

# **RESIST-TB:**

## **Research Excellence to Stop TB Resistance**

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### **Report on the RESIST-TB Protocol Workshop, Amsterdam, 5-6 October 2009**

In light of the growing interest in MDR-TB trials and the movement of several new TB drugs through the pipeline, RESIST-TB recently organized a working meeting to produce three clinical trial protocols for studies to define the optimal use of new drugs for the treatment of MDR-TB. These protocols detail the specifics of what the next generation of clinical trials for treatment of MDR-TB should look like. Meeting participants included clinicians, researchers, NGO and NTP representatives and representative from pharmaceutical companies currently developing candidate new TB drugs. The workshop addressed the questions of what are the optimal companion drugs and what is the optimal duration of DR-TB treatment regimen. Phase III Trial designs were drafted considering two possible scenarios: first, that one drug becomes available several years before others; and second, that two drugs become available at approximately the same time.

### **Background**

Despite the global commitment to scale up diagnosis and treatment of drug-resistant TB (World Health Assembly Resolution 62.15) in response to the worsening MDR/XDR-TB global crisis, substantial gaps exist in our understanding of how to best treat and prevent this disease. Current treatments evolved in a total absence of randomized clinical trials and result in cure in 50-80% of patients treated. There is no preventive regimen of proven efficacy for close contacts of patients with DR-TB. Therefore, concerned patients, physicians, research scientists and other stakeholders met in Cambridge, Massachusetts, in June, 2008, and formed RESIST-TB.

The mission of RESIST-TB is to promote and conduct research to cure and prevent DRTB throughout the world. Research efforts will be conducted with the aim of identifying effective regimens for programmatic use. Our work is focused on producing results that will inform current problems in the management of patients with DR-TB. The most scientifically rigorous way to do this is through randomized, controlled trials of treatment for DR-TB.

### **Why do we need to undertake clinical trials for MDR-TB?**

DR-TB is a growing global public health problem. Drug-resistant isolates have been identified in nearly all countries surveyed since 1994 and nearly 500,000 cases of MDR-TB are estimated to emerge yearly worldwide. XDR-TB has been found in every region of the world and detected in 10% of MDR-TB isolates collected through a survey of the supranational laboratory network. The MDR-TB epidemic is burgeoning in some settings such as the former Soviet Union and certain provinces in China and India. In addition, evidence of overlapping of the HIV and MDR-TB epidemics in some populations threatens control of these two epidemics.

MDR-TB treatment programs have rapidly expanded in recent years. Since 2000, the GLC has approved treatment of MDR-TB in more than 30,000 patients in 67 projects in 52 countries. It is estimated that approximately three times that number, or 90,000 patients, are receiving MDR-TB treatment outside the GLC mechanism. In 2006 alone, more than 20,000 patients with MDR-TB were reported to the World Health Organization (WHO) by more than 60 countries. The increasing number of MDR-TB treatment sites provides a setting in which trials could be implemented. The MDR-TB Working Group of the Stop TB Partnership established the goal of treating nearly 1.6 million MDR-TB patients by 2015, an ambitious target that can be achieved only with shorter and simpler treatment regimens.

Treating MDR-TB is presently difficult, expensive, time-consuming and requires an appropriate infrastructure. According to WHO recommendations, treatment of MDR-TB should include at least 4 drugs with almost certain effectiveness, and be based on DST and/or patient drug history. An injectable agent (aminoglycoside or capreomycin) must be included among these drugs, for a minimum duration of 6 months. In some cases, more than 4 drugs should be started, i.e., when the susceptibility pattern is unknown, if an agent's effectiveness is questionable, or in clinically serious cases such as those with extensive, bilateral pulmonary disease. The drugs should be administered 6 days a week using directly observed therapy (DOT) throughout treatment, that should last at least 18 months beyond culture conversion, making it a very long undertaking (usually 24 months).

In the absence of any controlled trial comparing different regimens, the number and type of drugs required to treat a patient with MDR-TB is a matter of a controversy, even though specialists agree on basic principles, such as the minimum number of drugs to use and the inclusion of injectable agents. In contrast with evidence-based recommendations for treatment of drug-sensitive TB, however, recommendations for MDR-TB treatment are mainly based on expert opinion and observational studies: personal experience has largely become the basis for case management. Experts may differ in their approach to patient management according to their own experiences, which is not exempt from bias related to specific circumstances. As a result, treatment regimens vary substantially, from standardized 4-5-drug regimens given for less than 18 months, to individualized 24-month regimens utilizing more than 5 drugs. The efficacy of recommended MDR-TB treatment regimens may vary according to background sensitivity patterns and the drugs included in the combination. Drug interactions have been poorly documented to date. In addition, most of the drugs have substantial toxicity and potential for a number of adverse events, contributing to early interruption of treatment. This can lead to further failure or relapse, with serious consequences both at the individual and the community levels, in terms of patient survival and the spread and amplification of resistance.

Treatment outcomes of patients with MDR-TB remain suboptimal. The long duration and toxicity of drugs lead to relatively high default rates (around 15% in a cohort of patients from 9 GLC-approved sites from 2000-2003). Treatment success is slightly above 60% in GLC-approved sites. A review of earlier cohorts, largely HIV-uninfected, reported failure rates between 0% and 32% (crude weighted mean: 9.48%) and relapse rates between 0% and 17% (crude weighted mean: 2.43%). Mortality rates are even higher in people living with HIV, varying from 5% to 20%. In addition to

efforts aimed at improving the delivery of care, it is imperative to improve outcomes of MDR-TB treatment, either through the optimized use of currently available drugs or the introduction of new drugs.

### **The current TB drugs R&D landscape and the role of RESIST-TB**

The two most advanced compounds in the TB drug pipeline are currently in Phase IIb clinical trials and being tested in MDR-TB patients. The U.S. FDA recently clarified what will be required for a new MDR-TB drug to receive an indication through the accelerated approval process

(<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM183845.pdf> ). This means that the drug will be approved based on a surrogate endpoint, and the optimal use of the new drug (in combination with existing drugs) will not have been elucidated.

There is therefore the need to identify what trials need to be performed to define the best way for TB control programs to use the new drug to maximize the cure rate, minimize the emergence of resistance, and optimize the use of program resources, so that the maximum number of persons can receive treatment. This is important because current resources are likely to allow only a small fraction of those in need of treatment to receive it, and defining the minimal time that treatment is needed will allow more patients to receive the drug..

For this reason, RESIST TB recently organized a working meeting to produce three protocol documents to define the optimal use of new drugs for the treatment of MDR-TB. These trials detail the specifics of what the next generation of clinical trials for treatment of MDR-TB should look like. Meeting participants included clinicians, researchers, NGO and NTP representatives and representative from pharmaceutical companies currently developing candidate new TB drugs. The workshop addressed the questions of what are the optimal companion drugs and what is the optimal duration of DR-TB treatment regimen. Phase III Trial designs have been drafted considering two possible scenarios: first, that one drug becomes available several years before others; and second, that two drugs become available at approximately the same time.

Prevention of MDR-TB is an equally important goal, and a trial to define an effective “preventive therapy” regimen that could be given to close contacts of persons with infectious MDR-TB. Such treatment would have a critical impact on decreasing the number of persons with MDR-TB who needed treatment. For this reason, the RESIST TB workshop also focused on designing a protocol for prevention of TB among close contacts using a new drug, either alone or in combination with existing drugs.

### **Participants in the Workshop**

RESIST-TB	TAG
NEAT	Tibotec
TBTC	Otsuka
ACTG	Pfizer
MRC	Sequella
TREAT-TB	

## One New Drug

### Treatment of MDR-TB with One New Drug: the STRONG\*-1 Study

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Objectives: Safety, efficacy, and tolerability of OBT+ new drug for 12 months versus OBT+ placebo for treatment of MDR-TB

Design: Prospective, randomized, double-blind clinical trial

Subjects: Pulmonary MDR-TB  $\pm$  XDR-TB; All ages

Study Arms: Arm 1: OBT for 18 m w/ placebo for 1<sup>st</sup> 12 m.

Arm 2: OBT for 18 m w/ drug A for 1<sup>st</sup> 12 m.

Arm 3: Drug A+OBT for 12 months.

Sample Size: 120 subjects in Arm 1, 480 in Arm 2 & 3 each

Primary Combined Endpoint: Death, rx failure, absence of culture conversion after 6 months of rx, relapse, default.

\*Shortened Treatment Regimen with One New Generation

### Treatment of MDR-TB with One New Drug: the STRONG\*-2 Study

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Objectives: Safety, efficacy, and tolerability of 6-9 months of one new drug plus OBT vs. 12 months of one new drug plus OBT.

Design: Prospective, randomized, double-blind clinical trial

Subjects: Pulmonary MDR-TB  $\pm$  XDR-TB; All ages

Study Arms: Arm 1: A+OBT for 6-9 months

Arm 2: A+OBT for 12 months

Sample Size: 480 subjects per arm

Primary Combined Endpoint: Death, treatment failure, absence of culture conversion on solid medium after 6 months of treatment, relapse, default.

\*Shortened Treatment Regimen with One New Generation

## Two New Drugs

### Treatment of MDR-TB with Two New Drugs: the TOSTIDO\* Study

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Objectives: Safety, efficacy, and tolerability of two new drugs+ companions for 6 months vs. one new drug+OBT for 12 months

Design: Prospective, randomized open-label clinical trial

Subjects: Pulmonary MDR-TB (no XDR-TB); all ages

Study Arms: Arm 1: ABZQ for 6 months

Arm 2: 12 months of A+OBT

Sample Size: 575 subjects per arm

Primary Combined Endpoint: Failure, relapse, death, or default

\* Treatment Outcome Shortening with Two Investigational Drugs+Others

## Treatment of MDR-TB contacts

### Preventive Therapy of MDR-TB Contacts: the OPTICOM \* Study

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Objectives: To compare safety, efficacy and tolerability of Drug A to INH for preventing active TB

Design: Prospective, randomized, double blinded clinical trial

Subjects: Close household contacts in adults and children with and without HIV

Study arms: 1) Drug A

2) INH

Sample size: 2530 in each arm

Primary endpoint: Active TB

\* Optimal Preventive Therapy In Contacts Of MDR-TB