# Introducing compassionate use treatment for extensively drug-resistant tuberculosis patients in Armenia

## Overview

Multidrug-resistant tuberculosis (MDR-TB) has posed a growing public health threat in Armenia, currently among the world's 27 countries for highest MDR-TB burden.[1] In this context, extensively drug-resistant tuberculosis (XDR-TB) has also emerged, accounting for approximately 10% of diagnosed MDR-TB patients in 2011.[1] While a number of new TB therapies have been advanced, approved treatment options for XDR-TB patients in Armenia were limited, leaving diagnosed patients with few treatment options. Having worked on MDR-TB control in Armenia since 2005, Médecins Sans Frontières (MSF), in partnership with the Ministry of Health, undertook an initiative to formalize the compassionate use of TB drugs to allow patients with no other treatment alternative access to experimental therapies. A committee of experts was convened to develop a protocol for the compassionate use of in-development medicines, which was approved by a local ethics committee and the Ministry of Health. A humanitarian waiver was granted to allow importation of the medicines. In 2012, a confidentiality agreement was signed with the pharmaceutical company developing the TB drug Bedaquiline, allowing XDR-TB patients and others meeting the eligibility criteria to receive this treatment. As of July 2013, eligible patients began receiving treatment, with 62 patients having benefited to-date. Patients receive a 24-week course of Bedaquiline tablets added to a multidrug TB treatment of two years. MSF has supported the compassionate use initiative with technical knowledge for establishing this programme, as well as providing necessary funding, procurement of drugs, training of providers and support for local TB specialists to deliver the new treatment. The compassionate use initiative is part of the National TB Programme's national policy framework for strengthening Armenia's response to MDR-TB and XDR-TB.

## Problem definition

The resurgence of tuberculosis (TB) in Armenia throughout the early and mid-2000s sparked public health concerns, with incidence rates at 49 per 100 000 people.[2] In this context, rates of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) have been of particular concern (Box 1). Estimates from 2011 showed that 19% of all new TB cases and 56% of re-treatment cases were MDR-TB, of which 9% were diagnosed as XDR-TB.[1] Treatment success rates for all TB types are well below the 85% target set by WHO.

In early 2010, despite the growing need for TB care in Armenia, existing treatment options for both TB and MDR-TB remained limited. Nearly half of all patients who began treatment were unable to complete the full course of TB treatment due to a combination of contributing factors, including low adherence rates, poorly managed side-effects and treatment intolerance.[1]

Box 1

What problems did the initiative seek to address?

- High rates of MDR-TB and XDR-TB.
- High death and failure rates amongst MDR-TB and XDR-TB patients.
- Limited number of approved treatment options for MDR-TB and XDR-TB patients.
- Poor patient adherence to TB treatment due to side-effects and treatment intolerance.

## Health services delivery transformations

### Timeline of transformations

Despite strong political commitment throughout the mid-2000s to addressing TB, rates of MDR-TB and XDR-TB continued to grow. In recent years, efforts have focused on addressing this problem through the National Response Plan to Combat Drug-Resistant TB 2013–2015.

Médecins Sans Frontières (MSF) has worked closely with the Ministry of Health in the rollout of TB-related projects since 2005, including the development of a compassionate use drug programme (Table 1). In January 2013, the local Armenian ethics committee approved the use of Bedaquiline for XDR-TB treatment on humanitarian grounds. By April 2013, patients began receiving the treatment, with 62 patients having so far received medicines through this initiative.

### Description of transformations

**Selecting services.** Through the introduction of the compassionate use of medicines, patients presenting with a TB-related life-threatening condition without alternative treatment options may now be considered to gain access to the use of Bedaquiline. The drug has been made available free of charge through a pharmaceutical company led compassionate use programme, supported by MSF. Compassionate use is limited to patients who have XDR-TB or pre-XDR-TB and meet strict age and other eligibility requirements. Patients receive a 24-week course of Bedaquiline tablets given along with a two-year regimen of other supporting antibiotics, such as Linezolid and in some cases Imipenem, as well as other standard anti-TB drugs thought to be effective. In parallel to exploring novel drug therapies, extending services to include palliative care for XDR-TB patients that do not qualify for the compassionate use of Bedaquiline has been advanced.

Table 1
What were the chronological milestones for the initiative?

| | |
|---|---|
| Late 1990s–early 2000s | TB control strategies based on WHO-recommended Directly Observed Treatment Short course (DOTS) initiated across Armenia. |
| 2005 | MSF begins work on MDR-TB related projects in Armenia. |
| Late 2006 | National Tuberculosis Control Programme 2007–2015 adopted by the government. |
| Early 2012 | MSF begins work to establish compassionate use of TB drugs in Armenia. |
| October 2012 | National TB Programme signs confidentiality agreement with pharmaceutical company for the use of Bedaquiline. |
| 2013 | National Response Plan to Combat Drug-Resistant TB 2013–2015 adopted by the government. |
| January 2013 | Armenian ethics committee and Ministry of Health approve use of Bedaquiline for XDR-TB patients on humanitarian grounds. |
| February 2013 | First Bedaquiline request submitted to pharmaceutical company. |
| March 2013 | First Bedaquiline importation to Armenia. |
| April 2013 | Bedaquiline treatment becomes available to patients meeting eligibility criteria. |
| April 2015 | End of compassionate use of Bedaquiline and beginning of its routine use supplied through the Global Drug Facility. |
| Present | Continued implementation of compassionate use initiative led by MSF for other in-development medicines; Armenian government continues to implement the National TB Programme. |

**Designing care.** Establishing national guidelines, specifying eligibility for treatment have been put in place through a partnership between MSF and the National TB Control Programme, according to the pharmaceutical company's criteria. Patients receive a baseline clinical assessment and, if guideline criteria are met, begin treatment once approved. This includes directly observed treatment of all drugs in the treatment regimen for the entire two year duration. The new drug Bedaquiline is given as daily treatment for the first two weeks, then three times per week until 24 weeks of treatment.

**Organizing providers.** TB services continue to be delivered within the existing vertical TB-specialist

system, including the National TB Centre in Abovyan staffed by 239 physicians, 291 nurses, 15 bacteriologists and 29 laboratory technicians.[1] The compassionate use initiative is delivered out of this Centre, with MSF providers and select specialist physicians trained to dispense Bedaquiline. Patients can be followed in smaller TB centres closer to their homes once they are stable on treatment.

**Managing services.** MSF manages the compassionate delivery of TB medicines, including the procurement, distribution and dispensing of medicines, through the National TB Centre. Funding for the initiative has been made available through MSF, providing additional human resources and trainings to assist with the delivery of services. The initiative has benefited from the National TB Programme's use of standardized electronic data collection and reporting systems developed by WHO for regular tracking and supervision of services provided.

**Improving performance.** Training has been provided to health workers dispensing the new medicines on topics including assessing the eligibility of patients, dispensing the new medicine, performing clinical assessments to identify side-effects, interpreting electrocardiogram results, delivering intravenous medication and other basic skills. Training was also provided to enhance communication competencies in an effort to ensure providers effectively and respectfully discuss treatment options with patients.

## Health system enabling factors

This initiative has been supported by continuous political commitment to TB control, evidenced by the development and implementation of Armenia's National TB Programme (Table 3). While a legal framework for the compassionate use of TB drugs remains to be developed, the initiative was advanced through approval granted by the local ethics committee and the Ministry of Health; a small yet important step towards large-scale legal changes needed for the compassionate use programme to take place.

Table 2
How was the delivery of health services transformed through the initiative?

| Before | After |
|---|---|
| **Selecting services** | |
| Treatment for TB available free of charge to population; no approved treatment options for XDR-TB patients; new drug therapies in development but not currently available. | Compassionate use treatment with Bedaquiline made available to XDR-TB patients who meet strict eligibility criteria; palliative care options for XDR-TB patients are being explored. |
| **Designing care** | |
| No guidelines for compassionate use treatment for TB in Armenia. | Patient eligibility criteria set by pharmaceutical company developing Bedaquiline; national protocol for compassionate use of TB drugs established by compassionate use expert committee. |
| **Organizing providers** | |
| Specialized TB providers concentrated in vertically organized TB hospital settings; role of primary care physicians in TB control increasing but still limited. | Compassionate use TB treatment delivered by TB specialists and MSF physicians at the National TB Centre and other TB settings. |
| **Managing delivery** | |
| TB control activities managed by National TB Centre; MSF provides support for delivery of MDR-TB interventions. | MSF leads delivery of compassionate use TB initiative and provides necessary funding and resources for the service. |
| **Improving performance** | |
| Clinical skills of TB providers narrow and limited to direct TB treatment; TB providers have little knowledge or skills for even basic clinical activities outside of treatments for the lungs. | Comprehensive training on all aspects of delivery for new TB drugs, clinical monitoring and treatment of side-effects carried out for select TB providers; training on effective patient communication also conducted. |

Table 3
How has the health system supported transformations in health services delivery?

| System enablers | Example |
|---|---|
| Accountability | • Ministry of Health has overall responsibility for TB control; National TB Centre is accountable to the Ministry for provision of TB care.<br>• National TB Centre is responsible for developing TB policies under the Ministry; National Tuberculosis Control Programme 2007–2015 guides national TB control interventions.<br>• Legal framework for compassionate use initiatives currently absent; approval for initiative secured through a humanitarian waiver granted by the local ethics committee and Ministry of Health. |
| Competencies | • Initiative supported a general increase in pharmacovigilance. |
| Information | • Ongoing tracking and evaluation of patient outcomes related to TB. |
| Innovation | • Introduction of compassionate use treatment to Armenia. |

Aligning the initiative with existing infrastructure and the ongoing monitoring of the National TB Programme has helped to ensure the compassionate use programme is appropriately resourced. The Ministry of Health continues to support the initiative as part of the National TB Programme's national policy framework for strengthening Armenia's response to MDR-TB and XDR-TB.

## Outcomes

To date, 62 XDR-TB patients have accessed treatment through the initiative. Initial results are promising although most patients have not yet completed the full two-year treatment. The early six-month conversion rates (patients who are no longer positive for TB after six months of treatment) are above 80%, which is much higher than previously available treatments.[3]

## Change management

### Key actors

This initiative was introduced by MSF, drawing from their experience with compassionate use of medicines in high-income countries, but working closely with the Armenian government to tailor these experiences to the national context.

MSF guided the initiative's design but was "very well supported" by the Ministry of Health, the National TB Centre and other actors (Box 2). An external compassionate use committee with MSF representatives as well as external experts gave support to the drug-resistant TB committee in establishing protocols; WHO provided additional guidance and expertise. Contacts formed with the pharmaceutical company Janssen provided Bedaquiline for distribution to patients through the initiative.

Box 2
Who were the key actors and what were their defining roles?

- **MSF**. Long-term actor in MDR-TB interventions in Armenia; led development of compassionate use TB initiative; provided funding and resources for initiative; conducted provider trainings; continues to coordinate delivery of compassionate use initiative.
- **National TB Centre.** Subdivision of the Ministry of Health appointed to oversee TB control; responsible for setting TB policies and overseeing delivery of National TB Programme.
- **Drug-resistant TB committee.** Members include National TB Centre and MSF physicians; responsible for selecting patients for compassionate use treatment based on eligibility criteria and overseeing treatment.
- **Janssen**. Pharmaceutical company supplying Bedaquiline treatment; developed guidelines on eligibility criteria for compassionate use initiative; supplied drugs to eligible patients.
- **Local ethics committee.** Granted approval to allow compassionate use of TB drugs.
- **Ministry of Health**. Approved compassionate use of TB drugs and their importation through a humanitarian waiver.
- **MSF-PIH compassionate use committee**. Members include TB specialists from MSF, Partners in Health (PIH) and external experts; developed protocol for compassionate use TB initiative; oversee approval processes for potential compassionate use patients.

### Initiating change

Patients' needs were "a key motivating factor" for the initiative. MSF had been working in Armenia on MDR-TB interventions since 2005 and had experience contending with the growing problem of drug-resistant TB. While new treatment options were in the pipeline, these were not yet approved for sale leaving XDR patients with no available treatment options.

*These patients were otherwise dying; we needed to make these drugs available for compassionate use. The drugs were never going to be registered and cleared before it would be possible to treat patients today. So when waiting is not an option, we need to do something.*

The idea of compassionate use drug programmes "is not so novel. The same has been done for HIV treatment. So already a lot of thinking has gone into the compassionate use of medicines." Prior experience in the compassionate use approach from other contexts allowed the initiative design process to move quickly, and facilitated an understanding of what resources were necessary for effective implementation. As the initiative aligned closely with existing national TB policies and programmes, patients' needs were "already well documented and understood" and the necessary monitoring and evaluation systems were in place.

### Implementation

The initiative's implementation was coordinated by MSF but relied on the supporting TB systems already in place from the National TB Programme. Procurement of the first batch of Bedaquiline from the pharmaceutical company took several months but supply channels quickly became stable and streamlined for approved patients. The initiative is no longer required for Bedaquiline, as the drug is now available through routine use, however similar initiatives are now being used to give access to new drugs.

### Moving forward

While the initiative remains supported by MSF, the Armenian government continues to increase their commitment to TB control. An extension to the National Response Plan to Combat Drug-Resistant TB 2013–2015 is being drawn up to provide future guidance on XDR-TB interventions. This plan is beginning to lay the groundwork for a more sustainable delivery model, including negotiations of low cost drug supplies from The Global Fund and working to establish a legal framework to allow for other compassionate use initiatives to be implemented in the future.

### Highlights

- Prior experience of compassionate use initiatives in other contexts supported the initiative's effective implementation and provided an immediate solution to the lack of available treatment options.
- Donor support and a close partnership with the national government allowed for the removal of institutional barriers, including the lack of a legal framework.
- Closely aligning reforms with ongoing programmes reduced the investment needed in new infrastructure in addition to greater professional acceptance.

1 World Health Organization Regional Office for Europe. (2014). Armenia. Compassionate use of new drugs. In *Best practices in prevention, control and care for drug resistant tuberculosis*.
2 World Bank. (2014). *World Databank: World development indicators.*
3 Yeghiazaryan L. (2015). *Armenian experience on treatment of XDR and pre-XDR patients with new drugs under compassionate use program*. [PowerPoint slides]. Retrieved from http://www.tb-symposium.org/documents/en/presentations/Lusine_Yeghiazaryan_BDQ_practical_use_eng.pdf.