THE IMPLEMENTATION OF NEW DRUGS AND SHORTER TREATMENT REGIMENS IN KYRGYZSTAN

CHALLENGE TB IMPLEMENTATION BRIEF

BACKGROUND

Until very recently, all patients in the Kyrgyzstan with drug-resistant tuberculosis (DR-TB) received a treatment regimen for 20-24 months. These treatment regimens included the use of injectables agents for 8 months, which caused permanent disabling side effects in some patients. Only 54 percent of patients with multidrug-resistant TB (MDR-TB) presented a successful final treatment outcome, while 22 percent abandoned treatment (data from the 2015 cohort). Patients with extensively drug-resistant TB (XDR-TB) had a cure rate of only 11 percent.

Bedaquiline (Bdq) and delamanid (Dlm) are the first new drugs to appear on the market to treat TB in 40 years. Since their introduction, they have brought renewed hope to patients as they presented new therapeutic options for patients with DR-TB. The shorter MDR-TB regimen, as its name implies, is a regimen that is 9-11 months long and thus shorter than the conventional regimen that was being used in the Kyrgyzstan, and as such presents benefits for both patients and the health system.

Patient Story

Eight-year-old Syuta (pictured above) lost her mother to extensively drug-resistant TB. The treatment she took for two years failed to help her. The introduction of new drugs and treatment regimens came too late to save her life and bring her home to her children. Syuta and her three brothers were orphaned and are now being raised by their grandmother.

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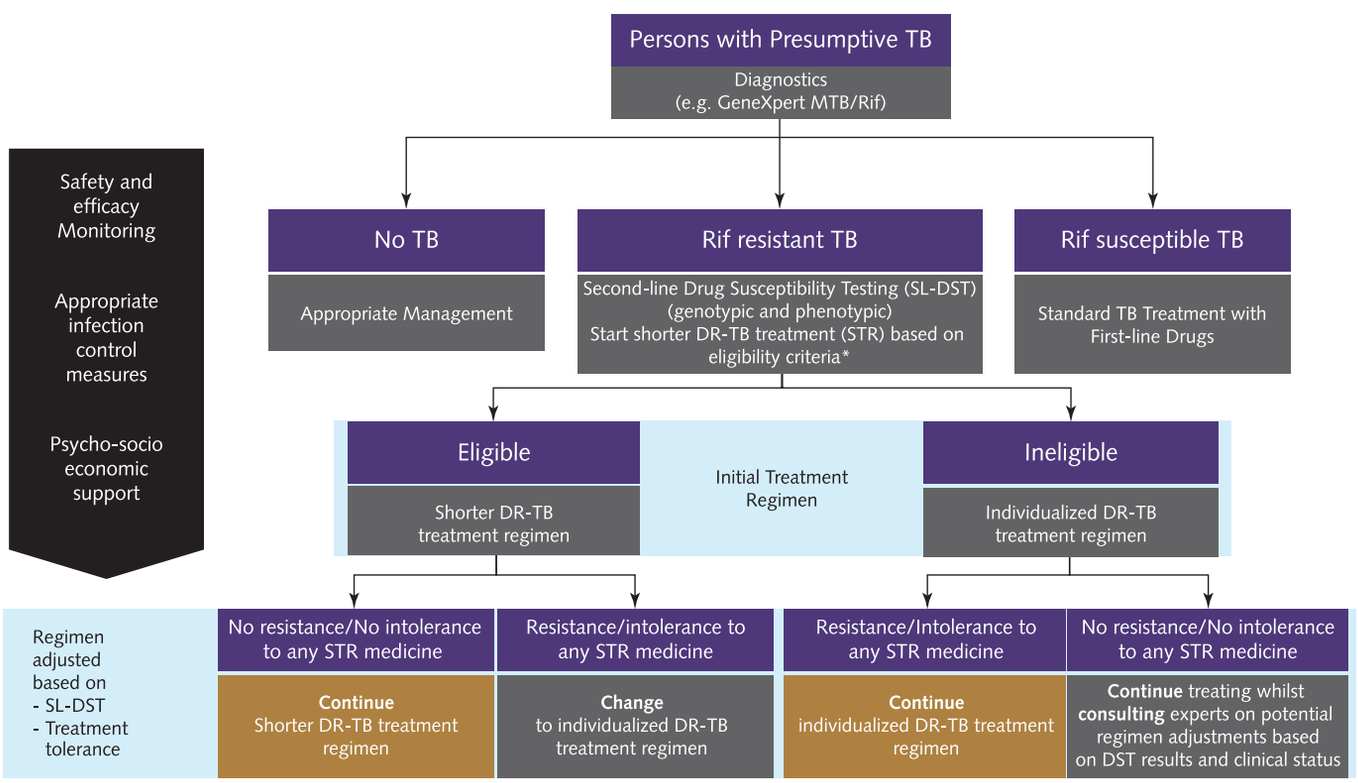
INTERVENTIONS

The USAID-funded Challenge TB project (CTB), supported the Kyrgyzstan National TB program (NTP) in the introduction of new DR-TB diagnostic and treatment approaches (in partnership with the Global Fund, the World Health Organization (WHO), and the United Nations Development Program (UNDP)).

CTB supported the NTP in the implementation of the triage approach, which is the core component needed for the successful introduction of new DR-TB treatment regimens. The patient triage approach helps to allocate the appropriate treatment for the patient by using second-line line probe assay (SL-LPA) for the early detection of second-line drug (SLD) resistance among rifampicin-resistant TB (RR-TB) patients, followed by the early initiation of the most effective regimen for each patient. Patients without resistance to second-line injectables (SLI) and/or fluoroquinolones were put on the shorter DR-TB treatment regimens (STR). Patients with more extensive resistance to SLDs were put on standard-length treatment (20-24 months) with the addition of new and/or re-purposed drugs.

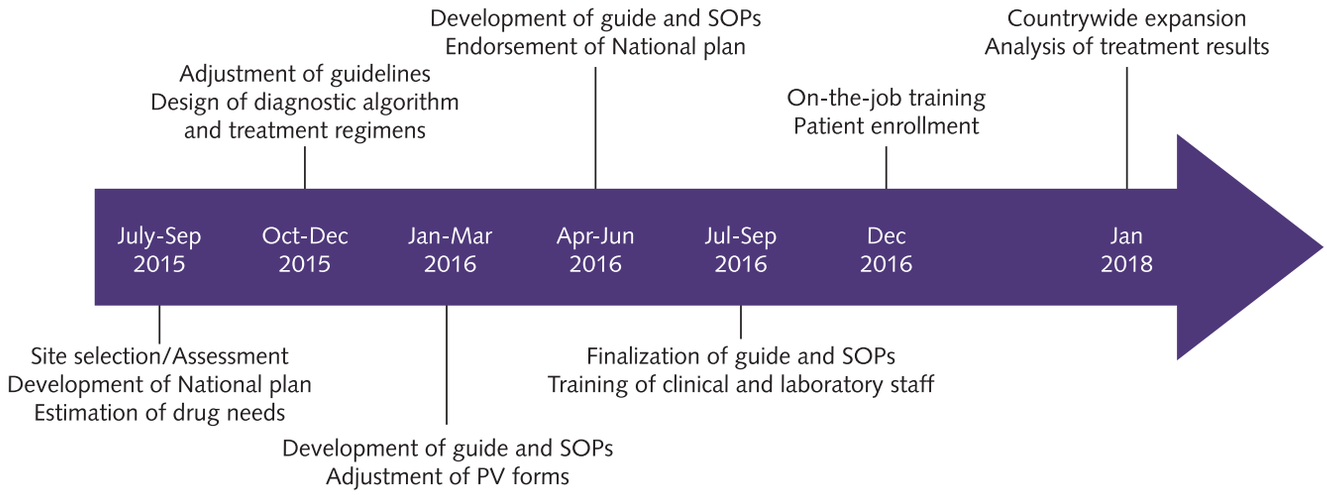
FIGURE 1: PATIENT TRIAGE APPROACH



* Not eligible for the shorter treatment regimen are patients having 1) Resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance); 2) Exposure to one or more second-line medicines in the regimen >1 month (unless susceptibility to these medicines is confirmed); 3) Intolerance to any medicine in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions); 4) Pregnancy; 5) Disseminated, meningeal or central nervous system TB; or any extra-pulmonary disease in an HIV patient.

To introduce new drugs and regimens (ND&Rs), CTB used a multifaceted approach, providing support in different areas, including advocacy, regulatory frameworks, staff capacity-building, clinical mentoring, data analysis and sharing, and policy improvement.

FIGURE 2: TIMELINE OF THE INTRODUCTION OF NEW DRUGS & REGIMENS IN KYRGYZSTAN



ADVOCACY, POLICY, AND REGULATORY FRAMEWORK

Even though WHO had released recommendations for the use of both bedaquiline and delamanid, the guidelines from WHO in 2013 and 2014 were interim with conditional recommendations. Phase III trial data for bedaquiline and delamanid were not available until the latter years of the CTB project, and WHO only issued guidelines on the STR in 2016. In addition, the STR had mainly been used in regions with lower levels of drug-resistance than in the Central Asian Republic (CAR) countries. Hence there was initial reluctance on the part of the Ministry of Health and the National TB Program (NTP) representatives to endorse the use of the new drugs and regimens in Kyrgyzstan. CTB experts facilitated multiple advocacy meetings and workshops to increase knowledge, interest, and awareness among national experts, and coordinated efforts among partners to unify the approach. CTB also supported the adjustment of national guidelines, standard operating procedures, and the national introduction plan.

SCALING-UP DIAGNOSTIC CAPACITY

As access to diagnostic tests differed per region, previous national clinical guidelines included four versions of the diagnostic algorithm reflecting the unequal access to timely diagnosis of TB and DR-TB. None of the algorithms included rapid molecular tests for early diagnosis of XDR-TB. There were severe delays in reporting results to clinicians and treatment was started late, reducing the chances of patients being cured. CTB, in collaboration with partners, designed a new diagnostic algorithm based on the triage approach, including the rapid detection of RR-TB and testing for SLD resistance among RR-TB patients using rapid molecular tests. Partners supported the introduction of SL-LPA, specimen transportation, and timely communication of test results to clinicians.

INDIVIDUALS' COMPETENCY DEVELOPMENT

CTB focused on providing short- and long-term technical assistance to build in-country capacity and to develop the competencies of the members of the national and regional MDR-TB Consilia (who recommend treatment regimens for patients and discuss difficult cases), and of healthcare providers such as doctors and nurses in all regions. The aim was to improve the quality of daily practices in the management of DR-TB.

To improve the ability of staff to manage the patients, a learning program based on a "blended learning approach" (self/interactive learning using e-platforms for distance consultations) was organized. This approach made the best use of the human, financial, and time available, and ensured that the new competencies could be used immediately by the trained staff. The 'blended learning' approach also allowed for the implementation of web-based consultations with experts, followed by clinical mentoring done during supportive supervision visits.

The 'Quality Improvement Tool for Clinical Management of DR-TB patients' (QI tool) was developed under the CTB Core BDQ Coordination Project to support the quality improvement of clinical management and allow the standardization of all the necessary activities. (https://www.challengetb.org/library/pmdt). It allowed continuous support to field staff providing competency-based on-the-job training based on the gaps identified. The QI tool was also presented during the webinar and is freely available with to anyone providing TB care in similar or different settings (https://vimeo.com/313161261).

Thanks to this continuous competency development approach, front-line healthcare workers were empowered to interpret molecular tests results; they are now more confident in the selection of the correct DR-TB treatment regimens.

Staff competency building activities were initiated in two pilot sites – Bishkek city and Chui oblasts. A few months after the initiation of patient enrollment in first two pilot sites, the development of competencies, such as the interpretation of molecular test results, regimen selection and design, safety monitoring, etc. using the above-mentioned approach, was gradually extended throughout the country. The NTP staff from the first pilot sites were involved as facilitators, mentors, and supervisors, which assisted in making new treatments available countrywide in less than a year.

ACTIVE DRUG-SAFETY MONITORING AND MANAGEMENT

2015 WHO guidance for active drug-safety monitoring and management (aDSM) of DR-TB treatment programs triggered the introduction of active pharmacovigilance (PV) in many countries, including Kyrgyzstan. CTB supported the necessary adjustments in early detection of adverse events (AEs), revising the list of mandatory baseline and follow-up tests, and providing on-the-job training on the clinical management of AEs. CTB also supported advances in recording and reporting of AEs to national and international level, fostering collaboration between the NTP and the PV center.

DRUG MANAGEMENT

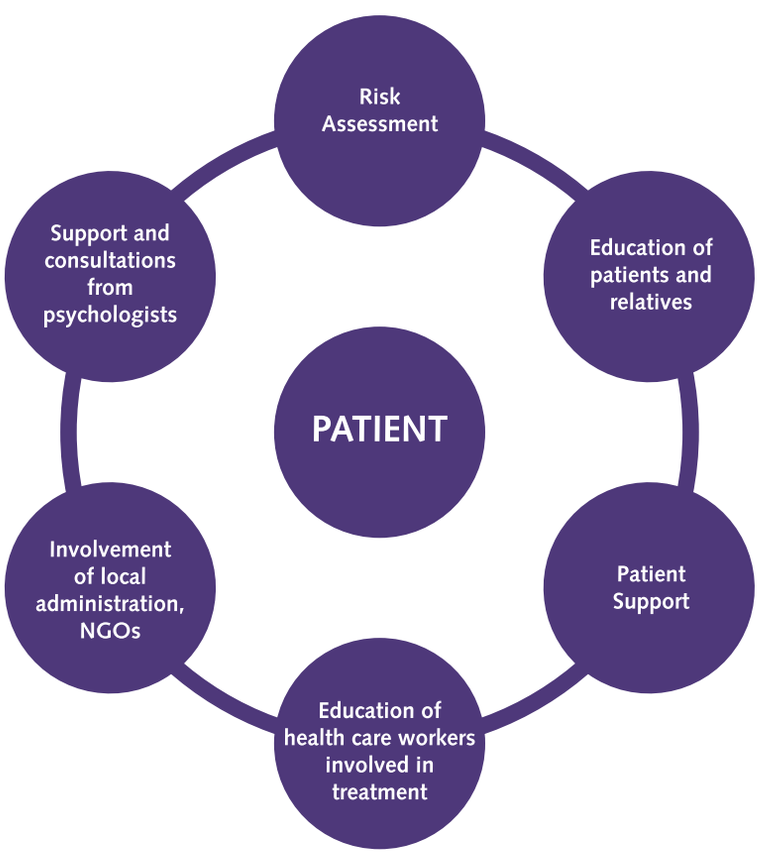
As previously there was only one regimen for the treatment of DR-TB patients, there was no clarity on the proportion/number of DR-TB patients eligible for new regimens. The issue was further complicated by a lack of an electronic reporting system. It was not clear how many patients who previously failed or discontinued treatment needed treatment with regimens containing new drugs. CTB in close collaboration with UNDP/Global Fund supported the estimation of drug needs before the initiation of patient enrollment, as well as during the introduction process, including placing of extra drug orders to ensure access to new treatments for every patient in the country. The estimation of drug needs included an estimate of the number of patients for each regimen, the scale-up of the QuanTB

tool, as well as the recalculation of needs based on enrollment progress. In collaboration with GDF and the Sentinel project, KNCV supported the importation of pediatric formulations of second-line TB drugs.

CASE MANAGEMENT

Introduction of individualized case management was key to the success and safety of the new treatments. The high number of patients giving up on treatment not only furthers the spread of TB but creates a risk of resistance. CTB multiplied efforts to keep patients on treatment by developing a case management model providing constant education, clinical supervision, psychological support, and social aid to the patients on treatment. Project staff worked with every patient individually, produced a TB companion guide in local languages, and provided patients with more comfortable treatment solutions such as video observed treatment to ensure they completed treatment. In less than two years, patients returned to treatment more than 200 times.

FIGURE 3: CASE MANAGEMENT MODEL

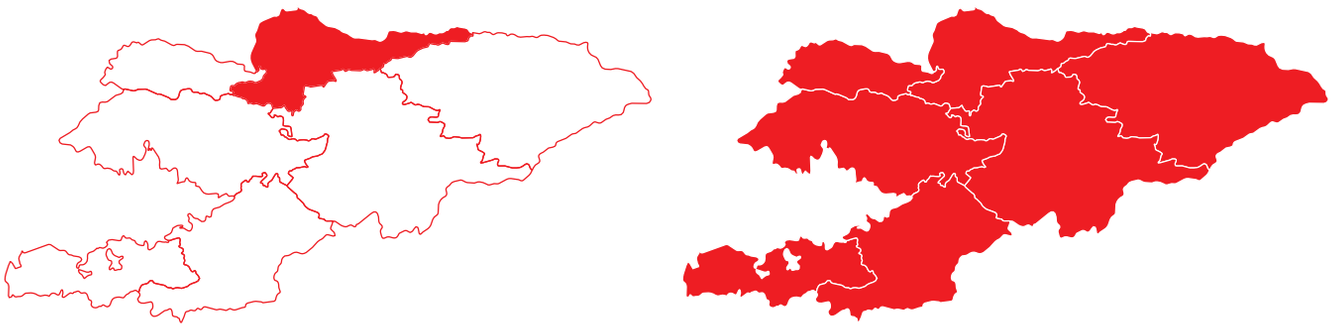


RESULTS/ACHIEVEMENTS

Between 2017 and 2018, 1,009 DR-TB patients were enrolled on new treatment regimens, 7 percent of whom were children.

Access to new treatments was expanded countrywide in record time – with Kyrgyzstan being one of the first countries to give full access.

FIGURE 4: THE AVAILABILITY OF ND&RS IN KYRGYZSTAN, 2017 VS. 2018



Since June 2017, SL-LPA (rapid molecular test for resistance to second-line drugs) has been available in Kyrgyzstan, and thanks to the support of different partners, it is now available in two laboratories that cover the whole country. This has helped to reduce the time for XDR-TB diagnosis from several months to just a few days.

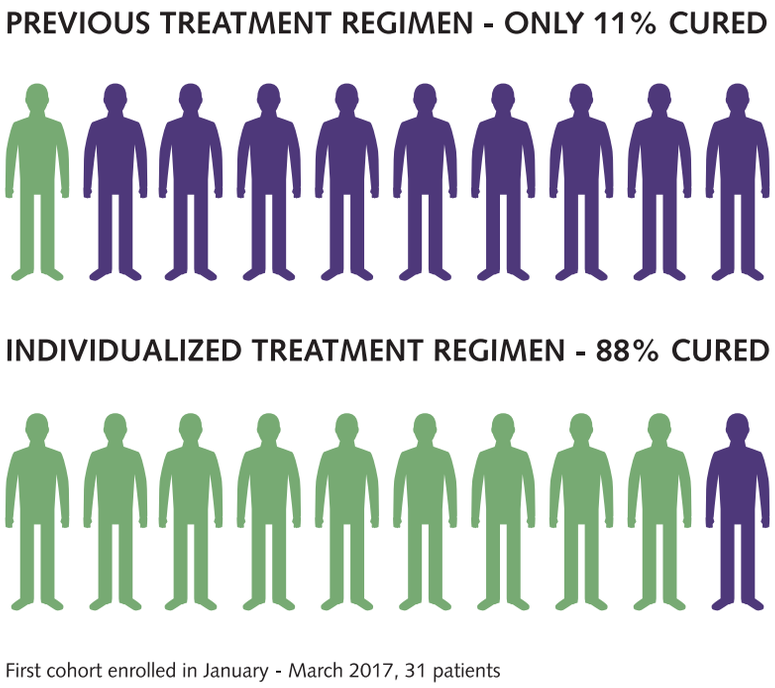
Patients on the STR are treated in just 9 months instead of 24, and data from the 2017 cohort show that 78 percent of patients were successfully treated, with only one patient suffering a relapse 8 months after they were cured. In 2018, there were 181 patients enrolled on the STR, of which 23 patients have already successfully completed treatment.

FIGURE 5: COMPARISON OF TREATMENT LENGTH AND OUTCOMES FOR THE LONG CONVENTIONAL REGIMEN VS. THE SHORTER REGIMEN

The preliminary treatment results using regimens containing new drugs for patients with more complicated forms of DR-TB including XDR-TB are encouraging, 88 percent of those enrolled between January and March 2017 were cured. This is even more impressive considering that all of these had XDR-TB and some were in palliative care before the treatment containing new drugs became available.

Some patients with XDR-TB that presented a complex resistance pattern and thus were unable to receive an effective regimen with enough active drugs had Bdq extended beyond 24 weeks. This was done following the guidance of the WHO provided in the 'best practice statement on the off-label use of Bdq and Dlm for the treatment of drug-resistant TB' and with the support of the national authorities. In the 2017 cohort, due to the advanced disease and/or wide drug resistance profile 36 percent of patients (72/199) received Bdq for the extended duration (beyond 6 months as currently recommended by WHO) without a significant increase in the number of reported AEs.

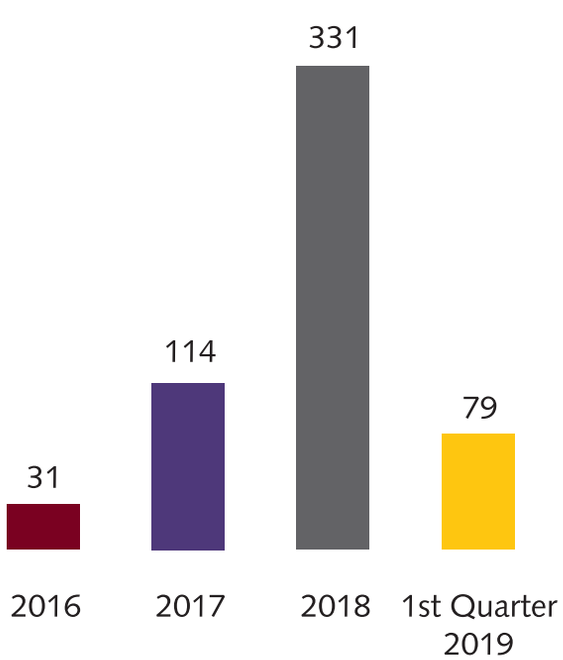
FIGURE 6: COMPARISON OF TREATMENT OUTCOMES LONG BETWEEN THE CONVENTIONAL REGIMEN VS. INDIVIDUALIZED TREATMENT REGIMENS CONTAINING NEW DRUGS FOR XDR-TB PATIENTS.



First cohort enrolled in January - March 2017, 31 patients

All safety monitoring tests are available in every region, and the national health insurance fund covers their cost (previously it was mainly covered by the Global Fund or patients had to frequently pay out-of-pocket). The collaboration between the NTP and the PV center is continuously improving with regular joint meetings, and the reporting of AEs has increased tenfold compared to 2016.

FIGURE 7: REPORTS OF ADVERSE EVENTS RELATED TO THE USE OF NEW DRUGS & REGIMENS.



After initial struggles with shortages of new drugs, because the needs in-country were much higher than expected, bedaquiline and delamanid are now available for all patients in all regions of Kyrgyzstan including prisons. All regional DR-TB Consilia are capable of correctly enrolling patients on new treatments.

AUTHORS
Gunta Dravniece, Bakyt Myrzaliev, Marion Biremon, Ieva Leimane, Fraser Wares, Emmy van der Grinten

PHOTOS
Marion Biremon
Olivier Le Blanc

LAYOUT/GRAPHICS
Tristan Bayly

Patient Story

Ainura's life has been plagued by TB. After losing her two parents and her brother to the disease, she fell sick and embarked on an 11 year-long battle for life. Until recently, no treatment could cure her of XDR-TB, and she had to put her daughters in an orphanage to keep them from getting infected. The new drugs were a miracle, she was cured and reunited with her family.

CONCLUSIONS

Patients are thankful for the substantially shorter duration of treatment and the shorter period of injectable use. Acceptance by clinicians took longer than expected, and the scale-up of enrollment was slower than anticipated.

The results from Kyrgyzstan are inspiring, and were shared in many national and international meetings. Fortunately, this is not the end of the development, the foundations for the introduction of innovations in Kyrgyzstan have been built, and the country is now preparing to adopt upcoming innovations in the diagnosis and treatment of TB, such as new genome sequencing and injectable free DR-TB treatment regimens that take less than 9 months.

www.challengetb.org

www.kncvtbc.org

info@challengetb.org

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