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Abbreviations and acronyms

AFB	acid-fast bacilli
ART	antiretroviral therapy
CDC	United States Centers for Disease Control and Prevention
CPT	co-trimoxazole preventive therapy
DOT	directly observed therapy
DOTS	internationally recommended strategy for TB control
DRS	drug resistance surveillance
DST	drug susceptibility testing
FIND	Foundation for Innovative New Diagnostics
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GLC	Green Light Committee
HIV	human immunodeficiency virus
HPF	high-power field
HRD	human resource development
IUATLD	International Union Against Tuberculosis and Lung Disease
LFT	liver function test
MDR-TB	multidrug-resistant tuberculosis
NTM	nontuberculous mycobacteria
PIH	Partners In Health
PPD	purified protein derivative
PPM	public-private mix
SCC	short-course chemotherapy
TB	tuberculosis
TSH	thyroid-stimulating hormone
UNAIDS	Joint United Nations Programme on HIV/AIDS
UVGI	ultraviolet germicidal irradiation
WHO	World Health Organization

Antituberculosis drug abbreviations

Am	Amikacin	Lfx	Levofloxacin
Amx/Clv	Amoxicillin/Clavulanate	Lzd	Linezolid
Cfx	Ciprofloxacin	Mfx	Moxifloxacin
Cfz	Clofazimine	Ofx	Ofloxacin
Clr	Clarithromycin	PAS	<i>P</i> -aminosalicylic acid
Cm	Capreomycin	Pto	Protionamide
Cs	Cycloserine	R	Rifampicin
E	Ethambutol	S	Streptomycin
Eto	Ethionamide	Th	Thioacetazone
Gfx	Gatifloxacin	Trd	Terizidone
H	Isoniazid	Vi	Viomycin
Km	Kanamycin	Z	Pyrazinamide

Preface

When, in the early 1990s, the World Health Organization (WHO) resumed leadership in control of tuberculosis (TB) worldwide, the primary focus was to support Member States in setting up proper national TB control programmes. Leadership was crucial at a time when the prospects for TB control were universally bleak in the face of a rampant epidemic. Emphasis was placed on establishment of the key and essential elements of TB control based on current knowledge, and on their assertive promotion. Thus, the DOTS strategy was launched in 1994–1995 and Member States were supported in its implementation. DOTS was, and remains, the most cost-effective approach to detecting and curing cases and to preventing the onset and spread of drug resistance. Prevention was therefore promoted as the main tool for combating drug-resistant TB.

Management of existing cases, especially of the most feared variant, multi-drug-resistant TB (MDR-TB), was left to the individual initiative of national programmes. Best practice guidelines detailing the choice of regimens were published in 1996 to guide clinicians in TB treatment, but no programmatic recommendations were made available by WHO. The focus had to remain on DOTS implementation, since very few countries had an acceptable standard of basic TB control. In essence, the few resources available for TB were prioritized to build, expand and strengthen basic TB control programmes in order to diagnose and cure the majority of TB patients while preventing the emergence of drug resistance. At that time in the mid-1990s, the international community had only just started to become aware of the burden imposed by TB on the societies of developing countries. It was not yet conceivable that already overburdened national programmes could undertake the complex, lengthy and extremely costly (often unaffordable) management of drug-resistant, often chronic, cases of TB. Besides, knowledge about the spread of drug resistance was lacking and there was no standard method of acquiring reliable information.

In 1997, WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) reported for the first time standardized information on drug resistance from surveys or surveillance systems conducted since 1994 in some 35 countries. This information confirmed what many had feared: drug resistance was widespread and MDR-TB was at a critically high level in some

parts of the world, especially in some countries of the former Soviet Union.

Stimulated by this new evidence, many realized that the time had come to address MDR-TB in a more proactive way than previously. WHO, in particular, decided to explore what could be done together with some key partners, such as the Harvard Medical School, the United States Centers for Disease Control and Prevention (CDC) and Médecins Sans Frontières. At two historic meetings – in Cambridge, Massachusetts, in April 1998, during which the term “DOTS-Plus” was coined, and in Geneva, Switzerland, in January 1999 – experts agreed on the need to face MDR-TB programmatically, i.e. no longer solely through individual practitioner’s efforts but through wider DOTS-Plus pilot projects implemented by, or in collaboration with, national TB control programmes. For this purpose, a formal WHO working group, named “DOTS-Plus for MDR-TB”, was established in March 1999 to assist countries and support efforts to assess the feasibility of DOTS-Plus and to produce sound policy recommendations. This working group was later adopted by the Stop TB Partnership in 2001 as its very first “implementation” working group.

While formulating draft guidelines for the management of MDR-TB, the new working group soon encountered an insurmountable obstacle: the price of most second-line antituberculosis drugs recommended for use in the treatment of MDR-TB was unaffordable to countries in need. New frontiers in drug procurement would need to be explored and negotiations with producers embarked upon in order to make these drugs affordable to the poorest countries. The era of a renewed, human rights-based approach to medicine and public health had just begun, and the advent of the principle of access to care for all favourably influenced those discussions. It was decided that a coalition of partners strongly motivated to make MDR-TB treatment affordable would be more effective than any individual group in the negotiations with the pharmaceutical industry.

The Green Light Committee (GLC) was thus born in June 2000: hosted by WHO as a partnership among five categories of participants (governments of resource-limited countries, academic institutions, civil society organizations, bilateral donors and WHO), it successfully negotiated prices of drugs with producers; solicited creation of, and adopted, sound policies for proper management of drug-resistant TB; established strict criteria to review proposals for DOTS-Plus projects; assisted countries in developing such proposals and ensured their proper implementation; and finally, provided access to quality-assured second-line drugs at concessionary prices to those projects considered technically and scientifically sound and not at risk of producing additional drug resistance. In brief, the GLC rapidly became a model of good practice which, by providing access to previously unaffordable drugs, ensured that their use was as safe and rational as possible to prevent the emergence of “su-

per”-resistant strains of *Mycobacterium tuberculosis*. In 2002, the GLC was adopted by the newly established Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) as its mechanism for screening proposals for DOTS-Plus financing. This was another historic milestone, and the GFATM is today the leading financial mechanism supporting the management of MDR-TB in resource-constrained settings.

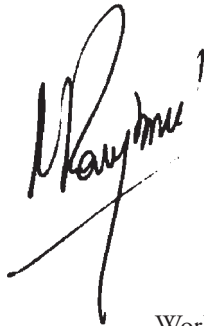
The Scientific Panel of the WHO Working Group on DOTS-Plus for MDR-TB produced its first set of guidelines – *Guidelines for establishing DOTS-Plus pilot projects for the management of multidrug-resistant tuberculosis* – in 2000, following discussions that began at a meeting in Madrid in September 1999. That document was based on the little evidence available at the time, gathered mostly from small-scale projects carried out in previous years and without established standards. Much more evidence has become available in subsequent years. First, the cost-effectiveness of DOTS-Plus has been shown in different settings, including Peru. Second, reasonably high cure rates have been achieved in country-wide programmes to treat MDR-TB, for instance in Latvia. Third, growing favourable evidence of feasibility and cost-effectiveness (still unpublished) has accrued from a number of DOTS-Plus projects in several settings around the world. By September 2005, 35 GLC-approved projects had been implemented in some 29 countries around the world, providing treatment to more than 10 000 cases of MDR-TB in resource-limited settings.

This new evidence mandates a revision of the previous guidelines in order to make available an updated set of recommendations. The new guidelines address this need and provide guidance on current best practice in the management of drug-resistant TB, especially MDR-TB, that should be adopted worldwide. The challenge is huge. WHO estimates that some 300 000–600 000 new cases of MDR-TB may emerge every year, with a global prevalence that may be as high as one million cases. Most of these patients would have no access to proper care and treatment without the existence of the GLC, the DOTS-Plus Working Group and funds made available through the powerful financial mechanisms existing today, such as the GFATM, the World Bank and some bilateral donors.

The new guidelines are also needed in the context of the new Stop TB Strategy, launched in 2005 by WHO and the Stop TB Partnership. This strategy, building on – and enhancing – DOTS, explicitly identifies the management of MDR-TB as a priority. The strategy recognizes the need to provide care to all patients affected by TB, whether the disease is caused by drug-susceptible or drug-resistant bacilli, and the need to avoid jeopardizing TB control efforts where drug-resistant TB is highly prevalent. Therefore, the management of MDR-TB now needs to be integrated into comprehensive national TB control plans in order to comply with the new Stop TB Strategy. Advocacy, built on a solid rationale and the proper demonstration of feasibility

under different programmatic circumstances, is crucial to ensure that the integrated programmes will be fully adopted by all national TB control programmes.

In conclusion, the new guidelines represent the best current knowledge in the management of drug-resistant TB and MDR-TB and offer ample options for tailoring diagnosis and care to different epidemiological and programmatic conditions worldwide. The recommendations, compiled by leading experts, should be followed without hesitation by all national TB control programmes and their partners as the most solid programmatic standards. At the same time, it is imperative to stress that the five elements of the DOTS strategy remain the cornerstone of TB control and the most effective tool for preventing the onset and dissemination of drug resistance. Without the essential elements of TB control fully in place, management of MDR-TB will undoubtedly fail in the long term. These guidelines focus on care for MDR-TB patients, in the hope and expectation that, in future, the occurrence of massive numbers of cases can be prevented through sound TB control practices.

A handwritten signature in black ink, appearing to read 'M. Raviglione', is positioned above the printed name and title.

Dr Mario Raviglione
Director
Stop TB Department
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Introduction

The emergence of resistance to drugs used to treat tuberculosis (TB), and particularly multidrug-resistant TB (MDR-TB),¹ has become a significant public health problem in a number of countries and an obstacle to effective global TB control. In many other countries, the extent of drug resistance is unknown and the management of patients with MDR-TB is inadequate. In countries where drug resistance has been identified, specific measures need to be taken within TB control programmes to address the problem through appropriate management of patients and adoption of strategies to prevent the propagation and dissemination of drug-resistant TB, including MDR-TB.

These guidelines offer updated recommendations for TB control programmes and medical workers in middle- and low-income countries faced with drug-resistant forms of TB, especially MDR-TB. They replace two previous publications by the World Health Organization (WHO) on drug-resistant TB (1–2). Taking account of important developments in recent years, the new guidelines aim to disseminate consistent, up-to-date recommendations for national TB control programmes and medical practitioners on the diagnosis and management of drug-resistant TB in a variety of geographical, political, economic and social settings. The guidelines can be adapted to suit diverse local circumstances because they are structured around a flexible framework approach (see Chapter 2), combining a consistent core of principles and requirements with various alternatives that can be tailored to the specific local situation.

The new guidelines expand upon the most recent general WHO guidelines on TB, *Treatment of tuberculosis: guidelines for national programmes* (3), which includes specific considerations for chronic and MDR-TB cases, classified together under WHO diagnostic Category IV. Detailed strategies are described for the diagnosis of resistant strains of TB and the management of regimens designed to treat Category IV patients.

The term DOTS-Plus has been used recently to refer to piloting of the management of drug-resistant TB within the context of basic DOTS pro-

¹ MDR-TB is defined as tuberculosis caused by *Mycobacterium tuberculosis* resistant in vitro to the effects of isoniazid and rifampicin, with or without resistance to any other drugs. Resistance is defined by specific laboratory criteria (see Chapter 6).