RESIST-TB:

Research Excellence to Stop TB Resistance

ANNUAL REPORT FOR 2012

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 helping provide access to effective curative and preventive treatment for drug-resistant tuberculosis (DR-TB). Efforts in 2012 were sponsored by the Centers for Disease Control and Prevention, Médecins Sans Frontiers, Partners In Health, Treatment Action Group, International Union Against Tuberculosis and Lung Disease and the World Health Organization.

Our 2012 activities centered on 1) scientific advocacy through the publication of two articles, which outlined specific research priorities on existing TB drugs in support of optimized treatment regimens and dissemination of knowledge through our website and eNewsletter; 2) building capacity for TB clinical trials through assessment of clinical trials site capacity; 3) proposing specific research on new TB drugs; and 4) influencing public policy through the Union Conference symposia in 2012, the White Paper on early access to new drugs, and other varied activities.

SCIENTIFIC ADVOCACY

DRUG EFFICACY

Over the past year, the Drug Efficacy (DE) Working Group conducted thorough and detailed literature reviews on existing first- and second-line anti-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 that highlighted optimized doses, efficacy, and future research recommendations for each drug. Review I, entitled "Old Drugs, New Purpose: Retooling Existing Drugs for Optimized Treatment of Resistant Tuberculosis," was published in the Clinical Infectious Diseases Journal[1]. The aim was to identify research questions important for optimizing future treatment regimens and the authors concluded that highest priority should be placed on optimizing the dosing of PZA, injectables, and INH.

[1] Dooley KE, Mitnick CD, Ann DeGroote M, Obuku E, Belitsky V, Hamilton CD, Makhene M, Shah S, Brust JC, Durakovic N, Nuermberger E. Old Drugs, new purpose: retooling existing drugs for optimized treatment of resistant tuberculosis. Clin Infect Dis 2012; 55(4): 572-81.

Review II, entitled "World Health Organization Group 5 Drugs for the Treatment of Drug-Resistant Tuberculosis: Unclear Efficacy or Untapped Potential?," was published in the Journal of Infectious Diseases[2]. This review concluded that:

1. Clofazimine and beta-lactams may have unrealized potential in the treatment of DR-TB and warrant further study.
2. Serious toxicity or intrinsic resistance limited the utility of other group 5 drugs.
3. Better understanding of structure-toxicity relationships may lead to better-tolerated analogs of existing, poorly tolerated drugs.

WEBSITE AND eNEWSLETTER

The website (www.resisttb.org) is in the process of being updated to make it 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. A monthly eNewsletter was initiated in May of 2012, highlighting information about new DR-TB related publications, updates and events. The reach of the eNewsletter has been steadily expanding and currently has a regular subscription of over 200 individuals and organizations.

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. The three MDR-TB clinical trial concepts drafted during the Amsterdam meeting drove the creation of multiple proposals and concepts that were submitted to funding organizations in 2012 (shown below): These are consistent with our Strategic Goal of *identifying an MDR-TB treatment regimen that cures 95% of all MDR-TB patients with less than 5% relapse*.

1) In March, RESIST-TB submitted a proposal to evaluate combinations of bedaquiline (TMC-207), sutezolid (PNU-100480), PA-824 and SQ-109 along with an optimized background therapy for MDR-TB treatment. The trial proposal was approved by ACTG in June. The study protocol is now nearing completion (Study A5319).

2) In 2011 and 2012, RESIST-TB led the coordination and design of a phase 2 study proposal that examines the pharmacodynamics of high-dose levofloxacin in the treatment of MDR-TB (Opti-Q). This concept has been approved by TBTC (TBTC Study

[2] Dooley KE, Obuku EA, Durakovic N, Belitsky V, Mitnick C, Nuermberger EL. World Health Organization group 5 drugs for the treatment of drug-resistant tuberculosis: unclear efficacy or untapped potential? J Infect Dis 2012; [epub ahead of print].

32) and was submitted to NIH for review in September. It received an encouraging score in January 2013 (11th percentile). If funded by NIH, the study will be performed as a collaboration between CDC and NIH.

3) The RESIST-TB preventive therapy concept was adapted and submitted for further development to both ACTG and TBTC. The submission resulted in the ACTG chartering a protocol team to develop a trial proposal based on this concept (Study A5300).

SITE CAPACITY DEVELOPMENT

Promoting clinical trials is unlikely to be productive if site capacity is insufficient to perform MDR-TB clinical trials. 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. We have identified adequate numbers of patients, skilled laboratory and pharmacy capacity, data management capacity, and good clinical practices training as important characteristics of potential sites. Over the past year we reviewed and updated site assessment tools and prepared a detailed capacity survey in 2012. Ten potential sites were identified in Africa, Asia, Europe and the Americas with the following results:

- Total MDR-TB patients treated in 2010: 2806
- Total XDR-TB patients treated in 2010: 187
- 100% of sites have lab capacity and ties to the local NTP
- 100% of sites deliver DOT to patients
- 70% of sites have electronic data capacity
- 80% of sites perform follow-up for at least 12 months
- 80% of trials have clinical trials experience

In the coming year, RESIST-TB will focus its efforts on providing assistance with improvement of electronic data capacity and developing experience in long-term follow up.

PUBLIC POLICY

UNION CONFERENCE

RESIST-TB continues to influence public policy by ensuring that drug resistant tuberculosis is brought to the forefront of TB clinical trials priorities.

The RESIST-TB annual meeting at the 2012 Union Conference in Kuala Lumpur, Malaysia 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. STREAM Study (Appendix A):

- Adapted the 'Bangladesh' regimen with the objectives of 1) assessing whether the regimen has a rate of favorable outcomes that is not inferior to that of a standardized control regimen; 2) comparing the proportion of patients who experience grade 3 or greater adverse events compared to the control regimen.
- Recruiting has started in South Africa; screening started in Ethiopia and Vietnam; permission at advanced stage in India.

II. Salvage Regimen and NC-002 Trial (Appendix B):

- Moves a novel regimen from 20week EBA to 2-month 'SSCC' study and enrolls DS and DR patients in a single trial with the same regimen.
- Proposal to initiate global study of combinations of new chemical entities in patients with XDR-/TDR-TB.

III. MARVEL Study (ACTG A5319) (Appendix C):

- Study combination regimens for 8 weeks to identify those that should move forward to Phase 3 trials.
- Identify regimens that can be used by HIV-infected and HIV-uninfected persons
- Identify regimens that perform as well as HRZE in DS-TB
- Identify regimens that are safe and at least as well tolerated as current MDR-TB treatment regimens.

IV. Otsuka – Delamanid Phase III MDR-TB trial (Appendix D):

The trial, already underway, aims to enroll 390 patients with the objective of determining whether 6 months of OPC-67683 is effective in the treatment of MDR-TB in combination with other MDR-TB medication over an 18-24 month course of treatment.

RESIST-TB's External Relations sub-Group also coordinated the MDR-TB symposium at the 2012 Union meeting (Symposium 28: "Advances in the Treatment of MDR-TB"). RESIST-TB has proposed a symposium for the 2013 Union Meeting on the latest developments in prevention of MDR-TB. It will address the role of implementation of rapid treatment to reduce infectiousness in source cases; the methods of optimizing design and administrative controls to prevent nosocomial transmission; the role of preventive treatment of children exposed to MDR-TB; and potential new agents that could be used to treat latent MDR-TB.

EXPANDED ACCESS WORKING GROUP

Another important policy priority has been to promote early access to new TB drugs – a priority that has increased urgency now that bedaquiline has received regulatory approval and delamanid may also receive approval soon. 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 compassionate use
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 second line drugs

This manuscript will be published by IJTLD in February, 2013.

EXTERNAL RELATIONS SUB-GROUP

The External Relations sub-Group of the Steering Committee filed a statement with the U.S. FDA in support of accelerated approval of bedaquiline in November, 2012 (Appendix E).

Goals for 2013

In the coming year, RESIST-TB will continue to provide leadership in scientific advocacy, MDR-TB clinical trials design and preparation, and public policy development. We will:

- Collaborate with Médecins Sans Frontières to design a strategy for optimizing combinations of new and existing drugs for MDR-TB treatment in a "New MDR Regimen" article.
- Outline gaps in basic science, diagnostics, treatment and community action knowledge by identifying the "Top 10 questions to turn the tide on MDR-TB."
- Implement a "GeneXpert Diagnostic Roll-out Surveillance Project," in collaboration with World Health Organization, to monitor and report on increases in MDR-TB diagnosis.
- Track the roll-out of bedaquiline and delamanid and determine in different geographic regions and record which companion drugs are being used. This effort will be undertaken in collaboration with Janssen and Otsuka.
- Develop an approach to XDT/TDR treatment in collaboration with GATB.

RESIST-TB continues to fill an important and unmet need. By trying to address the existing gaps in the treatment and prevention of MDR-TB, the organization takes on important projects that are not being addressed by others. The successful continuation of these activities is recognized as critical to the continued progress of research and advocacy on MDR-TB.