Phase III Clinical Trial Results at the 48th Union World Conference on Lung Health: Implications for the Field[1]

Preliminary results from two phase III drug-resistant TB (DR-TB) clinical trials were presented at the 48th Union World Conference on Lung Health: stage 1 of the STREAM trial[2] and the Otsuka 213 delamanid trial[3]. As this is the first time we have data from phase III trials specifically for DR-TB, their completion marks an important advance in evidence-based treatment of DR-TB. However, the interpretation of these phase III trial results is complicated, and thus there remain multiple questions about how these results should affect clinical practice in the field. This document will briefly review the findings of these studies as presented at the Union meeting and reviewed later with the study investigators. It will then discuss possible implications for decisions made at country level, while formal WHO review and recommendations are pending. Of note, some data presented were preliminary, and although no major changes in findings are anticipated, the final data merit careful review and additional analyses.

Stage 1 of the STREAM Study

The study hypothesis was "to determine whether a standardized regimen utilizing existing drugs that has been used in one country setting with excellent treatment outcomes can be used in other settings with comparable success." In order to assess this, a multicenter study in Ethiopia, South Africa, Mongolia, and Vietnam was undertaken using a non-inferiority, open-label study design which compared a standardized 9-11 month regimen[4] with the 20-24 month longer standard of care regimen. The study was sponsored by USAID and the International Union Against TB and Lung Disease. Total enrollment was 424 participants; 282 in the study arm and 142 in the control arm. In terms of resistance, 99.1% of participants' TB was susceptible to both the fluoroquinolone and injectable agents and 85% was susceptible to ethionamide. The primary efficacy outcome was the proportion of patients with a favorable outcome at 132 weeks after randomization, having not previously had an unfavorable outcome or been retreated (i.e. recurrent TB).

In terms of efficacy, the longer control arm showed favorable clinical outcomes in 80.6% of participants while the shorter regimen arm showed favorable clinical outcomes in 78.1% of participants. Although these numbers appear similar, the study failed to demonstrate non-inferiority of the shorter regimen—meaning the shorter regimen was not shown to be as effective

as the longer regimen. This is likely due to the fact that the longer arm had much higher rates of favorable clinical outcomes than anticipated and thus the study was "under-powered" (i.e. did not have enough participants enrolled) to confirm non-inferiority of the shorter regimen. Though the study was not powered to detect differences in subgroups, there was a concerning trend toward increased death in people with HIV (who had a higher mortality rate of 18% when given the shorter regimen compared with 7% among persons who did not have HIV), although this difference was not statistically significant.

In terms of safety, the results showed similar rates of treatment emergent adverse events and of serious adverse events in both arms—although formal tests of hearing loss were not part of the study and only "whisper testing" was used. QTcF prolongation of greater than 500msec—a disturbance in the heart's electrical activity that is a risk factor for the development of a serious cardiac arrhythmia—was reported in about 10% of patients receiving the shorter treatment regimen (compared with 5% in the longer regimen), leading the investigators to recommend ongoing electrocardiogram (ECG) monitoring for persons on the shorter regimen. This is in addition to the standard elements of active drug safety monitoring and management (aDSM) that should accompany DR-TB treatment, including active monitoring for hearing loss, with regimen adjustment if adverse events are noted. There appeared to be substantial short-term cost savings to both the health system and individual participants who were assigned to the shorter regimen arm.

<u>Otsuka 213 Delamanid Trial</u>

The study hypothesis was "to determine whether delamanid is effective in the treatment of multidrug-resistant tuberculosis (MDR TB) in combination with other MDR TB medications during 6 months of treatment." In order to assess this, a multicenter study was undertaken in Estonia, Latvia, Lithuania, Moldova, Peru, the Philippines, and South Africa and sponsored by Otsuka—the company that makes delamanid. The study was a randomized, placebo-controlled trial of 511 participants where delamanid (341 participants) or placebo (170 participants) was given for six months in addition to an "optimized backbone regimen." The primary outcome was time to sputum culture conversion over the first six months of treatment.

A total of 327 participants were culture positive at baseline and eligible for the efficacy analysis. Participants in the delamanid arm had a more rapid culture conversion compared with those in the placebo arm (6 to 13 days, depending on the three analytic methods used) The *p* value for the primary efficacy analysis was 0.056 (not significant) but the *p* values for the efficacy analysis using 2 more sensitive techniques (known as "last observation carried forward" and "book ending") were 0.0281 and 0.0052 respectively (both statistically significant). Rates of favorable treatment outcomes at 24 months were similar in the delamanid and placebo arms at 81.4% and 81.2% respectively, but the study was not powered to detect differences in long-term treatment outcomes. And as in stage 1 of the STREAM trial, the control arm had much higher rates of favorable outcomes than anticipated.

In terms of safety, the use of delamanid was not associated with an increased rate of treatment emergent adverse events, and QTcF prolongation >500msec was seen in a small proportion of patients in both arms (5.3% of the participants who received delamanid compared with 2.9% of those who received placebo). In a secondary analysis, including delamanid in the regimen appeared to be protective against the development of additional resistance while on treatment, with only 1.8% of participants who received delamanid developing additional resistance to the fluoroquinolones, compared with 3.6% in the placebo arm.

Field Implications

While there are promising findings from each study in terms of cost savings of the shorter regimen, and the safety of delamanid as well as its effectiveness in preventing additional resistance, neither trial was able to fully confirm its primary objective as specified in their study protocols. This means there is uncertainty about the implications of these studies for clinical practice. With stage 1 of the STREAM study, the rates of favorable outcomes were "close,"[5] but the results also leave open the possibility that the shorter regimen may not be as effective as the longer one. While it may be an appealing therapeutic option for many individuals who qualify to receive it given that treatment has to be taken for a much shorter period of time, we advise:

- Individuals with DR-TB should be made aware of the phase III study results prior to initiating the regimen;
- Countries using the shorter regimen should carefully select and monitor patients and their outcomes closely, especially among persons with HIV;
- The shorter regimen should only be used in those with susceptibility to the second-line drugs in the regimen, since almost all participants in STREAM stage 1 had documented susceptibility to the fluoroquinolones (99%), the injectable agents (99%), and ethionamide (85%). Countries that are not yet able to offer such testing should be strongly encouraged and supported to develop adequate drug susceptibility testing as part of plans to "roll out" the shorter regimen.
- Because the rates of adverse events seen with both the shorter regimen and the longer standard of care were similar, and high, aggressive monitoring and management of adverse events must be included as a part of its implementation.

Once the final analysis of the study is done, there may be more clarity about which groups of persons living with DR-TB would benefit most from the shorter regimen. Additional suggestions may be provided once those analyses are available.

In terms of delamanid, the use of the drug was not associated with a significantly faster time to culture conversion in the primary analysis but was associated with a statistically significant reduction in time to culture conversion using two additional analytic methods. The study also did not demonstrate better longer-term outcomes when delamanid was added to an optimized regimen, but the study was not powered to assess this. The good safety profile of delamanid and

protection from development of resistance mean it is still an important therapeutic option for patients who have resistance or intolerance to other anti-tuberculous agents. We advise:

- Delamanid should be included in country guidelines and procured by National TB Programs;
- Delamanid should be prioritized for people at high risk of treatment failure (most notably for HIV-positive individuals), children, and patients requiring the combination of bedaquiline and delamanid due to high levels of drug resistance or drug intolerance.

An important finding from both of these trials was the higher rate of favorable outcomes seen in the longer standard of care treatment arm than expected. Though the longer standard of care treatment performed better in these clinical trials than anticipated, with about an 80% treatment success rate in each, it bears mentioning that an 80% treatment success rate is not an acceptable goal, as it means 1 out of every 5 patients treated had a poor outcome. This number not only reflects significant human suffering but will make it impossible to achieve the "End TB" targets[6].

While there have certainly been some improvements in the overall treatment of DR-TB in the past few years, the higher rate of treatment success seen in these studies compared with operational cohorts has important implications for standards of care in the field. Certainly, it is true that clinical trials are able to carefully select participants and exclude the sickest and highest-risk individuals from being in the study, and this inevitably leads to better outcomes. Field clinicians and National TB Programs will never have this luxury, nor should they. However, there are some interventions that may have been associated with the stronger performance of the standard of care regimen in these studies that should become standard for all DR-TB patients:

- First, routine drug susceptibility testing was offered to all participants, yet universal DST is still not available in the field—with the recent WHO Global TB Report showing that only 39% of persons with TB were offered testing to rifampin with the Xpert MTB/RIF. Among those found to have rifampin resistance, only 39% were tested for resistance to fluoroquinolone and injectables (WHO recommends 100%)[7].
- Second, enhanced efforts were made to ensure participants were not lost to follow up and were engaged in their care throughout the trials. Clinical studies do have increased funding to support this type of work, but it is clear that this dedication to patient follow up needs a great deal more attention in routine clinical care.

Having phase III trials for the treatment of DR-TB is a much-needed breakthrough, and those who designed, executed, and, most especially, participated in these trials should be commended. Translating these study results, however, into definitive practice recommendations will be challenging given that neither study was able to fully confirm its primary hypothesis while both suggested benefits when the study drug or regimen was used. Overall, these two studies demonstrate that that there is unlikely to be a "magic bullet" or "one-size-fits-all" solution for the

treatment of DR-TB. We need to invest in better diagnosis and treatment support throughout therapy, as well in research and development, to ensure the best possible outcomes are achieved for all individuals with the disease.

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[1] This statement is issued by the leadership committee of DR-TB STAT. The views expressed here do NOT reflect the views of all members of DR-TB STAT nor do they reflect the views of DR-TB STAT's funders, including the Stop TB Partnership and the Global Drug Resistance Initiative.
[2] http://www.isrctn.com/ISRCTN78372190
[3] https://clinicaltrials.gov/ct2/show/study/NCT01424670?term=NCT01424670&rank=1
[4] The regimen consisted of 4-6 months of high-dose isoniazid, pyrazinamide, ethambutol, kanamycin, high-dose moxifloxacin, clofazimine and ethionamide followed by 5 months of pyrazinamide, ethambutol, clofazimine and high-dose moxifloxacin.
[5] https://www.nytimes.com/2017/10/13/health/tuberculosis-treatment-drugs.html
[6] http://www.who.int/tb/post2015_strategy/en/
[7] http://www.who.int/tb/publications/global_report/en/