DTS-Plus & Green Light Committee

Improving access to second-line anti-TB drugs

Current global tuberculosis (TB) efforts are threatened by high levels of multidrug-resistant TB (MDR-TB) in some parts of the world. The World Health Organization (WHO) and its international partners have established the Working Group on DOTS-Plus for MDR-TB (Working Group) in order to address MDR-TB effectively. The aim of the Working Group is to develop evidence-based policy guidelines for the management of MDR-TB. Pilot projects shall constitute evidence to guide the creation of specific policy to be used by WHO Member States. One of the short-term goals of the Working Group is to increase access to expensive second-line anti-TB drugs for DOTS-Plus pilot projects in low- and middle-income countries. This brochure explains the relationship between MDR-TB, DOTS, and DOTS-Plus and how projects can become a DOTS-Plus pilot project that can benefit from concessionary prices negotiated for second-line anti-TB drugs by the Working Group.



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What is MDR- TB?

Drug-resistant TB is caused by inconsistent, partial or incorrect treatment of drug-susceptible TB. MDR-TB is the acronym for Multidrug-Resistant Tuberculosis. MDR-TB is a specific form of drugresistant TB that is resistant to at least isoniazid and rifampicin, the two most powerful first-line anti-TB drugs.

It is essential that patients complete their treatment in order to be cured. This does not always happen when the supply of drugs is unreliable or when patients start to feel better as symptoms subside and decide themselves to stop treatment. The potential result is the emergence of MDR-TB. MDR-TB may also arise when physicians administer improper treatment to patients or when the drugs used are of insufficient quality.

Drug-susceptible TB can be cured in six to eight months with firstline anti-TB drugs (ethambutol, isoniazid, pyrazinamide, rifampicin, and streptomycin). MDR-TB is curable but requires extensive chemotherapy that takes up to two years and is more toxic to patients. The second-line anti-TB drugs needed for chemotherapy (amikacin, capreomycin, ciprofloxacin, cycloserine, ethionamide, kanamycin, levofloxacin, ofloxacin, para-aminosalycylic acid [PAS], and prothionamide) are often prohibitively expensive. MDR-TB patients who do not have access to second-line anti-TB drugs are often deemed incurable.

Is MDR-TB really a problem?

In the 1940s there were no drugs to cure TB. Today, strains of *Mycobacterium tuberculosis* that are resistant to a single anti-TB drug have been documented in all countries surveyed by WHO/IUATLD during 1994–1999. Moreover, strains of *Mycobacterium tuberculosis* resistant to all major anti-TB drugs have emerged. The most recent

WHO/IUATLD *Drug Resistance Surveillance Report*, which surveyed fiftyeight different countries and geographical areas between 1996 and 1999, revealed the presence of new MDR-TB "hot spots" in addition to those recorded in the first report. MDR-TB "hot spots" in addition to those recorded in the first report. MDR-TB was shown to range from 0% to 14.1% among new TB cases. Recent data indicate that MDR-TB needs to be managed aggressively and that treatment of MDR-TB with first-line anti-TB drugs is usually not effective. In an era of globalization with increasing international travel and migration, any country is a potential target for MDR-TB outbreaks. Recently, an increase in outbreaks of MDR-TB in the United States and Western Europe have proven to be partially linked to sources in other countries.



The DOTS Strategy combines 5 elements

- Political commitment to effective TB control
- Case detection by sputum smear microscopy among symptomatic people
- Standardized treatment regimen of 6–8 months of short-course chemotherapy (SCC) with first-line anti-TB drugs, administered under proper case management conditions, including direct observation
- Uninterrupted supply of all essential anti-TB drugs
- Standardized recording and reporting system allowing assessment of treatment results

What is DOTS?

DOTS is the acronym for Directly Observed Treatment, Short-course and is the brand name for the WHO-recommended strategy for TB control.

Of crucial importance is that health and community workers provide the proper environment for patients to receive the full course of first-line anti-TB drugs during the short-course chemotherapy; strict adherence to the treatment is imperative in the prevention of development of drug resistance. DOTS is best organized in such a way that patients receive treatment without having their daily life disrupted. The medication can be given by anyone who is willing, trained, responsible, acceptable to the patient and accountable to the TB control services. This approach makes it possible that patients, for example, receive medication at home or in the workplace and facilitates adherence to treatment.



Since DOTS was introduced on a global scale in 1991, approximately 3.5 million people have been cured of TB. In China, cure rates among new cases are 96%. In Peru, widespread use of DOTS for ten years has led to the successful treatment of 91% of cases. In some parts of the world (China and India) the price of a six-month supply of anti-TB drugs for DOTS is as low as US\$ 10–20 per patient. The World Bank has described the DOTS strategy as one of the "most cost-effective of all health interventions."

How poor TB control and MDR-TB reinforce each other

Emerging drug resistance is often a reflection of poor TB control in general and poor DOTS implementation in particular. From a public health perspective, poorly supervised or incomplete TB treatment is worse than no treatment at all, since inaccurate treatment can cause severe harm in the form of drug resistance. When patients fail to complete standard treatment regimens or are given the wrong treatment regimen they may remain infectious. The bacilli in their lungs may develop resistance to anti-TB drugs. People they infect will have the same drug-resistant TB strain. In areas with minimal levels of MDR-TB, DOTS will effectively manage the TB epidemic. In areas with significant levels of MDR-TB, however, the DOTS strategy needs to be modified to incorporate the proper administration of second-line anti-TB drugs.

The DOTS-Plus strategy

DOTS-Plus for MDR-TB is a comprehensive management initiative under development that is built upon the five elements of the DOTS strategy. DOTS-Plus takes into account specific issues, such as the use of second-line anti-TB drugs, that need to be addressed in areas where there are significant levels of MDR-TB.

The goal of DOTS-Plus is to prevent the further development and spread of MDR-TB. DOTS-Plus is not intended as a universal option and is not required in all settings. DOTS-Plus should be implemented in selected areas in order to combat an emerging epidemic. The underlying principle is that proper implementation of DOTS will prevent the emergence of drug resistance and should be the first step in fighting MDR-TB. It is not possible to conduct DOTS-Plus in an area without having an effective DOTS-based TB control programme in place.

The Working Group has identified access to second-line anti-TB drugs as one of the major obstacles to the implementation of DOTS-Plus pilot projects. While access to second-line anti-TB drugs must increase, these drugs should only be used in DOTS-Plus pilot projects that meet the standards set forth by the Scientific Panel of the Working Group in the Guidelines for the Establishment of DOTS-Plus Pilot Projects for the Management of MDR-TB (the Guidelines). Adherence to the Guidelines results in proper management of existing cases of MDR-TB while preventing the rapid development of resistance to second-line anti-TB drugs.

The Guidelines are based on the recommendations of the Scientific Panel of the Working Group and will be further developed based on evidence provided by DOTS-Plus pilot projects. In addition to explaining the DOTS-Plus concept, the Guidelines define the minimum requirements necessary to establish and maintain DOTS-Plus pilot projects. Sample protocols are available to design standardized or individualized treatment regimens with second-line anti-TB drugs to be used in DOTS-Plus pilot projects.



Green Light Committee:



Increasing access to essential anti-TB drugs by lowering costs

The Working Group has worked extensively with the pharmaceutical industry to form partnerships to combat MDR-TB. As part of this collaboration, members of the pharmaceutical industry have agreed to provide preferential prices to DOTS-Plus pilot projects. In order for projects to benefit from any pricing arrangements negotiated by the Working Group, the Green Light Committee must validate those projects.

The Green Light Committee has been established by the Working Group for this purpose and is a subgroup of the Working Group. WHO is a permanent member of the Green Light Committee and houses the Secretariat.

It is the task of the Green Light Committee to review project applications and determine whether projects are in compliance with the Guidelines. DOTS-Plus pilot projects adhering to the Guidelines carry the greatest chance of programmatic success and the least chance of creating resistance to second-line anti-TB drugs, the last line of defence against TB. Some members of the pharmaceutical industry have already refused to sell second-line anti-TB drugs to projects that are not validated by the Green Light Committee.

How can you apply?

Project managers can submit an application to the Green Light Committee through the WHO Secretariat. Specific instructions for the application process are available from WHO. Decisions by the Green Light Committee, in principle, will be taken rapidly after submission, provided that the application contains all requested documentation.

The Green Light Committee may consult independent external experts for technical advice regarding the project. The Green Light Committee may decide to request a visit to the project site in order to conduct a more in-depth assessment. If a project is found to meet the requirements set forth in the Guidelines, the project will be given the option of benefiting from the preferential pricing arrangement negotiated by participants of the Working Group for this purpose.

If the project is not found to meet the requirements outlined in the Guidelines, the project manager will be provided with a written statement highlighting the reasons for non-compliance. The project manager will be invited to re-submit a request, but only after having adequately addressed the criteria in the Guidelines. During the course of a validated DOTS-Plus pilot project, the project may be reassessed by the Green Light Committee to ensure that it remains compliant with the Guidelines.



For further information on DOTS-Plus for MDR-TB and the Green Light Committee please contact:

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