

RESIST-TB:

Research Excellence to Stop TB Resistance

ANNUAL REPORT FOR 2011

RESIST-TB is an organization of concerned patients, physicians, research scientists and stakeholders. Its mission is to promote and conduct clinical research to cure and prevent drug-resistant tuberculosis. RESIST-TB is committed to addressing the substantial existing gaps in knowledge and to help and provide access to effective treatment for and prevention of drug-resistant tuberculosis. Their efforts were sponsored by the [Centers for Disease Control and Prevention](#), [Médecins Sans Frontiers](#), [Partners In Health](#), [Treatment Action Group](#), [TREAT-TB/IUATLD](#), and the [World Health Organization](#).

RESIST-TB aims to mobilize action towards better regimens for DR-TB treatment. In 2011 their activities focused on promoting scholarly advocacy through the Drug Efficacy working group, which recommended research in support of optimized treatment regimens; building capacity for TB clinical trials through the progress of the Site Development and 2 New Drugs working groups, as well as our leadership and support of the Opti-Q trial; and influencing public policy through a White Paper on early access to new drugs that was developed by the Expanded Access working group.

Scholarly Advocacy

Over the past year, the [Drug Efficacy \(DE\) Working Group](#) conducted thorough and detailed literature reviews on existing first- and second-line TB drugs. Despite the lack of clinical trials to determine optimized combinations of new and existing drugs for MDR-TB, the DE committee compiled a comprehensive summary and analysis of the literature reviews that highlighted optimized doses, efficacy, and future research recommendations for each drug. The aim was to identify research questions important to optimizing future treatment regimens. Their efforts culminated in two reviews, currently under review at prominent infectious diseases journals, which concluded that:

1. High priority should be given to optimizing the dose of PZA, injectables, and INH.
2. Better understanding of the potential of oxazolidinones, riminophenazines, and beta-lactams to DR-TB may inform the development of new agents in the class and spur new and important discoveries.
3. Further research focusing on optimizing doses and duration of drugs is paramount.

Clinical Trials

RESIST-TB is the largest international organization that focuses on championing and promoting research and clinical trials for MDR-TB. In October of 2009, RESIST-TB organized a working meeting in Amsterdam, Netherlands, to produce three concepts for clinical trials of new drugs for the treatment of MDR-TB. Meeting participants included clinicians, researchers, NGO and NTP representatives and representatives from industry. The workshop and resulting documents addressed the questions of what the optimal companion drugs are and what the optimal duration of DR-TB regimen should be. Phase III trial designs were drafted considering two possible scenarios: first, that one drug becomes available several years before the others; and second, that two drugs become available approximately at the same time. The third concept was developed to define an effective “preventative therapy” regimen that could be given to close contacts of persons with infectious MDR-TB.

The three concepts drafted during the Amsterdam meeting drove the creation of multiple proposals and concepts that were submitted to funding organizations in 2011. RESIST-TB aims *to identify an MDR-TB treatment regimen that cures 95% of all MDR-TB patients with less than 5% relapse*. It is with that focus in mind that they submitted:

- 1) The 2 New Drugs Working Group proposal to TBTC for a trial to evaluate bedaquiline (TMC-207) and other drugs along with an optimized background therapy for MDR-TB treatment. The trial proposal has been reviewed by TBTC. RESIST-TB is at present incorporating its suggestions in the revision of the proposal (currently under review).
- 2) RESIST-TB has led the coordination and design of a study that examines high-dose levofloxacin in the treatment of MDR-TB (Opti-Q). This concept has been approved by TBTC and submitted to NIH for review.
- 3) The RESIST-TB Preventative Therapy Working Group concept was submitted for development to ACTG and TBTC. The submission resulted in the ACTG developing a trial based on this concept.

Site Capacity Development

Promoting clinical trials is inadequate if there is insufficient capacity at the site to perform MDR-TB diagnosis, treatment, and monitoring. The RESIST-TB Site Capacity Working Group has begun the process of reviewing potential new sites that could provide increased capacity for MDR-TB clinical trials. They have identified adequate numbers of patients, laboratory capacity, and good clinical practices training and experiences as key determinants for potential sites. Over the past year they have reviewed and updated the site assessment tools, in preparation for a detailed capacity survey to be undertaken in early 2012.

Public Policy

RESIST-TB has sought to influence public policy by ensuring that drug resistant tuberculosis is brought to the forefront of TB clinical trials priorities. To accomplish this, the recently updated website (www.resisttb.org) has become more accessible and user friendly. Henceforth, the most up-to-date news, events, developments, and publications related to MDR-TB will be regularly publicized on the front page.

The RESIST-TB annual meeting at the 2011 IUATLD Conference in Lille, France drew a large audience interested in hearing about the newest developments in MDR-TB trials as well as RESIST-TB's efforts in promoting those trials. Updates and data on the [three recent trials](#) were presented:

I. Tibotec – TMC-207 Phase III Planned confirmatory trial:

- The trial aims to enroll 600 patients with the objective 1) of providing additional efficacy and safety to support traditional approval; 2) of investigating how to best use TMC207 in clinical practice; and 3) of evaluating and MDR regimen that will potentially decrease the burden of MDR treatment.

II. Treat TB/USAID/MRC – STREAM Phase III Trial:

- The study aims to enroll 387 patients in an adapted 'Bangladesh' regimen with the primary objective 1) of assessing, in a randomized comparison, whether the study regimen has a rate of favorable outcomes that is not inferior to that of standardized control regimen (using a pre-specified margin of inferiority); and 2) of comparing the proportion of patients who experience grade 3 or greater adverse events during treatment or follow-up on the study regimen as compared to the control regimen.

III. Otsuka – OPC-67683 Phase III MDR-TB trial

- The trial aims to enroll 390 patients with the objective of determining whether Delamanid is effective in the treatment of MDR-TB in combination with other MDR-TB medication during 6 months of treatment.

RESIST-TB also proposed and organized a symposium at the IUATLD Annual Meeting, in collaboration with the Global Alliance for TB Drug Development, on recently completed scientific studies of new drugs for MDR-TB and XDR-TB. This popular symposium addressed murine studies of new drugs for MDR-TB and XDR-TB, recently completed studies of PNU-100480, PA-824 and TMC-207, and a thought-provoking presentation on the prospects for scale-up of MDR-TB Treatment.

Another important policy priority has been to promote early access to new TB drugs – a priority that has increased urgency now that new drugs are nearing regulatory approval. The RESIST-TB Expanded Access Working Group, with the collaboration of the CPTR Access and Appropriate Use Working Group, drafted a White Paper on compassionate use and expanded access to new drugs for DR-TB. It highlighted six steps that would be required for successful early access programs:

1. Expand and harmonize regulations permitting CU
2. Expand availability of susceptibility testing
3. Support the development of clinical centers for MDR-TB treatment
4. Promote research on drug compatibility with new TB drugs
5. Promote revised MDR-TB treatment recommendations
6. Promote a harmonized regulatory pathway for companion SLD

This manuscript has been submitted for publication to an international medical journal.

Goals for 2012

In the coming year, RESIST-TB will continue to provide leadership in scholarly advocacy, MDR-TB clinical trials design and preparation, and public policy development. They will push for development and implementation of trials of 2 new drugs for treatment as well as a preventative therapy trial. The Site Capacity Working Group will undertake a survey of potential sites and advocate for resource allocation to bring these sites to clinical trial readiness. All of the RESIST-TB Working Groups will continue to develop and research articles as well as organize presentations in order to educate the public on MDR-TB advances. Another important goal for the coming year will be to further the collaboration among trials groups and sponsors and to build up a significant email distribution list for effective outreach purposes. Lastly, our Annual Meeting and our Scientific Symposium at the IUATLD World Conference on Lung Health in Kuala Lumpur will raise awareness of new initiatives and recent accomplishments, respectively, that hold the promise of shorter, more effective and less toxic treatment regimens for Drug-Resistant TB.