.

3. DOTS-Plus is a management initiative designed to address MDR TB that consist of (i) DOTS, the WHO strategy for TB control, and (ii) pilot treatment protocols based on individualized or standardized treatment regimens of second-line anti-TB drugs.

4. Pilot projects based on individualized or standardized treatment regimens of third-line anti-TB drugs should be launched in specialized units of countries with strong DOTS programmes and countries with high levels of MDR TB which are successfully starting a DOTS programme. The implementation of these pilot projects should not proceed without the approval and support of the relevant governments.

5. Countries not implementing DOTS should not attempt to launch pilot projects of MDR TB management.

6. Upon review of the feasibility and efficacy data of the pilot projects, WHO will draw appropriate policy guidelines and recommendations on the management of MDR TB.
7. WHO/IUATLD efforts on expansion and assessment of trends in prevalence of Drug Resistance within the WHO/IUATLD Global Project on Drug Resistance Surveillance (DRS) are strongly supported.

8. WHO will continue to support the efforts of the advocacy/fund-raising committee, which aims to launch pilot projects based on both individualized or standardized regimens of second-line drugs.
Introduction to Meeting

The World Health Organization (WHO) and the International Union against Tuberculosis and Lung Diseases (IUATLD) joint Global Project on Drug Resistance Surveillance (DRS) in 35 countries/geographic areas recently reported that drug resistance tuberculosis (TB) is present everywhere and that primary multidrug-resistant (MDR) to at least rifampicin and isoniazid is a serious problem in some of these countries/areas. Among these countries/areas, Latvia (14.4%), Estonia (10.2%), Dominican Republic (6.6%), Ivory Coast (5.3%), Argentina (4.4%), and Russia (Ivanovo Oblast) (4%) were classified as “Hot Spots” for MDR TB. Furthermore, rates greater than 2% of primary MDR TB were found in 54% of the countries not implementing DOTS as compared to 22% of the countries implementing it in over 90% of the population.

The DOTS strategy, the WHO policy package for TB control, recognized by the World Bank as one of the most cost-effective of all health interventions, can prevent the upsurge of MDR TB by curing over 90% of TB infectious cases, as shown in various settings including Peru, China, and New York. While DOTS cures the majority of TB patients and prevents new drug-resistant cases from arising, patients with MDR TB are generally not cured by standard 4-drug short-course chemotherapy. Therefore, significant further transmission of MDR TB could continue to spread.

In developed countries MDR TB is managed with individual tailoring of third-line drug regimens and strong laboratory support for drug susceptibility testing (DST). A study using this approach is being carried out in Lima, Peru. However, the feasibility of a wider implementation and the efficacy of this approach in developing countries have yet to be proven. Therefore, other specific management strategies might be necessary to address MDR TB as a public health threat in low-income countries. These include standardization of third-line drug regimens for chronic TB cases, likely MDR-TB cases, in order to maximize resources and overcome the lack of DST.

A conference co-sponsored by WHO and held on 4-5 April 1998 at Harvard University, Cambridge, USA, to review the dimensions and dynamics of MDR TB and discuss strategies to address it, concluded that the problem demands substantial increase in global investment in TB control.

In light of the above, the Global Tuberculosis Program (GTB) of WHO has convened this meeting to review the recommendations of the Harvard Meeting, to discuss and outline the next steps to address MDR TB, to discuss feasibility treatment protocols, and to outline advocacy/fund-raising efforts.

Proceedings

Dr. M. Espinal of the Surveillance, Epidemiology, and Respiratory Health Unit (SEP) of GTB presented the current priorities of the WHO/IUATLD Global Project on DRS. Surveillance of MDR TB is being extended to include both trends in countries that have already reported and collection of more representative data in countries with a major TB burden including China, Russia, Nigeria, and India.
Two study protocols (annex) aiming to assess the feasibility and efficacy of MDR TB treatment programmes in developing countries based on third-line drugs were then presented and discussed. One was based on individualized treatment of MDR TB cases in the light of a detailed treatment history and results of DST for each patient. The other was a proposed standardized treatment regimen for chronic TB patients (likely to have MDR TB).

Drs P. Farmer and J. Kim from the Harvard group presented the general concepts of their protocol reporting on the individualized MDR TB community-based treatment program in urban Peru. This project is carried out by a local Non-Governmental Organization (NGO) in conjunction with the National TB Programme. It includes support to patients - both technical and social. Although preliminary data from 55 patients are encouraging, showing 83% smear conversion, the sample is still too small and the results too preliminary to draw final conclusions. Final data from this project should provide useful information on which to make appropriate recommendations for the management of MDR TB in developing countries. Replicability and cost-effectiveness assessment of this programme should follow. In order to replicate this protocol, the authors will revise it in the light of suggestions and comments made in the meeting. Substantive comments were two: first, it was suggested that an end point for treatment completion be selected (rather than stating that the regimen length will be “at least 24 months”). The second comment was to standardize the case definition with regard to retreatment cases failing standard short-course chemotherapy. It was felt that this protocol could be generally suitable for middle-income countries.

A second draft protocol to evaluate the effectiveness of a standard regimen for the third line treatment of chronic excretors (likely MDR TB) of acid-fast bacilli was prepared and presented by Dr H. Rieder, IUATLD, who was contracted by WHO to develop such a protocol. This protocol addresses only countries in which the diagnosis of TB is based on the microscopy examination of spontaneously expectorated sputum specimens. Thus, for the purpose of enrolment, sputum smear-positivity must be persistent. The suggested standard regimen is capreomycin (CM), ethambutol (EMB), pyrazinamide (PZA), ofloxacin (OFL), and ethionamide (ETH) for 3 months followed by a continuation phase of EMB, OFL, and ETH for 18 months. Since ethambutol (EMB) is recommended in both the initial and continuation phase of first-line treatment and second-line retreatment regimens, resistance to EMB is therefore a risk. One suggestion was that EMB should be replaced by paraaminosalicylic acid (PAS) because the PAS granules produce fewer side effects than CSN. Difficulties include its expense, bulk, and the requirement for cold storage. It was pointed out that regimens using both EMB and PAS quite commonly produce hypothyroidism, but the suggestion is that PAS should replace, not supplement, EMB. One suggestion was that an arm of the study of the WHO/IUATLD protocol might be supplemented with vaccination with M. vaccae, but this was left open. This protocol will be also revised in light of the previous comments and suggestions. It could be suitable for low-income countries.

It was agreed that implementation of a pilot program of any regimen should be carried out by a specialized unit where it could be more carefully controlled. In the case of the Harvard Protocol, routine DST is necessary, as it involves individualized treatment decision. On the other hand, in the case of the WHO/IUATLD protocol,
DST should be included with the primary objective of defining the causes of failure rather than as a basis for treatment of individual patients. Cost of the standardized regimen for MDR-TB would be about 2,500 $US per patient, compared to 15-30 $US for standard treatment (first line). Cost of the individualized approach was estimated as up to 8,000 $US (for the most expensive regimen used in Peru for an individual patient).

Following the presentation of the proposed protocols, a very helpful and detailed account of all the reserve drugs and side-effects based on the experience acquired by the National Jewish Medical & Research Center was presented by Dr M. Iseman.

The meeting put emphasis on the importance of only initiating pilot projects in DOTS countries. Thus, the appropriate name for this initiative should be “DOTS-Plus”. It was also agreed to test both protocols. The individualized regimen approach currently under application in Peru should provide final results, undergo cost-effectiveness analysis, and be replicated in other settings. The standardized regimen approach should also be tested in several settings and cost-effectiveness analysis produced. Each protocol might be appropriate to different kinds of countries (e.g., individualized approach in middle-income countries and the standardized approach in low resource countries). Analysis and review of the feasibility and cost-effectiveness data provided by pilot projects should follow and appropriate recommendations regarding the management of MDR TB made.

Possible countries considered.

It was recommended that pilot projects to test the treatment protocols (individualized and standardized) should be implemented in DOTS countries only. Target countries to test these protocols will be those with (i) strong DOTS control program, and (ii) those successfully starting DOTS where high levels of MDR TB due to previous mismanagement are detected. Final decision to implement the protocols will be responsibility of the governments of the potential countries.

Individualized approach:

Possibilities include Ivanovo Oblast and Tomsk Oblast in Russia. Also, Latvia, Kazakhstan, Vietnam, and Peru (currently under implementation).

Standardized approach:

Suggested possibilities were South Africa, Malawi, Zimbabwe, Leningrad Oblast (Russia), Vietnam, Peru, and IUATLD model programmes.

Exploring possible suitable sites for pilot projects

Participants at the meeting will explore informally the suitability and interest of countries. They were asked to make clear, however, that this was an informal approach, which would not guarantee the ultimate choice of these settings. The main purpose of this exploration is that when a short list of countries was developed, representatives of the governments of these countries would be approached to discuss
the feasibility of launching pilot projects and to finalize appropriate protocols. Further meetings should then be specific to particular pilot projects.

Resource and Advocacy

Dr H. Hiatt, chairman of the advocacy fund-raising committee reported on the progress in approaching numerous potential donor bodies. Some of these have very specific interest in community building.

The preliminary approaches were based mainly on gathering resources for potential replication of the individualized approach carried out in Peru. As a result of this discussion, however, it was also agreed that funding would be sought for both types of projects (individualized and standardized). These approaches to donors have a major potential advocacy impact for the global control of TB in general. It was concluded that efforts to raise resources should continue unabated. It was made clear, though, that particular countries or areas should not be publicized as potential pilot project sites before the governments and professionals of the host countries agree with the possibility of such involvement. It was agreed that, in light of the discussion, the advocacy fund-raising committee could approach potential donors with the support of WHO.

Next Steps

1. The authors in the light of the discussions and any further thoughts will amend the draft protocols reviewed at this meeting. It was suggested that each technical report should have an appendix on important criteria for selection of a country implementing such a program (e.g., DOTS should be in place, local laboratory capacity for culture and susceptibility testing). A Revised Version of both protocols should then be sent to WHO.

2. The advocacy fund-raising committee lead by Dr H. Hiatt will continue its efforts to support the implementation of pilot projects of both treatment approaches.

3. WHO/IUATLD and the Harvard Group will explore the suitability of potential countries to launch pilot projects.

4. Further meetings to discuss DOTS-Plus should be country specific. An informal meeting of those participants attending the Bangkok IUATLD meeting should be considered.

5. WHO would decide the overall composition and chairmanship of a formal working group or task force after appropriate consultations.
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Background and introduction

A report commissioned by the World Health Organization (WHO) outlines the problems associated with the treatment of chronic tuberculosis cases. A large proportion of such cases harbor strains resistant to both isoniazid and rifampicin (defined here as multi-drug resistance (MDR)) and would probably fail another course of treatment [1]. Since these patients would have failed a standard International Union Against Tuberculosis and Lung Disease (IUATLD) / WHO first-line treatment regimen not containing rifampicin in the continuation phase and a second-line retreatment regimen containing rifampicin throughout in order to be classified as chronic tuberculosis patients, therapy for these patients could be considered third-line treatment.

In industrialized countries, where susceptibility testing and drug serum monitoring can be routinely performed, drug regimens can be tailored to individual patient situations. However, it is argued that, in countries where such testing either cannot be performed or is unreliable, a standard third-line regimen be considered for national programs capable of implementing such a policy. Given the relative lack of the required drugs, the regimen also would fit well with the finding by Goble et al. that, regardless of susceptibility test results, the most successful regimens were those which included multiple drugs which the patient had not previously received [2]. The low number of reserve drugs available imposes obvious limits on the potential range of effective drug combinations available for treatment of chronic excretors.

With an individual approach, selecting from the whole array of available drugs with activity against *Mycobacterium tuberculosis*, it is apparently possible to obtain persistent sputum smear conversion in a large proportion of cases as shown in Northern Lima, Peru [3]. Nevertheless, an individual approach requires particularly tight control, considerable resources, and sophisticated laboratory support. For this reason, a standard third-line regimen is proposed here that is likely to give reasonably good results, and is based on drugs which are expensive, but not as expensive as some that have been used in individual treatment in more affluent countries [2].

There is, at best, only empirical evidence supporting the use of such regimens. The addition of the epidemic with the human immunodeficiency virus (HIV) to the epidemiological picture and a desire for data to confirm these findings argues for a trial of such a regimen. The danger of rapid dissemination of MDR strains via highly susceptible HIV infected patients makes it particularly urgent to explore which regimens may be the most effective. This might vary between countries, depending on which of the more standard drugs have been used locally in unreliable combinations. In particular, ethambutol may be a less reliable reserve drug if it has been extensively used in an unsupervised continuation phase. The problem of multiple-drug resistant tuberculosis and therefore of chronic tuberculosis patients is a man-made one. In wild strains, fewer than one in $10^{12}$ *M. tuberculosis* organisms will be resistant to both isoniazid and rifampicin. Their relative proportion will only increase as the result of inadequate and improper use of anti-microbial agents, selecting surviving naturally resistant mutants. A number of reports have demonstrated how improper treatment increases the proportion of multiple-drug resistant cases and how the proper application of substantial resources can bring a rapid and significant reduction in the number and proportion of multiple-drug resistant cases [4-6]. While the importance of a third-line regimen for the treatment of chronic cases can not be denied on an individual, clinical basis, the most important contribution to the solution of the problem of chronic tuberculosis cases and multiple-drug resistance is going to come from improved program and individual case management.
Trials of third-line treatment regimens can have benefits beyond the simple evaluation of that regimen. Methods for the evaluation of the efficacy of new anti-tuberculosis drugs have been particularly troublesome. Studies of new drugs added to regimens for the treatment of multiple-drug resistance have often not been very informative because of the variability of the individually tailored regimens given to each patient. Often the patients in these studies had *M. tuberculosis* organisms which were already resistant to so many drugs that the new drug was the only one to which they were susceptible. The patient to patient variability in this type of salvage trial makes the results extremely difficult, if not impossible, to interpret. However, a trial of a standard third-line regimen treatment would provide an opportunity to randomly allocate patients to an alternative drug. If the drug was truly useful, i.e., bactericidal on the magnitude of isoniazid or rifampicin, then effects would stand out and could be detected with relatively small sample sizes. Such a trial would not only provide the benefit of confirming the efficacy of the standardized regimen but it could also provide important information on new compounds, early in their development cycle. As this proposal is written, there are very few, if any new compounds which might be justified for inclusion in such a trial.

In every national program designed on WHO / IUATLD guidelines there are patients who have failed on a first-line regimens (in some programs with, in some without, rifampicin in the continuation phase). These failures would have been treated subsequently with a standard second-line regimen with rifampicin throughout. [7-9]. For programmatic purposes, such patients remaining sputum smear-positive are said to be *chronic excretors*. It should be emphasized that in these programs many patients who received the second-line regimen will not necessarily have drug resistance. Those qualifying for the second-line regimen include relapses and returns after default. In others failure may have been due to inadequate supervision. The high success rate of the second-line regimen in many programs suggests that few of these patients harbored MDR bacilli. In addition, some of the apparent failures of the the second-line regimen may also have been due to inadequate supervision.

Accordingly, national programs following the WHO DOTS strategy / IUATLD model approach will have relatively small numbers who have genuinely failed the second-line regimen as the strategy has one of its primary objectives a drastic reduction in MDR. Theoretically, only those who had multi-drug resistant strains at the outset should appear as chronic cases at the end of retreatment. Usually, such cases must be given low priority in a national program out of necessity, because the resources required to treat such patients are prohibitive. As the comparison of regimens in appendix 1 shows, the least expensive third-line regimen is over 200 times as expensive as the least expensive first-line regimen and almost 100 times as expensive as a second-line regimen. It is thus unlikely that a third-line regimen can ever become a routinely available service in the poorest countries, unless vastly greater resources are made available internationally.

In some countries which have not had longstanding good national control programs most of the MDR cases would have resulted from poor treatment, either in a poor national program or by private practitioners. Although we do not yet have reliable data from the countries most at risk, on a global basis this category is (numerically and in practice) likely to present the greatest challenge to control.

It may be concluded from the above analysis that a standardized third-line regimen for chronic cases might have to differ, depending on the likely patterns of local resistance in
MDR cases. This applies in particular to MDR resulting from treatment outside a good national DOTS program.

A further consideration to the second-line regimen following a non-rifampicin containing first-line regimen should be made. While it matters probably little whether streptomycin or ethambutol is given as the fourth drug in the intensive phase, the companion drug of isoniazid in the continuation phase does. If this companion drug is thiacetazone, and the patient genuinely fails treatment, the likelihood that thiacetazone resistance (in addition to probably initial resistance to isoniazid) has been acquired is considerable. Nevertheless, the retreatment regimen will always contain at least two drugs (rifampicin and ethambutol in the continuation phase) to which the organism is still likely to be susceptible. In contrast, if the first-line regimen contains ethambutol as the companion drug of isoniazid in the continuation phase, ethambutol resistance may have been acquired in the continuation phase and the patient receives potentially effective mono-therapy (rifampicin) in the continuation phase of the retreatment regimen, increasing the probability of acquiring rifampicin resistance. The IUATLD has thus recommended for such a situation to use pyrazinamide throughout the second-line regimen [7]. Nevertheless, the choice of the second-line regimen, in turn, will also affect the choice of drugs in a third-line regimen.

Currently available first-line regimens (for sputum smear-positive patients at least, who receive every dose of rifampicin directly observed) recommended by WHO for category I patients [9] can be broadly categorized into two groups.

- Regimens with the four most potent drugs during a two-month intensive phase (isoniazid, rifampicin, pyrazinamide, and streptomycin or ethambutol as a fourth companion drug), followed by six months of isoniazid with thiacetazone or ethambutol as a companion drug.

- Regimens with the four most potent drugs during a two-month intensive phase (isoniazid, rifampicin, pyrazinamide, and streptomycin or ethambutol as a fourth companion drug), followed by four months of isoniazid plus rifampicin.

A re-treatment regimen (in the terminology of this protocol designated as “second-line regimen”) recommended by WHO and IUATLD for category II patients (relapse, treatment failure, and resumption of treatment after interruption) basically consists of:

- Eight months of isoniazid, rifampicin, and ethambutol, supplemented by pyrazinamide during the first three months, and supplemented by streptomycin during the first two months.

This second-line regimen is recommended by WHO irrespective of whether the first-line regimen included rifampicin throughout or not.

A patient is thus classified to have chronic tuberculosis (WHO category IV) if remaining sputum smear-positive after completion of a fully supervised second-line regimen. This protocol deals with the treatment of these patients.

It is, nevertheless, important to note, that true failures on a rifampicin-throughout first-line regimen are likely to harbor MDR tuberculosis and their benefit from the second-line regimen thus might be minimal. On the other hand, an evaluation of cases treated with a rifampicin throughout regimen in Algeria has shown that a remarkable proportion had still fully
susceptible strains after a first course, and even a second course of treatment (Pierre Chaulet, written communication, September 4, 1999, table 1). It thus may be useful to evaluate whether the criteria for declaring failure on a second-line regimen might need to be loosened or kept tight as proposed in this protocol. In this protocol, this situation is not addressed, and it considers only cases meeting the original definition of a chronic excretor.

Before embarking in this study, countries will have to consider that among chronic excretors the perhaps most difficult to treat patients will be included, i.e., patients who have absconded over and over again, and will be likely to do so again, unless sufficient support is provided to increase the probability of adherence. This will require human resources well and above the resources needed for the purchase of medications.

Benefits and ethical considerations

The antituberculosis drugs proposed in this protocol are not usually available in low-income countries, and chronic excretors do not have any further option for treatment. The reason for this state of affairs is primarily a lack of resources of drugs that cost 100 to 200 and more times as much as those needed for the usual recommended first- and second-line treatment. Furthermore, neither efficacy nor effectiveness nor feasibility of a third-line regimen has been established.

Any patient thus receiving a third-line regimen in the context of this study will contribute to a better characterization of the place of a third-line regimen in a national tuberculosis program. For the individual, it will carry the benefit of increased chances of cure from a condition otherwise judged as incurable. This individual benefit is judged to far outweigh the risks (from drug toxicity) of treatment.

Only rarely will it be possible to enroll every chronic excretor into the study in a given country. The major impediments include logistic difficulties to setting up a country-wide system at this point in time, and limitations in availability of resources to purchase all the necessary drugs. It also seems to be inappropriate to allocate large amounts of resources into a strategy that has not yet been proven efficacious and efficient.

This situation offers the opportunity to study the efficacy of the regimen in comparison to a control group not receiving treatment. It is not deemed ethical, however, to randomize eligible patients into a group receiving and a group not receiving the third-line regimen. It is rather proposed to compare the group of eligible patients (who receive the third-line regimen) with a group who are not eligible for treatment. While such an allocation is scientifically much less rigorous than random allocation, the ethical repercussions are much less serious.

It will have to be ensured that an ethics approval committee in each country reviews and approves any protocol that might be derived or expanded from this generic protocol.
Goals and Objectives

Goal

This generic protocol addresses two distinct situations, but both using the same core regimen to treat chronic excretors.

Chronic excretors

This protocol addresses only the setting of countries in which the diagnosis of tuberculosis (and failures and relapses) is based on the microscopic examination of spontaneously expectorated sputum specimens.

Patients who have bacteriologically failed after completing a directly observed throughout standard WHO / IUATLD re-treatment regimen containing rifampicin plus isoniazid throughout are potentially eligible for inclusion (appendix 2).

The definition of failure is a patient who has taken a full course of a WHO / IUATLD recommended regimen containing rifampicin plus isoniazid throughout and remains or becomes again sputum smear-positive at the end of re-treatment (the second-line regimen). It must be ensured that the patient has indeed taken virtually all of the prescribed drugs. With such effective regimens, failure to do so is far more common as a cause of "failure" than MDR. For the purpose of enrolment into the third-line regimen, sputum smear-positivity must be persistent. Persistent sputum smear-positivity is defined as a patient who fails a second-line regimen and has, on at least three occasions, each at least one week apart from the previous, a sputum smear graded as ≥1+ (at least 10 bacilli per 100 oil immersion fields) on microscopic examination using the Ziehl-Neelsen technique of staining. These patients are defined as chronic excretors in the context of this protocol.

Feasibility study

It is far from clear to what extent the difficulties with the organization of a third-line regimen can be overcome. Difficulties include notably securing additional funds for expensive drugs in usually already very tight budgets; organizing one or several centers of excellence which can deal with a much more complicated treatment; organizing and maintaining a regular supply of drugs for a third-line regimen; etc. It is thus proposed that some countries may simply assess the practicability of organizing such a service. This will be called feasibility study in the following.

In this first situation, a standardized third-line regimen is proposed. It is administered to carefully selected patients under program conditions. In this setting, no control treatment arm is required, and end points of evaluation differ from the second setting. It might nevertheless be worthwhile to consider the ethical implications and acceptability of using non-eligible patients as a comparison group. This setting is characterized by a small number of chronic excretors, too small to allow meaningful assessment of comparative regimens. Often, these will be countries which have adhered to a conventional treatment approach recommended by IUATLD, using a non-rifampicin containing continuation phase in a first-line regimen, and a rifampicin throughout containing regimen for retreatment cases.
Efficacy

In the second setting, the number of potentially eligible patients is larger, allowing the use of a comparison treatment regimen. This situation might be found in areas that have used unobserved rifampicin throughout regimens. In the following, this will be called *efficacy study*. There could be three categories of patients with potentially MDR strains:

- patients who have had directly observed chemotherapy in the intensive phase but not in the continuation phase of a national program;
- patients in a national program without directly observed therapy, but with a theoretically appropriate regimen;
- patients treated outside the national program. Some of these may well have received one or more drugs not used in the standard regimens, but useful for a third-line regimen. This is the notorious group of chronic excretors, in some countries very large.

A determination of these categories has potential repercussions on the assignment of treatment in a randomized trial: The randomization (and the analysis) should be done separately for each category. The chemotherapy history may be particularly unreliable for the third of the above three categories.

Specific Objective

To evaluate the effectiveness, and, under certain circumstances, the efficacy of a 21-month regimen proposed by Crofton *et al* [1] under direct observation of drug intake. It consists of ethionamide, capreomycin, ethambutol, ofloxacin, and pyrazinamide during a 3-month intensive phase, followed by ethionamide, ethambutol, and ofloxacin during an 18-month continuation phase, in curing patients with sputum smear positive, pulmonary tuberculosis who are classified as chronic excretors. This is the minimum required duration of treatment. It might be modified by the results of sputum smear examination: the continuation phase may be only initiated after microscopic sputum conversion is documented, and then the continuation phase of 18 months is added. Thus, some patients might be treated for a longer period than 21 months.

There are several reasons for the choice of this regimen. First of all is its appeal of a lower cost compared to other available third-line regimens. It is, However, not the least expensive one (see appendix 1). The utilization of the polypeptide capreomycin rather than the aminoglycoside kanamycin increases the cost, but cross-resistance between the two aminoglycoside antibiotics streptomycin and kanamycin is more likely than between capreomycin and streptomycin. This could be important in countries where primary resistance to streptomycin is frequent.

Among the thiocamides, ethionamide is given preference over prothionamide because it appears to be better tolerated than the latter, and is also less expensive.

Ofloxacin is chosen among the quinolones because it is the best documented in the group and is also the currently least expensive of the quinolones.
Pyrazinamide is usually only given in the intensive phase of both the first- and the second-line regimen. There is thus a reasonably high expectation that the drug has retained its efficacy and is therefore given again in the intensive phase of the third-line regimen.

The regimen will thus include at any time at least two drugs to which the strain is likely to be susceptible, i.e., ofloxacin and ethionamide, plus supplemented by a third, capreomycin, during the intensive phase (unless one or more of these drugs has been used before as may be the case in countries where the private sector plays an important role). Finally, patients whose strain is still susceptible to ethambutol, will benefit from this relatively inexpensive (as part of the third-line regimen) drug that is usually very well tolerated.

The regimen of choice is indicated in bold in appendix 1. This regimen is henceforth referred to as the standard third-line regimen. The most questionable drug in this regimen is ethambutol whose susceptibility might have been lost with a fairly high probability in genuine failures on a second-line regimen or in patients inadequately treated.

Additional objectives when studying efficacy

In areas where the number of patients is sufficiently large, and the infrastructure is available, the efficacy of an alternate regimen is compared to the standard core regimen.

Possible arms of a comparison arm include:

Replacing ethambutol by cycloserine

To evaluate in certain settings the comparative efficacy of ethambutol versus cycloserine in the regimen to improve the cure rate of a standard third-line regimen for the treatment of sputum smear microscopy positive, pulmonary tuberculosis. The use of cycloserine instead of ethambutol depends on the context of the situation. As mentioned above, countries which have used ethambutol extensively might expect a high level of resistance to the drug. It is in such settings where a difference between regimens using either ethambutol or cycloserine could probably best be demonstrated.

Replacing ofloxacin by levofloxacin

To evaluate in certain settings the comparative efficacy of ofloxacin versus levofloxacin in the regimen to improve the cure rate of a standard third-line regimen for the treatment of sputum smear microscopy positive, pulmonary tuberculosis.

Replacing a daily continuation phase with a thrice-weekly continuation phase

To evaluate feasibility, efficacy, and toxicity of providing an 18-month continuation phase consisting of daily ethionamide, ethambutol, and ofloxacin versus thrice-weekly ethionamide, ethambutol, and ofloxacin. If there is no difference between the regimens, ambulatory, directly observed therapy could obviously become easier to administrate.
Increasing the duration of capreomycin administration

Because capreomycin might be of particular importance in the treatment, the optimum length of its administration might be assessed.

Changing the duration of treatment

The optimum length of treatment is not really known for the third-line regimen. It thus might be considered to compare a shorter with a longer duration of treatment with the standard regimen.

Adjunct treatment with M. vaccae

To evaluate in certain settings the usefulness of *M. vaccae* as an adjunct to the standard third-line regimen. Patients are randomly allocated to receive the standard third-line regimen plus a suitable placebo or the standard third-line regimen plus *M. vaccae*. Programs opting for this adjunct therapy should be aware that the randomized trial in South Africa was not able to demonstrate efficacy (unpublished data).

Sample Size

If the true conversion rate is 50%, then about 40 patients would have to be observed to determine and estimate the conversion rate with a 95% confidence interval of plus / minus 15%. About 90 patients would have to be observed to reduce the confidence interval to plus / minus 10%.

For settings using an additional arm in addition to the standard third-line regimen, the following considerations on sample size should be made. To detect a significant difference from a sputum conversion of 50% at six months on the standard third-line regimen and 75% at six months with an alternative regimen, or to detect the difference between a 75% cure ratio on the standard third-line regimen and a 95% cure rate with an alternative regimen, approximately 58 patients must be followed in each group, for a total of about 116 patients. Assuming that about 20% of patients will be lost to follow-up, approximately 73 patients should be enrolled in each group. A loss of 20% of patients is assumed here for deaths, absconders, and transfers. If HIV infection is highly prevalent among the patients, the proportion dying is likely to increase, and the sample size would have to be adjusted accordingly. These calculations assume a two-tailed test, with a 95% confidence interval (type I error) and 80% power (type II error).

Quite obviously, if smaller differences are sought, the required sample size will increase accordingly.
Outcome Measure

Basic outcome measures

Basic outcome measures include the minimum required for the feasibility study, notably:

- Collection of specimens for sputum smear microscopy at three-month intervals
- The proportion of patients converting sputum to acid-fast bacilli smear negative by the end of three months and six months of therapy (the smear conversion ratio)
- The proportion of patients with acid-fast bacilli smear negative sputum after six months of treatment and maintaining that status throughout the completion of 21 months of treatment (the smear cure ratio).
- Susceptibility test results to at least isoniazid, rifampicin, streptomycin, and ethambutol on the pre-treatment isolate. In countries taking part in the WHO / IUATLD Global Project on Surveillance of Drug Resistance, susceptibility testing to these four drugs has been established under the supervision of designated supranational reference laboratories. In other countries, it will be essential to establish such links to ensure that proficiency testing of the results is carried out according to international standards [10, 11]. If it is not feasible to have susceptibility tests carried out according to these standards, it will be necessary to make arrangements with external laboratories to ensure testing of all strains from eligible patients.

Additional outcome measures

Additional outcome measures are measures that go beyond treatment completion and are particularly recommended for sites that opt for the efficacy study with one or two experimental arms. These measures include:

- Collection of specimens for culture and susceptibility testing at three-month intervals
- The proportion of patients converting sputum to culture negative by the end of three months and six months of therapy (the culture conversion ratio)
- The proportion of patients with culture negative sputum after six months of treatment and maintaining that status throughout the completion of 21 months of treatment (the culture cure ratio)
- Where possible, support from laboratories should be sought to test for susceptibility of all administered drugs on the pre-treatment isolate and all positive cultures during treatment
- Active follow up beyond treatment completion for at least 24 months for the determination of treatment recurrence frequency
- Collection of strains from cases with recurrent disease during follow-up
- Proportion of patients in whom the regimen has to be 1) altered (e.g., change of one or more drugs) or 2) abandoned, because of drug toxicity
- Determination of the RFLP patterns of the initial and recurrent strain to distinguish reinfection from relapse strains
Inclusion Criteria

Potentially eligible for inclusion in the study are patients meeting the definition of a chronic excretor as defined above.

A patient must provide informed consent to be treated with the proposed treatment regimen. The patient must be informed fully about the type of treatment, its risks and benefits, and the right to withdraw from treatment at any point in time.

Eligibility for implementation of this protocol will only include countries which have adapted the WHO DOTS strategy.

The treatment regimen proposed here is very expensive (see appendix 1) and is associated with a high frequency of adverse reactions. The regimen will not usually be applicable on a countrywide basis in low-income countries as this would likely lead to uncontrolled enrolment by insufficiently qualified personnel.

To make the regimen as effective as possible, it is thus important that the selection be rigid (see exclusion criteria below) to guarantee the highest possible success in terms of completion of the treatment once a decision to enroll a patient has been taken, and to prevent the emergence of further resistance.

Exclusion Criteria

Exclusion from the basic third-line regimen

- Inability or unwillingness to give informed consent for participating in the study.
- Inability or unwillingness to take treatment with the standardized regimen or the alternative comparison regimen in the efficacy study (e.g., known intolerance of a study drug, terminal illness, permanent residence outside the study area).
- Patients whose susceptibility test result shows susceptibility to rifampicin. Patients meeting the inclusion criteria, and not presenting with any of the above exclusion criteria should be enrolled into the study. Once susceptibility test results become available, expected after six weeks to three months, patients showing susceptibility to rifampicin can be taken off the third-line regimen. These patients should be given a standard WHO / IUATLD retreatment regimen, as this regimen is likely to cure the patient if direct observation of drug intake is ensured throughout treatment. If drug susceptibility test results do not become available, as might be the case in a considerable proportion of cases (Data from Algeria, Pierre Chaulet, written communication, September 4, 1998), these cases should continue to receive the third-line regimen, but their results should be analyzed separately.
- Patients known to be HIV positive may or may not be enrolled in the study, as the sulfur-containing ethionamide may cause adverse reactions similar to those observed with thioacetazone. However, expert opinion suggests that ethionamide is actually much better tolerated in HIV-infected patients than other sulfur-containing drugs such as
sulfamethoxazole (H. William Harris, written communication, September 17, 1998). Thus, it is proposed that HIV infection is not an absolute exclusion criterion for the study.

**Exclusion from a cycloserine arm**

- Any psychiatric illness
- Epilepsy
- Alcoholism

**Procedures**

National tuberculosis programs agreeing to participate in the study, are required to provide the following before initiating the third-line treatment program:

- To utilize this generic protocol as a basis for a detailed research protocol
- To identify a specialized treatment unit in the capital of the country in which all eligible patients will be taken care of. In large countries, more than one such center might be designated
- To have arrangements to ensure that drug supply can be guaranteed for the estimated number of patients for at least three years, with regular audit of drugs to ensure that supplies are not deviated to patients not included in the project
- To prepare a list of all known chronic excretors. This list should be comprehensive for the entire catchment area from which the patients are to be enrolled. If patients from the private sector are also eligible, it will be necessary to collaborate with these physicians to establish such a list
- To determine eligible patients on the list of chronic excretors
- To conduct a thorough pre-enrolment interview with each patient
- Continuity of staff must be guaranteed
- To ensure that all infrastructure for bacteriologic services are in place and functioning before the enrolment of patients

**Data Collection**

**Core Data**

The following data will be collected for all patients:

- Study ID number
- Age
- Sex
- Body weight
- Date and result of diagnostic acid-fast bacilli sputum smear examinations
o Assigned regimen  
o Date regimen started  
o Date regimen completed  
o Number of directly observed doses of each drug  
o Number of self-administered doses of each drug  
o All periods off regimen due to non-adherence  
o Date and result of all acid-fast bacilli sputum smear examinations during treatment  
o Outcome of treatment and date outcome assigned.

In addition, the study manager should retain sufficient identifying and locating information to allow follow-up of the patient during treatment.

All treatment should be given directly observed throughout treatment on at least 5 days per week. Patients should be daily interviewed about the presence or absence of signs and symptoms of adverse effects to study drugs. Adverse effects should be recorded whenever they are diagnosed and the period off medication due to adverse effects should be noted.

In centers choosing the feasibility study and non-eligible patients as control group, the patients not eligible for enrolment should have their bacteriologic status checked at 3, 6, 12, 15, 18, and 21 months recorded to provide a comparable bacteriologic ascertainment to the treatment group. This is proposed because the outcome without a third-line regimen is not known, and cure on the third-line regimen may be falsely attributed to the efficacy of the regimen, rather than a favorable natural course of the disease.

Centers opting for follow-up after successful completion of treatment should require that patients be seen at six-month intervals after the completion of treatment, questioned about signs and symptoms of tuberculosis, and clinical specimens should be obtained for acid-fast bacilli smear examination and for culture where applicable (2 spot and one overnight specimen). Each patient should be seen four times after the completion of therapy to complete 24 months follow-up. Active follow-up of patients failing an appointment is essential. Knowledge about the outcome of each patient during follow-up must be secured.

Where feasible, the efficacy study should plan to extend the two-year follow-up to a five-year follow up.

Additional Data

Where feasible, HIV testing will be performed on all patients at the beginning of treatment at the completion of treatment at 21 months, and at the completion of 24 months of follow-up after treatment. Alternatively, serum samples could be collected and banked so that serum can be tested for HIV antibodies for all treatment failures and individuals with a recurrence of tuberculosis and in a sample of matched controls. However, HIV testing is not a prerequisite for study participation. Nevertheless, because HIV infection profoundly alters treatment outcome (notably deaths), it is strongly recommended that due consideration is given to systematic HIV counseling and testing.

Diagnostic specimens of sputum will be cultured for M. tuberculosis and isolates tested for susceptibility to the four drugs recommended for testing in the WHO / IUATLD global
surveillance project. Because test results for rifampicin are among the most reliable, patients with two diagnostic isolates susceptible to rifampicin, should be removed from the trial and be given a standard WHO / IUATLD retreatment regimen. Isolates from diagnostic samples will also be banked and paired with any isolates obtained from treatment failure patients and from patients with a recurrence of tuberculosis so that RFLP patterns can be compared and judgment made as to whether the recurrence is a result of relapse or re-infection.

Susceptibility test results will not be used for patient management with the exception of susceptibility test results to rifampicin (see above). This is recommended for the following reasons:

- Drug susceptibility test results may not match treatment susceptibility in the individual
- Expertise in determining susceptibility patterns to pyrazinamide, quinolones, capreomycin, ethionamide, and cycloserine is not routinely available
- In the low-income countries addressed in this protocol, the priority in the determination of drug susceptibility test results is for surveillance
- Eligibility criteria for enrolment on the third-line regimen are so stringent as to make the clinical probability of multiple-drug resistant tuberculosis very high
- Susceptibility test results would be available only several months after action is required
- The point of the protocol is to evaluate a standard third-line regimen, not individual case management

Summary

In summary, three major points should be considered in any situation, where the implementation of a third-line regimen is sought:

- The basic recommended regimen consists of three months minimum (plus prolongation in patients still sputum smear-positive after this time) of capreomycin, ethionamide, pyrazinamide, ofloxacin, and ethambutol, followed by an 18-month continuation phase, consisting of ethionamide, ofloxacin, and ethambutol
- Possibly, modifications from the standard third-line regimen are necessary in areas where ethambutol resistance is highly likely.
- The final regimen should be decided in consultation with national experts in light of local circumstances
Acknowledgements:

The following persons have provided written comments for the development of this protocol: Thuridur Arnadottir, Maarten Bosman, Pierre Chaulet, Sir John Crofton, Lawrence J Geiter, H William Harris, Norman Horne, Dermot Maher, Brian Watt.

The development of this protocol was financially supported by the World Health Organization.

Prepared by Hans L. Rieder, International Union Against Tuberculosis and Lung Disease (IUATLD)
References


Table 1. Drug susceptibility pattern according to the number of courses of chemotherapy with a rifampicin throughout regimen of six months duration, Algeria. (Data kindly provided by Pierre Chaulet, written communication, September 4, 1999).

<table>
<thead>
<tr>
<th>Course</th>
<th>Cases</th>
<th>Still fully susceptible</th>
<th>Any resistance</th>
<th>Resistance to</th>
</tr>
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<tr>
<td></td>
<td>n</td>
<td>(%)</td>
<td>n</td>
<td>(%)</td>
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<tr>
<td>1</td>
<td>77</td>
<td>(73)</td>
<td>21</td>
<td>(27)</td>
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<tr>
<td>2</td>
<td>43</td>
<td>(35)</td>
<td>28</td>
<td>(65)</td>
</tr>
<tr>
<td>3</td>
<td>39</td>
<td>(2.5)</td>
<td>38</td>
<td>(97.5)</td>
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</tbody>
</table>
Appendix 1. First-, second-, and third-line regimens for suspected multiply drug-resistant tuberculosis and their FOB cost in US$

<table>
<thead>
<tr>
<th>Anti-tuberculosis drug</th>
<th>INH/ RMP/ PZA/ SM/ EMB</th>
<th>INH/ EMB/ KM/ AK/ CM/ ETH/ OFL/ CYC</th>
<th>Regimen cost US$</th>
<th>Relative cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbreviation used here</td>
<td>mg / tablet / vial</td>
<td>Unit size</td>
<td>Supplier's currency</td>
<td>Unit cost supplier</td>
</tr>
<tr>
<td></td>
<td>H (HR) Z S E (HE) (HT)</td>
<td>1000/150 100 400 1000 400/150 100/300 1000 1000 1000 250 200 250</td>
<td>NGL NGL NGL NGL NGL NGL</td>
<td>6.05 48.40 42.25 5.45 34.60 42.50 14.20</td>
</tr>
<tr>
<td>Cost of first-line regimens</td>
<td>2 S[HR]Z / 6 (HT)</td>
<td>4.39 3.83 3.29 1.29</td>
<td>12.79 1.1</td>
<td>2 S[HR]Z / 6 (HE) 4.39 3.83 3.29 7.70</td>
</tr>
<tr>
<td>Cost of second-line regimens</td>
<td>2 S[HR]ZE / 1 (HR)ZE / 5 E[HR]; 5 E[HR] 17.54 5.74 3.29 8.38</td>
<td>34.94 3.0</td>
<td>2 S[HR]ZE / 1 (HR)ZE / 5 E[HR] 17.54 5.74 3.29 7.83</td>
<td>28.73 2.5</td>
</tr>
<tr>
<td>Cost of third-line regimens</td>
<td>3 K-Et-Z-O-E / 18 Et-O-E 5.74 21.95 32.70 195.30 1,827.00 2,082.69 179.7</td>
<td>3 A-Et-Z-O-E / 18 Et-O-E 5.74 21.95 1,923.00 195.30 1,827.00 3,972.96 342.8</td>
<td>3 Cm-Et-Z-O-E / 18 Et-O-E 5.74 21.95 1,923.00 444.00 195.30 1,827.00 2,493.99 215.2</td>
<td>3 K-Et-Z-O-Cy / 18 Et-O-Cy 5.74 32.70 21.95 195.30 1,827.00 3,972.96 281.8</td>
</tr>
</tbody>
</table>
Sputum Smear-Positive Patients Only
Never treated previously for as much as 1 month

First-line regimen

Cure Completion **Failure** Transferred Absconded Death

Relapse

Return sm-pos

Second-line regimen

Cure Completion **Failure** Transferred Absconded Death

at end of treatment

Relapse

Return sm-pos

Eligible for third-line regimen
Protocol for the Implementation of Individualized Treatment Regimens for Multidrug Resistant Tuberculosis in Resource-Poor Settings

Prepared by:

Dr. Paul Farmer
Dr. Jim Yong Kim
Mrs. Carole D. Mitnick
Mrs. Mercedes Becerra
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Objective
In recent years, it has become clear that short-course, multidrug therapy including both isoniazid (INH) and rifampicin (RIF) can cure almost all patients sick with pansusceptible strains of Mycobacterium tuberculosis. There is ample evidence, however, that resistance to either of these drugs can compromise outcomes even when therapy is directly observed. When patients have multidrug-resistant tuberculosis (MDRTB)—that is, resistance to both isoniazid and rifampicin—they are exceedingly unlikely to be cured by short-course chemotherapy (SCC). Instead, amplification of resistance to other first-line drugs used in SCC is a more likely outcome of such interventions; retreatment regimens that add a single new drug, such as streptomycin, are also unlikely to cure MDRTB but do increase the likelihood of acquired resistance to the new drug. These patients remain ill and infectious with increasingly resistant strains.1,2

This protocol aims to evaluate the effectiveness of an MDRTB-control initiative based on the use of individualized treatment regimens (ITR) to improve treatment outcomes among patients failing to respond to empiric treatment or retreatment regimens. As a “DOTS-Plus” initiative, it will be implemented in resource-poor settings in which a DOTS-based national TB program (NTP) can assure case detection and treatment of all suspected TB cases.3 For further details on all aspects of the DOTS-Plus ITR strategy, please see the document, Community-Based Approaches to the Treatment and Control of Multidrug Resistant Tuberculosis, hereafter called the Handbook.

Patient Selection and Inclusion Criteria
Eligibility for this protocol is nested in three levels. Because of the potential for amplification of resistance to other first-line drugs if patients with suspected MDRTB are not identified, the inclusion criteria will become progressively more restrictive through the enrollment process. Generally speaking, the first level will identify patients likely to have active MDRTB. At the second level, active TB will be confirmed; those with resolved disease or infection only will be excluded from the ITR protocol. At the third level, patients whose strains are not resistant to at least INH and RIF will be excluded from the ITR protocol.

Level 1

Patients must fall into one of the four following groups to be eligible for evaluation for treatment:

4 Program in Infectious Disease and Social Change. Community-Based Approaches to the Treatment and Control of Multidrug-Resistant Tuberculosis. Boston, MA: Harvard Medical School, 1999.
1. **Patients most likely to have MDRTB.** This group shall comprise patients in a defined geographical area who are symptomatic and have failed to respond after four months of directly observed retreatment therapy. Because in most settings the possibility of a failure to ensure directly observed therapy must be excluded, a review of the patient's directly observed therapy will be conducted. If the patient has been receiving directly observed therapy correctly and is failing to respond to treatment, MDRTB will be considered possible. Failure to respond to therapy is defined as confirmed smear-positivity at four months after initiating the retreatment regimen.

2. **Incident cases of primary MDRTB.** This group shall be sought among incident TB cases who are close contacts (e.g. household members, co-workers, or other daily contacts) of either: (a) patients with documented MDRTB, or (b) patients who died of TB while receiving a directly observed treatment or retreatment regimen.

3. **All household contacts of MDRTB patients.** This group shall comprise members of the household of individuals in either of the first two categories.

4. **Patients who fail initial therapy.** This criterion, which will be further refined, will pilot the use of DNA probes for the rapid identification of *in-vitro* resistance to RIF in patients who fail to respond to initial treatment. Failure to respond to therapy is defined by three positive smear-microscopy examinations after four months of directly observed treatment.

Additionally, all patients must agree to directly observed ITR for 18 to 24 months in order to be eligible for participation in this protocol.

**Level 2**

All individuals identified through the first level of selection will undergo drug-susceptibility testing as well as clinical and radiographic evaluation procedures:

1. Patients will be asked to provide two sputum specimens for smear-microscopy examination and culture.

2. Participants will undergo complete clinical evaluation, including elicitation of history of present illness, past medical history (including all antecedent TB history), known drug allergies, and social history with documentation of known TB contacts.

3. A baseline chest radiograph will be obtained at the time of initial evaluation.

For all participants, active disease will be identified according to conventional bacteriologic, clinical, and radiographic criteria (see the Handbook). Patients without active disease will be excluded from the ITR protocol at this point. Household members and other close contacts will be tuberculin tested, and those who are non-reactive and who have not yet received BCG vaccination will be provided with the vaccine.

**Level 3**

All patients with active, suspected MDR disease will be screened for drug resistance. Cultured organisms will be tested for susceptibility to 12 antituberculous medications (see appendix 1). Patients whose isolates demonstrate pan-susceptible disease will be referred back to the NTP for treatment and monitoring under NTP guidelines. Pending definitive susceptibility results, participants will be placed on empiric ITR.
TREATMENT STRATEGY

1. The ITR will consist of:
   - a minimum of four (and, in some cases, as many as eight) drugs to which the
     patient’s isolate has demonstrated susceptibility;
   - high-end recommended doses (see appendix 2);
   - an 18-to-24-month regimen.
An initial, empiric ITR will be followed by a definitive ITR after final drug
susceptibility results become available.

2. Direct observation of every dose throughout the course of treatment is an essential
   component of this strategy.

3. The treatment strategy will be implemented by local health providers and community
   members, under the aegis of the NTP, with consultation from MDRTB experts as
   appropriate. Training, continuing education, and other forms of community capacity-
   building will be central to this DOTS-Plus program.

4. Complete drug-susceptibility testing of all *M. tuberculosis* isolates of those patients
   referred for evaluation requires transnational collaborative linkages between the NTP
   and a supranational reference laboratory.

Treatment procedures

Duration of treatment

ITRs will be administered for 18 to 24 months. The International Working Group on
MDRTB will provide a consulting TB specialist who will recommend, based on the
patient’s clinical status and susceptibility results, a treatment regimen. Each regimen will
include a parenteral anti-mycobacterial agent, which will be administered until at least
six consecutive months of smear- and culture-negativity have been documented. The
consulting TB specialist-clinician will determine both the overall duration of the ITR and
the duration of use of the parenteral medication after a thorough clinical evaluation.
Decisions regarding treatment termination will rely on radiographic, clinical, and
laboratory data (see the Handbook for more detail).

Design of the empiric ITR

Guidelines for the design of the individualized empiric regimen include the following:

1. Adequate empiric regimens must include at least four (although may include as many
   as eight) drugs, including one parenteral drug, to which the patient is likely to be
   susceptible. INH and RIF should be included in empiric ITRs in addition to the
   minimum of five other drugs when proof of resistance of the infecting strain to INH
   and RIF is lacking.

2. Resistance to a given drug must be considered likely if:
   - the patient has previously received the drug;
• the patient has previous documentation of *in vitro* resistance to the drug; or

• the patient has had close or long-term exposure to a patient with documented resistance to the drug.

3. When relying on previous drug-susceptibility testing, consider the following:

• **Discrepancies in drug-resistance patterns.** If there are discrepancies in an individual’s drug-resistance patterns over time, one should “fear the worst” and avoid reliance on any drugs to which even a single isolate has demonstrated resistance. If testing has been performed at more than one laboratory, and discrepant results are reported, design of a regimen should be guided by the resistance data from the mycobacteriology laboratory deemed most experienced. There are several supranational reference laboratories recognized by international TB experts; results from these laboratories should be considered the most reliable.

It is important to note, however, that discrepant results may be the consequence of any of a number of factors, including different testing methods, laboratory errors, or mislabeling of specimens. When discrepant results are encountered, the bacteriologist(s) responsible for the testing should be contacted in order to exclude laboratory error as the cause of discrepant susceptibility results.

• **Treatment since last available results.** If a patient has received treatment since the collection of the sample for which drug-susceptibility results are available, the acquisition of further resistance to drugs should be excluded. New specimens should be obtained prior to initiation of therapy and empiric regimens (while awaiting these results) should not rely on drugs to which the infecting strain may have acquired resistance.

4. A parenteral medication is an important component of the empiric regimen. Principles guiding the selection of these medications are detailed in the *Handbook*.

5. “Fourth-line” drugs (e.g., amoxicillin-clavulanic acid, clofazimine) may be used for reinforcement of an empiric ITR.

6. In the most difficult cases after all other treatment options have been exhausted, surgical intervention and the use of two concomitant parenteral drugs may be considered.

---

*Design of the definitive ITR*

As mentioned above, patients whose isolates demonstrate pan-susceptible disease should be referred back to the NTP for treatment at the patient’s local health center. There, patients will be placed on a standardized short-course regimen and evaluated by the NTP according to guidelines.

Patients whose isolates demonstrate MDRTB will see their empiric ITR changed to a definitive ITR, based on complete susceptibility testing. Drugs to which the strain demonstrates *in vitro* resistance will be discontinued; drugs which had not been included in the empiric ITR but to which the strain demonstrates *in vitro* susceptibility will be added to the ITR. Thus, all drugs used in the definitive regimen will be those to which the individual’s infecting strain has demonstrated susceptibility.
Changes to the definitive ITR during the course of therapy

The parenteral medication may be discontinued as early as six months after smear- and culture-conversion, based on the recommendations of the consulting TB clinician. Monitoring of response to treatment will be conducted in close collaboration with the NTP and will include:

- monthly smear microscopy and culture;
- monthly weight surveillance;
- chest radiograph every six months; and
- baseline examination of liver function and renal function with frequency of monitoring depending on the drugs used and the patient’s baseline clinical status, age, and co-morbid conditions.

After six months of ITR, treatment failure is suggested at any point by persistence of symptoms consistent with active tuberculosis, positive sputum microscopy or culture. Possibility of treatment failure will be thoroughly evaluated, and the possibility of incorrectly administered directly observed therapy must be excluded.

Monitoring side effects

Side effects are most common during the first several weeks of treatment. They are often mild; include nausea, vomiting, and diarrhea; and in our experience rarely necessitate the discontinuation of treatment. Frequent follow-up and intensive management of complications are necessary throughout the course of treatment (see Handbook).

Treatment delivery

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>RESPONSIBLE PERSON(S) AND THEIR ROLE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Directly observed therapy</td>
<td>DOT worker (i.e. community-health worker, family member, neighbor, shopkeeper) observes the ingestion of each dose of medicine in the patient’s home (while he or she is still smear-positive), or in a health center, place of employment, or other location.</td>
</tr>
<tr>
<td>Monitoring treatment</td>
<td>MDRTB promoter (community-health worker with special training in the treatment of MDRTB) visits the patient every other day and can be contacted by patient/family in an emergency; local physicians evaluate patients monthly and can be contacted in case of emergency.</td>
</tr>
<tr>
<td>Referral of patients in emergencies</td>
<td>DOT worker, MDRTB promoter, other health personnel.</td>
</tr>
<tr>
<td>Management of emergencies</td>
<td>Local physicians.</td>
</tr>
<tr>
<td>Design and modification of ITRs</td>
<td>Consulting TB clinician— (sees patients monthly, can be contacted regularly for clinical consultation).</td>
</tr>
<tr>
<td>Evaluation of DOTS-Plus program</td>
<td>NTP, external technical advisory committee.</td>
</tr>
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</table>
Ensuring treatment completion and success

Experience in treating MDRTB in the community has led to a deeper understanding of risk factors for poor outcome. While disseminated disease, high-grade resistance, poorly chosen drug combinations, underdosing, and severe parenchymal destruction are some of the clinical predictors of poor treatment response, numerous socioeconomic factors also shape a patient’s likelihood of continuing, and responding to, therapy. This protocol will incorporate the following interventions aimed at reducing the negative impact of such socioeconomic influences on treatment outcomes:

- subsidy of transportation costs;
- scheduling of appointments and tests at hours appropriate to patients’ work and family commitments;
- availability of free medical consultations, laboratory and radiology services;
- provision of free supplies such as syringes, needles, and drugs to control side-effects, under the supervision of clinical staff; and
- nutritional assistance.

OUTCOMES ASSESSMENT

Clinical measures

Smear-conversion rate: The proportion of all smear-positive patients who become smear-negative and culture-negative during treatment with ITR.

Likely cures: Of the patients who have received ITR for at least six months, the proportion who remain smear- and culture-negative.

Cures: Of the patients who have received ITR for 18 to 24 months, the proportion who remain smear- and culture-negative.

Absconders: Of the patients initiating ITR, the proportion who abandon treatment.

Deaths: Of the patients initiating ITR, the proportion who die during treatment. (The cause of death should be evaluated and recorded.)

Likely failure: Of the patients who have received ITR for at least six months, the proportion who remain smear- or culture-positive. Among these patients, a careful analysis will be carried out to ensure that these individuals are receiving their DOT correctly and are not among “cryptic absconders” (that is, patients who are not receiving proper DOT but who have not abandoned treatment).

Treatment failure: Of the patients who have received ITR for 18 to 24 months, the proportion who remain smear- or culture-positive.

Epidemiologic measures

Transmission events averted: Assuming that one patient with smear-positive, pulmonary, MDR disease infects 10-12 individuals per year, it is possible to estimate the
number of transmission events averted (TEAs) by effective therapy. Measurement unit is number of infections averted per person-year of ITR.

Nosocomial TEA: This represents an estimate of TEAs over defined intervals for smear-positive patients resident in health-care facilities.

Community-impact measures

The community-based approach places a premium on building local capacity for response to an outbreak of MDRTB (or other infectious disease threats to a community's well-being). Although such benefits are difficult to measure, we will consider at the following indicators:

- number of previously unemployed individuals trained and employed as DOT workers;
- number of community-health workers trained and employed as DOT workers and as MDRTB-promoters;
- increase in community involvement in TB treatment and control measured by the number of community residents participating in the program, the number who have expressed interest in participating, and the level of TB-related knowledge and awareness in the community;
- number of patients finding employment or becoming involved in other community-capacity building activities; and
- extent of collaboration between non-governmental organizations, governmental organizations, and health centers.

Prerequisites for the Implementation of an ITR-Based MDRTB-Control Initiative

1. Commitment of all participants:
   - national government;
   - local public-health authorities; and
   - reference laboratory.

2. DOTS: a DOTS-based program in place, or a strong commitment to implement a DOTS-based program on the part of the national government, is desirable prior to the initiation of DOTS-Plus.

3. Supervision: program-wide supervision of the DOTS-Plus program by those with strong technical knowledge willing to commit a minimum of two to three years.

4. Local human resources: trained staff (or staff willing to be trained) to manage local operations.

5. Evaluation and improvement: commitment of all collaborating parties to ongoing evaluation and program modification.

6. Secure drug supply: a consistent supply of all second- and third-line drugs must be assured.
DATA COLLECTION

Each patient's complete clinical history and drug-susceptibility data shall be recorded in a standardized manner. Data will be collected on structured forms comprising part of the patient history. Results will be evaluated by NTP staff. Please see Appendix 3 for sample data forms.
TABLE OF APPENDICES

APPENDIX 1: DRUG FORMULARY FOR COMMUNITY-BASED ITR MDRTB INITIATIVE

APPENDIX 2: TABLE OF CHEMOTHERAPEUTIC AGENTS USED IN THE TREATMENT OF TUBERCULOSIS

APPENDIX 3: DATA COLLECTION FORMS
   FORM 1: Initial clinical evaluation form
   FORM 2: DOT administration sheet
   FORM 3: Resistance results summary sheet
   FORM 4: Summary sheet for direct smear microscopy and culture results
   FORM 5: Side-effect & allergy monitoring form
   FORM 6: Health worker report
   FORM 7: Summary data for patients with suspected MDRTB
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Description</th>
<th>Administration</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Nicotinic acid hydrazide. Bactericidal. Inhibits mycolic acid synthesis most effectively in dividing cells. Hepatically metabolized.</td>
<td>Low dose: 5 mg/kg PO QD</td>
<td>Adverse reactions 5.4%. Most commonly, rash (2%), fever (1.2%), jaundice (0.6%), peripheral neuritis (0.2%). Anemia, agranulocytosis, thrombocytopenia, eosinophilia, optic neuritis, positive ANA, vasculitis, and hypersensitivity have all been reported. Interacts with phenytoin.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Bactericidal. Produced by <em>Streptomyces</em> sp. Inhibits protein synthesis by blocking mRNA transcription and synthesis. Hepatically metabolized.</td>
<td>10 mg/kg PO QD</td>
<td>Adverse effects &lt;4%. Rash (0.8%), fever (0.5%), GI upset (1.5%). Hepatitis; thrombocytopenia (in rare cases), cholestatic jaundice, gynecomasia, renal insufficiency. Interacts with drugs metabolized by p450 system. Orange-colored urine, saliva, sputum, tears, and sweat.</td>
</tr>
<tr>
<td>(Rifampicin)</td>
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<tr>
<td>Pyrazinamide</td>
<td>Nicotinamide derivative. Bactericidal. Mechanism unknown. Effective in acid milieu (e.g. cavitary disease, intracellular organisms). Hepatically metabolized, renally excreted.</td>
<td>25-35 mg/kg PO QD</td>
<td>Hepatotoxicity, hyperuricemia; occasionally, rash, GI upset, arthralgia, dysuria, malaise, fever, impairment of diabetic control.</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Bacteriostatic. Inhibits lipid and cell wall metabolism.</td>
<td>15-25 mg/kg PO QD</td>
<td>Adverse effects &lt;2%. Reduced visual acuity (0.8%), rash (0.5%), fever (0.3%). Retrobulbar neuritis is dose-related; increased risk with renal insufficiency. Less commonly: pleuritis, arthralgia, GI upset, malaise, headache, dizziness, disorientation, hallucination.</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Description</td>
<td>Administration</td>
<td>Side Effects</td>
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</tr>
<tr>
<td>Streptomycin</td>
<td>Aminoglycoside. Bactericidal. Inhibits protein synthesis through disruption of ribosomal function. Less effective in acid, intracellular environment. Renally excreted.</td>
<td>1 g IM QD</td>
<td>8.2% incidence of adverse reactions. Otoxicity and nephrotoxicity dose-related (both cumulative and peak concentrations), increased risk with renal insufficiency, may be irreversible.</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Aminoglycoside. Bactericidal.</td>
<td>15 mg/kg IM or IV QD</td>
<td>Otoxicity and nephrotoxicity dose-related (both cumulative and peak concentrations), increased risk with renal insufficiency. Pain at injection site.</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Aminoglycoside. Bactericidal. Inhibits protein synthesis through disruption of ribosomal function. Less effective in acid, intracellular environment. Renally excreted.</td>
<td>1 g IM QD</td>
<td>Otoxicity and nephrotoxicity dose-related (both cumulative and peak concentrations), increased risk with renal insufficiency. Pain at injection site common.</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Polypeptide. No demonstrated cross-resistance with aminoglycosides.</td>
<td>1 g IM QD</td>
<td>Well tolerated. Otoxicity and nephrotoxicity dose-related (both cumulative and peak concentrations); increased risk with renal insufficiency.</td>
</tr>
<tr>
<td>Para-aminosalicylic acid</td>
<td>Bacteriostatic. Hepatic acetylation, renally excreted.</td>
<td>4 g PO TID</td>
<td>Adverse effects in 10%. GI upset (nausea, vomiting, diarrhea), hypersensitivity in 5-10% of patients; rarely, hepatitis.</td>
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<td>Delayed-release granules should be administered with acidic food or drink.</td>
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<tr>
<td>Drug Name</td>
<td>Description</td>
<td>Administration</td>
<td>Side Effects</td>
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<tr>
<td>Fluoroquinolones</td>
<td>Likely bactericidal. DNA-gyrase inhibitor. Levofloxacin appears to be active moiety, and may well be the drug of choice. Not FDA-approved for use during pregnancy—associated with arthropathies in studies with immature animals. Renally excreted. Cross-resistance among fluoroquinolones thought to be near complete.</td>
<td>Ciprofloxacin: 750 mg PO BID&lt;br&gt;Sparfloxacine: 200mg PO BID&lt;br&gt;Ofloxacine 400mg PO BID&lt;br&gt;Levofoxacin 500mg PO QD&lt;br&gt;Adjust doses for creatinine clearance &lt; 50 ml/min</td>
<td>Well tolerated, well absorbed.&lt;br&gt;Occasionally, GI upset, dizziness, hypersensitivity. Has been associated with seizures in MDRTB patients receiving multiple drugs with CNS side effects.&lt;br&gt;Prolong half-life of theophylline.&lt;br&gt;Antacids with Al, Mg, CaSO₄ or FeSO₄ may inhibit GI absorption of quinolones.&lt;br&gt;Sparfloxacine may cause a photosensitivity reaction in up to 8%; also should not be used in persons receiving any drug that prolongs the Q-T interval..&lt;br&gt;Ofloxacine may cause a mild transaminitis.</td>
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<tr>
<td>Ciprofloxacin</td>
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<tr>
<td>Sparfloxacine</td>
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<tr>
<td>Ofloxacine</td>
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<tr>
<td>Levofloxacine</td>
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<tr>
<td>Cycloserine</td>
<td>Alanine analogue. Bacteriostatic. Interferes with cell-wall proteoglycan synthesis. Renally excreted.</td>
<td>750-1000 mg PO QD&lt;br&gt;Administer with pyridoxine 150-300 mg QD</td>
<td>Neurological and psychiatric disturbances, including psychosis, convulsions, peripheral neuropathy, especially when taken with isoniazid. These adverse reactions may be lessened by pyridoxine coadministration.&lt;br&gt;Interacts with phenytoin. Effects may be potentiated by alcohol.</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Description</td>
<td>Administration</td>
<td>Side Effects</td>
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<tr>
<td>Ethionamide</td>
<td>Derivative of isonicotinic acid. Bacteriostatic. Cross-resistance with thiacezzone occurs. Hepatically metabolized, renally excreted.</td>
<td>750-1000 mg PO QD Increase gradually to maximum dose.</td>
<td>GI upset (nausea, vomiting, abdominal pain, loss of appetite) and metallic taste in mouth common. May cause hypothyroidism when taken with PAS. Rarely, hepatitis, arthralgias, impotence, gynecomastia, photosensitive dermatitis.</td>
</tr>
<tr>
<td>Thiacetzone</td>
<td>Weakly bactericidal. Inhibition of mycolic acid synthesis.</td>
<td>150 mg PO TID</td>
<td>GI upset (nausea, vomiting) and hypersensitivity common. Jaundice, reversible bone-marrow suppression, cutaneous reactions including Stevens-Johnson syndrome, especially in HIV-infected patients. May potentiate ototoxicity of aminoglycosides.</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>Beta-lactam antibiotic with a beta-lactamase inhibitor.</td>
<td>500 mg PO TID</td>
<td>GI upset. Administer with food. Hypersensitivity reactions.</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Semisynthetic erythromycin derivative. Efficacy shown against M. avium complex. In vitro killing of susceptible strains of M. tuberculosis.</td>
<td>500 mg PO BID</td>
<td>GI upset much less common than with erythromycin. May cause metallic taste in mouth.</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>Substituted iminophenazine bright-red dye. Bacteriostatic. Transcription inhibition by binding guanine residues of mycobacterial DNA.</td>
<td>200-300 mg PO QD Initiate dose at 300 mg and may lower to 200 mg when skin begins to bronze.</td>
<td>Discoloration of skin, GI upset, and crystal deposition causing discoloration of the eye. Less commonly, phototoxicity reactions, malabsorption, and severe abdominal distress.</td>
</tr>
<tr>
<td>Rifabutin/ Rifapentine</td>
<td>Rifamycin spiroperidyl derivative. Cross-resistance with rifampin &gt;70%.</td>
<td>150-300 mg PO QD</td>
<td>Considered to be of comparable or lesser toxicity as RIF. Hepatotoxicity, GI upset, hypersensitivity.</td>
</tr>
</tbody>
</table>
REFERENCES


FORM 1.  INITIAL CLINICAL EVALUATION FORM

Name of patient: ___________________________ Patient ID: ___________________________

Date of evaluation: ___________________________

Name of interviewer: ___________________________ Health facility: ___________________________

Age of patient: ___________________________ Date of birth: ___________________________

Sex: __M__ __F

Patient address: ___________________________

### Treatment Summary:

<table>
<thead>
<tr>
<th>Treatment #</th>
<th>Date treatment started</th>
<th>Date treatment completed</th>
<th>Regimen received (e.g. H_{3}R_{2}E_{2}Z_{2})</th>
<th>Treating health facility</th>
<th>Treatment months remaining smear pos.</th>
<th>Received regular treatment? (circle one)</th>
<th>Condition at completion (cured/failed/abandoned)</th>
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<tr>
<td>1</td>
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<td>C F A</td>
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</table>

### Drug-Susceptibility Summary:

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>Date of sample</th>
<th>Date of result</th>
<th>Laboratory</th>
<th>Resistant to:</th>
<th>Sensitive to:</th>
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</table>

Check all drugs that the patient has received:

<table>
<thead>
<tr>
<th>INH</th>
<th>RIF</th>
<th>EMB</th>
<th>PZA</th>
<th>SM</th>
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<tbody>
<tr>
<td>KM</td>
<td>CM</td>
<td>AMK</td>
<td>FQ</td>
<td>THA</td>
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<tr>
<td>CS</td>
<td>PAS</td>
<td>THZ</td>
<td>AMX-CLV</td>
<td>RFB</td>
</tr>
<tr>
<td>CLR</td>
<td>Other</td>
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</tbody>
</table>
Past contact summary (to be used to determine possible sources of infection for the index case):

<table>
<thead>
<tr>
<th>Name of contact</th>
<th>Relation of contact to patient</th>
<th>Did the contact have multiple treatments? (circle one)</th>
<th>Did the contact die of TB? (circle one)</th>
<th>Did the contact have documented MDRTB? (circle one)</th>
<th>If the contact had MDRTB, to which of the following drugs was he or she resistant:</th>
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</table>

Health worker? ____

Occupation: ___________________

Drug addiction: __Y__ N

Ever been in jail? __Y__ N

Ever in an institution? __Y__ N

Smoke(d) tobacco? __Y__ N

Previous thoracic surgery? __Y__ N

Date of surgery: ________________ Procedure: ________________________

Review of symptoms:

<table>
<thead>
<tr>
<th>Cough</th>
<th>Phlegm</th>
<th>Hemoptysis</th>
<th>Respiratory distress</th>
<th>Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night sweats</td>
<td>Weight loss</td>
<td>Cachexia</td>
<td>Diarrhea</td>
<td>Nausea or vomiting</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Oxygen dependency</td>
<td>Chest pain</td>
<td></td>
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</tbody>
</table>

Physical Exam: __Heart Rate__ __Respiratory Rate__ __Blood pressure__ __Weight__

Other symptoms: __________________________

Chest X-ray: __Bilateral__ __Unilateral__ __Cavitary disease__ __Severe parenchymal destruction__

Grade: _______
Current contacts of patient (to be used to guide possible screenings and interventions for these individuals):

<table>
<thead>
<tr>
<th>Name of contact</th>
<th>Relation to patient</th>
<th>Symptomatic? If yes, describe symptoms (e.g. cough, weight loss, fever)</th>
<th>Has contact received BCG?</th>
<th>Is contact PPD-positive?</th>
<th>Comments</th>
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</table>
FORM 2. DOT ADMINISTRATION SHEET

Name of patient: ____________________________  Health facility: ____________________________
Age of patient: ______  Date of birth: ______  Sex: ☐ M  ☐ F  Occupation: ____________________________
Patient address: ____________________________

Initial AFB:  Date: ___________  Result: ___________  Lab ID#: ___________
Initial Culture:  Date: ___________  Result: ___________  Lab ID#: ___________
TB:  ☐ Pulmonary  ☐ Extrapulmonary (specify site): ____________________________
Susceptibility Testing:  Date ______  Resistant to: ____________________________  Sensitive to: ____________________________
                  Date ______  Resistant to: ____________________________  Sensitive to: ____________________________

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Adverse Reaction
Monthly Weight
AFB control
Culture control
LMP

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Adverse Reaction
Monthly Weight
AFB control
Culture control
LMP

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Adverse Reaction
Monthly Weight
AFB control
Culture control
LMP
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Adverse Reaction

Monthly Weight

AFP control

Culture control

LMP

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Adverse Reaction

Monthly Weight

AFP control

Culture control

LMP

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Adverse Reaction

Monthly Weight

AFP control

Culture control

LMP

<table>
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<th>Date</th>
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<th>Month</th>
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Adverse Reaction

Monthly Weight

AFP control

Culture control

LMP
FORM 3. RESISTANCE RESULTS SUMMARY SHEET

Name of patient: ____________________________________________
Date treatment begun: _______________________________________
Health facility: _____________________________________________

<table>
<thead>
<tr>
<th>Data sample</th>
<th>ID no</th>
<th>INH 0.1</th>
<th>INH 0.2</th>
<th>INH 0.4</th>
<th>INH 1</th>
<th>INH 5</th>
<th>RIF</th>
<th>PZA</th>
<th>EMB</th>
<th>SM 2.0</th>
<th>SM 10</th>
<th>KM</th>
<th>CM</th>
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<th>ETH</th>
<th>CPX</th>
<th>CS</th>
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Observations:

21
FORM 4. SUMMARY SHEET FOR DIRECT SMEAR MICROSCOPY AND CULTURE RESULTS

Name of patient: 
Date treatment begun: 
Health facility: 

<table>
<thead>
<tr>
<th>Month</th>
<th>Date of sample</th>
<th>Local Laboratory ID #</th>
<th>Result of Direct Smear Microscopy</th>
<th>Results of Culture</th>
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Observations:
# Form 5. Side-Effect & Allergy Monitoring Form

## Name of Patient:

__________________________

Health worker: ____________________________

Date: ____________________________

Date of initial presentation of symptoms: ____________________________

## Adverse Reaction:

- Abdominal pain
- Constipation
- Decreased hearing
- Diarrhea
- Dizziness
- Fatigue
- Fever
- Headache
- Joint pain
- Nausea
- Psychosis
- Rash
- Ringing in ears (tinnitus)
- Skin coloration changes
- Tremors
- Vision changes
- Vomiting
- Other: ____________________________

## Description of symptom:

- __________________________________________
- __________________________________________
- __________________________________________
- __________________________________________

## Management:

- __________________________________________
- __________________________________________
- __________________________________________

## Evolution:

- __________________________________________
- __________________________________________
- __________________________________________

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23
# Health Worker Report

**Date:** ______________

**Name of patient:** ____________________________

**Health Worker:** ____________________________

## Patient complaints, signs, symptoms

<table>
<thead>
<tr>
<th>Date of event</th>
<th>Description</th>
<th>Pending follow-up</th>
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</table>

## MDRTB Regimen

<table>
<thead>
<tr>
<th>Date</th>
<th>Missed doses, regimen changes</th>
<th>Pending follow-up</th>
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## Other medications used (non-TB drugs)

<table>
<thead>
<tr>
<th>Date</th>
<th>Medication</th>
<th>Dose</th>
<th>Duration of use</th>
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</table>

## Laboratory analyses

<table>
<thead>
<tr>
<th>Date</th>
<th>Laboratory tests</th>
<th>Result</th>
<th>ID number</th>
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## Other consults, tests, observations:

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24
### FORM 7. SUMMARY DATA FOR PATIENTS WITH SUSPECTED MDR TB
(adapted from WHO Guidelines for the Management of Drug-Resistant Tuberculosis, 1997, Table 1)

<table>
<thead>
<tr>
<th>Drugs and Chemotherapy</th>
<th>Drugs Taken (more freq. duration)</th>
<th>Smear Results</th>
<th>Culture Results</th>
<th>Susceptibility Test Results</th>
<th>Radiological Results</th>
<th>Clinical Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of diagnosis:</td>
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<td>Date of starting first course of chemotherapy:</td>
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<td>Date of completing or stopping first course of chemotherapy:</td>
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<td>Date of starting second course of chemotherapy:</td>
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<td>Date of completing or stopping second course of chemotherapy:</td>
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<td>Date of starting third course of chemotherapy:</td>
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<td>Date of completing or stopping third course of chemotherapy:</td>
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25
DRUG FORMULARY FOR COMMUNITY-BASED ITR
MDRTB INITIATIVE

- amikacin
- amoxicillin-clavulanic acid
- capreomycin
- clarithromycin
- clofazimine
- cycloserine
- ethambutol
- ethionamide
- fluoroquinolones
- isoniazid
- kanamycin
- para-aminosalicylic acid (PAS)
- pyrazinamide
- rifabutin
- rifampin
- streptomycin
- thiacetazone