REGIONAL GREEN LIGHT COMMITTEE FOR EUROPE MISSION: MONITORING IMPLEMENTATION OF THE NATIONAL MUTIDRUG AND EXTENSIVELY DRUG-RESITANT TUBERCULOSIS RESPONSE PLAN

ARMENIA

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Acronyms

aDSM	active drug-safety monitoring and management
AMX/CLV	amoxicillin-clavulanate
BDQ	bedaquiline
CC (+/-)	culture (positive/negative)
CFZ	clofazimine
DLM	delamanid
DOT	directly observed treatment
DR-TB	drug-resistant tuberculosis
DST	drug-susceptibility testing
DS-TB	drug-susceptible tuberculosis
ECG	electrocardiogram
FLD	first-line drugs
FQ	fluoroquinolone
GDF	Global Drug Facility
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
Imi/Cls	imipenem/cilastatin
LPA	line-probe assay
LZD	linezolid
MGIT	mycobacteria growth indicator tube
MDR-TB	multidrug-resistant tuberculosis
MOH	Ministry of Health of Armenia
MSF-F	Médecins Sans Frontières-France
M/XDR-TB	multidrug and extensively drug-resistant tuberculosis
NFM	new funding model
NRL	National Reference Laboratory
NTC	National Tuberculosis Centre
NTM	non-tuberculosis mycobacteria
NTP	national tuberculosis programme
PDR-TB	polydrug-resistant tuberculosis
PHC	primary health care
PMDT	programmatic management of drug-resistant tuberculosis
rGLC-Europe	Regional Green Light Committee for Europe
RR-TB	rifampicin-resistant (tuberculosis)
SLD	second-line drugs
SLI	second-line injectable
SNRL	Supranational Reference Laboratory
SS (+/-)	sputum-smear (positive/negative)
TB	tuberculosis
UPS	uninterrupted power supply
USAID	United States Agency for International Development
UVGI	ultraviolet germicidal irradiation (lamp)
XDR-TB	extensively drug-resistant tuberculosis
YCTBD	Yerevan city tuberculosis dispensary

1. Terms of reference

Objectives and deliverables

The objectives and deliverables were to:

- assess progress on implementation of the national strategic plan for 2016–2020, including its multidrug and extensively drug-resistant tuberculosis (M/XDR-TB) component, and develop recommendations for future activities;
- assess progress made and readiness for effective introduction of new drugs, specifically bedaquiline (BDQ), by the national TB programme (NTP);
- assess the effectiveness of implementing the current drug-resistant TB (DR-TB) control project supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), including TB drug management;
- advise on the estimated number of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) patients for 2017/2018; and
- assess readiness for effective start-up of a nine-months treatment short course for suitable patients.

Key issues to be elaborated and reviewed

The key issues elaborated and reviewed were:

- identifying the need for technical assistance and recommended actions for programmatic management of DR-TB to fulfill the national TB strategic plan for 2016–2020;
- assessing case-finding strategies and identifying barriers to the timeous start of DR-TB treatment, including TB in children;
- reviewing and providing recommendations on existing guidelines on DR-TB;
- assessing medical/clinical aspects of management and treatment of MDR-TB and XDR-TB;
- assessing the status of introduction of new TB drugs;
- assessing active drug-safety monitoring and management (aDSM); and
- ensuring follow up of TB and DR-TB patients in relation to adherence to treatment, patient-centered approach and social support.

Expected outcome of the mission

The expected outcomes were:

- a Regional Green Light Committee-Europe (rGLC-Europe) monitoring mission report with recommendations; and
- areas of technical assistance from the WHO Regional Office for Europe and rGLC-Europe identified.

2. Background

The rGLC-Europe support the scaling-up of DR-TB and implementation of the national M/XDR-TB response plan, including access to new TB drugs, in Armenia. The last monitoring mission was conducted in September 2015. In 2012, the Ministry of Health of Armenia (MOH) endorsed the national M/XDR-TB response plan for 2012–2015, which was developed by the NTP and key stakeholders with support from the rGLC and the Regional Office. The government endorsed the national strategy to fight TB for 2016–2020 on 24 March 2016. The document was developed by the National Tuberculosis Centre (NTC) with technical assistance from key stakeholders and articulated strategic directions for the NTP, including scaling-up access and use of new drugs for the management of DR-TB.

This mission report presents findings and a summary of discussions on most aspects of programmatic management of DR-TB (PMDT), with a focus on the use of new drugs for treatment of DR-TB in Armenia.

3. Follow-up of the previous mission recommendations

The NTP in Armenia has shown good progress in relation to management of DR-TB, with most recommendations from the previous monitoring mission achieved. Of 35 key recommendations, none had not been implemented, 14 showed various level of progress and required improvement/attention, and 19 had been completed but required ongoing attention and support (Tables 1 and 2).

Table 1. Implementation of recommendations from previous rGLC-Europe mission: MOH level

	Recommendation	Responsibility
1	Ensure adequate and sustainable financing of the NTP, considering existing donor funding.	
2	Update the national M/XDR-TB response plan for 2012–2015 in line with the start of the new funding model (NFM) GFATM grant, transition of Médecins Sans Frontières-France (MSF-F) and other ongoing projects.	
3	Improve capacity of health providers at all levels in the management of TB and DR-TB, including the prison sector, primary health care (PHC) and HIV/AIDS services in line with updated national guidelines.	
4	Ensure availability of financial resources from the government for procurement of anti-TB medications for drug-susceptible TB (DS-TB) from 2016 onward.	
5	Address issues of TB among labour migrants and ensure treatment compliance strategies (continuous recommendation).	
6	Consider using the United States Agency for International Development (USAID) BDQ donation programme for future drug orders.	
7	Support the procurement process of all TB medications coming through international mechanisms, especially new TB and repurposed companion drugs.	

Table 2. Implementation of recommendations from previous rGLC-Europe mission: NTP level

	Recommendation	Responsibility
1	Update the national M/XDR-TB response plan for 2012–2015 in line with the start of the NFM GFATM grant, transition of MSF-F and other ongoing projects.	
2	Improve coordination of the TB programme at marz level through assignment of marz coordinators selected from the pool of district TB doctors, and equip marzes with vehicles to perform regular supervision and monitoring.	
3	Update the national guidelines on DR-TB in line with the WHO companion handbook on PMDT (2015), particularly chapters on the use of new TB and repurposed companion drugs (Group 5).	
4	Consider an update of the existing protocol for management of polydrug-resistant TB (PDR-TB) (PDR regimen C) in line with Chapter 6, "Mono- and poly-resistant strains (drug-resistant TB other than MDR-TB)" of the companion handbook to the WHO guidelines for the programmatic management of DR-TB (2015).	
5	Issues of pharmacovigilance, especially related to drug-safety monitoring, should be considered as one of the key elements in expanded access to new TB drugs.	
6	Consider electrocardiogram (ECG) follow-up six months after completion of therapy with BDQ if the regimen contains clofazimine (CFZ) and fluoroquinolone (FQ).	
7	Improve capacity of health providers at all levels on management of TB and DR-TB, including in the prison sector, PHC and HIV/AIDS services, in line with updated national guidelines.	
8	Ensure availability of the updated version of the national DR-TB guidelines and updated diagnostic algorithms at all treatment sites.	
9	Strengthen surgical management for patients with TB and DR-TB.	
10	Address the issues of palliative care for TB and DR-TB patients.	
11	Consider expanding criteria for inclusion to home-based care in Yerevan and other sites where the initiative is available to cover patients at high risk of defaulting therapy due to sociobehavioural reasons.	
12	Consider creating mobile teams in marz centres with more than 20–25 TB and DR-TB patients on treatment to serve as an alternative to the existing TB outpatient system.	
13	Analyse the effectiveness of the new system of social support in relation to its impact on strengthening adherence to therapy. Assessment should be performed on a quarterly basis during Year 1 of new GFATM implementation.	
14	Ensure regular provision of supplies for adequate laboratory performance and avoid shortages of cartridges for Xpert MTBRIF, tubes for mycobacteria growth indicator tubes (MGIT), test kits for Hain line-probe assay (LPA), and UPS blocks for Xpert MTBRIF.	
15	Consider conducting external quality control on liquid media at the Supranational Reference Laboratory (SNRL) on a regular basis.	
16	Consider hospitalizing patients with known drug-susceptibility testing (DST) status to any inpatient facility. The use of rapid molecular diagnosis of drug resistance should guide further administrative triage of patients according to DST status.	

17	Upper-room ultraviolet germicidal irradiation (UVGI) lamps are recommended for use at least in all inpatient facilities (wards, corridors, procedure rooms, directly observed treatment (DOT) points), including in the penitentiary sector. Regular monitoring of performance and appropriate use by qualified engineers is essential.	
18	Health personnel at the Centre for Detainees of the prison sector who have contact with any infectious patient should wear respirators. Patients at all inpatient sites, at minimum, should wear surgical masks and follow cough etiquette. The NTC, in collaboration with the prison sector, should conduct regular monitoring of infection control in the Centre for Detainees and other prison inpatient facilities (continuous recommendation).	
19	Consider using the USAID BDQ donation programme for future drug orders.	
20	Rational adjustments to forecasting and future drug orders of second-line drugs (SLD) should be considered, taking into account patients' adherence to treatment.	
21	Consider revision of future drug orders for PDR-TB once the national guidelines are finalized (withdrawal of PDR-C regimen).	
22	Consider eTB Manager as a basis for the information system for TB.	
23	Conduct regular monitoring of data-collection and entry at county-level TB dispensaries and laboratories (continuous recommendation).	
24	Consider the possibility of adding X-ray digital photos to eTB Manager.	
25	Address issues of TB among labour migrants and ensure treatment compliance strategies (continuous recommendation).	
26	Ensure that TB patients at the Centre for Detainees have equal access to tertiary-level care, including surgery.	

4. Current mission main recommendations (summary)

The current mission main recommendations are summarized in Table 3.

Table 3. Current mission main recommendations (summary)

	Recommendation	Responsibility
1	Ensure availability of updated version of the national DR-TB guidelines and updated diagnostic algorithms at all treatment sites	MOH, NTC
2	Strengthen surgical management for patients with TB and DR-TB	NTC, partners
3	Address the issues of palliative care for TB and DR-TB patients, especially those who completed therapy with new TB drugs	NTC, partners
4	Consider replicating best practices from the compassionate use programme and the end TB project into the routine system of DR-TB patient management	NTC
5	Consider conducting analysis of the use of imipenem/cilastatin (Imi/Cls) over six months in DR-TB patients	NTC, partners
6	Conduct training for DR-TB doctors on the updated version of the national guidelines with a focus on the use of new TB drugs, active drug safety and improvement in patient management	NTC, partners
7	Improve the capacity of TB doctors on interpreting ECGc (calculating QT interval and QTcF) to monitor patients on therapy with BDQ, delamanid (DLM), CFZ and FQ	NTC
8	Consider conducting training for specialists (cardiologists, ophthalmologists, neurologist) from the general health-care system who might potentially be involved in treating patients with TB on the PMDT to improve management of patients with DR-TB, especially those on new TB drugs	NTC
9	Consider conducting training on medical management of DR-TB and HIV coinfection for NTP; a HIV specialist from the National AIDS Centre should be a part of DR-TB committee meetings when discussing cases with coinfection, especially those on therapy with new TB drugs	NTC, partners
10	Ensure complete implementation of the minimum of aDSM requirements for patients treated with new TB drugs at the Centre for Detainees (HbA1C, ECG monitoring)	NTP, prison sector, partners
11	Consider including the minimum of clinical laboratory and instrumental monitoring tests into the MOH decree under the category for DR-TB patients who receive therapy with new TB drugs	NTP
12	Consider expanding criteria for inclusion to home-based care in Yerevan and other sites where the initiative is available to cover patients at high risk of defaulting therapy due to sociobehavioural reasons with no consideration for drug-resistance status	NTC
13	Scale-up alternatives to mandatory daily DOT for patients at low-to-medium risk of defaulting using modern technology tools (Video DOT)	NTC, partners
14	Address the issues of DOT and find ways to introduce additional workforce to the staff of the TB unit at the Centre for Detainees to perform DOT of patients on new TB drugs at evenings and weekends	Prison sector, partners
15	Improve coordination of the TB programme at marz level through assignment of marz coordinators selected from the pool of district TB doctors	NTC

	Recommendation	Responsibility
16	Consider hospitalizing patients with known DST status to any inpatient facility; the use of rapid molecular diagnosis of drug resistance should guide further administrative triage of patients according to DST status	NTC, partners
17	Upper-room UVGI lamps are recommended for use at least in all inpatient facilities (wards, corridors, procedure rooms, DOT points), including in the penitentiary sector; regular monitoring of performance and appropriate use by qualified engineers is essential	NTC, penitentiary sector, partners
18	Consider using the USAID BDQ donation programme for drug orders for programmatic use of BDQ	NTC
19	Rational adjustments to forecasting and future drug orders of BDQ and DLM should be considered, taking into account the need for extended use of BDQ and DLM beyond 24 weeks	NTC
20	Implementation of aDSM should be embedded in the national system of pharmacovigilance	NTC
21	Uninterrupted supply of the whole spectrum of Group 5 drugs – BDQ, DLM, CFZ, linezolid (LZD) and Imi/Cls + amoxicillin/clavulanate (AMX/CLV) for treatment of patients with DR-TB under programme conditions beyond the endTB project should be ensured	NTC, partners
22	Regular monitoring of data collection and entry at county-level TB dispensaries and laboratories should be conducted (continuous recommendation)	NTC
23	The possibility of adding X-ray digital photos to eTB Manager should be considered	NTC
24	The introduction of the new form summarizing clinical laboratory and instrumental monitoring and updating the national TB register should be considered	NTC
25	Issues of TB among labour migrants should be addressed and treatment compliance strategies ensured (continuous recommendation)	MOH, NTC

5. General country/region profile

Findings and summary of discussion

Management of patients with MDR-TB with international donor funding in Armenia started in July 2006, when the gGLC-Europe approved the MSF-France-supported project for treatment of 90 MDR-TB patients in two pilot districts of Yerevan, Malatia-Sebastia and Shengavit. In February 2009, the rGLC-Europe approved a request from MSF-F for a cohort expansion of an additional 200 MDR-TB patients, which brought the total approved to 290 patients and covered three more districts of Yerevan.

The rGLC-Europe approved an application from the NTP in April 2008 for the treatment of an initial cohort of 180 patients, with MSF-F as the technical partner, bringing the total to 470 patients. The NTC and MSF-F cohorts were approved separately, with different mechanisms of drug procurement. In December 2011, following a suggestion from the GFATM, the Round 8 and Round 10 GFATM grants were consolidated, with total funding of €7 million to 31 December 2014. The no-cost extension period was approved by the GFATM until September 2015 and the start of the NFM GFATM grant, which will run to 30 September 2018. Armenia had accessed BDQ and other repurposed companion drugs under the compassionate use programme in 2013. The endTB

project was launched in Armenia in spring 2015, focusing on increasing access to new TB drugs for DR-TB – BDQ and DLM – for programmatic conditions.

Several GLC-Europe monitoring missions (conducted in October 2008, March 2009, September 2009, May 2010, May 2011, June 2012, May 2013, July 2014 and September 2015) have marked the progress made on programme implementation by the NTP, with most recommendations fulfilled. The previous rGLC-Europe monitoring mission had taken place in September 2015 with the purpose of evaluating progress on implementation of the national M/XDR-TB response plan for 2012–2015. The current mission focused only on the use and scale-up of access to new TB drugs.

According to the latest WHO TB report, Armenia is no longer considered as a high-burden country for TB and MDR-TB. The latest available data submitted to WHO (2015) show that main TB indices suffered decline compared to previous years, with TB incidence (including HIV+TB) reported as 41 (36–46) per 100 000 people and a total number of around 1200 cases registered (1100–1400), TB prevalence (including HIV+TB) of 66 (31–115) per 100 000, and TB mortality (excluding HIV+TB) of 5.7 (4.8–6.7) per 100 000 (2014) (Table 4) – Attachment 3.

Data presented by NTC slightly differ from those presented to WHO in 2015: they exclude cases with HIV+TB, with the latest TB incidence rate of 28.1 per 100 000 and TB mortality of 1.5 per 100 000. TB case notification show declines in the number of new and retreatment cases notified in 2015 compared with previous years (Tables 5 and 6).

Table 4. Incidence, prevalence and mortality rates of TB, 2013–2015

Year	Incidence	Prevalence	Mortality
2013	36.6	46.7	1.6
2014	34.7	45.3	1.6
2015	28.1	37.1	1.5

Source: NTP.

Table 5. TB case notifications, 2015 (WHO)

Percentage:	Total new and relapse
tested with rapid diagnostics at the time of diagnosis	18
of pulmonary	100
% with known HIV status	72
% of bacteriologically confirmed among pulmonary	45
Total	**1 090**
Total cases notified	1 104

Source: WHO.

Table 6. TB case notifications, 2013–2015 (NTP)

Case notifications	2013		2014		2015	
		%	Total	%	Total	%
New cases						
Smear-positive	299	28.6	246	23.5	238	28.3
Smear-negative	748	71.4	800	76.5	604	71.7
Smear unknown	–	–	–	–	–	–
Extrapumonary TB	249	23.8	249	23.8	224	26.6
Other	–	–	–	–	–	–
Total new	1 047		1 046		842	

Retreatment cases						
Relapse	54	14.9	46	14.4	34	12.5
Treatment after failure	16	4.4	11	3.5	15	5.5
Treatment after default	14	3.9	12	3.8	11	4
Other	279	76.8	250	78.3	213	78
Total retreatment	363		319		273	

Source: NTP.

Despite successes in managing drug-susceptible TB and the fact that Armenia is no longer a high-burden country, DR-TB still posed major challenges to the effectiveness of the NTP (Annex 3; Tables 4 and 5). More than 150 patients in Armenia are estimated to have MDR/rifampicin-resistant TB (RR), with 101 cases laboratory-confirmed and started on treatment. With almost 100% coverage with DST to SLDs (second-line injectable (SLI) and FQ), the NTP reported a high level of FQ resistance (around 33% of all MDR/RR-TB patients diagnosed (MDR+FQ and XDR-TB) in 2015 and 34.4% during six months of 2016), which posed significant challenges in the management of high demand for new TB drugs. Most FQ-resistant patients observed during the mission were former labour migrants.

Armenia has faced issues of outgoing labour migration, mostly to the Russian Federation and Ukraine, over several years. Often, patients default treatment to enable them to work outside of the country. Simultaneously, treatment of TB and DR-TB was challenging for patients diagnosed outside of Armenia, especially in the Russian Federation, due to lack of access to quality-assured care. This jeopardized the success of the NTP and the existing reservoir of DR-TB was at risk of being constantly enlarged by patients becoming infected with DR-TB or being improperly treated outside of Armenia. Taking into account that estimates for MDR/RR-TB were higher than the actual number of diagnosed cases in 2015 (67% – see Table 7), the estimated number of patients with FQ resistance was assumed to be up to 60 patients per year, all of whom require new TB drugs. The 15–20% of patients with MDR/RR-TB who were diagnosed with resistance to SLI also required therapy with new TB drugs (Table 9).

Table 7. DR-TB care, 2015

	New cases: % (range)	**Previously treated cases: % (range)**	**Total**
Estimated MDR/RR-TB cases among notified Pulmonary TB cases			150 (130–180)
Estimated % of TB cases with MDR/RR-TB	11 (8–14)	47 (41–53)	
Percentage notified tested for RR	0	0	436
MDR/RR cases tested for resistance to SLD			101
Laboratory confirmed cases	MDR/RR-TB: 101, XDR-TB: 8		
Patients started on treatment	MDR/RR-TB: 268, XDR-TB: 8		

Source: NTP.

Table 8. Number of notified/diagnosed cases: TB-S, RR/MDR-TB, 2014/2015

	TB-S	**MDR-TB**	**%**
2014	1 365	119	9
2015	1 115	109	10

Source: NTP.

Table 9. Number of notified cases with FQ, SLI resistance and XDR-TB, 2015/2016

	A	B	C	D	E		
	No diagnosed RR/MDR-TB	**Out of patients in column A enrolled into therapy**	**Out of patients in column A resistant to FQ**	**Out of patients in column A resistant to SLI**	**Out of patients in column A diagnosed with XDR-TB (laboratory-confirmed)**	**Number of patients started therapy with new TB drugs (BDQ and/or DLM)**	**Number patients from columns C, D and E without therapy with new TB drugs (BDQ and/or DLM)**
2015	109	109	17 (15.6%)	25 (22.9%)	19 (17.4%)	30	21
2016 (six months)	67	67	9 (13.4%)	10 (14.9%)	14 (20.9%)	18	6

6. Coordination of the programme and financing

Findings and summary of discussion

On 24 March 2016, the government endorsed the national strategy to fight TB in Armenia for 2016–2020. The document was developed by the NTC with technical assistance from key stakeholders and articulated strategic directions for the NTP, including scaling-up access and use of new TB drugs for the management of DR-TB. Most activities in the plan were taken from the GFATM consolidated grant. The plan served as the strategic and operational document, with a detailed operational plan and budget for programme management of DR-TB for 2016–2020, and was in line with the updated roadmap for the WHO European Region for 2016–2020.

The NTC was the leading institution in Armenia responsible for TB policy and methodology development, monitoring and evaluation of NTP performance, and provision of medical care and services. Coordination and management of the NTP was centralized with the creation of the NTC in 2014, after which the NTC became extremely efficient in finance and management. The NTC had sufficient human resources and capacity to adequately coordinate activities in relation to methodology, data collection and supervision, and medical management of TB and DR-TB.

Management of the GFATM grant was under the Project Implementation Unit within the MOH. Armenia completed implementation of Phase 1 of the consolidated grant, which received approval for no-cost extension until September 2015 with a budget of $7 million. The NFM GFATM grant started on 1 October 2015, with a budget of $9.2 million until 30 September 2018. Activities in the NFM GFATM included ongoing support for the NTP, especially in scaling-up access to rapid molecular diagnosis – 13 Gene Xpert modules and cartridges, laboratory consumables for conventional DST on BACTEC MGIT-960 and LPA, infection control equipment and 500 upper-level UVGI lamps – and drug procurement of first-line drugs (FLD) Ethambutol and Pyrazinamide and SLD for DR-TB, including new TB drugs. The application also aimed to support HIV diagnosis among TB patients, management of HIV-TB coinfection and operational research.

MSF-F has been one of the key partners of the NTP in Armenia for over a decade, contributing to the decrease of reservoir of DR-TB in the country. MSF-F has a plan of activities focusing on technical assistance, programme-monitoring, operational research and capacity-building, and has developed a strategy for transitioning from its role as one of the leading technical-assistance partners. At the time of the visit, MSF-F was continuing to support and implement a series of activities, including providing technical assistance on PMDT and introduction of new TB drugs through the endTB project, developing the protocol for palliative care, improving the algorithm for TB case-detection, investing in surgical management of TB, DR-TB and PDR-TB, and developing management of non-tuberculosis mycobacteria (NTM) infection (direct procurement of medicines, including ancillary medicines for side-effect management). Further technical and financial assistance from MSF-F will be highly beneficial for the NTP, especially in supporting the scaling-up and use of new TB drugs for treatment of DR-TB.

The Regional Office, rGLC-Europe and WHO country office continue to play an important role in coordinating activities on TB control, providing technical assistance and promoting policy dialogue at national and international levels.

7. Treatment strategies and administration

The NTC developed and released the new version of the national guidelines for TB and DR-TB in 2016, endorsed by the MOH through Decree 2462 of 5 August (available only in Armenian language). The updated Armenian guidelines do not match the recent new version of the WHO guidelines on PMDT, but do not contradict current WHO policy and approaches to patient management and care. They do not include the new grouping of TB drugs, but are based on the classification of TB drugs described in the WHO compendium handbook to the guidelines on PMDT of 2015. The new TB drugs – BDQ, DLM, LZD, CFZ and carbapenems – are listed and presented as Group 5 agents in the national classification of TB drugs. The new document contains information on regimen design for DR-TB based on the 2015 grouping of TB drugs, dosages, diagnostic algorithms, protocols on side-effect management, and required registration and treatment forms.

The NTP had been using the clinical guide from the endTB project, which was developed by the project for management of patients with new TB drugs (Attachment 2). The endTB project clinical guide includes detailed information on treatment regimen design with Group 5 drugs, dosages, drug-to-drug interactions (especially with antiretroviral medicines), clinical monitoring, and diagnosis and management of adverse drug reactions, as well as off-label use of new TB drugs. It does not contradict any of the latest WHO recommendations on management of patients with DR-TB, and several sections on new TB drugs have been included in the new national guidelines.

Regimen design with the use of new TB drugs

Treatment regimens for all DR-TB patients, including PDR-TB, and for the use of new TB drugs were designed by the DR-TB Committee, which had regular weekly meetings at the NTC. The role of the DR-TB Committee included discussion of the treatment strategy, regimen design, management of adverse and sever adverse reactions, causality assessment, referrals between sectors and outcome definition. Approaches to case definitions match the WHO criteria and are based on the site of the disease, prior treatment history and type of drug resistance.

Treatment regimens for DR-TB were individualized, reflecting several factors in design of the appropriate minimum number, and combination, of effective drugs in the regimen. Besides DST, the history of previous use of FLD and SLD, information on contacts, comorbid and pre-existing conditions, and information on adherence had to be considered when building the regimen. The

total of Group 5 drugs in the regimen was influenced by the number of Group 4 drugs considered to be effective. The ultimate goal of the regimen with new TB drugs, especially for XDR-TB, is to have at least four effective SLDs in the regimen. Criteria for duration of the intensive phase and the whole course of chemotherapy match WHO recommendations, with the minimum duration of the intensive phase no less than eight months and minimum duration of the whole course of treatment no less than 20 months for patients never before treated for MDR-TB. Extension over 20 months is possible for previously treated patients with DR-TB and others with massive pulmonary destruction. Criteria for stopping the injectable agent are based on strong evidence of culture conversion – up to four consecutive negative cultures – and clinical response to treatment. No limitations are set for prolonging the duration of the intensive phase and the whole duration of treatment.

Duration of use of BDQ and DLM is 24 weeks, with dosages and frequency described in the WHO interim guidance and updated national guidelines. LZD has been used for the entire treatment at 600 mg daily with pyridoxine 50 mg daily. CFZ became available in Armenia in 2006 and has been used for the management of patients with pre-XDR and XDR-TB, administered as 200 mg once daily for two months, followed by 100 mg daily for the duration of therapy. Imi/Cls is administered as 1000 mg twice daily: two vials are administered by 40–60 minutes infusion twice daily (four vials daily) seven days per week during hospitalization and six days per week during the ambulatory phase. Patients on Imi/Cls require long-term access to central veins because of twice-daily intravenous injections. Implantable access systems, such as Port-a-cath, are the preferred option offered to patients. It was noted that infusions of Imi/Cls had been administered for more than 12 months of therapy, even for the entire treatment of up to 24 months in patients with XDR-TB. AMX/CLV is added to regimens with Imi/Cls (carbapenem). Dosing of AMX/CLV is based on the clavulanic acid component (125 mg 30 minutes orally before the intravenous infusion of Imi/Cls).

The off-label use of medicines[1] was made possible by the decision of the DR-TB Committee on individual cases after discussion with the International Medical Committee of the endTB project, comprising international experts on DR-TB with relevant experience on use of new TB drugs. Extended and concomitant use of BDQ and DLM has been used in patients with extensive pulmonary damage who show a slow positive response to therapy and for whom bacteriological conversion has been achieved. Each case has been discussed individually by the DR-TB Committee and sent for expert opinion to the International Medical Committee. Both the extended and concomitant use of BDQ and DLM has not contradicted WHO guidelines, which states the evidence indicating when benefits overcome potential risks of death is insufficient. The cases reviewed by the rGLC consultant had clinical indications for either extended use of BDQ and DLM or co-administration of BDQ and DLM performed under strict clinical and laboratory monitoring by NTP and MSF-F. BDQ had been extended up to 48 weeks in several patients.

Eligibility criteria for treatment with new TB drugs

The following categories of patients with DR-TB are eligible for treatment initiation with new TB drugs.

1. Patients for whom the construction of a regimen with four likely effective SLDs (from Groups 2 to 4), including a FQ and an injectable is not possible:
    a. XDR-TB (resistance to a FQ and at least one injectable);
    b. pre-XDR-TB (resistance to a FQ or at least one SLI, but not both);

[1] According to the 2016 WHO guidelines, off-label use of medicines is the extended use of BDQ and DLM, concomitant use of BDQ and DLM, or the use of BDQ and DLM in patients younger than 18 years or who are pregnant or lactating.

c. patients with two or more Group 4 drugs (Ethionamide/Prothionamide (Eto/Pto), Cycloserine (Cs), Paraaminosalycic acid (PAS) compromised;

d. contact with a patient with a strain with resistance pattern of a, b, or c;

e. patients unable to tolerate MDR-TB drugs necessary for construction of the regimen (for example, ototoxicity due to an injectable agent); and

f. patients who are a "failure" of an MDR-TB regimen, by WHO 2013 definitions.

2. Other patients who have high risk of unfavourable outcome but do not fit one of the above categories:

   a. patients with extensive or advanced disease (X-ray demonstrating multiple cavities, bilateral lesions, or extensive parenchymal damage or multiple system involvement);

   b. patients with increased likelihood of acquisition of additional resistance, treatment failure, or death due to comorbidities or other conditions (drug contraindication, patients with low body mass index, HIV, diabetes); and

   c. patients coming from catchment areas that have poor MDR-TB treatment outcomes despite good programmatic conditions (such as sites with extensive SLD resistance backgrounds).

According to the national requirements, all patients should have a sputum sample collected for second-line DST at the time of starting treatment with new TB drugs. Second-line DST is important because the second-line resistance pattern can affect the design of the treatment regimen. Based on the above criteria, however, the second-line DST is not a strict requirement for the use of new drugs: in some patients, treatment with new drugs is possible without second-line DST, based on a clinical history that a regimen with four likely effective drugs, including a FQ and an injectable, is not possible to build, or intolerance to a key SLD, or having a high risk of an unfavourable outcome.

Even if the new TB drugs have recently been included in national guidelines, all patients accessing BDQ and/or DLM signed the informed consent form prior to the start of therapy. Consent forms were available from the endTB project and had been collected by the MSF-F.

Active drug safety, monitoring and management

Main principles of the WHO-recommended aDSM were fully introduced into the treatment of patients with new TB drugs. MSF-F, an implementing organization of the endTB project, has been monitoring the implementation of active and systematic laboratory assessments of all patients on treatment with new TB drugs to detect drug toxicity and adverse effects. Adverse and severe adverse effects had been registered and managed by NTP doctors with technical assistance from MSF-F, who were also reporting the severe adverse effects to the international pharmacovigilance unit established in the endTB project. MSF-F, in collaboration with NTC, provided training that included the schedule of clinical and laboratory systematic assessments for all TB doctors involved in the management of patients with new TB drugs, and continued monitoring all sites with patients on new TB drugs. Considering that the NTP have recently released the new national guidelines, however, MSF-F should work closely with the NTC on introducing the best practices of the compassionate use programme and the endTB project to the management of patients with DR-TB. The aDSM was in place at all treatment sites visited, including the leading inpatient facility in Abovyan (NTC) and peripheral inpatient and outpatient settings. For methodological details of an aDSM within the endTB project, which was a more intensive type – the cohort event monitoring (Attachment 2).

ADSM for clinical monitoring of DR-TB patients on therapy with new TB drugs is more intense than for patients on conventional (traditional) MDR-TB regimens. Cohort event monitoring for patients

on new TB drugs includes thorough clinical assessment and bacteriological and laboratory testing at baseline, during, and six months after treatment completion. Sputum smear microscopy and culture testing are repeated monthly during the whole duration of therapy, as are other laboratory tests. The following laboratory and instrumental screening was mandatory at baseline and during the schedule of events described in the endTB guide (Attachment 2): brief peripheral neuropathy screen, ophthalmologic screening for visual acuity and colour-blindness, audiometry, ECG, complete clinical laboratory screening for liver and kidney function, presence of HIV and viral hepatitis B and C, HbA1C for diabetes mellitus, thyroid stimulating hormone and chest radiography. Diagnosis and management of adverse events are performed adequately for all patients on new TB drugs with clinical algorithms available and ancillary medicines purchased by NTC (GFATM grant) and MSF-F.

Most laboratory and instrumental tests have been regulated by the MOH (Article 3.4.2.3 of the MOH regulation "Chaporoshich") as part of the guaranteed package for TB and DR-TB and are available at most sites visited (except for several important tests, which are covered by MSF-F: electrolytes (K, Mg), HbA1C, albumin, lipase and thyroid stimulating hormone). Missing tests in the prison sector have also been covered by the MSF-F, but considering the aDSM requirements, the NTP should look at transiting funding for these tests from either state funding or the GFATM grant. Availability of narrow specialists at PHC level across the country is adequate, with most settings having access to cardiologists, neurologists, ophthalmologists and other narrow specialists.

Different strategies applied to adverse and severe adverse effects registered in patients receiving new TB drugs. Thorough monitoring throughout therapy has made it possible timeously to diagnose and address the events. QT prolongation had been reported in some patients on new TB drugs, requiring weekly ECGs and regimen adjustments. ECG interpretation (QT and QTcF calculation) and neurologic and ophthalmology screening (colour-blindness and visual acuity) had mostly been performed by MSF-F doctors and not those at treatment sites. There is therefore a need to improve the capacity of TB doctors at all treatment sites through regular training on how to perform the tests, which are considered part of good clinical practice.

Clinical monitoring of DR-TB patients on the conventional (traditional) MDR-TB regimen is complete, but lacks laboratory and instrumental tools that might be beneficial to overall patient management. Neurological examination and colour-blindness screening for early identification of neurotoxic reactions to some TB medicines (Eto/Pto, H) and audiometry for patients on an injectable agent for early identification of ototoxic effects, which would meet the eligibility criteria for the start of therapy with new TB drugs, should be performed routinely in inpatient and outpatient settings.

Surgical management of patients remains a challenge for the NTP. No full-time thoracic surgeon is available, meaning the NTC has to contract this specialist service from the general hospital. With MSF-F support, a surgeon from India is available for online consultations with the NTC.

Group 5 drugs are available for patients who have started therapy under the compassionate use programme (April 2013) with BDQ and who are enrolled under programme conditions in the endTB project managed by MSF-F from spring of 2015. Of the 62 patients who had started therapy under the compassionate use programme between April 2013 and April 2015, all had finished the 24-week course of therapy with BDQ, 55 had completed, and seven are still on treatment. Forty per cent of patients enrolled onto both the compassionate use programme and the endTB project had laboratory-confirmed resistance to a SLI agent (XDR-TB), 52% had pre-XDR-TB with resistance to FQ, and 8% were considered as pre-XDR with resistance to a SLI agent. Seventy-five out of a total cohort of 96 patients had been enrolled onto the endTB project, 36 on BDQ-containing

regimens, 31 on DLM-containing regimens and seven on regimens with concomitant use of BDQ and DLM. The use of new drugs has already been extended beyond 24 weeks in nine patients, seven in Bedaquiline (BDQ)-containing regimens and two on Delamanide (DLM)-containing regimens which, due to limited data, is currently considered off-label use but is not strictly prohibited, similar to concomitant use of BDQ and DLM.

Final outcomes for both cohorts (compassionate use programme and End TB project) are not yet available, but the compassionate use programme cohort showed a high rate of culture conversion during the first six months after initiation of therapy with BDQ (84% of 32 patients in preliminary results).

Management of patients with HIV coinfection has been included in the national guidelines. As noted by the NTC, antiretroviral treatment was usually initiated within eight weeks of the start of MDR-TB therapy, with no consideration of CD4 count. All antiretroviral medicines were taken under self-administration. The NTC has noted an increase in the number of patients coinfected with HIV over recent years, especially among those considered as labour migrants from the Russian Federation. Medical files on patients with coinfection lack information on levels of CD4 cells and viral load, which is essential for clinical decision-making and better coordination with HIV services. Even if the level of cooperation with HIV services was considered adequate, TB doctors' capacity to treat patients needs to be strengthened through knowledge of management of dual infection. A HIV specialist from the National AIDS Centre should join DR-TB committee meetings when coinfection cases are discussed, especially for patients on new TB drugs. HIV infection is often accompanied by hepatitis B and C: starting in late 2016, MSF-France is planning to initiate new treatment regimens for hepatitis C containing sophosbuvir (Sovaldi), a new Federal Drug Agency-approved medicine used for the treatment of chronic hepatitis C genotypes 1, 2, 3, 4, 5 and 6, usually in combination with other medications depending on the specific genotype.

The issue of NTM infection is being addressed through the NTM protocol developed by MSF-F. Previous rGLC-Europe missions advised that unlike TB, NTM infections should not be considered contagious. There is no evidence that NTM infection can be transmitted from one person to another, so the NTP should respect issues of infection control and consider providing NTP therapy in ambulatory settings (TB cabinets) and/or through the general health-care network.

Treatment of patients with new TB drugs in outpatient settings

Options for delivering DOT to DR-TB patients, especially those on new TB drugs, are available in urban and rural settings, with the aims of making care more patient-centred and improving adherence to therapy. The NTP is responsible for providing care and social support through funding available from the GFATM grant. Starting in late 2015, the NTP introduced monetary incentives transferred to patients' bank accounts: 13 000 drams ($27.50) per month for DR-TB patients and 8000 drams ($16.75) per month for DS-TB patients. Monetary incentives are paid only to those attending clinics daily for DOT and whose adherence to therapy is no less than 90% per month: 200 drams ($0.41)per day. The NTP decided that nutritional support would have less impact on adherence to therapy than monetary payments.

Most patients attend for treatment at the closest PHC facility (60 TB cabinets or around 100 health posts) in all 11 marzes, including Yerevan. Home-based care is available across the country for all patients on therapy, especially those being treated with new TB drugs, for whom the TB cabinet nurse visits at their place of residence. First initiated by MSF-F, the programme is delegated to the NTC to cover not only patients with DR-TB, but also those with regular TB. The original primary focus of home-based care was on patients at high risk of abandoning treatment due to behavioural and social challenges, elderly people and those with disabilities. With more programme experience gained, the NTC has identified two types of criteria for inclusion: temporary (smear-/culture-positive patients who refused hospitalization, those with temporary

disability or trauma, and those with severe adverse effects or dizziness); and permanent (people with disabilities, mothers with children under 5 years, those receiving the second infusion of Imi/Cls, and people aged over 70 years).

Two home-based care teams were functioning in Yerevan City at the time of the visit, covering 50% of home-based care patients each and delivering care from 09:00–15:00 six days per week (not on Sundays). Home visits in evenings were possible for DR-TB patients who required infusions of Imi/Cls at 12-hourly intervals. DOT in rural settings is organized at the nearest TB cabinets (PHC policlinic or ambulatory centre) and performed by trained nurses. Mobile home-based care is not available, but nurses visit patients at home when needed. The number of nurses in marzes varies depending on the number of patients who meet the criteria for home-based support. Transportation costs are reimbursed to the health provider if taxis or private vehicles are used for home visits to patients with DR-TB, but not for those on treatment for DS-TB. The quality of DOT for DS-TB therefore seemed questionable, as nurses may not be motivated to observe therapy, especially during the cold season. Cases of self-administered therapy were not identified, but close relatives had observed therapy of around 10% of patients in marzes. The working times of some TB cabinets in marzes does not completely meet treatment requirements (weekends), especially in cases of therapy with new TB and repurposed companion drugs (Imi). The NTP should consider options for performing DOT in sites with more than 10 DR-TB patients on therapy, especially those on new TB drugs.

MSF-F initiated video-DOT for patients on therapy with new TB drugs in 2016, first in Yerevan city, with 17 patients treated at the time of the mission. Video-DOT had been considered a new tool that provided an important alternative to mandatory daily visits to TB cabinets for patients with low-to-medium risk of default in order to decrease chances of self-administered therapy. It was provided mostly to patients who received DLM, LZD and CFZ to observe therapy seven days a week. Trained TB nurses equipped with smartphones used the tool via Skype in Yerevan city, monitored by MSF-F. Patients were required to come to TB cabinets to replenish the weekly supply of TB medicines and be clinically monitored by a TB doctor.

The recommendation to improve coordination of TB activities at marz level has not been completely achieved. None of the TB doctors in marzes have been assigned as marz coordinators to take responsibility for overall programme implementation and coordination of activities. Reporting has been centralized at NTC level, which makes it difficult to request TB data at marz level and means that responsibility for TB programme implementation is retained at the NTC. Coordination of the TB programme at regional (marz) level certainly requires improvement through identifying marz coordinators from the pool of dedicated TB doctors. This will increase ownership and responsibility for programme implementation at marz level, improve supervision and monitoring, strengthen coordination of activities with the NTC (including data-reporting) and, as a result, improve programme performance. The NTC should consider equipping future marz coordinators with vehicles to perform regular monitoring visits to patients and treatment sites, especially in remote areas. To decrease costs to the rural programme, the same vehicles could be used for mobile home-based care in marz centres.

In the main treatment site for TB in the prison sector, the Centre for Detainees, DOT of evening doses and during weekends has been very difficult to implement due to lack of personnel. TB doctors and nurses work Monday to Friday from 09:00–17:00, presenting difficulties for administration and observation of evening and weekend doses of DLM and Imi/Cls. There is an urgent need for the leadership of the Centre for Detainees and the Medical Department of the Ministry of Justice to address the issues of DOT and find ways to introduce additional workforce to the TB unit at the Centre.

Recommendations in relation to treatment strategies and administration are summarized in Table 10.

Table 10. Recommendations on treatment strategies and administration

	Recommendation	Responsibility
1	Ensure availability of updated version of the national DR-TB guidelines and updated diagnostic algorithms at all treatment sites	MOH, NTC
2	Strengthen surgical management for patients with TB and DR-TB	NTC, partners
3	Address the issues of palliative care for TB and DR-TB patients, especially those who completed therapy with new TB drugs	NTC, partners
4	Consider replicating best practices from the compassionate use programme and the end TB project into the routine system of DR-TB patient management	NTC
5	Consider conducting analysis of the use of Imi/Cls over six months in DR-TB patients	NTC, partners
6	Conduct training for DR-TB doctors on the updated version of the national guidelines, with a focus on the use of new TB drugs, active drug safety and patient management	NTC, partners
7	Improve the capacity of TB doctors on interpreting ECGc (calculating QT interval and QTcF) to monitor patients on therapy with BDQ, DLM, CFZ and FQ	NTC
8	Consider conducting training for specialists (cardiologists, ophthalmologists, neurologist) from the general health-care system who might potentially be involved in treating patients with TB on the PMDT to improve management of patients with DR-TB, especially those on new TB drugs	NTC
9	Consider conducting training on medical management of DR-TB and HIV coinfection for NTP; a HIV specialist from the National AIDS Centre should be a part of DR-TB committee meetings when discussing cases with coinfection, especially those on therapy with new TB drugs	NTC, partners
10	Ensure complete implementation of the minimum of aDSM requirements for patients treated with new TB drugs at the Centre for Detainees (HbA1C, ECG monitoring)	NTP, prison sector, partners
11	Consider including the minimum of clinical laboratory and instrumental monitoring tests into the MOH decree under the category for DR-TB patients who receive therapy with new TB drugs	NTP
12	Consider expanding criteria for inclusion to home-based care in Yerevan and other sites where the initiative is available to cover patients at high risk of defaulting therapy due to sociobehavioural reasons with no consideration for drug-resistance status	NTC
13	Scale-up alternatives to mandatory daily DOT for patients at low-to-medium risk of defaulting using modern technology tools (Video DOT)	NTC, partners
14	Address the issues of DOT and find ways to introduce additional workforce to the staff of the TB unit at the Centre for Detainees to perform DOT of patients on new TB drugs at evenings and weekends	Prison sector, partners
15	Consider creating mobile teams in marz centers with more than 10 TB and DR-TB patients on treatment to serve as an alternative to the existing system of outpatient TB programme	NTC
16	Improve coordination of the TB programme at marz level through assignment of marz coordinators selected from the pool of district TB doctors	NTC

8. TB laboratories

Findings and summary of discussion

Laboratory services in Armenia have gone through reorganization in recent years, with significant investment from various sources to improve capacity and performance. No significant changes in the infrastructure of the laboratory network have occurred since the last rGLC-Europe mission. Existing infrastructure and capacity guarantee universal access to smear, culture and DST for diagnosis and follow-up across the country. Transportation of samples from sites for sputum-smear microscopy, Xpert MTBRIF or culture and DST at the National Reference Laboratory (NRL) occurs routinely and no problems or delays have been identified. Transportation of samples from marzes to the NRL is organized twice weekly (on Tuesdays and Thursdays) by the NTC, with results reported by telephone and in paper format.

Laboratory services have achieved universal access to bacteriological diagnosis of TB and its drug resistance over the last three years. A series of diagnostic algorithms on smear microscopy, culture testing (liquid and solid media) and DST (GX, LPA, MGIT and LJ) is available, with the algorithms including criteria for selecting each method. Algorithms were included in the updated version of the national guidelines on PMDT (2016) and are available at all institutions involved in implementation of the NTP. The NRL served as the leading reference bacteriological laboratory for the whole country and is part of the NTC. DST on solid and liquid media and rapid molecular diagnosis are centralized at the NRL, which also serves as the methodology and quality-assurance centre for bacteriological services for the country.

Culture and conventional DST on solid media (only Cs) are performed on L-J media mostly for confirmation of culture results of RR-TB cases and is no longer considered the gold standard for diagnosis. Culture-testing and DST on liquid media prevailed due to higher sensitivity and adequate financing from the GFATM grant. Solid-media DST is almost no longer in use due to availability of other conventional methods of DST (LPA and MGIT) after diagnosis of RR-TB on Xpert MTB/Rif. The BACTEC MGIT-960 system is available only at the NRL and is used both for liquid media culture (diagnosis and follow-up) and conventional DST. The system performed around two thirds of all DST load in the country to FLD and SLD. First-line DST includes testing for the following drugs: Isoniazid (H), Rifampicine (R), Streptomycin (S) , Ethambutol (E), and separately to Pyrazynamide (Z), with results available seven days after the culture result. DST to SLD is performed for Amicacine (Am), Capreomycine (Cm), Ofloxacine (Ofx) and Eto. No shortages of reagents and consumables for BACTEC MGIT-960 were reported by NRL at the time of the visit.

Other options for DST include rapid molecular diagnosis methods, the PCR LPA or Hain test (MTBDRPlus and MTBDR*sl*) and GeneXpert MTB/RIF. The PCR LPA equipment was installed at the NRL in 2013 and performs DST to H, R, and E, Km, Cm and FQ separately. The new version of the MTBDRsl assay for detection of resistance to FQ and SLIs had been ordered and is expected to be implementated in 2017. Indications for MTBDRsl are set out in revised algorithms and are in line with the generally accepted international approach. According to the algorithm, Hain testing is performed for sputum-smear positive (SS+) new and retreatment cases (category 1 and 2), sputum-smear negative (SS-) and culture-positive (CC+) cases, SS+ cases with positive smear or culture results at the third month of therapy, and SS+ PDR-TB cases with positive smear and culture results at the third month of treatment. LPA is performed in parallel with MGIT. Time from collection of sample to arrival of DST results to FLD on PCR LPA is 2–3 days and up to three weeks on MGIT, which is appropriate for initiating an appropriate regimen once the result is available.

DST for new TB drugs of Group C (CFZ and LZD) and Group D2 (BDQ and DLM) has not yet been done for patients at SNRL level, but the NRL was asked to consider storing sputum specimens from samples taken as part of routine care to perform laboratory tests related to resistance, and the possibility of sending sputum specimens for DST to BDQ and/or DLM, as well as CFZ and LZD, has been discussed with MSF-F.

GeneXpert MTB/RIF (GX) became available in Armenia in 2012, with three four-module machines purchased through GFATM funding for the NRL, Yerevan city TB dispensary (YCTBD) and Republican HIV Prevention Centre. Five four-module Xpert machines were available at the time of the visit: two at NRL, one at the YCTBD, one in the Vanadzor infectious diseases hospital (Lori marz) and one in the Republican AIDS Centre in Yerevan. Protocol for rapid molecular diagnosis was available and matched the international criteria for diagnosis, including TB suspects, all HIV-positive cases, all new SS+ cases, patients with HIV coinfection and diabetes, and TB patients who remain SS+ at the end of the intensive phase. The protocol includes registration of patients in accordance with the results of rapid molecular testing (TB positive and rifampicin-susceptible, TB positive and RR, non-TB) and an algorithm for implementation. The protocol and algorithm were available at treatment sites visited during the mission and all five Xpert machines were functioning, with no shortages of cartridges reported by the NRL or sites.

With funding from the GFATM grant, the NTP has purchased 13 new two-module Xpert machines, which have been cleared by customs and are about to be distributed to all marzes (one each), with the ultimate goal of increasing access to rapid molecular diagnosis. The NTC should guarantee the availability of cartridges to avoid low use of Xpert machines.

The NTC laboratory coordinator and the NRL perform quarterly internal quality assurance of smear microscopy (SM) for the SM laboratories in the marzes (plus the two prison laboratories and all peripheral SM laboratories). The YCTBD performs external quality assurance for smear laboratories in Yerevan. There is also some sample exchange between the NRL and YCTBD for internal quality assurance purposes. The number of samples to be tested for internal quality assurance is based on the number laboratories receive and their positivity rates, in accordance with WHO recommendations. The NTC laboratory coordinator collects slides from smear microscopy points in marzes for quality control. Blinded testing is ensured, with a special form developed for reporting results. The NTC laboratory manager correlates the results. The NRL reported exceptionally high concordance among participating laboratories, the NRL and YCTBD.

The SNRL in Borstel, Germany performs external quality assurance once a year for DST on solid and liquid media, with an excellent concordance rate on solid media for FLD (H, R, S, E) of 100%, except for Z (specificity 88.2%) (2012 data). Concordance for SLD DST is 100% for Am, Ofx, and Cm and relatively acceptable for prothonamide (60% sensitivity and 80% specificity) (2012 data). External quality assurance on liquid media to FLD and SLD also shows high concordance. Regular external quality control on liquid media is recommended.

Recommendations in relation to TB laboratories are summarized in Table 11.

Table 11. Recommendations on TB laboratories

	Recommendation	Responsibility
1	Ensure uninterrupted and adequate supply of cartridges for Xpert MTBRIF, reagents and consumables for MGIT and Hain LPA	NTC, partners
2	Consider conducting external quality control on liquid media at SNRL on a regular basis	NRL
3	Consider storing sputum specimens from samples taken under routine care with new TB drugs to perform laboratory tests related to	NTC, SNRL, partners

	resistance	

9. TB infection control

Findings and summary of discussion

Improving infection control is one of the priorities of the Armenian NTC. Infection control activities are regulated by Epidemiological Control 3.1.1-010-08 and sanitary-epidemiological norms by MOH Decree N-21-N of 20 October 2008 and have not been updated. The NTC infection control coordinator is responsible for monitoring and supervising infection control at all treatment sites, including laboratories. The NTC team continues to lack licensed engineers to take responsibility for infection control maintenance and epidemiological aspects. The NTC has invested significant efforts in the past two years to improving infection control, especially in inpatient settings: a training curricula (including medico-epidemiological and engineering aspects of infection control) has been developed and a five-day seminar for specialists identified as hospital epidemiologists/focal points for infection control delivered.

National guidelines on infection control, reviewed by an external consultant and the Regional Office, are available in English and Russian languages. The guidelines were endorsed by local sanitary and epidemiological services and further endorsed by the MOH in 2013. No changes have been made to the guidelines since the last mission. The NTP conducted a comprehensive infection control assessment of each facility involved in the management of patients with TB and DR-TB in 2015: this meant 67 institutions were assessed, including the NTC, YCTBD, TB wards in Gyumri, Vanadzor and Kapan, two prison settings and 60 TB cabinets. The infection control checklist, which includes separate monitoring and evaluation checklists for inpatient and outpatient facility levels, was developed and has been reviewed by an external consultant.

Most patients starting therapy with new TB drugs are hospitalized in specialized DR-TB wards at the NTC. In the rare cases in which patients refuse to be admitted to the NTC, hospitalization at the nearest TB inpatient facility (Vanadzor) or home-based care is arranged. No forced-treatment legislation for TB exists in Armenia, so the NTC, with assistance from partner organizations, has developed alternatives for hospitalization and addressed non-adherence through patient-centred models of care. Criteria for hospitalization to the specialized ward at NTC for patients who started therapy with new TB drugs does not differ from DR-TB patients on conventional/traditional MDR-TB regimens. Discharge from hospital is possible upon bacteriological conversion (after 2–3 months of therapy) and confirmation of adequate DOT at the patient's place of residence.

The NTC, with technical assistance from the WHO country office and the Regional Office, started working on developing the strategic document to address the issue of excessive hospitalization of TB suspects and patients to inpatient facilities in 2013. The NTC closed the three regional inpatient facilities, which did not meet modern standards of infection control, in 2014. Since then, the NTC and YCTBD are the only inpatient institutions that admit confirmed TB cases and suspects for diagnosis and treatment. All patients diagnosed with any DR-TB are admitted to specialized DR-TB departments at the NTC. Patients with DS-TB from across the country, except Yerevan city, are hospitalized in TB wards at the NTC.

The specialized DR-TB ward has 100 beds and is located on the second and third floors of the NTC, with triaging of patients by wings according to the DST and smear/culture status:

1. PDR, smear/culture positive

2. DR-TB, smear/culture negative
3. MDR-TB, smear/culture positive
4. pre-XDR-TB and XDR-TB, smear/culture positive.

All four wings of the DR-TB ward are equipped with engineering ventilation and upper-level UVGI lamps. To decrease risks of nosocomial transmission, patients receive food and medicines in their rooms. Each room has a separate washroom, and all four wings have separate exits.

Patients with DS-TB and TB suspects are hospitalized in the 60-bedded specialized DS-TB ward at the NTC. Patients with smear- and culture-positive results stay in separate wings of the ward. Confirmation of diagnosis has improved due to increased access to rapid molecular diagnosis of TB and drug-resistance, and takes 2–14 days (3–7 on average) from initiation of therapy. Even if progress has been noted, TB suspects are still referred to the NTC for diagnosis confirmation from PHC facilities in marzes with unknown Xpert results. The number of suspects hospitalized in the DS-TB ward failed for diagnosis of TB is often uncertain, but patients found to have pneumonia, chronic obstructive pulmonary disease and cancer are hospitalized for up two weeks. Sputum for culture and DST is usually collected on admission to the ward and not prior, with several cases of DR-TB being diagnosed and referred to the specialized DR-TB ward for treatment. Before being diagnosed with DR-TB, patients share facilities in the ward, including the cafeteria, bathrooms, corridors and even rooms. The upcoming installation of 13 Xpert modules in all marzes through the GFATM grant offers an opportunity to hospitalize only patients with known TB and RR status to TB inpatient facilities, consequently decreasing the chances of nosocomial transmission. No shortage of Xpert cartridges were noted during the visit. Infection control approaches on hospitalizing patients with known DST status should be considered as an essential tool in decreasing nosocomial transmission of infection.

The NRL is located on the territory of the NTC in a new separate building with ventilation. Personal protective measures are followed properly, with respirators, robes, hats and gloves available for all medical and non-medical personnel. No incidence of TB and DR-TB among laboratory personnel has been reported since the last visit. Class 2 biosafety cabinets are available for all culture and DST methods used in the laboratory, with infection control monitoring (filter exchange, air flow at biosafety cabinets, etc.) supposedly implemented on a regular basis. NRL staff did not express any problems with exchange of high-efficiency particulate air filters for biosafety cabinets during the mission, although organizational constrains were present previously. Ignoring biosafety might result in increased risk of infection for personnel and reduce laboratory performance. Administrative separation of infectious from clean zones is performed adequately, with a separate entrance for sample-collection available. Sterilization of materials, utilization of disposables and cleaning of rooms with detergents and disinfectants is performed in accordance with existing sanitary-epidemiological regulations.

No changes in infection control measures in the Centre for Detainees of the prison sector since the last visit were noted. Even though the total number of TB patients detained has generally decreased, infection control still requires attention. All patients were on appropriate treatment regimens and achieved positive therapeutic responses, but the risk of nosocomial transmission remains. It is possible that this will decrease once upper-room UVGI lamps are procured, installed and properly monitored. All patients with DR-TB are detained in a specialized TB ward with a separate entrance; no contact with other detainees was identified. Administrative isolation of infectious patients from those whose smear/culture had converted was taking place. Upper-level UVGI lamps had been installed in the TB unit (corridor and rooms) and doctors' office, but most of them were outdated and malfunctioning. Replacement and installation of 490 modern UVGI lamps purchased through the GFATM grant is expected later in 2016. There is a need for a

qualified engineer specialized in infection control to perform regular maintenance and evaluation of all lamps installed at all inpatient facilities, including penitentiaries.

Recommendations relating to TB infection control are shown in Table 12.

Table 12. Recommendations on TB infection control

	Recommendation	Responsibility
1	Consider hospitalizing patients with known DST status to any inpatient facility; the use of rapid molecular diagnosis of drug resistance should guide further administrative triage of patients according to DST status	NTC, partners
2	Upper-room UVGI lamps are recommended for use at least in all inpatient facilities (wards, corridors, procedure rooms, DOT points), including in the penitentiary sector; regular monitoring of performance and appropriate use by qualified engineers is essential	NTC, penitentiary sector, partners
3	Health/administrative personnel of health facilities, the Centre for Detainees and bacteriological laboratories where there is a high risk of nosocomial infection of TB and DR-TB should use personal respirators of biosafety class not lower than FFP2 (or N95, according to the United States of America Standard 42CFR84): • at least two types/forms of respirators are recommended for use by health/administrative personnel of health facilities and bacteriological laboratories; • a fit test should be considered as the gold standard by every health/administrative worker prior to using a new form of respirator; and • use of surgical masks is strongly recommended for TB and DR-TB patients, at least in inpatient facilities (continuous recommendation)	NTC, penitentiary sector, partners

10. Drug management – new TB drugs

Findings and summary of discussion

All TB medicines, including new TB drugs, are provided free of charge to all TB and DR-TB patients regardless of immigration status, gender, age and race. Drug procurement of new TB drugs is donor-dependent, with two main sources of funding – the endTB project implemented by MSF-F, and the NFM GFATM grant – and is centralized at the NTC, which is responsible for selection, forecasting, drug-ordering and distribution directly to TB facilities, including the prison sector.

Procurement of FLD and SLD is performed through the Global Drug Facility (GDF) with funding available from the GFATM grant and managed by the MOH and NTC. Two separate drug orders had been submitted to the GDF by the NTC in 2015 and 2016, arriving in February and August respectively. The first order was based on dynamic inclusion of 228 patients (58 patients per quarter) and included FLD (Z, R, E) and SLD (Km, Cs, PAS, AMX/CLV, Cm, Mfx, Lfx, Eto and CFZ) split in two separate shipments (February and October 2016). The order included regimens for the management of patients with PDR-TB, MDR-TB, pre-XDR-TB and XDR-TB. The final quantity of all items was adjusted using 16.67% buffer stock (approximately two months' supply) and subtracting present stock and backorders in the supply chain. Quantities of BDQ, DLM, LZD and Imi/Cls had been provided by MSF-F through MSF-Logistique for patients on the compassionate use

programme and having programmatic use of new drugs. The NTC started ordering BDQ using the USAID-Janssen BDQ donation programme in July 2016. Drug orders are usually placed every six months to ensure timeous arrival of medicines to the country and buffer stock at the central warehouse. They are cleared by the rGLC-Europe prior to submission. Drug-ordering is performed using a standardized GDF form with stratification of the number of PDR-TB, MDR-TB and XDR-TB patients to be enrolled.

MSF-France has not been responsible for SLD procurement for MDR-TB since 2014, but continues with procurement of BDQ, DLM, CFZ, LZD and Imi-Cls for programmatic use for treatment of patients with DR-TB through the endTB project, with funding from UNITAID. MSF-F initiated the use of new TB drugs under the compassionate use programme in April 2013, resulting in 62 patients receiving therapy with a BDQ-containing regimen. This transitioned to programmatic use in April 2015 with the launch of the endTB project managed by MSF-F and implemented in close partnership with the NTP. The compassionate use programme for use of DLM was also initiated by MSF-F: it started on 5 November 2015, with DLM donated by Otsuka Pharmaceuticals, and transitioned to programmatic use within the endTB project in April 2016. At the time of the visit, MSF-F was using its organizational procurement system – MSF-Logistique – and delivering drugs for the remaining patients on the compassionate use programme (LZD and Imi-Cls only) and for programmatic use of new drugs within the endTB project (DLM, LZD and Imi-Cls). The NTC orders and procures CFZ for remaining patients on the compassionate use programme and those treated under programmatic conditions in the endTB project, with BDQ ordered via the USAID-Janssen BDQ donation programme. No shortages of new TB drugs was noted, with the procurement system adequately managed and coordinated between two organizations – NTC and MSF-F.

Of the 62 patients who started therapy under the compassionate use programme since 2013, all had finished the 24-week course of therapy with BDQ, 55 had completed and seven were still on treatment. Seventy-five patients had been enrolled out of a total cohort of 96 planned within the endTB project: 36 on BDQ-containing regimens, 31 on DLM-containing regimens and seven on regimens with concomitant use of BDQ and DLM. The use of new drugs has already been extended beyond 24 weeks in nine patients: seven in BDQ-containing regimens and two on DLM-containing regimens, which is currently considered as off-label use due to limited data but is not strictly prohibited, similar to concomitant use of BDQ and DLM. No problems in extending the use of BDQ beyond 24 weeks for some individual cases were foreseen, considering that Armenia is eligible for free procurement of BDQ under the USAID-Janssen BDQ donation programme.

BDQ-containing regimens for patients with XDR-TB and pre-XDR-TB under programmatic use of new TB drugs includes BDQ (100%), LZD (90%) and CFZ (70%) (Table 13). Around half of patients on a BDQ-containing regimen had Imi/Cls or MPN in the regimen and were taking AMX/CLV (1000 mg twice daily) (Table 14).

Table 13. Distribution of Group 5 drugs in BDQ-containing regimens

	BDQ (%)	LZD (%)	CFZ (%)	Imi/Cls + AMX/CLV (%)
Compassionate use	100	100	80	60
Programmatic use	100	90	70	50

Table 14. Availability and stock of second-line and new TB drugs

Name	Type	Expiration	NTP	Other
Kanamycin 1 000 mg	Vial	July 2018, September	Yes	–

		2018, October2018		
Amikacin 500 mg, 2.0 ml	Vial	–	–	MSF-F
Capreomycin 1 000 mg	Vial	June 2018, October 2018	Yes	–
Levofloxacin 250 mg	Tablet	July 2020, December 2020	Yes	–
Levofloxacin 500 mg	Tablet	–	–	–
Levofloxacin 750 mg	Tablet	–	–	–
Moxifloxacin 400 mg	Tablet	April 2019	Yes	–
PASER 4 g	Sachet	March 2018, September 2018	Yes	–
Cycloserine 250 mg	Tablet	December 2018, January 2019	Yes	–
Prothionamide 250 mg	Tablet	July 2017, October 2020	Yes	–
Amoxicillin/clavulanic acid 500/125 mg	Tablet	–	–	–
Amoxicillin/clavulanic acid 875/125 mg	Tablet	December 2017, April 2019	Yes	–
Pyrazinamide 400 mg	Tablet	September 2018, March 2019, November 2019	Yes	–
Pyrazinamide 500 mg	Tablet	–	–	–
Bedaquiline 100mg	Tablet	April 2017, June 2017, November 2017	Yes	–
Delamanid 100 mg	Tablet	–	–	MSF-F
Clofazimine 100 mg	Tablet	March 2019, April 2020, March 2020	Yes	–
Linezolid 100mg	Tablet	–	–	MSF-F
Imipenium/cilastatin 500mg	Vial	–	–	MSF-F
Meropenem 1 000 mg	Vial	–	–	–

Ancillary medicines are available through GFATM financing and procured from the same source under the GFATM grant. Pyridoxine (vitamin B6) is included in drug orders from GDF and features in all DR-TB regimens containing LZD, with an average dose of 150 mg per day during the whole course of chemotherapy. The list of ancillary medicines is available at all treatment sites for regular use by doctors. A national system of pharmacovigilance exists, with side-effects registered in MOH-approved yellow forms and reported spontaneously only upon withdrawal of the drug. The yellow form includes information on the compromised drug, side-effects and symptoms, and actions taken. Once completed, they are supposed to be sent to the National Drug Authority for further analysis. No system of active pharmacovigilance is present, but cohort event monitoring is conducted within the endTB project, with active reporting to the endTB pharmacovigilance unit in

Geneva, Switzerland. Registration of side-effects for TB drugs is therefore not taking place routinely for DS-TB and DR-TB (MDR-TB and PDR-TB), but only for patients under compassionate use of BDQ and those who have started therapy within the endTB project with new TB and repurposed companion drugs. The national side-effect monitoring form is available during the inpatient stay for all TB patients, including those with DR-TB, but is not recorded in the national TB register.

MSF-F has committed to procure antibiotics for the management of NTM.

Recommendations relating to drug management for new TB drugs are shown in Table 15.

Table 15. Recommendations on drug management for new TB drugs

	Recommendation	Responsibility
1	Consider using the USAID BDQ donation programme for drug orders for programmatic use of BDQ	NTC
2	Rational adjustments to forecasting and future drug orders of BDQ and DLM should be considered, taking into account the need for extended use of BDQ and DLM beyond 24 weeks	NTC
3	Implementation of aDSM should be embedded in the national system of pharmacovigilance	NTC
4	Uninterrupted supply of the whole spectrum of Group 5 drugs – BDQ, DLM, CFZ, linezolid (LZD) and Imi/Cls + amoxicillin/clavulanate (AMX/CLV) for treatment of patients with DR-TB under programme conditions beyond the endTB project should be ensured	NTC, partners

11. Information system and data management

Findings and summary of discussion

The national recording/reporting system for regular TB patients corresponds to international recommendations and covers the civilian and prison sectors. Case definitions, outcome definitions for DS-TB and DR-TB match WHO requirements. Recording and reporting forms for DS-TB and DR-TB differ but are eligible for use by all programme implementers and contain all essential information on case registration and treatment. The eTB Manager system is used by the NTP as a national TB register platform, integrating data across all aspects of TB control and including information on suspects, patients, medicines, laboratory-testing, diagnosis, treatment and outcomes for DS-TB and DR-TB. There is no separate DR-TB electronic database available, but DR-TB data are entered in the national TB registry and can be extracted. The platform is available at every treatment site, with TB doctors responsible for entering data requested by national TB forms.

During the mission, the consultant reviewed the following elements in eTB Manager for patients who receive therapy with new TB drugs: bacteriological status, DST, regimen and dosages, and adherence to treatment (which was complete). All new TB drugs had been listed in the platform and entered in the treatment-regimen section, with changes in the regimen possible (dose decrease, withdrawal or addition of medicines). The eTB Manager was used for epidemiological analyses by the NTP and routine clinical management of patients by TB doctors at sites, and seemed an ideal tool to serve as a national TB register. The NTP should nevertheless consider the option of introducing a new summary form covering most laboratory and instrumental tests, which could then be entered into the national TB register and be used for clinical purposes by

doctors, as well as acting as a tool for identifying any adverse events associated with the use of TB drugs.

The MSF-F, as the primary implementer of the endTB project in Armenia, has been using a separate web-based electronic medical record system (based on the Bahmni system) for entry of standardized clinical data for patients treated with new TB drugs. The endTB project electronic medical record system is open-source and contains all clinical information on patients treated with new TB drugs within the endTB project, including pharmacovigilance (registration of adverse and severe adverse effects). Separate forms have been developed for the purposes of the project, to be filled in by MSF-F clinicians for all patients on new TB drugs enrolled into the endTB project. It is expected that the electronic medical record system will meet the needs of clinical, research and reporting purposes. The software has not been employed for clinical use by physicians yet, but this is planned.

Recommendations relating to information system and data management are shown in Table 16.

Table 16. Recommendations on information system and data management

	Recommendation	Responsibility
1	Regular monitoring of data collection and entry at county-level TB dispensaries and laboratories should be conducted (continuous recommendation)	NTC
2	The possibility of adding X-ray digital photos to eTB Manager should be considered	NTC
3	The introduction of the new form summarizing clinical laboratory and instrumental monitoring and updating the national TB register should be considered	NTC

12. Ethics of TB prevention, care and control

Findings and summary of discussion

Treatment of TB and MDR-TB, including regimens with new TB drugs, is free of charge regardless of race, ethnicity, religion, age and gender. Access to treatment is equal to every diagnosed DR-TB patient, irrespective of place of residence in the country. Initiation of treatment is possible at the patient's choice, either in hospital or at his or her place of residence.

Armenia has been facing issues of labour migration in recent years, mostly to the Russian Federation and Ukraine, with patients often defaulting treatment for work outside of the country. Treatment options for patients with DR-TB who have returned to Armenia for treatment, including with new TB drugs, is often difficult, considering poor access to care offered to foreign nationals in neighbouring countries. Most diagnosed cases with DR-TB, especially with resistance to FQ, are associated with labour migration.

The recommendation on the ethics of TB prevention, care and control is shown in Table 17.

Table 17. Recommendation on the ethics of TB prevention, care and control

	Recommendation	Responsibility
1	Issues of TB among labour migrants should be addressed and treatment compliance strategies ensured (continuous recommendation)	MOH, NTC

Annexes

- Annex 1. Agenda of the rGLC mission
- Annex 2. endTB Clinical and Programmatic Guide for Patient Management with New TB Drugs. Version 3.3.
- Annex 3. WHO TB Country Profile for Armenia, 2015.