

WHO Stop TB Department

Tuberculosis that is “resistant to all drugs”: Frequently Asked Questions

January 2012

What is “totally drug resistant” tuberculosis (“TDR-TB”)?

In 2006, the first reports of extensively drug-resistant tuberculosis (XDR-TB), an even more severe form of drug resistant TB than multidrug-resistant TB (MDR-TB), began to appear.^{i,ii} MDR-TB is defined as resistance to isoniazid and rifampicin, with or without resistance to other first-line drugs (FLD). XDR-TB is defined as resistance to at least isoniazid and rifampicin, and to any fluoroquinolone, and to any of the three second-line injectables (amikacin, capreomycin, and kanamycin). Within a year of the first reports of XDR-TB, isolated cases were reported in Europe that had resistance to all first-line anti-TB drugs (FLD) and second-line anti-TB drugs (SLD) that were tested.^{iii,iv,v} In 2009, a cohort of 15 patients in Iran was reported which were resistant to all anti-TB drugs tested.^{vi} The terms “extremely drug resistant” (“XXDR-TB”) and “totally drug-resistant TB” (“TDR-TB”) were given by the respective authors reporting this group of patients. Recently, a further 4 patients from India with “totally drug resistant” tuberculosis (“TDR-TB”) were described^{vii}, with subsequent media reports of a further 8 cases.^{viii}

Is the term “totally drug resistant” clearly defined? Is it recognised by the WHO?

The term “totally drug resistant” has not been clearly defined for tuberculosis. While the concept of “total drug resistance” is easily understood in general terms, in practice, *in vitro* drug susceptibility testing (DST) is technically challenging and limitations on the use of results remain: conventional DST for the drugs that define MDR and XDR-TB has been thoroughly studied and consensus reached on appropriate methods, critical drug concentrations that define resistance, and reliability and reproducibility of testing.^{ix} Data on the reproducibility and reliability of DST for the remaining SLDs are either much more limited or have not been established, or the methodology for testing does not exist. Most importantly, correlation of DST results with clinical response to treatment has not yet been adequately established. Thus, a strain of TB with *in vitro* DST results showing resistance could in fact, in the patient, be susceptible to these drugs. The prognostic relevance of *in vitro* resistance to drugs without an internationally accepted and standardised drug susceptibility test therefore remains unclear and current WHO recommendations advise against the use of these results to guide treatment.^x

Lastly, new drugs are under development, and their effectiveness against these “totally drug resistant” strains has not yet been reported.

For these reasons, the term “totally drug resistant” tuberculosis is not yet recognised by the WHO. For now these cases are defined as extensively drug resistant tuberculosis (XDR-TB), according to WHO definitions.

How easily do MDR or XDR-TB or “TDR-TB” spread?

TB bacilli with different levels of resistance spread in the same way and with the same risk of infection as fully drug susceptible strains. For more information please click [here](#)

What does the WHO recommend should be done to address MDR or XDR-TB?

The discovery of patients with MDR or XDR-TB emphasizes the importance of ensuring that all care for tuberculosis, whether in the public or private sector, must conform to international standards^{xi} in order to prevent the emergence of drug resistance. Almost all countries must, in addition, ensure appropriate diagnosis and treatment of cases of MDR-TB.^{xii, xiii} National regulations for the quality and dispensing of anti-TB drugs, particularly of the second-line drugs, need to be strictly enforced.

To achieve this, most countries require simultaneous scale-up of the diagnostic and treatment services for drug-resistant TB, and the provision of adequate and continuous supplies of quality assured SLDs for both MDR- and XDR-TB to meet the increased demand.

MDR and XDR-TB raise many difficult issues concerning the management of patients, for example, whether to isolate patients, the need for institutional, palliative or end-of-life care, and the compassionate use of new drugs. The reader is referred to the WHO’s Guidelines for the programmatic management of drug-resistant tuberculosis.^x

Are there any treatment options for patients with XDR-TB?

XDR-TB severely reduces the options for treatment, but, yes, there are still options available, although they have not been studied in large cohorts. For such cases additional drugs will need to be procured from among the group of agents that is known to have some action against tuberculosis but is not routinely recommended for treatment of MDR-TB.^{ix} These include clofazimine, linezolid, amoxicillin/clavulanate, thioacetazone, imipenem/cilastatin, clarithromycin and high-dose isoniazid. Efficacy is not assured, however, and both toxicity and cost for some of these compounds are high. Potential purchasers should be aware that international availability of some of these agents is limited at present.

Will the new drugs in development soon be available for treatment of XDR-TB?

Several new drugs belonging to new classes of anti-mycobacterial agents are under development, but until they are shown to be effective in properly conducted clinical trials, WHO cannot recommend their routine use. In particular **WHO advises strongly against simply adding a single new drug to a failing regimen**. The use of experimental drugs outside clinical trials (compassionate use) has been addressed by the WHO^x.

What strategies underlie WHO’s recommendations for dealing with drug resistance?

The WHO-recommended Stop TB Strategy provides the framework for the effective large-scale treatment and control of both drug-susceptible and drug-resistant disease.^{xiv} The Global Plan to Stop TB, 2011 – 2015, developed by the Stop TB Partnership, including WHO, estimates funding needs for implementation levels needed to achieve global targets.^{xv} Critical weaknesses in many countries’

current capacity and approaches to the treatment and control of MDR-TB and XDR-TB have been identified and the policy approaches necessary to address them have been described.^{xvi}

Are countries aware of the need to respond to drug resistant TB? How are they doing?

In 2009, the Beijing Call for Action^{xvii} and the approval of the World Health Assembly Resolution 62.15^{xviii}, with 193 Member States present, signalled a step forward in countries' commitment to, and planning for, the treatment and control of MDR-TB. Planning, funding, and implementation have, however, fallen behind the milestones that were set. In 2010, only 20 out of 36 countries with a high burden of TB or MDR-TB had at least one laboratory capable of performing TB culture and DST per 5 million people. Much of Africa and the Indian subcontinent remain poorly served. Globally in 2010, only 4% of new and 6% of previously treated TB patients were reportedly tested for susceptibility to isoniazid and rifampicin, while the Global Plan targets are 20% or more, and 100%, respectively. The number of reported cases of MDR-TB was only 18% of the estimated number of cases among TB patients notified in 2010. And only around one quarter of them were treated in accordance with recommended international guidelines. Data (unpublished) collected by WHO show that just over a half of MDR-TB patients in recent cohorts completed their treatment successfully, and among patients with XDR-TB, death is more common than successful treatment; default and treatment failure rates are also high.

Are sufficient financial resources available in countries to address MDR-TB?

According to the 2011 WHO Global TB report, funding for MDR-TB in 2011 was US\$0.7 billion, US\$ 0.2 billion less than the need estimated in the Global Plan to Stop TB.^{xix} Of the reported funding, US\$ 0.5 billion (71%) was accounted for by three upper-middle income countries: Kazakhstan, the Russian Federation and South Africa. The funding required for MDR-TB to reach the 2015 target of universal access to care rises from US\$ 0.9 billion in 2011 to US\$ 2 billion in 2015; most of this funding is needed in middle-income countries. Thus, much more funding needs to be mobilized in high MDR-TB burden countries to ensure proper diagnosis and treatment.

What measures will be taken by the WHO at the global level, to address "TDR-TB" specifically?

To facilitate discussion and to make surveillance consistent, an initial step is for WHO and partners to develop a consensus on whether a new definition is needed, and if so what the term and definition should be for such patients, taking into account the technological limitations of DST that still exist in 2011. If "totally drug-resistant" TB defines a subset of XDR-TB with different characteristics to other XDR-TB cases, particularly with respect to the outcome of such cases, then an internationally recognised definition may be needed. This should be seen as a call for national TB programmes and research groups to make data available on the outcomes of all highly resistant cases.

WHO is organising an Expert Group Meeting in March, 2012 to assess additional data on DST accuracy obtained since 2008. This meeting will be expanded to include a consultation on possible definitions for "totally drug-resistant" TB. WHO is also convening another Expert Group Meeting in March to assess the latest evidence behind a new molecular line probe assay for detecting XDR-TB.

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