Shortening treatment for MDR-TB
Final results from Stage 1 of the STREAM trial

Key messages

- We urgently need more effective, safer and shorter regimens for multidrug-resistant tuberculosis (MDR-TB).
- These regimens should be less onerous and costly for both patients and health systems alike.
- STREAM Stage 1 is the first ever phase III randomised controlled trial of a treatment regimen for MDR-TB.
- STREAM Stage 1 compared a 9–11-month MDR-TB regimen to the 20-month regimen previously recommended by WHO.
- STREAM Stage 1 in Ethiopia and South Africa included an assessment of the costs, under each regimen, faced by participants and health systems.
- The final results from STREAM Stage 1 show that the 9–11-month regimen is non-inferior to the 20-month regimen, in terms of efficacy. In other words, the efficacy of the 9–11-month regimen is comparable to that of the 20-month regimen.
- Overall there were similar rates of severe side-effects between the 9–11-month regimen and the 20-month regimen, but there were differences in the types of side-effects caused by the two regimens.
- ECG monitoring was very useful and was required throughout treatment for the 9–11-month regimen. This is likely to be challenging in most routine programme settings, where access to ECG monitoring is limited.
- The STREAM Stage 1 9–11-month regimen presents substantial advantages, despite the need for regular ECG monitoring it requires.
  - The 9-month regimen reduces the treatment time from at least 20-months to 9–11-months.
- Treatment retention is more challenging for longer regimens. In the trial, patients were seen every four weeks; this is unlikely to be feasible in programmatic settings and may have contributed to the better than expected outcomes in the 20-month regimen arm.
- Although analysis of health economics data is ongoing, the 9–11-month regimen provides potential cost savings to patients and health systems compared to the 20-month regimen.
- While the 9–11-month regimen required patients to take more pills while they were on treatment, it reduced the overall pill burden by approximately two-thirds compared to the 20-month control regimen, due to the shorter period of treatment.
- Based on the STREAM 1 results, we have decided to modify regimen B during the remainder of STREAM Stage 2 by replacing moxifloxacin with levofloxacin. This will permit us to assess whether a 9–11-month regimen containing levofloxacin might reduce the risk of QT prolongation when compared to a regimen containing moxifloxacin and the need for continuous ECG monitoring, which could make the shorter levofloxacin-containing regimen more feasible to use under programmatic conditions.
- There is still an urgent need to improve the efficacy, and safety of MDR-TB treatment, so research into other shorter regimens is vitally important.
- STREAM Stage 2 is evaluating an all oral, bedaquiline-containing regimen that is potentially as effective and more tolerable than the injectable-containing regimens currently in use. It is also evaluating the comparative cost of the two regimens, for both the patient and the health system.
The need for shorter treatment regimens for MDR-TB

MDR-TB is a global public health crisis. Worldwide in 2017, an estimated 558,000 people developed TB that was resistant to rifampicin (RR-TB), the most effective first-line drug, and of these, 82% had MDR-TB.

The WHO TB treatment guidelines in effect when STREAM Stage 1 began in 2012 recommended a regimen that lasts at least 20 months, with an 8-month intensive phase. They recommend that the regimen is made up of at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or p-aminosalicylic acid (PAS), if cycloserine cannot be used. The guidelines acknowledge that these recommendations were based on low-quality evidence because they were not based on data from randomised trials.

A prospective observational study conducted in Bangladesh reported a cure or treatment completion rate of 84.5% in 515 patients treated with a 9–11-month regimen with high-dose gatifloxacin, clofazimine, ethambutol and pyrazinamide throughout, supplemented by prothionamide, kanamycin and double-dose isoniazid during the four-month intensive phase. However, it was felt that additional, higher-quality evidence from a randomised control trial was needed to support the efficacy and safety of this regimen in other settings, including in HIV-co-infected patients.

We know from programmatic data that the 20-month regimen has a number of important drawbacks, including:

- The length of the regimen is challenging for both patients and the health system, and the proportion of patients completing treatment is often low.
- The drugs used in the regimen have significant side-effects, most notably hearing loss, which can be permanent.
- The proportion of patients with favourable outcomes is relatively low, with standardised regimens having a globally reported treatment completion or cure rate of only around 50% according to analyses from WHO (although there is variation between countries and data includes patients with pre-XDR and XDR-TB who were not included in STREAM).
- The cost of the regimen is substantial both for patients and health systems.

In 2016 the WHO guidelines were updated to recommend a shorter, 9–11-month regimen (the STREAM Stage 1 regimen), for patients with MDR-TB who were not previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents was excluded or considered highly unlikely. This change was made because of these widely-acknowledged challenges with the 20-month regimen and because of favourable results from the shorter regimen in cohort studies.

This briefing paper presents final effectiveness and safety results from Stage 1 of the STREAM trial, which tested the 9–11-month regimen recommended in the 2016 WHO guidelines against the 20-month regimen recommended in the 2011 guidelines.

About STREAM Stage 1

STREAM Stage 1 is the first phase III randomised controlled trial of a treatment regimen for MDR-TB. The trial compared a 9–11-month MDR-TB regimen to the previously recommended 20-month regimen. It opened to recruitment in July 2012.

STREAM Stage 1 was carried out in Ethiopia, Mongolia, South Africa and Vietnam; 424 participants were randomised to receive either:

- Arm A (control arm): the locally mandated standardised 20-month regimen in use at the study site (provided that it complied with 2011 WHO guidelines)
- Arm B (intervention arm): a 9–11-month regimen consisting of moxifloxacin, clofazimine, ethambutol and pyrazinamide given for 9–11-months, supplemented by kanamycin, isoniazid and prothionamide in the first four months. All drugs were given in a single dosage daily, except for kanamycin, which was given three times per week from week 12.

In Arm B, the intensive phase could be extended by one or two months for patients whose smear had not converted by four or five months, respectively, extending the overall treatment time to up to 10 or 11 months, respectively.

The 9-month regimen has a number of potential advantages over the 20-month regimen. It is much shorter and therefore likely to be easier for patients and health systems. In addition, while the 9–11-month regimen requires patients to take more pills while they are on treatment, it reduces the overall pill burden by approximately two-thirds compared to the 20-month control regimen, due to the shorter period of treatment. This is particularly important for patients co-infected with HIV, who may have to take large numbers of pills to treat the two diseases.

STREAM Stage 1 in Ethiopia and South Africa included an assessment of the costs, under each regimen, faced by participants and health systems, and the financial well-being of participants.
The Design of STREAM Stage 1

Because of the shorter duration and potential lower costs of the shorter regimen, a non-inferiority design was considered appropriate.

The primary efficacy outcome of STREAM Stage 1 was the proportion of patients with a favourable outcome at 132 weeks post-randomisation. A patient was defined as having a favourable outcome if their last two culture results, taken on different occasions, were negative, unless the patient was previously classified as unfavourable. The last of these two cultures must be taken within the time period allowed for the 132-week assessment.

Unfavourable outcomes included:
• Positive culture results at 132 weeks or at the last time the patient was seen before week 132
• A change of two or more drugs in the assigned regimen or extension beyond replacement of any missed treatment
• Restarting treatment
• Death from any cause
• Lost to follow-up before 18 months

The primary safety outcome of STREAM Stage 1 was occurrence of any grade 3 or greater adverse events, as evaluated by the Division of AIDS criteria.

Was the 9–11-month regimen non-inferior to the 20-month regimen?

The 9–11-month regimen was statistically non-inferior to the 20-month regimen in terms of efficacy. 78.8% of assessable participants had a favourable outcome (vs. 79.8% in the 20-month regimen). The upper 95% confidence interval for the difference was 9.5%, which falls within the 10% non-inferiority margin.

There was no evidence that efficacy results were worse in HIV-infected participants than the results for HIV-negative participants.

Safety of the 9–11-month regimen

There were very similar rates of severe adverse events between the short and long regimens, with 48.2% of participants on the 9–11-month regimen experiencing Grade 3–5 adverse events, compared to 45.4% on the 20-month regimen.

Most common grade 3–5 adverse events included conduction disorders (10% in the 9–11-month arm vs 5% in the 20-month arm), which increase the risk of serious and potentially fatal arrhythmias, and metabolism and nutrition disorders (15% in the 9–11-month arm, and 20% in the 20-month arm). There was limited evidence of a difference in mortality between arms, although more deaths were observed on the short regimen in the first year after starting treatment. This observed difference was more pronounced in patients coinfected with HIV.

Five of the MedDRA System Organ Classes accounted for the majority of severe adverse events. Cardiac disorders affected more participants allocated to the short (10%) than the long (5%) regimen, whereas metabolic disorders, in particular Hypokalaemia, were more common on the long. Slightly more participants on the short than the long regimen had hepatobiliary events (9% vs 6%) but there was no difference in the frequency of either ear and labyrinth or respiratory disorders.

An independent data monitoring committee (IDMC) met six-monthly throughout the trial to review data. At no time did they recommend interrupting or stopping the trial for safety reasons.

Cost implications of the 9–11-month regimen

Although analysis of health economics data is ongoing, the 9–11-month regimen provides potential cost savings to patients and health systems compared to the 20-month regimen.
Conclusions

Until now there has been a lack of strong supporting evidence to underpin MDR-TB treatment guidelines. The results from STREAM Stage 1 help to fill that gap.

We know from programmatic data that the 20-month regimen has a number of important drawbacks, including the difficulty of completing such a long treatment, the significant side-effects of the drugs used, poor cure rates, and the cost of the regimen. Shorter, more effective and safer regimens are urgently needed.

The final results from STREAM Stage 1 suggest that the efficacy of the STREAM 9–11-month regimen is comparable to that of the 20-month regimen, supporting the use of a shortened regimen for patients with rifampicin-resistant TB. There were very similar rates of Grade 3–5 adverse events between the short and long regimens. However, conduction disorders were more common on the shorter, high dose moxifloxacin-containing regimen, which made ECG monitoring essential throughout treatment.

The STREAM 9–11-month regimen presents substantial advantages, despite the ECG monitoring required. The 9–11-month regimen reduces treatment times, may improve retention under programmatic conditions, and reduces the overall pill burden for patients.

Nevertheless, there remains an urgent need to improve the efficacy and safety of MDR-TB treatment, so further research into shorter regimens is vitally important. STREAM Stage 2 is evaluating an all oral regimen that is potentially as effective and more tolerable than the injectable-containing regimens currently in use. In addition, in STREAM Stage 2 moxifloxacin will be replaced by levofloxacin to permit assessment of whether this results in a reduced risk of QT prolongation.

STREAM 2 is also evaluating whether the fully oral 9–11-month regimen will result in cost-savings for patients and/or health systems, and includes a health-related quality of life assessment.

Recommendations

1. Global technical agencies should interpret the results of STREAM stage 1 carefully, in the light of the programmatic realities they face, and the recent Rapid Communication from WHO on MDR-TB treatment, to determine the best way forward.

2. There is still an urgent need to improve the efficacy and safety of MDR-TB treatment. Hence, research into other shorter regimens is vital.

Further information

A description of the STREAM Stage 1 study is available at https://_trialsjournal.biomedcentral.com/articles/10.1186/1745-6215-15-353.

STREAM is registered on ISRCTN, number 78372190 at http://www.isrctn.com/ISRCTN78372190.

For more detailed information on the design and implementation of the trial, see: www.Treattb.org.

You can read more about STREAM Stage 2 at http://err.ersjournals.com/content/25/139/29 and https://clinicaltrials.gov/show/NCT02409290.

For more detailed information on the design and implementation of the trial, see: www.Treattb.org.

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