Meeting Report
6th Semi-annual Global TB Community Advisory Board Meeting

May 29–30, 2014
New York, New York, USA

TB CAB Meeting in New York City
29-30 May, 2014

TB Drug/Combinations Pipeline Update

Dr. Neil Schluger (Columbia University) presented on the current pipeline of drugs for TB and how clinical trials are proceeding. Neil outlined the current state of global TB epidemiology, including the emergence of MDR-TB, for which only 10-15% of inflicted people are being treated. The WHO estimates only about a 2% decline in TB incidence per year—this is not enough to eliminate TB by 2050, nor is it a reliable estimate. Improving this trajectory must include a new regimen for TB as well as massive treatment of LTBI. Neil outlined the pros and cons of current therapy for active and latent TB, explaining how shorter and simpler regimens will lead to increased completion and cure rates. Based on the current pipeline, which contains only a handful of new or repurposed drugs in phase II and III, an achievable goal on the horizon would be to decrease treatment time to two or three months in the next ten years. There are no drugs in phase I. Neil did note the promise of new drugs bedaquiline and delamanid, which should have no pre-existing resistance, for improving drug-resistant (DR-TB) treatment. For shortening therapy for drug-susceptible TB (DS-TB), though quinolone-based short-course treatments have not proven non-inferior to the standard of care, they still have cured the majority of patients in trials. A way forward may be to determine who is at risk of relapse and in need of longer-term care to allow for most patients to be placed on shorter treatment. Unfortunately, funding for TB R&D is declining with little private sector investment. The TB CAB discussed the challenges that of uncertainty regarding the best animal model, limited clinical trial capacity, and lack of surrogate endpoints and biomarkers of activity.

Statistics and Clinical Trial Interactive Training

Patrick Phillips (UK Medical Research Council Clinical Trials Unit at University College London) presented an overview of clinical trial design and statistics to the TB CAB, and then delved in more detail into examples of determining power for the STREAM study and examining a paper on delamanid's phase IIB trial. Patrick explained type I (concluding there is a difference between two interventions when there is no difference) and type II errors (concluding that there is no difference when there is one), and how power and significance to minimize these errors influence trial design. Patrick also described trials according to the classification of explanatory trials (proof-of-concept under highly controlled conditions) and pragmatic (closer to implementation in practice) trials. The TB CAB also discussed with Patrick the implications of accelerated approvals and limited data for TB treatment in practice. Patrick explained the difference between superiority and non-inferiority trials, and how margins of non-inferiority are determined. The group also learned about intention to treat (ITT), a concept where all randomized patients are included in the analysis according to the treatment they were allocated to, and what pre-determined modifications are permissible for analysis (MITT). In the review of the delamanid paper, the TB CAB discussed the difficulty of interpreting the data given the poor study design.

Access and Research Gaps for Existing TB Drugs

Lindsay McKenna (Treatment Action Group) introduced the new TB drug guide that TAG published in May 2014. Lindsay suggested research and access advocacy priorities for six drugs, (bedaquiline, clofazimine, delaminid, linezolid, moxifloxacin, and rifapentine). The group discussed intellectual property blocks to generic competition and affordable access, and how secondary patents are potentially more easily contested than basic patents. The group discussed how small markets for some medicines challenge generic manufacturing. The TB CAB identified the need for advocacy for bedaquiline, clofazimine, linezolid and rifapentine to get onto the Essential Medicines List (EML), as the next meeting for the EML will be in spring 2015. The group discussed how regulators are not being stringent enough in terms of requiring rigorous phase three trials for DR-TB. There is a need for better consensus on what the control arm for DR-TB trials should look like.

Diagnostics Update

Colleen Daniels (Treatment Action Group) led a discussion updating the TB CAB about diagnostics advocacy and the need for a faster, point-of-care test. She described findings from the roll-out of GeneXpert, and reviewed with the TB CAB the urine LAM assay. Colleen described the slow-moving diagnostics pipeline and suggested a good way forward would be investing in technology for whole genome sequencing, which can allow for tailoring treatment based on individual profiles. Colleen explained the varying jargon to describe the diagnostics development process. The group discussed options for bringing down the cost of GeneXpert machines. Colleen updated the group that India did not renew an import license for Alere to be able to distribute Qiagen's TB Gold test in India, which is not suitable for diagnosis of active TB. Colleen also gave an update from the recent Global Laboratory Initiative meeting, which featured discussion on the importance of integrating TB diagnosis into other laboratories, as funding is too limited to expect TB-only laboratories. The group discussed a patient-centered approach to diagnosis.

TB CAB Strategy Session

The TB CAB strategy session focused on discussing the scope of the work of the group, and at what level (global, regional, national and local) the CAB as a whole and individual members work. The group reviewed the broad goals they created in 2011 and the Terms of Reference from 2013. Some members indicated that a lack of translated materials was a barrier to dissemination of information to networks. Unfortunately, the TB CAB lacks resources to pay for translations; this could be done by volunteers or perhaps working with partners, e.g. Global Coalition of TB Activists. Some members expressed concern that the conversations at the global and CAB level were not engaging those working on the ground, but the majority felt that the TB CAB was tackling important issues that local communities weren't able to, and that the focus was still relevant and the right one. Most members felt that it was the responsibility of individual CAB members to bring to the group issues from their countries to take forward, and that the CAB has successfully taken action when this has been done in the past. The group did discuss the need to be more inclusive and bring in more members (either list-only or rotating in given funding limitations).

Strategizing on Accessible Drug Pricing

Sharonann Lynch (Médecins Sans Frontières) and Kelly Catlin and Ateen Paliwal (Clinton Health Access Initiative) spoke with the group about how to approach accessible drug pricing. For CHAI, there are three stages of intervention: preparation, mobilization, and registration implementation. Some price reduction strategies include: building and consolidating demand, enhancing competition, optimizing product design, and having actual negotiations. Another way to bring down cost is to try and limit the risk for a manufacturer. Well-designed tenders can split volumes between manufacturers to avoid monopolies, and include several factors as part of the selection criteria. CHAI is not very involved in the TB drug market and although some of these reduction strategies (which CHAI uses in the HIV market) would work in TB, not all of them will be as effective (e.g. finding cheaper process chemistry may be difficult for DR-TB drugs requiring fermentation).

Sharonann discussed strategies to make DR-TB medicines more available, affordable, and adapted to needs, and highlighted especially the role of generic competition in bringing down the cost of HIV medicines. She discussed intellectual property, and how TRIPS flexibilities and compulsory licensing can lower prices. The group discussed the need for generic competition, reducing manufacturing costs, and the problem of the Global Fund institutionalizing tiered pricing (which segments the market, and ignores local disparities and willingness to pay).

Human Rights and Treatment Access Issues

Brian Citro (University of Chicago) spoke with the group about how human rights can play a role in TB treatment. The group discussed why a rights-based approach to TB advocacy is worth pursuing: generally individuals living with TB are members of groups that are marginalized; these are groups where human rights have been an effective tool in the past. The barriers faced in a TB epidemic include: financial and physical access, and stigma and discrimination. A rights-based approach to TB treatment would mean shifting the focus of treatment towards the rights of the individuals, including the right to health and the right to life. The right to privacy may also come into question with TB treatment; the burden is on the government to prove why someone should not have that right, but the reality is that most people are not well-protected. The group discussed the dichotomy between public health concerns and constitutional rights. The group also discussed how the government has a responsibility to ensure the right to health; this does not necessarily mean that the government has to be the provider of healthcare. Brian explained how there is rationale for rights-based advocacy directed toward non-government actors (e.g. pharmaceutical companies, private correctional facilities).