Report of HIV/TB Research Frontiers meeting in conjunction with the 2016 conference on retroviruses and opportunistic infections (CROI 2016)

The 10th meeting on HIV/TB research in conjunction with CROI 2016 was organised by the World Health Organization (WHO) in Boston, USA on February 22, 2016. The meeting was chaired by Haileyesus Getahun of WHO and Constance Benson of University of California, San Diego, USA.

The objective of the 2016 meeting was to discuss the implications of a novel WHO drug resistance surveillance data especially on pyrazinamide and fluoroquinolones on the development of future TB regimens, in designing clinical trials as well as its long term impact in clinical care of patients.

However, the meeting was opened with a presentation by Haileyesus Getahun (link to presentation) summarising the key impacts of the outcome of the meetings over the last 10 years. The data driven meetings have promoted discussion and debate and generated novel ideas that impacted policy and programme implementation for HIV-associated TB. The key ones include:

- Suggestion in 2007 to conduct studies to evaluate the WHO 2007 smear negative TB algorithm (link to the guidelines), which subsequently showed its impact in reducing mortality and further accelerated its implementation;
- Suggestion in 2008 to develop a simplified clinical algorithm to enhance the provision of isoniazid preventive therapy (IPT) that led to a unique collaboration of researchers, US Centres for Diseases Control and Prevention and WHO to conduct individual participant data meta-analysis (link to PLoS Medicine paper) and the development of the WHO guidelines (link to 2011 guidelines). Almost a million PLHIV were started on IPT in 2014;
- Other suggestions include the development of a combined isoniazid and co-trimoxazole pill in 2008 and the role and importance of presumptive TB treatment for PLHIV to prevent early mortality in 2007 and 2009 that led to the start of several clinical trials.

It was underlined that the novel research and implementation ideas that were generated from these meetings have an indelible role in contributing to the nearly 6 million PLHIV lives saved since 2005 through the implementation of collaborative TB/HIV activities.

Matteo Zignol of Global TB Programme of WHO presented (link to presentation) summary of unpublished data that assessed the prevalence of resistance to fluoroquinolones (ofloxacin, moxifloxacin) and pyrazinamide among 5000 new and previously treated, rifampicin-susceptible and resistant TB cases from five countries. The study was also intended to assess the proportion of cross resistance among the fluoroquinolones and evaluate the correlation between phenotypic and genotypic drug resistance testing. The key conclusion of the study included that the proportion of pyrazinamide resistance was similar to proportions of rifampicin resistance and there is strong association in the resistance pattern of the two drugs in all sites (Africa, Asia and Eastern Europe). However, there was higher ofloxacin resistance than rifampicin resistance among new patients in Asia, which is probably attributed to the higher use of fluoroquinolones
in the private sector. Eric Nuermberger of Johns Hopkins University commented (link to presentation) on the presentation. He mentioned the importance of fluoroquinolones for multidrug resistance TB treatment and the potential for higher doses of moxifloxacin and gatifloxacin to maintain efficacy against strains with low-level fluoroquinolone resistances. He pointed out that there has so far been little effort to understand their dose response relationships with regard to efficacy and toxicity as the current dosage was set for other infections (e.g. community acquired pneumonia) than MDR TB. He also said the findings of the study likely limit the value of pyrazinamide as a component of MDR-TB regimen to the roughly half of patients whose isolates lack pncA mutations, as pyrazinamide lacks efficacy against pncA mutants in animal models. He further argued that with further exploration of the PZA dose-response relationships that govern efficacy and toxicity, it may be possible to identify low-level PZA resistance, such as that associated with rpsL and even some pncA mutations, that could be overcome with higher PZA doses. Studies to better link genotypic and phenotypic DST results with such knowledge of dose-response relationships should enable more rapid and individualized treatment decisions in the future.

Rada Savic of University of San Francisco, USA (link to presentation) discussed the implications of the results for ongoing research and the design of future clinical trials. She questioned whether we are using the right endpoints at the right time. She particularly challenged the use of culture conversion at 2 month as a surrogate marker for drug efficacy because of the incomplete understanding of its predictive capacity. She highlighted the existence of large variability in drug response among patients (e.g. due to type of lesion) and also the increasing number of hard to treat patients could impede the development of one regimen that fits for all and further challenging programmatic management of drug resistance TB. Mel Spigelman of TB Alliance (link to presentation) commented on the presentation and shared insights in TB drug development. While he agreed that there is challenge to develop one regimen that fits for all, he pointed out that the heterogeneity of the disease as well as the differences in the state of resistance in different geographies would optimally call for different regimens for either different patient populations or in different countries. However, he also noted the enormous resource implications of providing either individualized therapies or different solutions for individual countries or patients. He also particularly emphasised the difficulty of moving from phase 2 to phase 3 trials due to lack of adequate tools and he suggested one potential approach would be using multiple phase 3 endpoints (duration of therapy) to overcome this challenge.

Participants in the meeting mentioned that the extent of the observed fluoroquinolone resistance after 50 years of use is not as severe as one would expect. It was concluded that the value of fluoroquinolones for the treatment of TB is worth exploring in future clinical trials. The possibility of using large number of drugs that withstand resistance in regimen for future trials based on their individual toxicity profile was also mentioned.

The role of the meetings in influencing global policy and programme implementation was noted and the importance of continuing the meeting in conjunction with future CROI was underlined by meeting participants.