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# RESIST-TB ANNUAL REPORT FOR 2013

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 2013 were sponsored by the World Health Organization, the Stop TB Partnership, the International Union Against Tuberculosis and Lung Disease, Treatment Action Group, Partners in Health, the U. S. Centers for Disease Control & Prevention, Médecins Sans Frontières, and the KNCV Tuberculosis Foundation.

Our 2013 activities centered on (1) DR-TB scientific advocacy through beginning the process of updating the 2008 research agenda on the programmatic management of DR-TB and dissemination of information through our updated website (www.resisttb.org) and eNewsletter; (2) DR-TB clinical trials development through evaluation and preparation of potential MDR-TB clinical trials sites and assisting in development of MDR-TB Clinical Trials proposals; (3) influencing public policy through the annual meeting at the Union Conference in 2013 and publishing articles in the scientific and lay press.

## SCIENTIFIC ADVOCACY

### RESEARCH AGENDA

Over the past year, the Research Agenda (RA) Working Group conducted an extensive review of available literature and resources on priorities in the programmatic management of DR-TB. The RA committee compiled a comprehensive list of the research questions that emerged from the review. These research questions were developed into a survey for external review that was distributed to over 500 unique contacts. The RA committee looks forward to drafting a manuscript for publication in 2014.

### WEBSITE AND eNEWSLETTER

The RESIST-TB website (www.resisttb.org) was redeveloped in 2013 to make it more user friendly and informative. The most recent news, events, developments, and publications related to MDR-TB will be regularly updated. Additionally, training resources and links to the new social media pages are accessible on the home page. A monthly eNewsletter highlights information about new DR-TB related publications, news updates and events. The reach of the eNewsletter has increased 50% in the past year and currently has a regular subscription of over 300 individuals and organizations.

## CLINICAL TRIALS

### SITE CAPACITY DEVELOPMENT WORKING GROUP

The Site Capacity Development Working Group has evaluated the patient populations, laboratory and research infrastructure available at each of 13 potential clinical trial sites. Eight clinical sites were identified as ready to implement trials and were listed on www.sitefinder.tghn.org for exposure to

clinical trial implementers. The remaining 5 sites require additional training in the following areas: (1) Good Laboratory Practice; (2) Good Clinical Practice; (3) Good Pharmaceutical Practice. The Working Group is compiling low-cost options for provision of training to these sites with the goal of bringing them to clinical trial readiness.

CLINICAL TRIALS WORKING GROUPS

RESIST-TB is the largest international organization that focuses on championing and promoting research and clinical trials for MDR-TB.

1. The Preventive Therapy Working Group has continued working on a concept adapted and submitted for further development to both ACTG and TBTC.

2. The M/XDR Regimens Working Group has focused on 3 projects in the last year, which include:
   - Proposal approved by ACTG for a trial evaluating combinations of bedaquiline, sutezolid, PA-824 and PZA for M/XDR-TB treatment (protocol currently in development).
   - NiX-TB trial of bedaquiline, an oxazolidinone, PA-824 and PZA for XDR-TB in development by the TB Alliance (protocol currently in development)
   - Phase 2 study of high-dose levofloxacin in the treatment of MDR-TB (Opti-Q), now funded by NIH, CDC and Macleods Pharmaceuticals (enrollment to begin in Q2/3-2014).

3. In collaboration with Médecins Sans Frontières, members of the RESIST-TB New Drugs Working Group developed a strategy for optimizing combinations of new and existing drugs for MDR-TB treatment. “Principles for designing future regimens for multidrug-resistant tuberculosis” was published online in the *Bulletin of the World Health Organization* on October 25, 2013 and focuses on principles for designing treatment regimens that are both proven safe in clinical trials and are clinically effective and programmatically practicable. This publication concluded that eight principles exist and future regimens should: (1) contain at least one new class of drug; (2) be broadly applicable for use against MDR and extensively drug-resistant *Mycobacterium tuberculosis* complex strains; (3) contain three to five effective drugs, each from a different drug class; (4) be delivered orally; (5) have a simple dosing schedule; (6) have a good side-effect profile that allows limited monitoring; (7) last a maximum of 6 months; (8) have minimal interaction with antiretrovirals.

GENE XPERT WORKING GROUP

The GeneXpert (GE) Working Group aims to better understand how GeneXpert technology is being utilized globally to increase diagnosis of DR-TB. GE has 3 basic goals for an ecological analysis during the initial stages of GeneXpert rollout, each of which will be monitored annually going forward. For the first year of analysis, the working group collected and compiled distribution of Xpert MTB/RIF rollout in the 27 high-burden MDR-TB countries, including cartridge sales by clinical site, as reported by Cepheid. Independently, trends were noted in MDR-TB diagnosis over the past decade, including that in the past 3 years since GeneXpert was first introduced in each country, areas using GE for MDR-TB diagnosis had a marked increase in such diagnoses, with no other clear explanation for this increase.

NIX-TB WORKING GROUP

The NIX-TB working group is a collaboration with the TB Alliance (TBA) to develop a salvage regimen for XDR-TB. The original proposal was for a regimen of bedaquiline, sutezolid, PA-824 and PZA, but due to the unavailability of sutezolid, this has been changed to a regimen of bedaquiline, linezolid, PA-824 and PZA. RESIST-TB has given input to the TBA on study design and enrollment criteria. It is hoped that the trial will begin enrollment in 2014.

## PUBLIC POLICY

EXPANDED ACCESS

Promoting early access to new TB drugs is an important policy priority. RESIST-TB is committed to surveillance of the following activities to examine opportunities for advocacy:

- Janssen's compassionate use (CU) program for bedaquiline has been in place since 2011. There are 230 patients enrolled in the CU program as of October 2013.
- European approval of delamanid was granted by the EMA in 2013; Otsuka is planning a delamanid expanded access (EA) program for future implementation, and this will be monitored by RESIST-TB*
- Although there are currently no plans for CU or EA for the remaining new TB drugs, RESIST-TB will watch closely to determine when such programs are justified

UNION CONFERENCE

RESIST-TB continues to influence public policy by ensuring that drug resistant tuberculosis stays in the spotlight at TB scientific meetings. The RESIST-TB annual meeting at the 2013 Union Conference in Paris, France, drew an audience of over 100 interested in hearing about the newest developments in MDR-TB trials, as well as RESIST-TB's efforts in promoting those trials.

The annual meeting featured a summary of RESIST-TB's efforts of 2013. Also included were an update by Dr. Sarah Meredith of the U.K. Medical Research Council on the STREAM trial, a 9-month treatment regimen based on a high-dose flouroquinolone and clofazamine; an update on the delamanid program by Dr. Jeffrey Hafkin from Otsuka; and an update on the Bedaquiline program by Dr. Myrian Haxaire-Theeuwes from Janssen. The annual meeting was closed with a panel discussion entitled "Moving from New Drugs to Programmatic Regimens for MDR-TB." The panel included experts and advocates from Treatment Action Group, WHO, KNCV Tuberculosis Foundation and TBTEAM.

## GOALS FOR 2014

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. Our plan for the upcoming year includes:

- Continue development of the research agenda on the programmatic management of DR-TB and submit the manuscript for peer-reviewed publication
- Monitor and report on increases in MDR-TB diagnosis through the GeneXpert Diagnostic Roll-out Surveillance Project in collaboration with WHO

*Compassionate use of and expanded access to new drugs for drug-resistant tuberculosis. Horsburgh CR Jr, Haxaire-Theeuwes M, Lienhardt C, Wingfield C, McNeeley D, Pyne-Mercier L, Keshavjee S, Varaine F; Research Excellence to Stop TB Resistance (RESIST-TB); Critical Path to TB Drug Regimens' Access and Appropriate Use Workgroup. Int J Tuberc Lung Dis. 2013 Feb;17(2):146-52

- Track CU/EA of new TB drugs through the roll-outs of Bedaquiline and Delamanid in collaboration with Janssen and Otsuka
- Accelerate progress towards improved DR-TB treatment in collaboration with ACTG, TBTC, DMID, GATB and other international partners.

RESIST-TB continues to fill an important and unmet need. By addressing the existing gaps in the treatment and prevention of MDR-TB, the organization draws attention to needed research and takes on important projects that are not currently addressed by the global tuberculosis community. The successful continuation of these activities is recognized as critical to the continued progress of research and advocacy on MDR-TB, ultimately resulting in more effective and better-tolerated treatment for MDR-TB and XDR-TB.