

STRENGTHENING THE TREATMENT OF DR-TB PATIENTS BY INTRODUCING NEW DRUGS AND REGIMENS IN ETHIOPIA



INTRODUCTION

A high-priority area for the USAID-funded Challenge TB (CTB) project across the 23 countries covered by the project, was to increase treatment coverage for rifampicin-resistant TB (RR-TB) and multidrug-resistant TB (MDR-TB) patients. The project focused on improving the quality of management of drug-resistant (DR-TB) patients, and actively helped countries to plan, implement, and introduce the new TB drugs (bedaquiline and delamanid) and regimens (the shorter treatment regimen), with the aim of improving the treatment outcomes of DR-TB patients and reducing the treatment gap. Thereby ensuring that every patient has access to the treatment they need and that no RR-/MDR-TB patient goes untreated.

This document highlights the activities, experiences, and lessons learned under the CTB project whilst supporting the strengthening of DR-TB patient treatment by introducing new drugs and regimens in Ethiopia.

Ethiopia is one of the World Health Organization's (WHO) 30 high TB, TB/HIV, and MDR-TB burden countries, with increasing concerns on the rising prevalence of MDR-TB. In 2017, WHO estimated 2.7 percent of new TB cases and 14 percent of previously treated TB cases had drug-resistant TB, and an estimated 2,700 RR-/MDR-TB cases emerged in the same year. However, in 2017/18, only 741 RR-/MDR-TB patients were diagnosed and put on treatment – just 25 percent of the estimated burden.



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CHALLENGE TB

Until 2016, the recommended regimen for MDR-TB required at least 20 months of treatment with drugs that are toxic, poorly tolerated, and of limited efficacy with low success rates (globally 55 percent in the 2015 cohort), particularly for patients with additional resistance to second-line drugs (SLD). The National TB Program (NTP) began the introduction of services for DR-TB patients in 2009, with the support of USAID and partners. The CTB project in Ethiopia, led by KNCV in partnership with MSH and WHO, supported the NTP in the implementation, service expansion, case-finding, enrollment on to treatment, and treatment follow-up services for DR-TB patients since its inception.

To address these challenges and based on 2016 WHO recommendations, Ethiopia began introducing bedaquiline (Bdq) and delamanid (Dlm) in late 2016. These are the first new anti-TB drugs (NDs) for many decades, and they enable faster, safer, less toxic, and more effective treatment under programmatic conditions. The introduction was technically and financially supported by several partners, namely CTB, the endTB project, and the global health committee [GHC]).

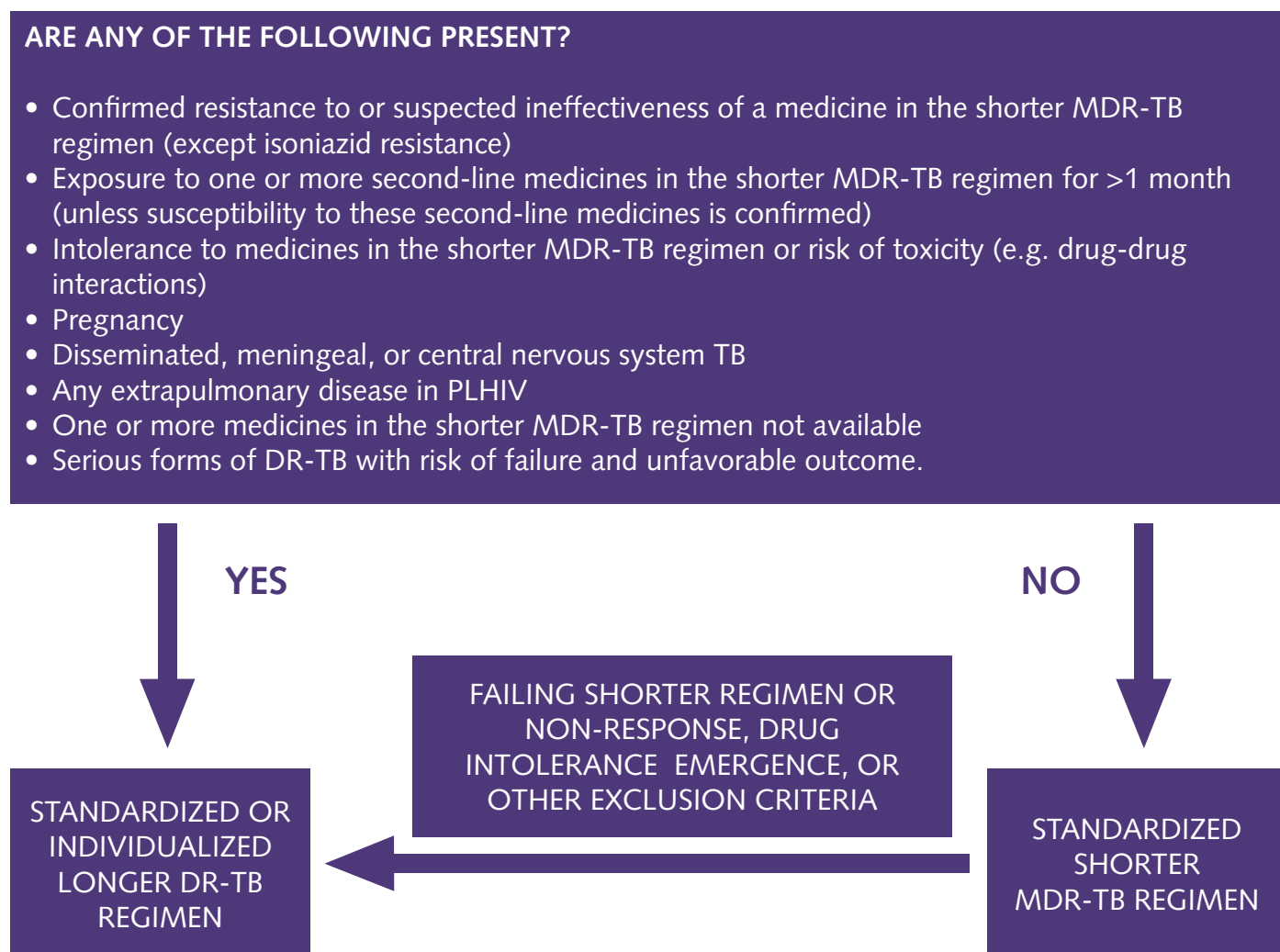
The objectives of CTB Ethiopia's support concerning new drugs and regimens for DR-TB patients were:

- To support the NTP to introduce and make accessible treatment with new TB drugs and regimens (ND&R) for eligible DR-TB patients in Ethiopia; and
- To support the NTP to improve the treatment outcomes of DR-TB patients treated with new TB drugs and regimens in Ethiopia.



CTB was the main partner supporting the NTP with the programmatic introduction of NDs and clinical management by procuring NDs, providing capacity building of health care workers (HCWs), supporting patient referral and linkage for treatment, patient support, and involved in treatment decisions regarding initiation on a ND-containing regimens (with Bdq and/or Dlm) as a member of the national clinical review committee (CRC). Since April 2018, Ethiopia has also adopted the WHO recommendation on the use of the shorter treatment regimen (STR) in eligible DR-TB patients (Figure 1). The STR is now available at all 60 Treatment Initiation Centers (TIC) throughout the whole country.

FIGURE 1: FINDING THE MISSING PATIENTS IN INDONESIA: TB NOTIFICATION 2014-2017



The country now has more than 300 GeneXpert machines in situ where sputum samples from those eligible are tested for RR-TB. After a diagnosis of RR-TB, patients are linked to the nearest TIC. A second sputum sample is sent to a regional laboratory for baseline culture and second-line (SL) drug susceptibility testing (DST) by line probe assay (LPA). Treatment is initiated after other baseline laboratory tests have been conducted, as per the national guideline protocol. Ethiopia implements a predominantly decentralized ambulatory model of MDR-TB service. In-patient care is limited and based on medical (e.g., advanced disease, additional SLD resistance) and/or psychosocial indications (e.g., homelessness). After initiating treatment, patients are linked to treatment follow-up centers (TFC) for directly-observed treatment (DOT), with a monthly follow-up at the TICs.

ACTIVITIES ACCOMPLISHED THROUGH CHALLENGE TB SUPPORT

STAKEHOLDER MEETINGS AND COLLABORATION

The NTP, in collaboration with other governmental stakeholders, including the Ethiopian Food, Medicine and Health Care Administration and Control Authority (EFMHACA) and the Ethiopian Public Health Institute (EPHI), and partners (CTB, WHO, Partners In Health [via the endTB project] and GHC), conducted a series of small group meetings to discuss the development of a national transition plan for introducing NDs for DR-TB patients and national ND technical guidelines, to plan ND procurement and shipments, to plan for the training of HCWs, to select ND TIC, to establish the national CRC and develop its terms of reference, and to revise the national consolidated TB guidelines by incorporating NDs and pharmacovigilance (PV).

There were also a series of meetings of the national PMDT technical working group (PMDT-TWG) organized by the NTP, at which CTB actively participated and made crucial inputs. In addition, international technical assistance (TA) via a PMDT expert from CTB HQ played an important role in the introduction of ND&Rs by providing technical guidance and strong advocacy messages at different stakeholder meetings, including at the national PMDT-TWG meetings and the Ethiopian Thoracic Society's annual conferences.

DEVELOPMENT OF POLICY DOCUMENTS

As members of the National PMDT-TWG, CTB staff were actively involved in the development of all DR-TB related national policies, plans, and related policy documents and training materials. For example, CTB staff were involved in the core writing teams that developed the 'National new drugs and shorter treatment regimen transition plan', the 'National guideline for the programmatic introduction of new drugs in Ethiopia' (which included PV and active drug-safety monitoring and management [aDSM]), the 'National CRC Terms of Reference', the 6th edition of the national consolidated TB and DR-TB guidelines incorporating new drugs and the shorter treatment regimen, and national documents related to the adoption of the 2019 WHO Consolidated Guidelines on the treatment of DR-TB (including the development of an addendum to the 6th edition of the national guidelines, a transition plan, and revision of the national PMDT training materials).

SITE ASSESSMENT AND SELECTION

CTB supported the NTP in site selection and baseline assessment of sites for ND treatment initiation in collaboration with other supporting partners (PIH and GHC) using a standardized national ND site assessment checklist. The CTB project also assisted in filling the gaps after the assessment, including the provision of TA and capacity building, provision of monitoring tools including Snellen and Ishihara charts, ECG, and audiometry machines, etc.

PHARMACOVIGILANCE/ADSM

CTB technically supported NTP and EFMHACA to revitalize the PV system, including aDSM, through workshops to develop an aDSM implementation plan and to incorporate aDSM in the national DR-TB policies, including guidelines and other documents. The project also technically supported the utilization of national and the Global TB Drug Facility (GDF) new drug reporting tools for reporting of adverse events (AEs) and serious adverse events (SAEs) to the national and international agencies (EFMHACA and GDF). In addition, TA will be continued with the objective of strengthening the PV system through the PAVIA project, in which KNCV is involved.

ADAPTATION OF RECORDING AND REPORTING SYSTEMS

CTB provided technical and financial support to the NTP to revise, print, and distribute revised national PMDT recording materials incorporating ND&R, including DR-TB registers, DR-TB follow-up registers, TB/DR-TB contact registers, DR-TB treatment cards, and DR-TB treatment support cards.

CAPACITY BUILDING AND LONG-TERM TECHNICAL ASSISTANCE

Since the introduction of the ND&Rs, CTB has conducted several rounds of PMDT training targeting HCWs and Regional Health Bureau (RHB) PMDT focal persons, and an international advanced DR-TB clinical training for 38 senior physicians from the TICs.

The project also financially and technically supported the training of more than 150 HCWs from the TICs on the utilization of machines for patient monitoring (e.g., audiometers and ECG machines). In addition, CTB supported two rounds of training on PV (including aDSM) for HCWs from every DR-TB TIC.

CTB also technically assisted in an audiometry training for HCWs and for DR-TB patient case consultations by the CRCs using the videoconferencing system established at the ALERT training center in Addis Ababa.

Since the introduction of ND&Rs, CTB's central and regional level laboratory and PMDT advisors have technically supported the NTP in the diagnosis, identification, and linkage of DR-TB patients eligible for NDs to the ND TICs for treatment. CTB has a central level PMDT expert and a DR-TB expert/clinician (at ALERT DR-TB TIC) who actively participate as members of the national CRC and in the clinical care of patients enrolled to ND at the ALERT Hospital's center of DR-TB excellence, where to date, 52 patients have been enrolled on regimens containing NDs.

DRUG PROCUREMENT (INCLUDING ANCILLARY DRUGS)

Through the inputs of its advisors, CTB has technically and financially supported the NTP and the Pharmaceutical Fund and Supply Agency (PFSA) to conduct annual national quantification exercises for anti-TB commodities, including SLDs. CTB has also supported PFSA in the monitoring and distribution of new and re-purposed drugs to the ND TICs.

CTB has also supported in the procurement and/or shipping costs of Bdq, Dlm, and re-purposed drugs (linezolid and clofazimine) for a limited number of patients in urgent need of the medication.

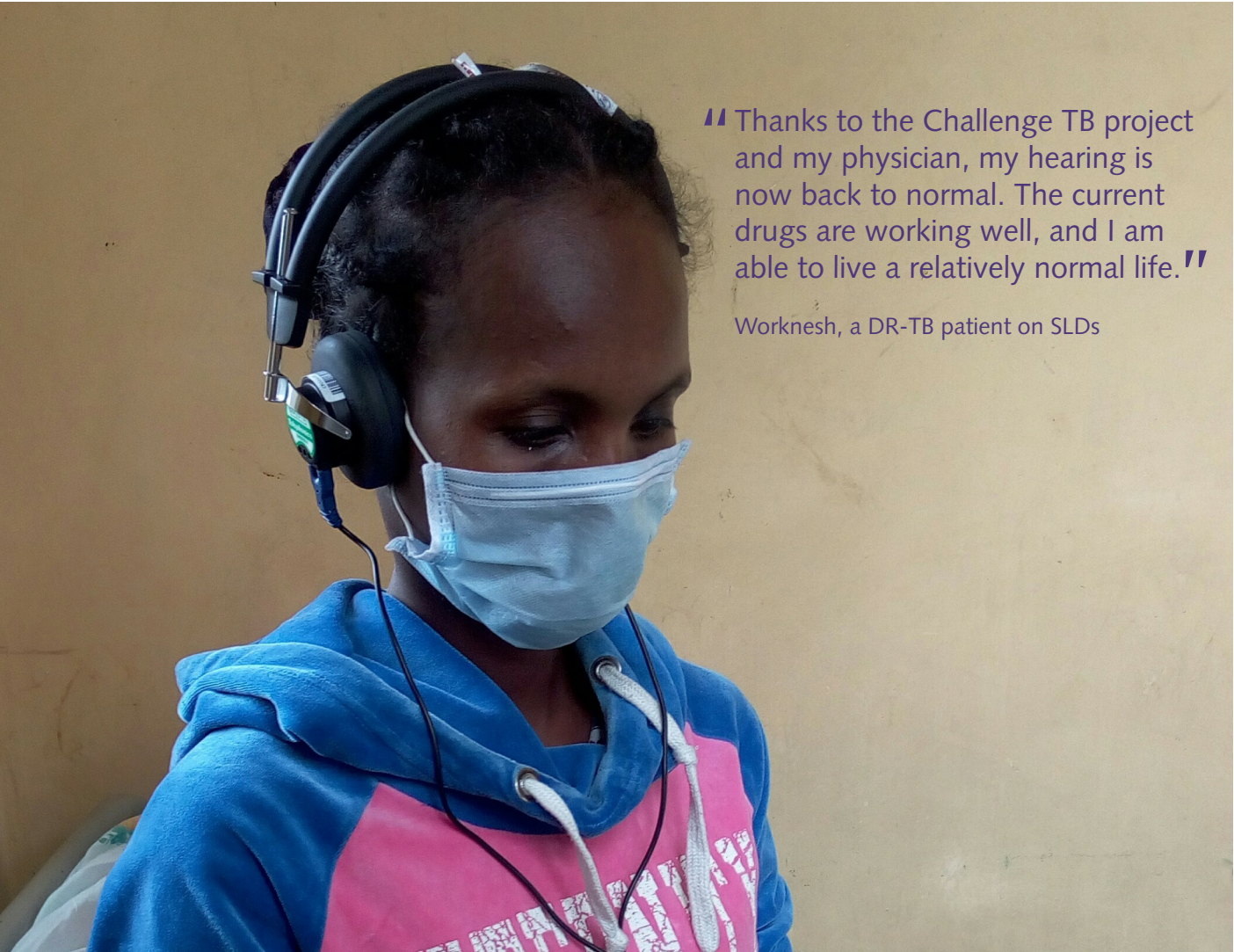
PATIENT SUPPORT PACKAGE - INCLUDING MONITORING FOR ADVERSE DRUG EVENTS

As part of the introduction of ND&R, and to improve the quality of patient care, CTB procured 40 audiometry machines for 40 TICs. In addition, CTB provided ECG machines, patients monitors, pulse oximeters, and other equipment to establish Critical Care Units for DR-TB patients at the ALERT and St Peter's TICs in Addis Ababa. The project also technically and financially supported a three-week training for 15 HCWs from St Peter's and ALERT TICs on critical care services.

CTB also provided the following support for patients at the ALERT ND TIC through:

- Procurement and provision of monthly food baskets;
- Patient transportation and house rent reimbursement;
- Per diem for mentoring of TFCs by ALERT TIC;
- Payment for outsourced investigations (laboratory and imaging);
- Cost of shipment of NDs to other ND/referring TICs.

CTB also procured and distributed 100,000 packets of therapeutic food supplements for malnourished DR-TB patients at all TICs in the country.



“ Thanks to the Challenge TB project and my physician, my hearing is now back to normal. The current drugs are working well, and I am able to live a relatively normal life.”

Worknesh, a DR-TB patient on SLDs

SUPERVISION, MONITORING, AND EVALUATION

CTB supported the NTP, both technically and financially, in conducting PMDT specific or integrated supportive supervision visits to TICs by central and regional NTP and CTB PMDT advisors. The supportive supervision had been conducted by involving DR-TB clinicians from TICs and by using a national DR-TB specific checklist adopted from quality improvement checklist developed by KNCV HQ. An international PMDT expert, together with CTB central PMDT and laboratory advisors, conducted a thorough assessment at high workload TICs to strengthen the use of ND&Rs.

After each supportive supervision, an action plan containing gaps and recommendations was developed, discussed and shared with the respective TICs panel and hospital management teams.

STRENGTHENING OF LAB NETWORK AND INFORMATION SYSTEMS

CTB TB central, regional, and cluster laboratory advisors played a significant role in technically assisting EPHI, the regional laboratories, and the GeneXpert sites in strengthening sample referral and timely result delivery for GeneXpert tests as well as culture and DST, including SL-LPA testing. The project also facilitated sputum sample referral and result delivery through the vans/vehicles introduced by CTB in the three large regions of Amhara, Oromia, and Addis Ababa. In addition, CTB played a significant role in placing and expanding the GxAlert laboratory information system at all GeneXpert sites to facilitate Xpert test result delivery at the national level, and to monitor the performance of each GeneXpert machine.

ESTABLISHMENT OF AND INVOLVEMENT IN NATIONAL AND REGIONAL CRCs

CTB technically facilitated and financially supported the decentralization of CRCs to the regions based on the national plan. Regional CRCs have now been established in Amhara, Southern Nations and Nationality Peoples (SNNP), and Tigray regions. The regional CRCs are currently active in reviewing DR-TB cases from TICs in the respective regions.

RESULTS

EXPANSION OF TICS AND TFCs

By the end of 2018, 60 DR-TB TICs were functional in the country, with the STR being available at all 60 TICs, and over 700 TFCs. CTB provides direct support to 56 of the TICs and over 650 of the TFCs. The project made a significant contribution to the expansion of TICs offering regimens containing NDs from three in 2016-17 to the current TICs offering ND (out of the total 60 TICs).

ENROLLMENT ON TREATMENT WITH NEW DRUGS AND REGIMENS

From July 2016 to January 2019, a total of 200 patients were enrolled on to regimens containing NDs (Table 1). Of these, 74.5 percent were enrolled on regimens containing Bdq, and 15 percent of patients were enrolled on to a regimen containing both Bdq and Dlm based on the recommendations of the CRC.

TABLE 1: NUMBER OF DR-TB PATIENTS ENROLLED ON REGIMENS CONTAINING NEW DRUGS (BY REGIMEN), JULY 2016 – JANUARY 2019

ND Containing Regimen	Total
Bdq	119
Dlm	51
Bdq and Dlm combined	30
Total	200

Although the burden of SLD resistance (and hence the burden of pre-XDR-/XDR-TB) in the country is not known, data from July 2016 to September 2018 shows that of 130 DR-TB patients who received a regimen containing either Bdq and/or Dlm, 31 were confirmed as pre-XDR, and 7 were confirmed as XDR-TB patients (Table 2). However, the largest group of patients (60) enrolled on NDs were those who were unable to tolerate their initial SLD treatment.

TABLE 2: NUMBER OF DR-TB PATIENTS ENROLLED ON TO A REGIMEN CONTAINING NEW DRUGS BY ELIGIBILITY CRITERIA, JULY 2016 - SEPTEMBER 2018

Eligibility Criteria	Total
XDR/Contact	7
Pre-XDR	31
Failure of standard regimen	9
Unable to tolerate SLDs	60
Advanced disease/comorbidity	23
Total	130

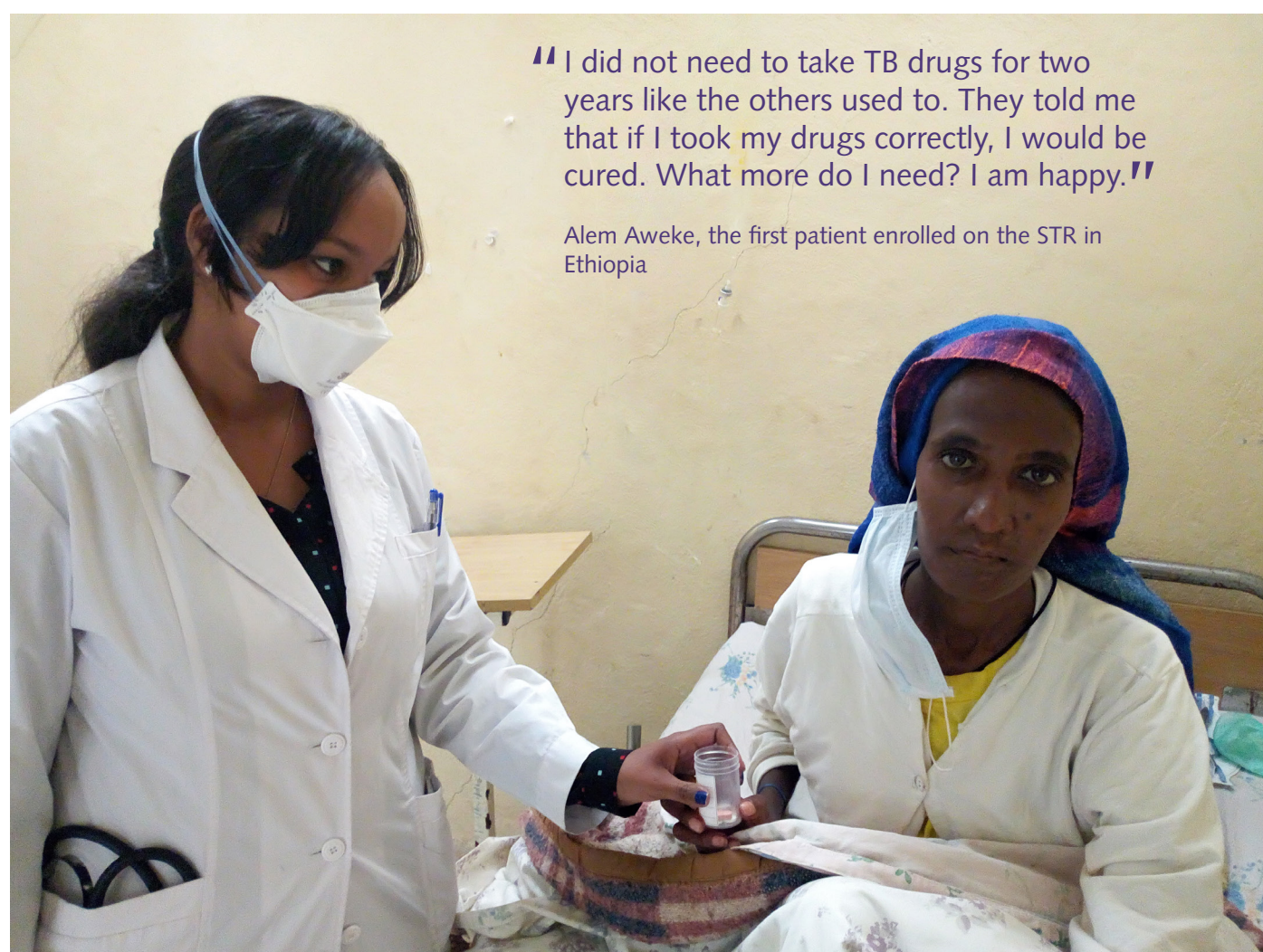
The CTB project supported the NTP, RHBs, and health facilities both financially and technically with the introduction of the STR and enrollment of eligible patients on treatment from April 2018. The STR is available at all 60 DR-TB TICs in the country and by the end of 2018, 83 patients had been enrolled on the STR.

ACTIVE DRUG SAFETY MONITORING AND MANAGEMENT (ADSM)

After the introduction of ND&Rs, adverse event reports from TICs showed a significant number of DR-TB patients developed moderate to profound hearing impairment after the use of injectables, their treatment was changed to an injection-free longer regimen (Table 3).

TABLE 3: THE FREQUENCY OF SAEs REPORTED TO NPV CENTER, ETHIOPIA, JULY 2016–JULY 2018. SOURCE: FMHACA ANNUAL NATIONAL TB REVIEW MEETING REPORT

SAEs		N (%)	Causality
1	Hearing impairment (hearing-loss)	6 (14.2)	Injectable SLDs: 28.6% of SAEs
2	Electrolyte disturbance	3 (7.1)	
3	Acute renal failure	3 (7.1)	
4	Myelosuppression	3 (7.1)	Linezolid: 21.4% of SAEs
5	Peripheral neuropathy	4 (9.5)	
6	Optic neuritis/decreased visual acuity	2 (4.8)	
7	Elevated liver enzymes (ALT or AST $\geq 1.1 \times$ ULN)	1 (2.4)	Bdq, Dlm, other TB drugs: 7.1% of SAEs
8	Prolonged QTcF interval	2 (4.8)	
9	Seizures	1 (2.4%)	Cs, INH
10	Other (disease progression, super imposed infection, respiratory failure, multiple organ failure, and intoxication)	17 (40.5%)	
Total		42 (100%)	



TREATMENT OUTCOMES OF PATIENTS ON NEW DRUGS

As yet, data concerning treatment outcomes for patients on the ND&R is limited due to the year of introduction of the drug and/or regimen, with the result that many patients are still on treatment due to long duration of the regimens. However, initial data from the ND TIC at the ALERT HOSPITAL in Addis Ababa show highly encouraging interim and final outcomes of treatment for patients with wide patterns of drug-resistance and/or intolerance to SLDs, who previously had poor outlooks and outcomes (Table 4).

TABLE 4: INTERIM AND FINAL TREATMENT OUTCOMES OF PATIENTS AT ALERT ND TIC, JANUARY 2017 TO JUNE 2018

ND Containing Regimen	# Cohort 6th month interim outcome	Culture conversion rate by month 6	# Cohort 24-month final treatment outcome	24-month Treatment Success Rate
Bdq	14	93%	9	66.7%
Dlm	7	86%	4	100%
Bdq and Dlm	6	100%	0	N/A
Total	27	92.6%	13	77%



LESSONS LEARNED AND NEXT STEPS

LESSONS LEARNED

- The introduction of individualized treatment regimens with new TB drugs is a long-awaited opportunity for patients with wider patterns of drug-resistance and for those who could not tolerate other standard DR-TB regimens.
- Improving access to treatment with ND&Rs improved the quality and decreased the costs associated with care delivery for both the patient and the program.
- Patient support packages and the treatment of malnutrition in DR-TB patients is a central component for improving treatment adherence and outcomes.
- Strengthening aDSM at all levels delivers the evidence on the safety of the ND&R needed to inform policy change for the better treatment of DR-TB patients.
- Regular supportive supervision and mentoring of HCWs at the TICs and TFCs by using a standardized tool and capacity-building of HCWs brought an improved quality care for DR-TB patients.
- Establishment of the CRCs for case consultation played a crucial role in the better design of regimens and appropriate management of AEs, resulting in better treatment outcomes.
- Regimens containing a second-line injectable agent have high rates of toxicity, particularly to hearing and kidneys. Routine audiometry and laboratory testing are compulsory components of care for these patients.

NEXT STEPS

Ethiopia now has three years experience in the introduction of and the management of DR-TB patients with ND&R. Detailed assessment and planning are a crucial initial part of the introduction. DR-TB patients can now access the STR at all the TICs in the country and NDs via an increasing number of TICs, although access to ND containing regimens still needs to be decentralized to additional TICs and selected TICs need upgrading to have in-patient capacity available. Experience and confidence in using and managing ND&Rs, including the associated AEs, is growing. Despite all the challenges faced by both the patients and the NTP, with the introduction of ND&Rs, the outlook for patients with DR-TB in Ethiopia is much more optimistic than it was just a few years ago.

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