

**PROCUREMENT OF SECOND-LINE ANTI-TUBERCULOSIS
DRUGS FOR DOTS-PLUS PILOT PROJECTS**

WHO Working Group on DOTS-Plus for MDR-TB

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EXECUTIVE SUMMARY

TB remains one of the world's leading infectious causes of adult deaths; furthermore, multidrug-resistant strains of the disease are emerging as a considerable threat to human health and a danger to TB control in numerous "hot spots" throughout the world. In this context, the concerns of this meeting were twofold: to advance the implementation of "DOTS-Plus" projects, which promise to offer effective treatment to patients with multidrug-resistant disease; and to safeguard the hard-won gains of global TB control achieved through DOTS programs. As the Working Group had previously identified the affordability, availability, quality, and control of second-line antituberculous medications as key to the success of DOTS-Plus programs, the meeting specifically focused on establishing a rational procurement strategy for second-line antituberculous drugs.

The first half of the meeting was directed at providing updates of the various potential and established DOTS-Plus pilot projects. Preliminary data regarding program efficacy was presented by the two Peru-based projects.

The second half of the meeting targeted the next steps in procurement of second-line drugs. Presentations by representatives of the pharmaceutical industry demonstrated their interest in treating MDRTB. Additionally, drug procurement specialists presented model procurement practices that could be implemented by the Working Group.

The meeting concluded with the following recommendations:

- 1) Create a scientific panel to standardise DOTS-Plus protocols and evaluate future protocols,
- 2) Develop a proposal to place second-line drugs on the WHO Model List of Essential Drugs, and
- 3) Initiate the process of a direct procurement strategy for second line drugs for present DOTS-Plus pilot programs, and direct the process of an overall pooled procurement strategy for second line drugs for future DOTS-Plus programs.

A meeting of the scientific panel of the DOTS-Plus Working Group was scheduled for September 13, 1999, in Madrid, Spain.

BACKGROUND

A 1997 WHO/IUATLD survey identified “hot spots” of multidrug-resistant tuberculosis (MDRTB). Additionally, the survey found that drug resistance is ubiquitous. After a series of meetings with international tuberculosis experts in 1998, the World Health Organisation (WHO), having recognised the importance of MDRTB, worked with various partners to create a pilot strategy (DOTS-Plus) to control MDRTB. Two of these international partners, Partners in Health and the National Tuberculosis Control Program of Peru, had already begun tackling the MDRTB epidemic and demonstrated that multi-resistant forms of the disease could be controlled, even in resource-poor settings. At a meeting on January 29, 1999, the international community joined forces with WHO to establish the “WHO Working Group on DOTS-Plus for MDRTB” and two sub-groups: one devoted to establishing a drug procurement system for second-line drugs, and the other to creating a laboratory network for testing susceptibility to these drugs. Additionally, it was decided that six pilot projects should be implemented as soon as possible.

AIMS OF THE MEETING

On July 5-6, 1999, the World Health Organization Working Group on DOTS-Plus for MDR-TB and the Program in Infectious Disease and Social Change at Harvard Medical School (PIDSC) hosted a meeting to advance the prospects for treatment of patients with multidrug-resistant tuberculosis in resource-poor countries. The meeting was made possible by the sponsorship of the Open Society Institute, WHO, Harvard Medical School, and Partners In Health (PIH). Participants worked in concert to lay the groundwork for appropriate MDR-TB case management, comprehensive evaluation of treatment programs, and joint procurement of affordable second-line antituberculous medications of high quality. Specifically, the Working Group formally convened to discuss the following topics:

- 1) Operations protocols for MDR-TB case management,
- 2) Feasibility studies of DOTS-Plus programs, and
- 3) Methods to secure an affordable supply of second-line drugs

Nine projects, some in planning stages and others already established, reported on their progress and presented preliminary data regarding the magnitude of the MDRTB problem at their respective project sites. These projects were Latvia (NTP Latvia, CDC, PHRI), Peru (NTP Peru), Lima (PIH/Socios en Salud/Harvard), Caucasus (ICRC), Tomsk (PHRI, MERLIN, WHO), Kemerovo (MSF, PHRI), Ivanovo (CDC, USAID, PHRI), Estonia (NTP Estonia, IUATLD, Nordic Countries), Russia (World Bank). In regard to drug procurement, representatives of the ICRC, IDA, and WHO proposed several different strategies for group procurement.

AGENDA

Dr. Howard Hiatt (Harvard Medical School) opened the meeting by reaffirming the importance of DOTS-Plus. He charged meeting participants to reach consensus on the implementation of DOTS-Plus. This included the development of a plan for the procurement

of existing antituberculous medications at prices affordable to the poorest countries and the elaboration of strategies through which the full capabilities of the pharmaceutical industry and others could be brought to bear on the development of new therapeutic agents for TB.

Dr. Arata Kochi (WHO) then outlined the meeting rationale and proposed three clear meeting objectives:

- (1) Develop operational protocols for MDR-TB case-management and guidelines for feasibility studies for DOTS-Plus programs,
- (2) Develop a plan to secure a steady supply of affordable second-line drugs, and
- (3) Develop new partnerships comprising of “a mix of old hands and new players” to improve international TB control.

PROGRAMME REPORTS

Dr. Marcos Espinal (WHO) reported on the results of a retrospective study of the impact of drug resistance on treatment outcomes under program conditions in Peru, Korea, Hong Kong, Ivanovo (Russian Federation), the Dominican Republic, and Italy. Standardised short-course chemotherapy (SCC) was found to be much more successful in treating MDR-TB (55% treatment success rate) under strong NTPs than weaker NTPs (20% success rate). But because overall success rates—derived from the sum of cures (based on negative smear) and completion—were unacceptably low, Dr. Espinal concluded that “short-course chemotherapy will cure only a fraction of MDR cases.” In response, Dr. Michael Kimerling (MSF-Belgium) referred to a cohort study in progress in Kemerovo that suggests that the WHO re-treatment regimen might actually lead to a higher proportion of drug-resistant disease and poorer clinical outcomes than no treatment at all.

Dr. Espinal remarked that the cost of SCC is between \$20 and \$40, while treatment with second-line drugs costs between \$1,000 and \$10,000. In view of this great disparity in costs, he argued that WHO recommendations should be guided by a cost-effectiveness analysis of different regimens and an assessment of their feasibility. In response, Dr. Paul Farmer (PIDSC, PIH) pointed out that any discussion of the relative cost of various regimens must take into account the epidemiologic and monetary ‘costs’ of treatment failure. Treatment failure, he argued, leads to increased disease burden, potentially “amplified” drug resistance patterns, and further transmission of MDR-TB strains. For these reasons, Dr. Farmer argued that a comparison of program efficiency based uniquely on the cost of drugs would not be accurate. Dr. Mario Raviglione (WHO) summarized the WHO position on the treatment of MDR-TB: (1) the implementation of sound TB control programs following the DOTS strategy remains a top priority for action; (2) WHO recognizes that MDR-TB is a considerable threat to the effectiveness of DOTS in some areas of the world, and thus strongly supports pilot projects to assess the feasibility and cost-effectiveness of DOTS-Plus interventions in a variety of settings, provided DOTS is in place or being simultaneously introduced; (3) based on the results of these pilot projects, WHO and its partners in the Working Group will formulate international policy recommendations on MDR-TB management. He then offered WHO’s working definition of DOTS-Plus: “a case-management strategy designed to manage MDR-TB using second-line drugs within the DOTS strategy in low and middle income countries.”

Dr. Farmer observed that the WHO re-treatment regimen had been developed at a juncture when rifampin (RIF) resistance was unknown, whereas in settings with endemic RIF resistance, the WHO re-treatment regimen had resulted in low cure rates and created further resistance. Dr. Farmer asked the meeting participants whether the WHO could be expected to change its recommendation for settings in which RIF resistance was established. Dr.

Raviglione replied that if current DOTS-Plus pilot projects demonstrated the necessity of changing the recommendations, WHO would take the requisite actions.

Dr. Jaime Bayona (SES) began the presentations by representatives of DOTS-Plus pilot projects with a description of his organization's work in Lima, Peru. Of 63 patients who had completed four or more months of treatment, over 85% were either cured or culture negative.

The results showed that while it was possible to cure MDR-TB in resource-poor settings, transnational collaboration and community involvement were necessary. Dr. Peter Cegielski (CDC) reported the results of the Ivanovo civilian project. Primary MDR-TB increased from 3.8% of cases in 1996 to nearly 10% in 1998. Of 26 primary MDR-TB cases in the study, 65% were caused by strains resistant to three or more drugs. The cure rate with SCC for patients with primary MDR-TB was 6%; treatment failed in 61% of MDR-TB cases; and death occurred in over one quarter of MDR-TB cases. Dr. Karin Weyer (TBRP, South Africa) noted her country's difficult TB situation, which was complicated by the world's most rapidly growing AIDS epidemic. With an annual TB incidence of 206,000 cases, even the estimated 1% incidence of MDR-TB generated over 2,000 new cases per year. In the national MDR-TB treatment project, seven of eight provinces chose to follow a standardised approach to treatment of MDR-TB. In preliminary data from the first year of treatment, two-thirds of patients receiving 'standardised' treatment achieved smear conversion; 100% of these went on to achieve culture conversion by 12 months. Results were similar for patients on individualised regimens. The 'standardised' regimens were also tested using a simplified dosing scheme, with a roughly comparable outcome.

Dr. Tim Healing (MERLIN) then began the presentation for the groups from Tomsk. Initial drug-susceptibility testing showed high levels of resistance to SM and INH, and 15% of isolates were MDR. In 1998, in spite of a leveling-off of TB incidence in the program area, preliminary data suggested that the incidence of DR-TB, and particularly MDR-TB, was rising rapidly.

Dr. Alex Goldfarb (PHRI) outlined the Tomsk project's general approach. First, the project aimed to expand DOTS coverage to the area's outlying prisons, homeless population, and most remote districts; second, it had tried to impose a rational hierarchy on the oblast's laboratories; third, the project had worked to streamline data management in the oblast; finally, it had begun to train Russian physicians and western consultants to work together as members of the same team. Only such a comprehensive approach, Dr. Goldfarb said, would be successfully reproducible on the national level. Dr. Mike Kimerling (MSF-Belgium) turned to the clinical aspects of the Tomsk and Kemerovo projects, which take a common approach. In the civilian population in Tomsk, the proportion of MDR-TB among new cases increased from 3% in 1997 to 6.2% in 1998, to 10% in the first quarter of 1999. There was also a significant proportion of poly-resistant non-MDR-TB. In the Tomsk prisons in 1998, almost one-third of new cases were MDR-TB. In the Kemerovo prisons, MDR-TB was somewhat less common, accounting for 17% of new cases. In closing, Dr. Kimerling estimated that there would be 459 new cases of MDR-TB in the Kemerovo prisons over the next year, in addition to 130 chronic cases.

Dr. Pascal Ollé (ICRC) opened the afternoon session by reporting on his organization's programs in prisons in Azerbaijan, Georgia, and Armenia. In Azerbaijan and Georgia, treatment results had been poor due to MDR-TB, weakness of the national programs, difficulties following released prisoners, and a black market, open to civilians and prisoners alike, for second-line drugs. The situation in Armenia, where health authorities had made a strong commitment to TB control and prevalence of TB was lower, was presented as a contrast to the two Caucasian republics. Dr. Manfred Danilovits (NTP Estonia) reported that his country was not yet committed to carrying out a DOTS-Plus pilot project, but that it hoped to commit to one in the future. Both primary and acquired drug resistance had increased markedly in 1998 over 1994-1997. For instance, the percentage of patients sick

with strains sensitive to four drugs had fallen from 71.2% between 1994 and 1997 to 61.2% in 1998.

Dr. Vaira Leimane (NTP Latvia) reported that in Latvia in 1998, primary and acquired multidrug resistance were 9% and 24%, respectively. Among patients with MDR-TB, 50% had resistance to three drugs, and another 45% had resistance to four or five drugs. In 1998, there were 727 patients with active MDR-TB in Latvia, including chronics. Of these, 21% were smear and culture negative, 27% were under treatment, 52% were chronics without treatment. Dr. Joana Godinho (World Bank) spoke about the TB situation in Russia. The 1997 case-notification rates were 82 per 100,000 in the civilian population, and 4,000 per 100,000 in prisons. TB mortality was 17 per 100,000 in the country as a whole, and over 500 per 100,000 in the prisons. The percentage of TB cases caused by MDR strains was 9%, and 22% in prisons.

Dr. Godinho then noted the request by the Russian Federation to the World Bank for a loan of US \$150 million to address TB and AIDS. The Bank had begun to flesh out the details, and hoped that the TB component of the project would reduce disease prevalence by 10%, and the case fatality rate by 40%, over 5 years. At the national level, the TB component would strengthen surveillance systems and standardize treatment protocols. At the regional level, the loan would support enhanced training and education, improved case finding and treatment, and TB treatment in the prisons. The loan would support oblasts that had shown a willingness to adopt the DOTS strategy and to integrate prisons into the project.

Dr. Ivan Sabogal (Peruvian NTP) reported on a standardized, empiric re-treatment scheme for MDR-TB implemented since October 1997 in Peru. Almost 85% of these patients, all of whom had failed a first re-treatment regimen, had MDR-TB. Of patients sick with MDR-TB, 86% had infecting strains that were resistant to at least three drugs. The culture conversion rate for patients with demonstrated MDR-TB for whom data were available (evaluated after 9 or 12 months of treatment) was 74%.

At the end of the first day, Dr. Raviglione summarised the main points of the day's discussion, noting the group's consensus on several key points:

- The importance of continued surveillance aimed at identifying MDR-TB "hot spots" and determining the size of the market for second-line antituberculous medications;
- The importance of a high quality network for drug-susceptibility testing, and the need to control the availability of second-line drugs by ensuring their use only within the framework of pre-existing or concurrently established DOTS programs, even by legal regulation in some instances;
- The need for a logical, standardised approach to the development of regimens for MDR-TB;
- The importance of close co-ordination between the nine pilot projects; and
- The need to consider active case finding, institutional intervention, and isolation as further means of identifying and controlling outbreaks.

Several participants proposed that a scientific panel be created within the working group, comprising clinical and public health experts. The purpose of this panel would be to review protocols for proposed DOTS-Plus programs and to assess whether protocols met WHO standards.

Some participants suggested that the cost-efficacy of DOTS-Plus needed to be demonstrated before the approach was more broadly implemented. To this end, a health economist based at WHO will initiate cost-efficacy analyses at one or two DOTS-Plus sites (the PIH/SES, H project and Peru NTP project were suggested, as they are already established).

Participants concurred that the entire Working Group should meet annually to review projects, share data, and discuss necessary improvements. It was agreed that the Working Group's final policy recommendations should be made only after careful analysis of several years of complete cohort data. Because a full course of treatment would take at least two years, rather than the six months of SCC, recommendations would be made final only in two to three years.

Drs. Jennifer Furin and Sonya Shin (PIDSC) opened the second day of the meeting by presenting their experience managing the side effects of second-line drugs used in the PIH/SES treatment project in Lima. Because of the severity of disease and drug resistance among this cohort of patients, the project aimed at aggressive management, using doses of medicines that were at the upper end of the recommended range. Yet, Drs. Furin and Shin reported that adverse effects were much less severe than the literature had suggested. Side effects of MDR-TB treatment were significant, but almost all could be managed without compromising the efficacy of therapy. Dr. Farmer noted that some tests for monitoring side effects (liver function tests and audiograms) had been stopped when it was determined that the tests were not providing clinically useful information. Drs. Furin and Shin concluded that side effects in this cohort were almost completely manageable through community-based, outpatient treatment.

DRUG PROCUREMENT

Dr. Richard Laing (Boston University School of Public Health) then began a discussion of drug procurement, noting that the aim of procurement was to secure drugs of good quality at the best possible prices, but that the cost of purchasing drugs was by no means the only cost in any system of procurement. Additional costs included those for transport, quality assurance testing, customs duties, storage, various mark-ups, sales taxes, and dispensing fees.

Dr. Laing then outlined four main methods of procurement: open tender, restricted tender, negotiated procurement, and direct procurement. The Eastern Caribbean Drug Service (ECDS) was presented as an example of a self-financing system of pooled, competitive procurement by restricted tender. In brief, the five small island nations that are members of the ECDS estimate their collective needs at an annual meeting and issue a tender to pre-qualified suppliers. The ECDS then adjudicates the tender. Countries place orders on an "as needed" basis through the ECDS secretariat, and suppliers ship directly to individual countries, which authorise payment upon receipt of goods. The ECDS funds its activities with a 15% surcharge, a cost the member states consider well worth bearing, in light of the large cost-reductions the system has achieved. Dr. Laing argued that the ECDS owes its success to the prompt payment and active monitoring of suppliers; to a dedicated professional staff backed by high-level political support; and to member states' pledge not to buy outside the system. He concluded that the ECDS model might be appropriate for a pooled procurement scheme for second-line antituberculosis drugs .

Dr. Gail Cassell (Eli Lilly & Co.) then gave the first of three presentations by representatives of the research -based pharmaceutical industry. She described the hurdles confronting the industry in developing new drugs against TB. Foremost among these was the necessity of recouping the industry's estimated cost of bringing a new drug to market—approximately \$650 million, taking into account the cost of developing the many drugs that never make it to market.

Dr. Giorgio Roscigno (Hoechst Marion Roussel) reported on the joint initiatives of the pharmaceutical industry and the WHO since the inauguration of Dr. Brundtland as Director-General of WHO in 1998. Two roundtables had been formed: one to address the question of access to existing pharmaceuticals for patients in poor countries and another to stimulate

research and development of new drugs for “neglected diseases,” with particular emphasis on malaria, AIDS, and TB. Dr. Roscigno related the obstacles perceived by industry to providing an affordable supply of second-line antituberculous agents. First, many of the agents were not registered in the countries in which they would be needed, and registration costs can constitute a sizeable disincentive when potential markets are small. Second, many of the agents were not on the WHO Model List of Essential Drugs. Third, existing estimates of medication requirements were highly imprecise. Fourth, without the assurance of a long-term commitment to treatment, production would proceed by small batches, resulting in higher cost than necessary. Fifth, without some standardisation of regimens, industry’s ability to forecast medication requirements would be hindered.

Discussion of pharmaceutical development continued with a presentation by Dr. David Jacobus (Jacobus Pharmaceuticals) describing his company’s formulation of para-aminosalicylic acid (PAS). This granular form of the drug has an acid-resistant coating that, with the granules’ small size, facilitates continuous release and gives the medication a longer half-life.

Dr. Peter Evans (WHO) contributed a perspective based on WHO’s experience with vaccine procurement. WHO uses a pre-qualification system that benefits other buyers as well, as the list of qualified manufacturers and reference prices is made public. Crucial to the function of this system are site visits to pharmaceutical manufacturers, which the WHO conducts jointly with the national regulatory authorities. The WHO reassesses producers every two years and engages in random testing of supplied vaccine. Dr. Evans noted that participating producers have asked for more, rather than less testing, as the WHO’s seal of approval gives them an advantage over unqualified rivals. Dr. Evans reaffirmed the importance of the Model List of Essential Drugs in vaccine procurement, and reiterated the importance of including second-line antituberculous drugs on the list. About 145 countries construct their national formularies based on the WHO list, and absence of a drug from the WHO list makes its registration virtually impossible in many cases. Countries without well-funded regulatory authorities rely especially heavily on the WHO list, since it provides assurance that drugs included are “right by science,” and that treatment guidelines exist.

Dr. Pascal Ollé (ICRC) then offered his organization’s perspective. Dr. Ollé noted that quality is itself a cost, and cautioned donors that buying drugs at the lowest price might not be the most cost-effective strategy in the long run. He also argued that no system could work without pre-qualification.

Guido Bakker (IDA) then described his organization’s work to the participants, posing four questions that he argued were crucial to the establishment of a workable procurement regime:

Who is the client?

What is the market size?

What products (including dosages and formulations) will be required?

Which drugs have the priority?

Mr. Bakker described how the IDA has succeeded in lowering the costs of many drugs in Africa by locating sources, assuring quality, and selling at cost. He expressed IDA’s commitment to making available all second-line antituberculous drugs within the next six months to one year.

Dr. Farmer presented the Open Society Institute/Harvard plan for publication of a report on the impact of drug-resistant TB, currently in preparation. One purpose of the volume, he noted, would be to review all available data on MDR-TB incidence and prevalence and to describe the course of key epidemics that will require second-line drugs for control. With

the assistance of all present, he concluded, the report would be presented at a gathering of donors later in the year.

Calculations of projects' drug needs had been performed during the course of the meeting, and once completed, Dr. Jim Yong Kim (PIH) initiated the discussion on pooled procurement. As some projects were ready to purchase and others less certain of their needs, the participants decided to establish a "hard" list of participants needing to purchase drugs immediately and a "soft" list of those who would purchase in the future.

After some discussion, three timetables were established: immediate, two months to one year, and more than one year. Organisations requiring immediate supplies would place orders directly with manufacturers, and others would follow in two months to one year. Dr. Evans, Dr. Raviglione, and Rajesh Gupta, all at WHO, would co-ordinate this second round of purchases in conjunction with Dr. Kim. These purchases would be pooled in so far as possible, and would take place by direct negotiation. In the long term, a mechanism would be developed to enable fully pooled procurement by restricted tender.

MEETING CONCLUSIONS

The meeting concluded with consensus on the following steps to advance the DOTS-Plus pilot projects:

- 1) A proposal would be drafted to place the following drugs on the WHO Model List of Essential Drugs: capreomycin, cycloserine, para-aminosalicylic acid, kanamycin, amikacin, ethionamide, ciprofloxacin, and ofloxacin.
- 2) A scientific panel would be formed to address the standardisation of DOTS-Plus protocols as part of the WHO "umbrella" for DOTS-Plus pilot programs. Guidelines for this standardisation would be developed and finalised at a meeting to be held September 13, 1999, in Madrid, Spain. All DOTS-Plus protocols would be reviewed by members of the subcommittee for approval.
- 3) Organisations requiring immediate supplies of drugs would procure them directly, and other groups would follow over the next two months to one year using a pooled procurement strategy co-ordinated by WHO and PIDSC/PIH. All organisations would collaborate over the next year to institute a common procurement system using restricted tenders.

WHO position on DOTS-Plus and procurement of second line drugs

Summary of WHO current position on MDR-TB

To achieve TB control worldwide, WHO considers implementation of sound TB control programmes following the DOTS strategy as a top priority for action.

Recognising that MDR-TB is a considerable threat to the effectiveness of DOTS in some areas of the world, WHO strongly supports pilot projects to assess the feasibility and cost-effectiveness of DOTS-PLUS* interventions in a variety of settings, provided DOTS is in place or being simultaneously introduced.

Based on the results of these pilot projects, WHO and its partners of the newly established Working Group on "DOTS-PLUS for MDR-TB" will formulate international policy recommendations on MDR-TB management.

**A working definition of DOTS-PLUS is the following: "DOTS-PLUS is a strategy under development designed to manage MDR-TB using second-line drugs within the DOTS strategy in low-and middle-income countries".*

- The WHO current position summarised in the above box spells out that **DOTS is the first priority** for action, as proper TB control prevents MDR-TB by minimising its creation.
- The box above also implies that second-line drugs for MDR-TB, as an essential component of DOTS-PLUS, are to **be used only where adequate measures are present** to protect the creation of additional MDR-TB. This means that pilot projects will be established only where the health system effectively guarantees that second-line drugs are administered following proper doctor and patient education and under strict vigilance.
- The current attempts to address MDR-TB must be considered in the context of **operational research "pilot" projects** that will establish the feasibility and cost-effectiveness of DOTS-PLUS.
- These pilot projects will need to have clear **"exit points"** in such a way that, in case one detects incorrect use of second-line drugs, the experiment can be stopped rapidly without compromising future usefulness of second-line drugs.
- It should be clear that final **WHO recommendations on DOTS-PLUS** will only be made in partnership with all collaborators **after accumulating evidence**. If pilot projects show negative results, WHO will may go back to the concept of using second-line drugs in special centres and for individual purposes, rather than producing a programmatic policy.
- As one of the main constraints to DOTS-PLUS is the procurement of quality second-line drugs, the WHO Working Group is currently working to **create a consortium of buyers** in order to negotiate reductions in cost with drug producers and enhance procurement procedures. Drugs to be considered are: amikacin, kanamycin, capreomycin, cycloserine, PAS, ethionamide/prothionamide, quinolones (ciprofloxacin and ofloxacin).
- **The negotiation with drug producers** needs to be fair, transparent and respectful of their interests. Therefore, once the estimated needs of drugs are available, WHO proposes a bidding mechanism open to all potential interested and qualified parties.
- Once a drug procurement mechanism is identified, every effort must be made to ensure that **the consortium of buyers will purchase only high quality drugs**.
- While the drug procurement system is now targeting pilot projects only, it could in the future become a **sustainable system for countries** to gain access to second-line drugs.

Annex 2

Common adverse effects observed and management strategies used in a cohort of 49 patients receiving community-based therapy for MDR-TB in Lima, Peru

ADVERSE EFFECT	SUSPECTED AGENT(S)	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Seizures	CS, INH, fluoroquinolones	<ol style="list-style-type: none"> 1) Initiate anti-convulsant therapy (e.g. phenytoin, valproic acid) 2) Increase pyridoxine to 300mg daily 3) Lower dose of suspected agent, if this can be done without compromising regimen 4) Discontinue suspected agent if this can be done without compromising regimen 	<ol style="list-style-type: none"> 1) Anti-convulsant is generally continued until MDR-TB treatment completed or suspected agent discontinued 2) History of prior seizure disorder IS NOT a contraindication to the use of agents listed here if patient's seizures are well-controlled and/or patient is receiving anti-convulsant therapy 3) Patients with history of prior seizures may be at increased risk for development of seizures during MDR-TB therapy 4) Seizures not a permanent sequelae of MDR-TB treatment
Peripheral neuropathy	SM, KM, AMK, CM, INH, THA, fluoroquinolones, CS, EMB	<ol style="list-style-type: none"> 1) Increase pyridoxine to 300mg daily 2) Change parenteral to CM if patient has documented susceptibility to CM 3) Begin exercise regimen, focusing on affected regions 4) Initiate therapy with tricyclic anti-depressant medications 5) Lower dose of suspected agent, if this can be done without 	<ol style="list-style-type: none"> 1) Patients with co-morbid disease (e.g. diabetes, HIV, alcoholism) may be more likely to develop peripheral neuropathy, but these conditions ARE NOT contraindications to the use of the agents listed here 2) Neuropathy is generally not reversible, although only a minority (approximately

		<p>compromising regimen</p> <p>6) Discontinue suspected agent if this can be done without compromising regimen</p> <p>7) Initiate therapy with neurontin</p>	<p>10%) of patients require continued intervention to keep symptoms controlled once MDR-TB treatment completed</p>
Hearing loss	SM, KM, AMK, CM, CLR	<p>1) Change parenteral to CM if patient has documented susceptibility to CM</p> <p>2) Lower dose of suspected agent, if this can be done without compromising regimen</p> <p>3) Discontinue suspected agent if this can be done without compromising regimen</p>	<p>1) If patients have received prior treatment with aminoglycosides, they may start therapy with hearing loss</p> <p>2) Hearing loss is generally not reversible</p>
Psychotic symptoms	CS, fluoroquinolones, INH, THA	<p>1) Initiate anti-psychotic medications</p> <p>2) Hold suspected agent for short period of time (1-4 weeks) while psychotic symptoms brought under control</p> <p>3) Lower dose of suspected agent, if this can be done without compromising regimen</p> <p>4) Discontinue suspected agent if this can be done without compromising regimen</p>	<p>1) Some patients will need to continue anti-psychotic treatment throughout MDR-TB therapy</p> <p>2) Prior history of psychiatric disease IS NOT a contraindication to the use of agents listed here but may increase the likelihood of development of psychotic symptoms</p> <p>3) Psychotic symptoms generally reversible upon MDR-TB treatment completion or discontinuation of offending agent</p>
Depression	Socioeconomic circumstances, CS, fluoroquinolones, INH, THA	<p>1) Improve socioeconomic conditions</p> <p>2) Group or individual supportive counseling</p> <p>3) Initiate anti-depressant medications</p>	<p>1) Importance of socioeconomic conditions should not be underestimated as contributing factor to depression</p> <p>2) Depression and depressive</p>

		<ol style="list-style-type: none"> 4) Lower dose of suspected agent, if this can be done without compromising regimen 5) Discontinue suspected agent if this can be done without compromising regimen 	<p>symptoms may fluctuate during therapy</p> <ol style="list-style-type: none"> 3) History of prior depression IS NOT a contraindication to the use of the agents listed here, (Peruvian NTP) reported on a standardized, empiric re-treatment scheme for MDR-TB implemented
Hypothyroidism	PAS, THA, especially when given in combination	<ol style="list-style-type: none"> 1) Initiate thyroxine therapy 2) Substitute equally efficacious agent for THA or PAS 	<ol style="list-style-type: none"> 1) Completely reversible upon discontinuation of PAS or THA
Nausea and vomiting	PAS, THA, INH, EMB, CFZ, PZA	<ol style="list-style-type: none"> 1) Rehydration 2) Initiate anti-emetic therapy 3) Lower dose of suspected agent, if this can be done without compromising regimen 4) Discontinue suspected agent if this can be done without compromising regimen 	<ol style="list-style-type: none"> 1) Nausea and vomiting ubiquitous in early weeks of therapy and usually abate with supportive therapy 2) Electrolytes should be monitored and repleted if vomiting severe 3) Reversible upon discontinuation of suspected agent
Gastritis	PAS, THA, INH, EMB, CFZ, PZA	<ol style="list-style-type: none"> 1) Antacids (e.g. calcium carbonate, H2-blockers, proton-pump inhibitors) 2) Hold suspected agent(s) for short periods of time (e.g. 1-7 days) 3) Lower dose of suspected agent, if this can be done without compromising regimen 4) Discontinue suspected agent if this can be done without compromising regimen 	<ol style="list-style-type: none"> 1) Severe gastritis, as manifest by hematemesis, melena or hematechezia not observed in this cohort 2) Dosing of antacids should be carefully timed so as to not interfere with the absorption of antituberculous medications 3) Reversible upon discontinuation of suspected agent(s)
Hepatitis	PZA, INH, RIF, fluoroquinolones, THA, EMB, PAS	<ol style="list-style-type: none"> 1) Stop therapy 2) Rule out other potential causes of 	<ol style="list-style-type: none"> 1) History of prior hepatitis should be carefully analyzed to determine most

		<p>hepatitis</p> <p>3) Re-introduce medications grouped serially while monitoring liver function, with most likely agent introduced last</p>	<p>likely causative agent(s); these should be avoided in future regimens</p> <p>2) Generally reversible upon discontinuation of suspected agent</p>
Renal failure	SM, KM, AMK, CM	<p>1) Discontinue suspected agent</p> <p>2) Consider using CM if an aminoglycoside had been prior parenteral in regimen</p>	<p>1) History of diabetes or renal disease IS NOT a contraindication to the use of the agents listed here, although patients with these co-morbidities may be at increased risk for developing renal failure</p> <p>2) Renal impairment may be permanent</p>
Optic neuritis	EMB	<p>1) Stop EMB</p>	<p>1) Not observed in this cohort of patients</p>
Arthralgias	PZA, fluoroquinolones	<p>1) Initiate therapy with non-steroidal anti-inflammatory medications</p> <p>2) Initiate exercise regimen</p> <p>3) Lower dose of suspected agent, if this can be done without compromising regimen</p> <p>4) Discontinue suspected agent if this can be done without compromising regimen</p>	<p>1) Symptoms of arthralgia generally diminish over time, even without intervention</p> <p>2) Uric acid levels may be elevated in some patients but are of little therapeutic relevance and anti-gout therapy (e.g allopurinol, colchicine) is of no proven benefit in these patients</p>

Furin, J.J., Mitnick, C.D., Becerra, M.C., Shin, S.S., Singler, J.M., Bayona, J., Alcantara, F., Sanchez, E., Bomann, M., Kim, J.Y., and Farmer, P.E. Absence of serious adverse effects in a cohort of Peruvian patients receiving community-based treatment for multidrug-resistant tuberculosis (MDR-TB). *International Journal of Tuberculosis and Lung Disease* 1999; 3(9 S1): S81.

**Projected Needs for Current DOTS-Plus Pilot Projects
N=4,720**

<u>Drug</u>	<u>Raw Quantity Needed (kg)</u>
Ethambutol	693,512.50
Streptomycin	12,380.00
Amikacin	16,000.00
Kanamycin	218,300.00
Capreomycin	236,854.40
PAS	3,926,258.40
Ciprofloxacin	75,600.00
Ofloxacin	6,954,810.56
Levofloxacin	690,000.00
Cycloserine	2,002,613.20
Ethionamide	5,135,063.20

**Estimated Global Needs for MDRTB Treatment
N=250,000**

<u>Drug</u>	<u>Raw Quantity Needed (kg)</u>
Ethambutol	36,732,653.60
Streptomycin	655,720.34
Amikacin	847,457.63
Kanamycin	11,562,500.00
Capreomycin	12,545,254.24
PAS	207,958,601.70
Ciprofloxacin	4,004,237.29
Ofloxacin	368,369,203.39
Levofloxacin	36,546,610.17
Cycloserine	106,070,614.41
Ethionamide	271,984,279.66

AGENDA

Meeting Co-Chairs **Dr. Jim Yong Kim, Harvard Medical School** **Dr. Mario Raviglione, World Health Organization**

Monday, July 5, 1999

Moderator: Dr. Lee Reichman

9:00	Welcoming Remarks	<i>Dr. H. Hiatt, Harvard</i>
9:15	Adoption of the Agenda and Introductions	<i>Dr. J. Kim, Harvard</i>
9:35	Rationale and Objectives of the Meeting	<i>Dr. A. Kochi, WHO</i>
9:50	Brief Overview of the Global MDR-TB Situation	<i>Dr. P. Farmer, Harvard</i>
10:10	Treatment Outcomes of Drug-Resistant Tuberculosis under Programme Conditions	<i>Dr. M. Espinal, WHO</i>
10:30	Break	
10:50	Update of the WHO DOTS-Plus Working Group	<i>Dr. M. Raviglione, WHO</i>
Presentations of Current Plans for DOTS-Plus Programs		
11:10	PIH/SES	<i>Dr. J. Bayona, SES</i>
11:25	MSF	<i>Dr. M. Kimerling, MSF</i>
11:40	CDC	<i>Dr. N. Binkin, CDC</i> <i>Dr. P. Cegielski, CDC</i>
11:55	South Africa	<i>Dr. K. Weyer, MRC, NTP, S. Africa</i>
12:10	MERLIN	<i>Dr. T. Healing, MERLIN</i>
12:25	PHRI	<i>Dr. A. Goldfarb, PHRI</i>
12:40	Discussion	<i>All</i>
13:10	Lunch	

Moderator: Dr. Arata Kochi

Presentations of Current Plans for DOTS-Plus Programs

14:30	Peruvian NTP	<i>Dr. I. Sabogal, NTP, Peru</i>
14:45	ICRC	<i>Dr. P. Ollé, ICRC</i>
15:00	Estonian NTP	<i>Dr. M. Danilovits, NTP, Estonia</i>
15:15	Latvian NTP	<i>Dr. V. Leimane, NTP, Latvia</i>
15:30	World Bank	<i>Dr. J. Godinho, World Bank</i>
15:45	Discussion	<i>All</i>

16:15	Break	
16:30	Overview of Drug Procurement Strategies	<i>Dr. R. Laing, Boston University</i>
17:00	Perspectives from the Research-Based Pharmaceutical Industry	<i>Dr. G. Cassell, EliLilly Dr. G. Roscigno, HMR Dr. D. Jacobus, Jacobus</i>
17:45	First Day Conclusions	<i>Dr. M. Raviglione, WHO Dr. J. Kim, Harvard</i>

Tuesday, July 6, 1999

Moderator: Dr. Nancy Binkin

9:00	Current Pricing and Availability of 2nd-Line Drugs	<i>Dr. J. Kim, Harvard</i>
9:10	Review of the Side Effects of 2nd-Line Drugs	<i>Dr. J. Furin, Harvard Dr. S. Shin, Harvard</i>
9:30	Issues in Accessibility and Control of 2nd-Line Drugs	<i>Dr. P. Evans, WHO Dr. G. Bakker, IDA Dr. P. Ollé, ICRC</i>
10:40	Break	
11:00	Preparing a Joint Tender for MDR-TB Drugs: Financing, Quality Standards, Logistics	<i>Dr. P. Evans, WHO Dr. G. Bakker, IDA Dr. P. Ollé, ICRC</i>
12:30	Lunch	

Moderator: Dr. Edward Nardell

14:00	Overview of New Anti-Tuberculosis Drug Development	<i>Dr. J. Kim, Harvard</i>
14:30	Update of the Harvard/OSI MDR-TB Impact Report	<i>Dr. P. Farmer, Harvard Ms. M. Nitchun, OSI</i>
15:00	Advocacy: Building Strategies and Partnerships	<i>Dr. L. Reichman, UMDNJ Mr. J. Kramer, ASTER Dr. N. Binkin, CDC Dr. E. Goemaere, MSF Dr. K. Lambregts, KNCV Dr. A. Goldfarb, PHRI</i>
16:00	Break	
16:20	DOTS-Plus: Where Do We Go from Here?	<i>Dr. A. Kochi, WHO All</i>

Annex 6

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