



**Capacity-building for consultants  
on the new WHO recommendations for the treatment  
of drug-resistant tuberculosis  
International online training  
15–18 June 2020**

## Abstract

WHO Regional Office for Europe held an online training session "Capacity-building for consultants on the new WHO recommendation for the treatment of drug-resistant tuberculosis" on 15–18 June 2020. The objectives of the training session included capacity-building of the new and existing rGLC/Europe consultants on the new WHO guidelines; increasing the pool of consultants to enable the smooth continuation of support to countries with regard to the introduction of the latest treatment policies based on the latest WHO recommendations, and assisting countries in the operationalization of the new guidelines. Members of the rGLC/Europe; representatives from the Stop TB Partnership, the Global Drug Facility (GDF), staff from WHO Headquarters Global TB Programme and from the Joint Tuberculosis, HIV and Viral Hepatitis Programme of the WHO Regional Office for Europe took part in the training session. During the meeting, staff and core experts from WHO Regional Office for Europe and rGLC experts shared updates on DR-TB treatment and related topics, in particular TB/HIV and paediatric TB and LTBI management and their implications for laboratory diagnosis, drug supply, infection control and clinical follow-up. The WHO Regional Office and Global TB Programme also addressed the challenge of COVID-19 pandemic, which is an overlapping threat hampering TB-related activities. Experienced and new rGLC members discussed the in-country mission Terms of Reference (TOR), expected results and possible complications. In view of the new WHO consolidated Guidelines on TB treatment (Module 4), issued on 15 June 2020, and up-coming operational research on short all-oral DR-TB treatment regimens, which will cover 11 countries in the WHO European Region, rGLC consultants were updated on WHO priorities and consultants' roles and responsibilities for operational research in the field. The WHO Collaborative Centre on DR-TB Treatment in Minsk, Belarus, involved the new and experienced rGLC experts in the real-life activities of the National DR-TB Consilium. The participants also practised using the QuanTB system.

The training session was prepared and organized with financial support of The Global Fund to Fight AIDS, Tuberculosis and Malaria (<http://www.theglobalfund.org>) under the Memorandum of Understanding between WHO and the TGF on the Regional GLC and Secretariats (April 2017).

**KEYWORDS:** TUBERCULOSIS, MULTIDRUG-RESISTANT TUBERCULOSIS, EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS, REGIONAL GREEN LIGHT COMMITTEE EUROPE

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## Abbreviations

ABC	abacavir
AE	adverse events
ADR	adverse drug reaction
aDSM	active drug safety monitoring and management
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral drugs
ATV/r	atazanavir/ritonavir
AST	aspartate aminotransferase
BDQ	bedaquiline
BPaL	bedaquiline, pretomanid and linezolid
Cs	cycloserine
CT	computer tomography
CFZ	clofazimine
ddl	didanosine
DLM	delamanid
DOT	directly observed treatment
DR-TB	drug-resistant tuberculosis
DRV/r	darunavir/ritonavir
DST	drug susceptibility testing
DTG	dolutegravir
E	ethambutol

EECA	Eastern Europe and Central Asia
ELI-TB	European TB Laboratory Initiative
FDC	Fix-dose combination
FTC	Emtricitabine
GDF	Global Drug Facility
GDG	Guideline Development Group
GDI	Global Drug-resistant TB Initiative
GF	Global Fund
GRADE	Grades of Recommendation Assessment, Development and Evaluation
HCV	hepatitis C
IC	Infection control
IGRA	Interferon Gamma Release Assay
IHD	ischaemic heart disorder
INH	isoniazid
LFX	levofloxacin
LPA	line probe assays
LPV/r	lopinavir/ritonavir
LTBI	latent TB infection
LZD	linezolid
M&E	Monitoring and Evaluation
MDR-TB	multidrug-resistant tuberculosis
MGIT	mycobacteria growth indicator tube
MSF	Médecins Sans Frontières
MFX	moxifloxacin

NTP	national TB control programme
OR	operational research
PLHIV	people living with HIV
PSM	procurement and supply management
PTO	prothionamide
PZA	pyrazinamide
QTcF	QT interval with Fridericia's correction
RAL	raltegravir
R&R	recording and reporting (R&R) system
rGLC/Europe	regional Green Light Committee/Europe
SHORRT	Short, all-Oral Regimens for Rifampicin-resistant Tuberculosis
SORT IT	Structured Operational Research Training Initiative
TDF	tenofovir disoproxil fumarate
TOR	terms of reference
TST	tuberculin skin test
USAID	United States Agency for International Development
WGS	whole genome sequencing
XDR-TB	extremely drug-resistant tuberculosis
ZDT	zidovudine
3TC	lamivudine

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## **Introduction**

The regional Green Light Committee for the WHO European Region (rGLC/Europe) was established in 2010 in response to the high burden of multidrug-resistant tuberculosis (MDR-TB) in the Region. It serves as the advisory body of WHO on the development and implementation of practical approaches for the prevention and management of multidrug and extensively drug-resistant tuberculosis (MDR/XDR-TB). It also provides technical assistance to the Member States of the WHO European Region and key partners in developing, updating and implementing a programmatic approach to the management of drug-resistant tuberculosis (DR-TB). The rGLC/Europe Secretariat is hosted by the WHO Regional Office for Europe.

WHO Regional Office for Europe held an international online training session for the consultants on the new guidelines on treatment of drug-resistant tuberculosis (DR-TB) on 15–18 June 2020. The objectives of the training session included capacity-building of the new and existing rGLC/Europe consultants on the new WHO guidelines; increasing the pool of consultants to enable the smooth continuation of support to countries with regard to the introduction of the latest treatment policies based on the latest WHO recommendations, and assisting countries in the operationalization of the new guidelines.

Members of rGLC/Europe; representatives from the Stop TB Partnership, the Global Drug Facility (GDF), the United States Agency for International Development (USAID); staff from the Global TB Programme, at WHO headquarters; and staff from the Joint Tuberculosis, HIV and Viral Hepatitis Programme and the Health Technologies and Pharmaceuticals Programme of the WHO Regional Office for Europe took part in the training session.

Dr Ogtay Gozalov, Medical Officer of the Division of Country Health Programmes, WHO Regional Office for Europe, opened the workshop. Dr Gozalov outlined the meeting objectives and schedule, welcomed new rGLC members, emphasized the role and the scope of consultancy, and discussed the overall template of the rGLC consultant report and, in particular, the need to get the report out within the time specified in the TOR. At the moment, given the rapid changes in WHO approaches for MDR-TB treatment, it is crucial for local NTPs to provide rapid and flexible responses. In terms of keeping the recommendations of rGLC consultant as targeted and as technically specific as possible, Dr Gozalov suggested asking NTPs to formulate detailed and specific requests to the rGLC, as no rGLC consultant can provide a comprehensive report, which could replace monitoring visits, normally organized by multidisciplinary teams. The COVID-19 lockdown has meant that in-person consultancies have been cancelled; remote consultancy should be carefully scheduled to provide the maximal possible output and avoid overwhelming national and local managers and participants to enable the consultancy to address the issues, brought up by the NTP, in the most interactive way possible.



## 1. Presentation of WHO consolidated guidelines on TB / Dr Fuad Mirzaev, Lead of Treatment Group, Division of Prevention, Detection, Treatment and Innovations, Global WHO TB programme

Dr Fuad Mirzaev outlined the history of the WHO DR-TB Guidelines starting with the first guidelines that were issued in 1996. The accumulation of experience, the improvement of the evidence behind the recommendations and the implementation of the GRADE approach, as well as the introduction of new drugs, mainly BDQ and DLM, created requests for a set of consolidated guidelines to streamline the information flow. The previous DR-TB consolidated guidelines were issued in March 2019. Rapid progress in DR-TB treatment made the revision of these guidelines necessary. Therefore, WHO has made a partial update of Module 4 *Drug-resistant tuberculosis treatment* and issued the document on 15 June 2020. To fill the gap between the evidence-based consolidated data and practical routine, which generates a lot of different questions and considerations, the new document is accompanied by the *Operational handbook on DR-TB treatment*.

The 2019–2020 updates, in comparison with the 2011–2017 recommendations, are the following:

- Significant changes
  - New longer all-oral regimens
  - New grouping of second line drugs
  - Composition of new shorter DR-TB treatment regimens
  - BPaL regimen
- Some changes
  - Number of medicines in longer regimens and their duration
  - Use of a shorter MDR-TB treatment regimen and additional requirements
  - Emphasis on OR, aDSM and DST
- No change
  - Treatment response monitoring
  - Start of ART with MDR-TB treatment
  - Use of surgery
  - Models of MDR-TB care (ambulatory/ hospitalization)

As of November 2019, new evidence available is related to:

- Programmatic implementation of shorter, all-oral BDQ-containing shorter regimen (9–11 months) in South Africa in 2017
- Nix-TB study on a novel 6-month regimen from TB Alliance in XDR-TB, or MDR intolerant or non-responsive patients
  - BPaL (6 months BDQ, pretomanid, LZD)
- END-TB observational study, which MSF, Partners in Health, and IRD (Interactive Research and development, Pakistan) held in 17 countries using BDQ >6months, and BDQ concurrently with DLM in longer regimens

The current guidelines consists of eight sections. Three of them have been significantly updated. These are:

*Section 2: Shorter all-oral bedaquiline-containing regimen for multidrug- or rifampicin-resistant tuberculosis*

*Section 3: Longer regimens for multidrug- or rifampicin-resistant tuberculosis*

*Section 4: The bedaquiline, pretomanid and linezolid (BPaL) regimen for multidrug-resistant tuberculosis with additional fluoroquinolone resistance*

The Operational Handbook follows these updates.

The key recommendation of *Section 2* is:

*2.1 A shorter all-oral bedaquiline-containing regimen of 9–12-months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) who have not been exposed to treatment with the second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded.*

*(Conditional recommendation, very low certainty in the evidence)*

In fact, the presented regimen (bedaquiline (used for 6 months), levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine for 4 months (with the possibility of extending to 6 months if the patient remains sputum smear-positive at the end of 4 months); followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide) was previously known as the DR-TB shorter regimen. Currently, the injectable drugs are being replaced with bedaquiline. The evidence behind this regimen is based on a bedaquiline 6-months course.

The prerequisite for this regimen use are:

- fluoroquinolone drug susceptibility testing (DST);
- availability of the treatment history to ensure that the patient has not previously received second-line drugs;
- absence of extensive (advanced) pulmonary lesions or severe extrapulmonary TB.

New data with regards to longer DR-TB treatment regimens informed the new regimen. In particular, no safety issues have been noted relating to bedaquiline use for longer than 6 months, bedaquiline and delamanid simultaneous use, and bedaquiline use during pregnancy. In the latter case, the only registered consequence was low body weight of neonates in comparison with neonates from mothers who did not use bedaquiline, but by the age of 1 year, no significant weight differences were observed. Longer regimens are suitable for patients who not fit the shorter DR-TB course inclusion criteria

**Section 3** is devoted to the longer treatment regimens, which could be applied for patients who do not meet the inclusion criteria for the shorter course. Being more flexible, this regimen allows an individual regimen composition. The Operational Handbook provides additional details on the composition of the different longer regimens.

Therefore, the new guidelines allow for tailoring of an all-oral regimen for any DR-TB case. If the patient has not been treated for DR-TB before, fluoroquinolone resistance is ruled out, and it is not an extensive (advanced) disease, the shorter bedaquiline-containment regimen is a first

choice treatment. In settings with high prevalence of resistance, some drugs within this regimen could be replaced by others. This should be done under the operational research conditions.

*Section 4* of the guidelines suggest a treatment regimen lasting 6–9 months, composed of BPaL used in patients with DR-TB who are resistant to fluoroquinolones, who have had either no previous exposure to bedaquiline and linezolid or have been exposed for no more than 2 weeks. This regimen is not recommended for the routine use and should be carried out under operational research conditions only. Routine programmatic use of the BPaL regimen is still not recommended primarily because of the unclear safety profile, although the NIX-TB study undertaken by TB Alliance (open label one-arm observational study with 108 patients enrolled; a global Individual Patient Database (IPD) >13 000 records overall from 38 studies in 55 countries was used as a comparator) demonstrated a success rate of about 90%. In some patients this regimen can be used if no other effective regimen can be composed (compassionate use according to existing ethical considerations).

The SHORRT operational research package is a tool that the Global TB WHO Programme recommends for the accumulation of new evidence on shorter regimens. WHO Regional Office for Europe is implementing the operational research on the SHORRT programme.

In summary the new guidelines propose:

- all-oral treatment regimens;
- modification of the treatment regimens;
- new data on bedaquiline safety for >6 months, in pregnancy, and simultaneously with delamanid;
- BPaL regimen is still recommended within operational research only;
- increased active drug safety monitoring and management (aDSM) and DST requirements;
- new scope for operational research in DR-TB treatment.

### **Summary of questions, comments and clarifications**

- The Operational Handbook provides information on the drug–drug interaction available to date. Several tables demonstrate interactions with antiretroviral (ARV) drugs, other antivirals, antibiotics, etc. The issue of interactions between different DR-TB drugs is also addressed.
- WHO Regional Office for Europe is starting to work on translating the consolidated guidelines into Russian. The draft document could be available within a month, but official approval can take longer, so hopefully the finalized document will be available in September/October 2020.
- The guidelines do not present the exact criteria of extensive disease. Definitely, bilateral cavitation is an exclusion criterion for the shorter regimen, whereas evaluation of such treatment acceptability with regards to the proportion of affected lung parenchyma is a physician’s responsibility. Formalistic and inflexible recommendations can just complicate the decision, as, in addition to lung lesion visualization, the disease clinical presentation, concomitant diseases and other factors should be taken into consideration.

## **2. TB programme and the COVID-19 pandemic/ Dr Masoud Dara, Coordinator, Communicable Diseases, Division of Country Health Programmes, WHO Regional Office for Europe**

As of 17 June 2020, in European Region there are almost 2.5 million of COVID-19 cases detected and almost 190 000 deaths. Spain, Italy and Germany are among the world leaders of the disease spread. Unlike TB, COVID-19 is a new acute disease, which is mainly transmitted by droplets and fomites, with airborne transmission as an additional route. Control of COVID-19 requires physical distancing, lockdown, hand hygiene and surface disinfection in addition to airborne precautions. There is no prophylactic treatment or vaccine for COVID-19, unlike TB. In addition, the lives lost and economic impact of TB is 1.5 million and \$ 12 billion, annually, versus 440 000 and US\$ 2 trillion so far in 2020 for COVID-19, but resource mobilization for TB is far behind that for COVID-19.

As COVID-19 is a long-term challenge that could affect the quality of TB services, urgent needs include the prioritizing of existing TB, HIV and hepatitis services; streamlining case detection, stocks, improvement infection control (IC) hierarchy for these disease; early COVID-19 detection among TB patients and health care workers; scaling-up new service models including mobile services and social contracting; and addressing the common risk factors of TB and COVID-19, in particular, smoking, diabetes, cardiovascular and chronic respiratory diseases. Rational use of existing TB staff expertise (mainly for COVID-19 detection, contact tracing and IC) and equipment (Xpert machines, for example), consideration of drug–drug interactions and documenting the coinfection management results are also essential.

During the recovery phase of the COVID-19 pandemic, it is necessary to prioritize funding/resources for health systems and particularly interventions affecting the most vulnerable groups; to attract, support, protect and retain the health workforce; to find missing patients and intensify outreach activities; to ensure access to the effective treatment and supply; to document the lessons learned; and to pursue the social mobilization, address stigma and accelerate health care reforms. Following-up the COVID-19 survivors, including cases of pulmonary fibrosis which could be similar to TB sequelae, is also important. The contact tracing system developed for TB can also be successfully be applied to COVID-19.

### **Summary of questions, comments and clarifications**

- GF allocated an additional \$ 2 billion for the COVID-19 response, and the most reasonable TB-related use of these costs are improved detection, IC and clinical management including remote and patient-oriented practices.
- The new manual, which WHO Regional Office for Europe developed, summarizes the successful video-DOT programmes mainly used in Belarus, Georgia and Moldova. It will be available in July 2020. The Russian translation is coming shortly. These manuals are well timed, as the COVID-19 pandemic is a challenge but simultaneously provides an opportunity to improve TB-related services and overcome stigma.

### **3. Practical considerations of Green Light Committee activities/ Dr Ogtay Gozalov, Medical Officer, Division of Communicable Diseases, WHO Regional Office for Europe**

Conflict of interests' disclosure is one of the key requirements for each WHO consultant. Improper practice by any WHO consultant can directly affect WHO goals and reputation.

On 1 July 2020, the new memorandum between WHO and the Global Fund to Fight AIDS, Tuberculosis and Malaria (GF), which is the direct donor of regional rGLCs, is expected. This memorandum will emphasize the following points:

1. rGLC Terms of Reference are to meet the local NTP needs, rather than WHO decisions.
2. There are no technical limitations on GLC consultancy. It can include areas beyond programmatic management of DR-TB, in particular, laboratories, IC, drug management, paediatric tuberculosis, latent tuberculosis infection (LTBI), etc.
3. Priorities should be identified in the Terms of Reference (TOR) for the consultancy mission.
4. rGLC and consultants cannot replace NTP activities, but can just catalyse activities, push innovations and provide technical support. This is a prerequisite for NTPs' ownership and leadership. Consultants have to stress this ownership throughout their missions.

Due to the COVID-19 lockdown, WHO and the GF reached an agreement on some modifications of rGLC activities. In particular, the traditional format of the rGLC consultant's report could not be developed, mainly because data verification and triangulation is only possible for in-person visits. As the consultants have to mainly work remotely, rGLC/Europe decided to implement a one-page report format, in which a consultant can briefly describe the summary of the TOR and the consultant's conclusions. Each mission should also yield a specific product (e.g. national standards, clinical guidelines, strategic plans, etc.). Countries are the final owners of such documents. In addition, the consultants should forward these drafts or the final version to rGLC/Europe. rGLC/Europe needs these documents to follow-up further approval by NTPs, receive feedback and support implementation, if needed. The NTP extensive review is a classic rGLC format, which is still in use. If an rGLC consultant was involved with a team of reviewers, their role should be reported as a part of the country mission deliverables. The time frame of each format preparation is rather different. Whereas the tradition format requires around 2 weeks, and a one-page review could be submitted immediately after the mission is completed; an NTP external review, being the product of a large team, usually takes several months.

Because of the expiration of the previous memorandum between WHO and the GF, and the signing of the new memorandum, rGLC/Europe has had to close all contracts with consultants and will open new ones with existing and new consultants. rGLC/Europe intends to hire new consultants for the next 18 months (until December 2021). To date, no missions have been cancelled due to the lockdown measures. All activities have been carried out remotely.

The overall role of the rGLC consultant is complex. The consultant should combine friendly support with expertise, wisdom and diplomacy. In addition, a consultant should demonstrate objectivity and integrity.

#### **4. Implementation of the new modified DR-TB treatment regimen in Belarus/ Dr Alena Skrahina, rGLC/Europe Head, Director of WHO Collaborating Centre for Implementation of New MDR and XDR-TB Treatment Regimens, Minsk, Belarus**

The TB incidence rate is continuously decreasing in Belarus, with a 2019 figure of 18.6 per 10 000 people. The trends for HIV are also favourable, and only 175 TB/HIV patient were detected in 2019. In addition, 1 182 DR-TB cases were detected in 2019. Whereas treatment success of DS-TB cases exceeds WHO target indicators, both in HIV-negative and HIV-positive cases (around 89% and 85 % respectively), treatment success of DR-TB in the 2018 cohort was only 64% in HIV-negative and 56% in HIV-positive patients. These challenges led to the prioritization of DR-TB in the National TB Strategic plan. This plan stressed the need for the rapid implementation of the new drugs and new regimens. Bedaquiline and delamanid have been used routinely in Belarus since June 2015 and June 2016, respectively. Other, repurposed drugs, such as linezolid, clofazimine, carbapenem, amoxicillin and clavulanate have been in use for many years.

Belarus is entering into a commitment to follow each of the new WHO guidelines. Sometimes this requires modification of the national strategic plans, including the budget. The GF Country Coordinating Committee supports these modifications with important technical roles played by rGLC/Europe and the WHO Regional Office. This allows the NTP to provide the necessary improvements of the Recording&Reporting (R&R) system, aDSM and also to submit annual reports to the national authorities, WHO and the GF Portfolio Manager. As this is a continuous cycle, currently, Belarus NTP is in process of updating the national guidelines. The WHO Rapid Communication on new drugs and regimens, issued in December 2019, provided a background for this update even before the full consolidated guidelines became available. Country readiness for implementation of the new regimens is based on the key elements of the national regulations and NTP capacity, as well as on the pharmacovigilance (PV) system. In particular, the National TB Policy is fully compliant with WHO recommendations, and clinical and laboratory capacities are also developing in line with the evidence-based data. Procurement, case management, national TB register, R&R, monitoring and evaluation (M&E) have been completely updated. National financial resources for such innovations are added with donor support, which GF, WHO and MSF provide.

Belarus has an advanced national PV system with the National PV Centre as a regulatory body, providing spontaneous reporting with 5.4 reports per 100 000 cases, experience with countrywide cohort event monitoring for TB/HIV, M/XDR-TB patients, and clinical staff who are trained in aDSM.

The MDR-TB Consilium is the key point for the implementation of the new regimens. In Belarus the Consilium is authorized to administer the new treatment even if it is not yet part of the existing national guidelines. Designing treatment regimens is the most important task of the Consilium. The following issues are also being discussed at the Consilium: adherence problems, management of comorbidities, safety and drug adverse events management, social support and surgery use.

The National aDSM system includes severe adverse events (SAEs) and adverse events of interest (AEI) monitoring, including peripheral neuropathy, myelosuppression (anaemia, thrombocytopenia, neutropenia), QTcF prolongation, optic nerve disorders, hepatitis,

hypothyroidism, hypokalaemia, acute kidney injury and ototoxicity. Obviously, given the exclusion of injectable drugs with shorter DR-TB treatment regimens, there is no longer a need to monitor hypothyroidism and ototoxicity. The overall algorithm of aDSM can vary depending on the particular regimen used.

The patient-centred models of care and treatment adherence improvements are expanding with GF and state support. The national budget has supported food incentives since 2015, and additional payments to DOT nurses is also provided. The transportation costs are still being covered from the GF budgets as well as the outpatient implanted central venous access port system. MSF is supporting the concomitant treatment of alcohol abuse. Video-observed treatment for TB patients demonstrates high levels of acceptability to patients, good treatment adherence and outcomes with treatment success rates of 86% in a cohort of 1 318, as of May 2020.

The patient-centred approach is of great demand in Belarus. Among 123 TB patients on the new DR-TB regimens, 74.6% have XDR-TB, 88.6% have previously been treated with second-line drugs; 65% are alcohol abusers, 33% have the history of imprisonment, 67% are unemployed, and 40% are on forced hospitalization. With MSF support, 40 patients already completed simultaneous TB and hepatitis C treatment with full success including zero hepatitis C viral loads. MSF is supporting the concomitant treatment of alcohol abuse. Out of 97 enrolled patients, about 54 are on the outpatient phase.

The Belarus NTP transition plan to the new MDR/XDR-TB treatment includes the following steps:

- analysis of the epidemiological situation and forecasting of rifampicin-resistant TB patients numbers in 2020–2021 (with a monthly patient enrolment plan);
- data collection for second-line drugs currently used and drugs in stock;
- determine the priority of the treatment regimens in accordance with the new WHO guidelines;
- planning for the gradual transition of all DR-TB patients onto new regimens;
- data analysis, assessment and calculation of the TB drugs need for 2020–2021;
- plan for government TB drugs procurement for 2020–2021, in consideration of the new regimens.

COVID-19 has affected the supply chain of LZD, MFX and Cs; therefore, some risk of treatment interruption has arisen.

BDQ was registered in the country in December 2018; this allows for drug procurement not only with GF support, but also from the national budget. The NTP has an experience of Global Drug Facility (GDF)-based procurement for the cost of the national budget, and in 2019 CFZ was procured through the GDF for 450 patients for the first time ever. Belarus pioneered the new shorter bedaquiline-containing regimen through a national operational research. As an early implementer of the new DR-TB regimens, Belarus received an additional \$ 1.15 million from the GF.

The proportion of patients on the new drugs increased from 8.5 in 2016 to 86% in 2019. The first cohort on bedaquiline-containing regimens demonstrate a 92% success rate; later on, this rate dropped to 76%. Among 107 patients, loss of follow-up, alcohol abuse and labour migration were the main reasons for treatment interruption.

The first patient was enrolled into the shorter all-oral regimen in September 2019. In December 2019 OR was stopped in order to streamline the regimen used and the inclusion criteria with those within the SHORRT initiative. A total of 272 patient were included, and 46 patients did not meet the inclusion criteria (in Belarus this included resistance to injectables). Currently, treatment success has been identified in 120 patients, and 91 are still on treatment.

Within the TB-REACH project, Belarus is implementing a pretomanid-containing 24-week regimen.

### **Summary of questions, comments and clarifications**

- In Belarus, 24.4% of patients experienced SAE related to LZD. The PV system has provided cohort analysis since 2014, and the drug has been in use in the country since 2012. The NTP has never used more than 600 mg, and quite often physicians have to decrease the dose to 300 mg or even cancel the treatment. Neurologists provide continuous support to TB physicians in the large clinics. Now all TB physicians are trained to detect neurotoxicity early. NTP procures tuning forks and other tools for this. Pyridoxine treatment is also widely used at an average daily dose of 100 mg per day.
- TB patients with alcohol abuse sometimes need treatment in an intensive care unit to interrupt a bout of heavy drinking. After that, NTP and/or MSF provide psychological support aimed at convincing the patient to undergo alcoholism treatment simultaneously with TB treatment. MSF provides training for such psychologists, equipped with so-call “free of alcohol rooms”, where patients can spend their leisure time, and where psychologists can provide consultations. Because of MSF support, these patients receive additional incentives and have access to naloxone, which is still not registered in Belarus. If needed, MSF is also providing clothes, support with passport renewals and employment. The project has been implemented for the last 2 years, and out of about 50 patients who were already on outpatient treatment, only two had interrupted treatment, but are back already. Scaling-up of this project is complicated because of the state requirement of mandatory registration of these patients into a drug abuse clinic, which patients try to avoid due to severe stigma. NTP is currently initiating an order related to postponing of such registration until the patient is in the harm reduction programme. The Belarus experience suggests that alcohol abuse is not a barrier for video-DOT, as the majority of such patients are compliant with video-DOT with NTP-provided smartphones.
- COVID-19 significantly affected the drug supply chain. GDF is ready to provide support to all NTPs in terms of the request adjustments to avoid overstocks and stock-outs.



## **5. Modified shorter DR-TB treatment regimens/ Dr Askar Yedilbayev, TB Unit Lead, Joint TB, HIV and viral hepatitis Programme, Division of Country Health Programmes, WHO Regional Office for Europe**

Out of the 30 countries, globally, with a high burden of TB, where MDR-TB makes up 87% of new MDR/RR-TB cases, nine countries are in the WHO European Region: Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Republic of Moldova, the Russian Federation, Tajikistan, Ukraine and Uzbekistan. No significant changes have occurred in the statistics for the WHO European Region in the last few years. As of 2018, the number of MDR/RR-TB cases is 77 000, the number of TB/HIV cases is 30 000, and 23 000 people died of TB.

Along with the reduction of total incidence and mortality rates, an increase in MDR-TB incidence rate has occurred. In the WHO European Region, MDR-TB incidence is six times higher than the worldwide incidence rate. In addition, the replacement of drug-susceptible with drug-resistant tuberculosis is being observed. The Russian Federation, Belarus, Kyrgyzstan and Kazakhstan demonstrate the highest MDR-TB proportions among new and re-treatment cases. In other countries the proportion of XDR-TB among MDR-TB cases varies from 10% to 20%. The main MDR-TB burden (85% of all MDR-TB cases) is found in four WHO European Region countries: Kazakhstan, the Russian Federation, Ukraine and Uzbekistan.

The slow increase of the treatment success in MDR-TB patients has not yet met the targets: in the 2016 cohort only a 3% increase was registered, reaching a 57% success rate for MDR-TB and 39% for XDR-TB. Access to the new regimen should improve the treatment success rate significantly.

In particular, the shorter regimen recommended (4–6 Km-Mfx-Cfz-Eto-Z-E-Hh / 5Mfx-Cfz-Z-E; later kanamycin was replaced by amikacin) is the modified STREAM regimen. The STREAM Stage 1 trial showed that in patients eligible for shorter MDR-TB regimens, the likelihood of treatment success was close to 80% in both arms. Observational studies of shorter MDR-TB regimens also showed an overall comparable likelihood of treatment success as with longer regimens; nevertheless, a higher risk of failure or relapse was registered with the shorter regimen when compared with the longer ones. In addition, there is no data on bedaquiline-containing 9-month regimens

The significant update to the WHO DR-TB Guidelines was presented at the Guideline Development Group meeting (November 2019), including:

- Additional programmatic data on the use of all-oral shorter regimens for MDR-TB/RR-TB from cohorts in South Africa.
- Results from the Nix-TB study on the use of BDQ, pretomanid and LZD in combination (BPAL) for patients with XDR-TB by TB Alliance.
- Additional programmatic data on the use of BDQ (including for use more than 6 months in duration) to treat MDR-TB/RR-TB from cohorts from high-incidence TB countries conducted within the End TB Observational study (17 countries).
- New programmatic data on the concurrent use of BDQ and DLM to treat MDR-TB/RR-TB from the End TB Observational study.

This meeting resulted in a WHO Rapid Communication, issued in December 2019. The document is mainly based on the data from the South African TB programme (starting from 2017 with more than 13 000 cases included). The comparison showed that replacing the injectable with BDQ resulted in significantly better treatment success and a considerable reduction in loss-to-follow-up in MDR-TB/RR-TB patients without previous exposure to second-line drugs and with confirmed fluoroquinolone-susceptible disease. The outcomes were similar irrespective of HIV status. Such an approach is only feasible if quick DST is accessible.

WHO stated that regimens that deviate significantly from those recommended may be explored under operational research conditions, making sure that the patient's best interests are served by collecting data on the use of future policy updates.

The priority for shorter and all-oral therapy for MDR-TB in the WHO European Region is due to:

- high level of drug resistance to medicines in standard second-line treatments;
- available infrastructure, including patient-centred models of care;
- experience and knowledge in treating MDR-TB for 20 years;
- high need for programmatic cost-efficiency;
- increased access and coverage for therapy with quality-assured medicines;
- desperate need to improve treatment success and quality of care;
- need for new evidence.

The intended research is a longitudinal observational single-arm study of 12 months duration, which does not presume modification of the routine programme performance. The primary outcome of interest is the proportion of patients who successfully complete treatment and suffer no recurrence. In addition, the study is focusing on incidence, timing and severity of SAEs and adverse events of interest (AEI); time to, and factors associated with, sputum culture conversion and favourable treatment outcomes. Frequency of amplification of resistance and relapse rates are also to be analysed.

Initially, 11 countries will take part in this intercountry OR: Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Tajikistan, Turkmenistan, Ukraine and Uzbekistan. Nine of these countries are high burden ones.

The overall OR objective is to determine the effectiveness, safety, feasibility, costs and impacts on the quality of life of all-oral shorter MDR/RR-TB treatment regimens under programmatic conditions.

The study will enrol all patients at a particular study site who have bacteriologically confirmed TB with rifampicin resistance and susceptibility to fluoroquinolone, and also children without culture confirmation from household contacts with confirmed rifampicin-resistant cases. The exclusion criteria are:

- previously received the second-line drugs for more than 1 month;
- extrapulmonary TB (i.e. no pulmonary disease), with meningitis, osteomyelitis or disseminated disease;

- resistance to drugs within the modified shorter treatment regimen;
- inability to take drugs in within the modified shorter treatment regimen (due to allergy or contraindicated drug–drug interactions);
- severe renal disease (creatinine clearance <30 ml/min);
- QTcF >500 ms;
- ALT or AST >3 times upper limit of normal;
- seriously sick patients (Karnofsky index <40).

The drugs choice is based on the priority for oral intake, with the expected balance of risks and benefits, resistance prevalence in the Region, DST results and accuracy, previous history of TB treatment, tolerability and drug–drug interactions.

The meta-analysis published in 2018 laid the foundation for this choice – *Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis, Lancet, 2018*. Of 12 030 patients from 25 countries in 50 studies, 7 346 (61%) had treatment success, 1 017 (8%) had failure or relapse, and 1 729 (14%) died. Compared with failure or relapse, treatment success was positively associated with the use of linezolid (adjusted risk difference 0.15; 95% CI 0.11–0.18), levofloxacin (0.15; 0.13–0.18), carbapenems (0.14; 0.06–0.21), moxifloxacin (0.11; 0.08–0.14), bedaquiline (0.10; 0.05–0.14), and clofazimine (0.06; 0.01–0.10). There was a significant association between reduced mortality and use of linezolid (–0.20; –0.23 to –0.16), levofloxacin (–0.06; –0.09 to –0.04), moxifloxacin (–0.07; –0.10 to –0.04), or bedaquiline (–0.14; –0.19 to –0.10). Compared with regimens without any injectable drug, amikacin provided modest benefits, but kanamycin and capreomycin were associated with worse outcomes. The remaining drugs were associated with slight or no improvements in outcomes.

Safety drug profiles were taken from the WHO Consolidated Guidelines, 2019. Frequency of SAE varied from 2.4% for bedaquiline to 17.2 for linezolid. The latter drug was nevertheless included into recommendations as it is highly associated with treatment success.

The Task Force selected three regimens for the WHO European Region:

- BDQ-LZD-LFX-CFZ-CS (adults);
- BDQ-LZD-LFX-CFZ-DLM (adults);
- DLM-LZD-LFX-CFZ (children).

The duration of all regimens is 39 weeks, with 7-days a week drugs intake. All patients with rifampicin resistance and no resistance for fluoquinolones are included. If no improvement is registered at the fourth month, it is safe to extend the treatment course to 20 months.

The minimal costs for the Regimen 1 is \$ 1, 066.84; delamanid-based Regimen 2 costs are much larger (\$ 3 632.78).

The implementation of all-oral modified shorter treatment regimens is not complicated and is very similar to the standard conditions of good programmatic management of MDR-TB. The monitoring objectives are to ensure effectiveness and safety of new regimens; to improve good clinical care of patients, and to increase the capacity of clinicians. Appropriate AE documentation is a cornerstone of these regimens implementation. It is expected that a total of around 4 500

patients in 11 countries will be enrolled. The approval of the national Institutional Review Board is a prerequisite.

The rapid implementation of the all-oral DR-TB treatment regimen is in great demand, especially in the context of COVID-19, as these regimens allow wide use of remote techniques including video-DOT.

### **Summary of questions, comments and clarifications**

- The consolidated guidelines on DR-TB did not change the rating on DLM, and this drug is still presented in Group C. This is due to lack of evidence on the safety profile (only 29 cases reported). Therefore, DLM use within the OR framework provides the opportunity to obtain these data and increase the data quality on its safety profile.

### **6. Implementation of the modified shorter all-oral regimen – Belarus experience/ Dr Elmira Gurbanova, rGLC/Europe**

Belarus started an OR of the modified shorter DR-TB treatment in 2018. In 2018, WHO announced a new classification of the second-line drugs and a new approach to DR-TB treatment. At that time, the so-called Bangladesh regimen was the core shorter DR-TB treatment regimen recommended by WHO. This regimen was not used much in Belarus, primarily because of the long history of TB drugs use, low confidence in DST and high prevalence of drug resistance. The WHO Rapid Communication (2018) was the first time that a recommendation for the NTP to evaluate any modification of shorter regimen under OR conditions was included. The Global Drug-resistant Initiative (GDI) immediately developed a generic protocol for a shorter DR-TB treatment regimen. As of 2018, the overall TB incidence rate in Belarus demonstrated a 10% annual drop; case detection was effective and treatment success reached the WHO target indicator of 85%. High DR-TB rates and low treatment success was and remains the most serious bottleneck of the national NTP. Although in the last cohort the treatment success reached 67%, which is higher than the regional average, it is not reaching the WHO target indicator of 75%. Such a challenge could be effectively met with OR, as the main purpose of OR is to demonstrate effective programmatic solutions in the country context. Evaluation of the current TB policy, the regulatory base and resources is the first step in OR preparation, and the rGLC consultant can provide valuable support for this. The consultant (not considering COVID-19 restrictions) is able to divide their mission into two stages. During the first, preparatory step, the consultant can request all available documents to clarify the country context (NTP reviews, epidemiological analysis, M&E missions, strategic plans, clinical guidelines and algorithms, PV standards, etc.). This is a good chance to find out the discrepancy between the national policy and WHO current recommendations and to initiate an update. In the case of Belarus, the national guidelines already contained all WHO updates for DR-TB treatment regimens and diagnostic approaches. The country visit is a chance to confirm that routine practices meet the requirements of the national policy or to identify inappropriate practices. Primarily, such conclusions could be based on the data, which have not yet been reported, and to case detection and management. Belarus represents a unique case in the WHO European Region, with over 90% cultural confirmation and 100% coverage of confirmed cases with first and second-line DST; therefore, no discrepancies were detected. Field visits to different sites and health care levels help to see the bigger picture of the real-life services. In Belarus the quality of services and data management was high at all

levels. PV also is very effective, including the cohort monitoring of AE for particular drugs. The NTP, with rGLC support and using the meta-analysis results, mentioned above, developed a modification of the shorter regimen, acceptable to the country context. This combination used the drugs from Group A and Group B, as the later guidelines recommend. The consultant's role was important in expanding the DST panel with bedaquiline, clofazimine and delamanid tests. The drug sources estimate of the number of patients enrolled and budgets are the most important parts of the technical assistance mission. Appropriate documentation of the mission results is critical as it the main source of evidence which allows GF and other donors to provide targeted support. Belarus NTP is a case in point, in which more than \$ 1 million was additionally allocated for OR, including direct costs, drugs and laboratory needs. This is in line with GF policy, which suggests using about 5–10% of M&E costs for OR. Consultants can also provide assistance on the formulation of research questions, development of research protocols, ethical considerations, staff training, etc.

The main purpose of OR is for changes of policy or practice, or for scaling-up interventions. Globally, this purpose is not always achieved. For instance, of 42 OR recently held in India, only seven yielded specific managerial solutions. Therefore, the results of the SHORRT initiative in Belarus and the WHO European Region in general should be taken into consideration during the next revision of the WHO DR-TB Guidelines. Ultimately, Belarus was able to start OR within the SHORRT programme and smoothly complete the preparation stage thanks to extensive experience both in shorter DR-TB regimen and OR.

The main prerequisites for a successful rGLC consultancy during the OR include awareness of new TB-related evidence-based data, readiness to meet the NTP's needs and to adjust to wills and ambitions with the existing capacity, technical expertise in the research protocol development and result analysis. SORT IT is an important resource of capacity-building in this direction.

#### **7. Piloting the video-supported treatment. An operational research in Belarus/ Dr Alena Skrahina, rGLC/Europe Head, Director of WHO Collaborating Centre of New MDR and XDR-TB Treatment Regimens Implementation, Minsk, Belarus**

Patient-oriented model of care is one of the key requirements for effective DR-TB treatment outlined in WHO Consolidated Guidelines on TB treatment, 2020. Video-DOT is an effective tool to increase quality, acceptability and feasibility of outpatient treatment. The video-DOT project started in the city of Minsk in October 2015 with GF support. A total of 10 patients were carefully selected considering the level of treatment adherence and reliability; they were provided with smartphones and the specially designed software. The enrolled patients mentioned saving 1–3 hours daily, transportation costs, and were satisfied with earlier treatment course completion because of taking pills on weekends.

The next video-DOT project started in October 2016 with annual enrollment of 150 patients and coverage of all country regions. Belarus Red Cross Society implemented the project with GF support and provided each patient with a smartphone (\$ 60) and Internet payment (\$ 9). After the completion of the treatment the patient keep the smartphone as an additional incentive.

As of 1 June 2020, 1 318 patients are on treatment, and 54% of them have DR-TB. All patients are on video-DOT. The most of patient are enrolled in Minsk and Gomel oblasts. To date 931 patients

are cured and completed the course, and 355 are still on treatment. A total of 98.6% patients confirmed high quality connection, no phones were lost, and six devices returned for the guarantee repair. In 2016 cohort treatment success was 86% on video-DOT versus 65% among the total cohort.

TB register contains the special module on video-DOT. A patient is obliged to forward the video file to the provider till 5 p.m. Patients are not able to change the date of video recording. If it is not done the provider is reaching the patient and clarifying the reason. Not sending the video for three times is a reason to take a smartphone away. The monitoring teams are rechecking these footages, especially in case of the treatment failure.

In general, video-DOT demonstrated high acceptability, high effectiveness and is a valuable solution especially in COVID-19 context.

### **Summary of questions, comments and clarifications**

- In Ukraine, video-DOT is in place in all oblasts of Ukraine, whereas coverage varies from 10% to 60%. NTP organized it within the routine services with no additional costs. Reluctance of providers is the main barrier. No special software was procured, and different messengers are used. All records are kept till the treatment completion. About 10% of them are randomly rechecked, and all records are being rechecked in the cases of treatment failure.
- In Moldova the first SMS-based remote monitoring was implemented in 2012–2013. About 100 patients were enrolled, and 99% completed treatment course. A specific apps is under development. NTP included video-DOT into the request to GF.
- In Georgia, video-DOT is also implemented, including 11 patients on rifapentine-containing preventive treatment regimen.
- In Uzbekistan, video-DOT is implemented in Navoi oblast with Telegram messenger. The patients are sending the photo to the providers.
- WHO Consolidated Guidelines on TB treatment suggests video-DOT as an effective alternative to conventional DOT. WHO Regional Office for Europe interviewed the regional NTPs about the software used for video-DOT. To date Belarus, Moldova and Georgia use the specially designed software, and in the other countries the commonly available messengers are used. WHO European Office for Europe has developed the manual on such techniques and will support the NTPs in choosing the most suitable technique for each national context. Currently, special software allows not only direct treatment observation, but also adverse events monitoring, training, etc. Therefore, *video-supported treatment* is a more suitable term to use than *video-observed treatment*.
- In Arkhangelsk, Russian Federation, there are three families in which some members are on video-DOT TB treatment and the rest are taking the rifampicin-containing preventive course under video-DOT conditions.

## **8. TB and pregnancy/ Dr Alena Skrahina, rGLC/Europe Head, Director of WHO Collaborating Centre of New MDR and XDR-TB Treatment Regimens Implementation, Minsk, Belarus**

TB cases identified during pregnancy are not routinely registered and reported to WHO. The data available are mainly estimates. Some case-control studies suggest that there is up to 11% risk of TB in HIV-positive pregnant women. Evidence suggests there is improvement of some disease courses (e.g. rheumatic arthritis) and worsening of others. TB risk is doubled in the period 6 months postpartum. In pregnant women, TB leads to twice as high a risk of pre-eclampsia, eclampsia and haemorrhage, a 12-times higher probability of hospitalization, and a 10-fold higher miscarriage risk. Neonates from mothers with TB are at a slightly higher risk of early perinatal death, low body weight and prematurity; vertical TB transmission is extremely rare, whereas vertical HIV transmission occurs twice as often.

In 2009, WHO recommended interviewing women starting TB treatment about current or planned pregnancies. Since then, the *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis* (2014) has suggested pregnancy testing screening for all DR-TB female patients.

The WHO guide *Systematic screening for active tuberculosis* (2013) recommends systematic TB screening if TB prevalence in the setting is more than 100 per 100 000. Currently, WHO does not recommend testing for LTBI in pregnant women.

It is well known that rifampicin accelerates the metabolism of oral contraceptives. Therefore, this contraception should not be recommended for women on rifampicin-containing regimens. High estrogen doses or non-hormone-based birth control could be a solution. WHO strongly suggests fertility control for all non-pregnant sexually active women on DR-TB treatment because of possible negative consequences both for the mother and for the infant. Pregnancy is not a reason for avoiding rifampicin and isoniazid-based preventive treatment, including those in HIV-positive pregnant women.

Given the possible negative consequences for the fetus in the case of DR-TB treatment, consensus is still not achieved about the term of pregnancy at which is safe to start treatment. New data about bedaquiline acceptability potentially increases the regimen safety. Overall, longer regimens using drugs with better safety profiles could be used. Because of the apparent low quality of evidence, OR results on DR-TB treatment outcomes with all-oral regimens would be valuable. As some second-line drugs may be associated with high risks for the fetus, GDI suggests avoiding enrolling pregnant women during the first trimester in the generic protocol for the SHORRT TB programme because of possible teratogenicity.

During 2008–2019, 35 women in the peripartal period underwent TB treatment in Belarus including 17 new and 18 re-treatment cases. The majority of them (32 patients) had DR-TB; all patients had pulmonary TB; two patients were HIV-positive and six had hepatitis C; some other had concomitant conditions including epilepsy, alcoholism and drugs misuse. In 25 cases patients conceived after the start of TB treatment; in one case TB was diagnosed during pregnancy, and in the other cases, women were diagnosed with TB after delivery. Treatment success was registered in 26 cases, treatment failure occurred in four cases, and two patients were lost to follow-up. A total of 18 pregnancies ended in childbirth on the due date, including two caesarean

sections; two premature births occurred. One miscarriage and 12 medical abortions were registered. Of 22 neonates, 15 had no health problems, six had low body weight, and one case of stillbirth was documented.

Overall, the following questions still need to be addressed:

- best practices in TB and mother and child health integrative care;
- R&R of TB, DR-TB and LTBI cases in pregnancy;
- TB prevention during pregnancy;
- best practice of TB and LTBI screening and diagnosis in pregnant women;
- best practices of childbirth control in TB female patients of fertile age;
- DR-TB contact tracing, follow-up and preventive treatment in pregnant women;
- the safest DR-TB treatment regimen in pregnant women;
- inclusion of pregnant DR-TB patients into clinical trials and OR.

#### **Summary of questions, comments and clarifications**

- The high proportion of medical abortions in eastern European countries could be due to prejudice towards TB in pregnancy, so both TB specialists and gynaecologists exercise some pressure by suggesting abortion. This was the case in Belarus and Ukraine. Another reason, especially before 2018 when the all-oral regimens were introduced, could be the wide use of injectables, which are associated with high teratogenicity.
- The NTP is responsible for the establishment of the effective integration between TB and mother and child care. It is realistic to allocate a special section in the TB strategic plan in each country for this.
- The family physician can be a key point both for TB screening and for pregnancy follow-up. These physicians can make timely referrals for pregnant women to TB specialists and gynaecologists. As they also provide observation after delivery, they are able to detect postpartum TB in women and follow-up neonates.
- No TB relapses occurred after the treatment completion among women treated for TB in the peripartum period.

#### **9. New drugs in DR-TB treatment in children. Case studies/ Dr Alena Skrahina, rGLC/Europe Head, Director of WHO Collaborating Centre of New MDR and XDR-TB Treatment Regimens Implementation, Minsk, Belarus**

At least 1 million children become ill with TB and 233 000 die each year. Children represent about 10% of all TB cases. The 2018 United Nations General Assembly High-Level Meeting on Tuberculosis and the current revision of the Roadmap for Childhood Tuberculosis together presented an important moment to consolidate and advance advocacy, commitment, resource mobilization and joint efforts by all stakeholders to provide health care and address the burden of TB among children. According to estimates, in 2018–2023 up to 40 million patients will undergo TB treatment including 3.5 million children, and there will be 1.5 million DR-TB patients, which includes 115 000 children. About 30 million people will receive preventive treatment including 4 million children.



Data originated from Belarus, were included into the clinical review *New and repurposed drugs for paediatric multidrug-resistant tuberculosis* published in the *American Journal of Respiratory and Critical Care Medicine* (2017). Although at the time of publication the cohort from Belarus consisted of only 15 patients, it was one of the largest cohorts among the study populations presented from different sites. The paediatric TB incidence rate in Belarus is as low as 1.2 cases per 100 000 (0.5 per 100 000 in the 0–14 years age group, and 5.7 per 100 000 in the 15–17 years age group). In 2018 and 2019, 21 and 23 paediatric patients, respectively, were detected. A total of 17.4% paediatric patients had DR-TB. As the MDR Consilium in Belarus allows the design of treatment regimens which are not yet included into the national guidelines, the first paediatric patient was put onto a bedaquiline-containing regimen in September 2015.

A total of 41 children and adolescent were enrolled into new treatment regimens in 2015–2019 with a median age of 16 years; 22 patients received BDQ, LZD, CFZ and 19 patients were on DLM, LZD, CFZ. To date, 38 patients successfully completed the treatment course, and three patients are still on treatment (receiving a BDQ-based regimen). Full DST are available for 34 patients, four patients are rifampicin-resistant on Xpert results, and in three cases the diagnosis was established based on clinical data and family contact with DR-TB patients. Ultimately, 24 patients were treated as XDR cases, 12 as pre-XDR and five as MDR-TB.

### **Case study**

*A 17-year-old HIV-positive female patient (vertical HIV transmission, on ART – ABC+3TB+EVF, low treatment adherence) with hepatitis C presented after chest X-ray screening in October 2018. On admission: CD4 340 cell/m<sup>3</sup>, viral load 34 000 copies/ml. Xpert test (ultra) was positive, rifampicin resistance detected and cultural test was positive. LPA detected resistance to rifampicin and isoniazid, and no second-line resistance was detected. Given the low treatment adherence the patient was put on the short-modified regimen with LFX, BDQ, CFZ, LZD, CS with pyridoxine 50 mg. After 2 weeks, the ART treatment was modified to DTG+TDF+FTC and co-trimoxazole was added. Daclatasvir and Sofosbuvir were given for hepatitis C. Drug–drug interaction databases Medscape and [hiv.druginteraction.org](http://hiv.druginteraction.org) allow such combinations; DTG intake should be given 2 hours before or 6 hours after pyridoxine, also increasing doses of co-trimoxazole should be avoided because of potential interaction with EVF. According to Medscape drug–drug interaction database, sofosbuvir+tenofovir, levofloxacin+bedaquiline, and emtricitabine+tenofovir pairs are can mutually enforce the probability of AE, which requires close monitoring.*

*After 9 months of treatment – negative culture, resolution of the pulmonary lesions on computer tomography (CT), Hepatitis C – <250 copies/mL, CD4 – 420 cell/mL, HIV viral load – <500 copies/mL.*

### **Summary of questions, comments and clarifications**

- The DR-TB notification rate among children, which is much lower than in adults, is due to lower cultural confirmation.

## **10. LTBI prevalence worldwide, diagnosis and treatment according to WHO recommendations/Dr Aleksander Skrahin, Intensive Care Unit Physician, National Institute of TB and Respiratory Diseases, Minsk, Belarus**

Treating LTBI is potentially the most significant contribution to TB elimination, which is the goal of the End TB strategy. The introduction of the new tools for active TB and LTBI treatment will enable the acceleration of TB decline from the currently reported 1.5% to 10% per year; this will allow the End TB targets to be achieved.

The most recent WHO LTBI guidelines (2018) outline the consolidated cascade of care, including risk group identification, ruling out active TB, testing and treatment options for LTBI. The guidelines are currently being updated, and the implementation guide is in preparation.

The challenges and bottlenecks of LTBI treatment include: the need to rule out active TB, concerns related to drug resistance, access to TB drugs, no standard regimens for DR-TB contacts, shortage of tests for LTBI, low treatment adherence and difficulties in registration.

LTBI treatment results is one of the top 10 End TB Strategy indicators; namely, the number of people enrolled on LTBI treatment divided by the number eligible for treatment, for three priority groups: people newly enrolled in HIV care; children aged <5 years who are household contacts of people with bacteriologically confirmed pulmonary TB; people aged ≥5 years who are household contacts of people with bacteriologically confirmed pulmonary TB. At the first United Nations (UN) High-Level Meeting on TB, held on 26 September 2018, Member States made a range of commitments to accelerate progress towards ending the TB epidemic. This included setting a new global target of providing TB preventive treatment to at least 30 million people in the 5-year period 2018–2022: 6 million people living with HIV (PLHIV), 4 million children aged under 5 years who are household contacts of people affected by TB, and 20 million other household contacts of TB cases. Despite this evidence of progress, substantial challenges with implementation and reporting remain.

Implementation of the interferon gamma release assay (IGRA) provide more specificity and sensitivity in comparison with the tuberculin skin test (TST), especially in populations who receive BCG vaccinations at birth, as IGRA is not affected by previous vaccinations.

According to the WHO guidelines (2018) the key LTBI risk groups include TB household contacts and PLHIV. Other at-risk populations for systematic testing and treatment include:

- patients initiating anti-TNF (tumour necrosis factor) treatment, patients receiving dialysis, patients preparing for an organ or haematological transplant and patients with silicosis (strong; systematic testing and treatment);
- prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people with problem drug use (conditional; low prevalence setting);
- people with diabetes, people with harmful alcohol use, tobacco smokers and underweight people: not recommended for systematic testing and treatment.

To rule out active TB, chest X-rays may be used as screening, but unavailability of chest X-rays should not be a barrier to further treatment. Adults and adolescents living with HIV with no

current cough, fever, weight loss or night sweats and infants and children living with HIV, who have poor weight gain, fever or current cough or who have a history of TB contact should be evaluated for TB.

The absence of clinical signs and chest X-ray abnormalities may be used to rule out TB in other HIV-negative at-risk groups before starting LTBI treatment.

Either TST or IGRA (QuantiFERON®-TB Gold and T-SPOT®.TB) can be used to test for LTBI. PLHIV with a positive LTBI test benefit more from preventive treatment than those with a negative LTBI test. LTBI testing by TST or IGRA is not a requirement for initiating preventive treatment in people living with HIV or child household contacts aged <5 years.

The following options are recommended for the treatment of LTBI:

1. 6 or 9 months of daily isoniazid (36H in PLHIV 10 years and older in high TB transmission settings);
2. 3 months of weekly rifapentine plus isoniazid (>2 years);
3. 3–4 months of daily isoniazid plus rifampicin;
4. 3–4 months of daily rifampicin.

For children, 3 months of daily isoniazid plus rifampicin is the preferred regimen.

Rifapentine-containing LTBI treatment is successfully being implemented worldwide. Paediatric rifapentine formulation are not available yet, which hampers implementation of rifapentine-based treatment in children. If paediatric fix-dose combinations (FDC) are not available, 6 months of daily isoniazid is an option.

Key considerations for drug–drug interactions during LTBI treatment for patients on ART are:

- EVF in daily doses of 400 mg and DTG are well-tolerated;
- DTG dose needs to increase to 50 mg twice a day if used together with rifampicin;
- DTG together with rifabutin is well-tolerated;
- Data on DTG simultaneous use with rifapentine are still controversial: one trial (Brooks et al., 2018) was terminated due to severe toxicity, another one demonstrated good tolerability (Kelly et al., 2018). Therefore, no official recommendations were issued.

WHO stipulates no risk of isoniazid and rifampicin resistance due to standard LTBI treatment, although ruling out active TB is a requirement, as larger bacterial population resistance amplification is possible in underdiagnosed active TB cases. Low toxicity is also confirmed.

The 1-month rifapentine plus isoniazid treatment in the BRIEF clinical trial demonstrated non-inferiority to a 3-months course, and, therefore, can be recommended shortly.

DR-TB preventive treatment approaches are still unjustified, as the clinical trials on DLM and LFX-containing regimens are still in progress.

As the positive predictive value of both the TST and IGRA in terms of active TB is low, a new test able to identify the risk of LTBI transformation into active TB is urgently required.

## Summary of questions, comments and clarifications

- Dialysis patients belong to the TB risk groups and, therefore, need LTBI testing and preventive treatment. This needs close integration with the dialysis services. In Belarus, the joint orders comprising both services exist. The nearest plans include provision for patients on immunosuppressive treatment and patients on dialysis with rifapentine plus isoniazid treatment under video-DOT conditions.
- Under high TB and HIV risk, 36-months preventive treatment is an option. In Belarus, preventive treatment is repeated in 1.5 year after 6-months course irrespective CD4 level.
- Effectiveness of preventive treatment needs better evidence as, worldwide, only about 17% patients complete the LTBI treatment course.
- During country missions, the consultants should follow WHO recommendations on LTBI priority groups. TST or IGRA is not a requirement for LTBI treatment, especially in PLHIV and household contacts. As well as children, adolescents and adults should also be considered for LTBI treatment.
- Ideally, specialists dealing with immunosuppressive therapy, dialysis or transplantation are able to identify and treat LTBI on their own or with the support of TB specialists. In Belarus such integration is in place.
- Mobile apps related to LTBI management are highly demanded.

### **11. New WHO recommendations on TB/HIV management/Dr Aleksander Skrahin, Intensive Care Unit Physician, National Institute of TB and Respiratory Diseases.**

Globally, the annual number of new HIV infection cases continued to decline gradually in 2018. Since a peak of 2.9 million (CI 2.3 million–3.8 million) new infections (all ages) in 1997, year-on-year declines have grown smaller. The annual number of new infections (all ages) since 2010 has declined from 2.1 million (CI 1.6 million–2.7 million) to 1.7 million (CI 1.6 million–2.3 million) in 2018, a 16% reduction which leaves the world far off the 2020 target of fewer than 500 000 new infections. Globally, 477 461 cases of TB among PLHIV were notified in 2018; equivalent to 11% of TB patients with an HIV test result. The number notified was only 56% of the estimated number of incident cases among PLHIV. Overall, the percentage of TB patients testing HIV-positive has fallen globally since 2008. This decline is evident in all WHO regions except the WHO European Region.

As is the case with AIDS-related mortality, the reduction in new HIV infections between 2010 and 2018 was strongest in eastern and southern Africa (28% decline). However, the annual number of new HIV infections has risen in Europe, especially, eastern Europe and central Asia (29% increase, 111 550 new cases as of 2018).

The dramatic decrease in the numbers of new infections happened as treatment scale-up was advanced in most of the regions. However, access to treatments still remains a challenge in some regions, where ART coverage remains low. Half of people with HIV in the WHO European Region are diagnosed late. The HIV treatment cascade suggests that the eastern European Region will

not meet the 90-90-90 targets by 2020. HIV drug resistance is a newly arising concern, which requires the expansion of genotype testing.

HIV is a main risk factor of DR-TB. According to the data, which Belarus NTP published in 2013, whereas among all new cases DR-TB was registered in 32.7%, in the new TB/HIV cohort this proportion was 51.1%; among 26 TB/HIV re-treatment cases, all patients had DR-TB versus 76% of DR-TB among all re-treatment patients. According to a study published in 2018 in eastern European countries, an adequate initial TB treatment was provided for 8% of patients with MDR-TB compared with 80% of those with pan-susceptible TB. By 12 months, an estimated 57.3% of MDR-TB patients had started adequate treatment. While 67% received ART, HIV-RNA suppression was demonstrated in only 23%. This suggested that ART use and viral suppression was well below the target of 90%, reflecting the challenging patient population and the environment in which health care is provided. Urgent improvement of management of patients with TB/HIV in eastern Europe, in particular for those with MDR-TB, is needed and includes widespread access to rapid TB diagnostics, better access to and use of second-line TB drugs, timely ART initiation with viral load monitoring, and integration of TB/HIV care.

WHO recommendations (2019) suggest the following first-line ART regimens:

1. Dolutegravir (DTG) in combination with a nucleoside reverse transcriptase inhibitor (NRTI) backbone is recommended as the preferred first-line regimen for people living with HIV initiating ART:

- adults and adolescents;
- infants and children with approved DTG dosing.

2. Efavirenz at low dose (EFV 400 mg) in combination with an NRTI backbone is recommended as the alternative first-line regimen for adults and adolescents living with HIV initiating ART.

3. A raltegravir (RAL)-based regimen may be recommended as the alternative first-line regimen for infants and children for whom approved DTG dosing is not available.

4. A RAL-based regimen may be recommended as the preferred first-line regimen for neonates.

The second-line ART regimens are:

1. DTG in combination with an optimized NRTI backbone may be recommended as a preferred second-line regimen for PLHIV for whom non-DTG-based regimens are failing.

- adults and adolescents;
- children with approved DTG dosing.

2. Boosted protease inhibitors in combination with an optimized NRTI backbone is recommended as a preferred second-line regimen for PLHIV for whom DTG-based regimens are failing.

In 2019, WHO guidelines provided further reassurance for DTG as the preferred drug for ART in first and second-line regimens including for pregnant women due to the declining estimate of neural tube defect risk and observed efficacy. This reassurance comes at a time when pretreatment resistance to EFV is increasing in low- and middle-income countries, creating demand for access to alternative drugs. WHO also suggest that, if stable, adults, adolescent and children with body weight >30 kg can be transitioned to TDF + 3TC + DTG.

WHO recommendations of updates on post-exposure prophylaxis are:

- TDF + 3TC (or FTC) is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis.
- DTG is recommended as the preferred third drug for HIV post-exposure prophylaxis for children for whom an approved DTG dosing is available.
- When available, ATV/r, DRV/r, LPV/r and RAL may be considered as alternative third drug options for post-exposure prophylaxis.

### **Summary of questions, comments and clarifications**

- As TDF is associated with kidney adverse reactions, especially on TB treatment, TAF (tenofovir alafenamide) could be safer for patients with compromised creatinine clearance. Such needs should be considered during development of procurement plans. In addition, the new TB treatment regimens are less likely to be associated with kidney lesions as injectables are not included. Therefore, the need for TAF is not so high. Despite FDC with TAF being available, WHO does not recommend it for wide use in place of TDF, mainly because of the low evidence behind TAF safety in pregnant women and TB/HIV patients.
- FDA recently allowed DTG in infants.
- EFV is still present in existing regimens mainly because of potential difficulties in DTG procurement. If DTG is available in the country, DTG-containing regimens are the preferred first-line and second-line combination.
- ddi is not recommended any more as a part of ART because of high toxicity.
- WHO does not recommend ABC use without genotyping. Its use under programmatic conditions could be limited by the need of such testing, which increase the expenditure of national programmes.
- Testing of HIV drug resistance can be implemented as a representative molecular epidemiologic survey. Nevertheless, as these tests are expensive, it is not a priority in eastern European countries, where EFV resistance is considered to be <10%, although the quality of evidence is not very high. Using integrase inhibitors in first-line regimens can prevent further spread of drug resistance. Therefore, genotyping is only a prerequisite of third-line therapy.

### **12. Drug–drug interactions in TB/HIV treatment and design of TB regimens/Dr Aleksander Skrahin, Intensive Care Unit Physician, National Institute of TB and Respiratory Diseases**

Concurrent treatment of TB and HIV is complicated by:

- the adherence challenges of polypharmacy;
- overlapping side-effect profiles of anti-TB and ARV drugs;
- immune reconstitution inflammatory syndrome, and;
- drug–drug interactions.

Not all cases of patients' deterioration on treatment is due to drug–drug interactions. This can also be the result of other concomitant conditions, AEs, other opportunistic infections, etc.

For drug–drug interactions, both pharmacokinetic and pharmacodynamic interactions can play a role.

Pharmacokinetics can be affected by resorption and metabolic interaction. The former is mainly affected with different concurrent drugs, in particular, ferric preparations and pyridoxine. The CYP family and UGT1A are the enzymes that commonly affect the latter mechanism. Some drugs can induce or inhibit activity of the CYP family and UGT1A.

The *Guidelines for the use of antiretroviral agents in adults and adolescents with HIV* (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2019) provides detailed information on biochemical interactions between different ARV drugs. Obtaining similar information on anti-TB drugs is more complicated, but the most important points are the following:

- BDQ and DLM as CYP3A4 substrates should not be given with strong CYP3A inducers or inhibitors;
- LZD, CFZ, MFX LFX metabolism does not involve the CYP family or UGT1A.

The most important pharmacodynamic interactions can increase the AE risk. For instance, ZDT with LZD can increase the risk of myelosuppression. All non-nucleoside reverse transcriptase inhibitors, as well as BDQ, DLM, CFZ, LZD, MFX and LFX can lead to QTcF prolongation; other drugs widely used in HIV-positive patients, such as methadon, ketonazole, fluconazole, etc., and genetic predisposal can further increase the risk.

Medscape drug–drug interactions <https://reference.medscape.com/drug-interactionchecker> is an important resource to clarify the potential interaction in pairs of anti-TB drugs and ARVs.

**13. MDR-TB Consilium role during the transition to the new WHO-recommended DR-TB treatment regimens. Case presentations: Longer and shorter treatment regimens; TB associated with HIV, Hepatitis C and COVID-19/ Dr Alena Skrahina, Dr Dmitryy Vetushko, Dr Varvara Solodovnikova, Dr Elena Nikolenko, Dr Dmitryy Klimuk, WHO Collaborating Centre of New MDR and XDR-TB Treatment Regimens Implementation, Minsk, Belarus**

All training participants received access to the national eTB-register after signing non-disclosure forms.

The following cases were presented and discussed.

1. A female patient with DR-TB and syphilis.
2. A 16-year-old adolescent with DR-TB cases with no cultural confirmation who had a household DR-TB contact with mother.
3. HIV-positive female patient with a DR-TB relapse.
4. HIV-positive male DR-TB patients who contracted COVID-19 in a TB hospital.

**14. Role of laboratory tests in the monitoring of AEs of DR-TB treatment, including shorter treatment regimens/ Dr Gulmira Kalmambetova, Head of National Reference Laboratory, Kyrgyzstan**

As suggested in the Operational Handbook on Tuberculosis (WHO, 2020), programmatic implementation of MDR-TB regimens requires policy and operational documents that govern

the main components of the possible revisions of the programme. Such documents include the National Strategic Plan for TB, treatment guidelines and algorithms, diagnostic algorithms, the essential medicines list, regulations (e.g. importation of clofazimine and pretomanid), orders and training materials. The TB treatment card may be changed to allow the tabulation of results of periodic testing for treatment responses and adverse reactions (this may have already been done for the purposes of aDSM). Primary care facilities should be in focus, as aDSM in specialized facilities are often more available than at the primary level, where patients receive outpatient treatment. Electrocardiogram, liver function and complete blood counts should be mandatory tests. In Kyrgyzstan, the NTP did not foresee these expenditures at the very beginning and this required an urgent correction later on. The laboratory specialist plays an important role in all national working groups or expert committees. Such practices are not in place in all NTPs. The laboratory NTP specialist role includes initiation of the national regulations, mapping of the regional laboratories including those able to provide tests for aDSM needs, calculation of the need for reagents and laboratory consumables, and participation in the MDR-TB Consilium.

There is a need to improve the quality of patient data using standardized variables, such as data on DST patterns, prescribed treatment, treatment outcomes and adverse drug reactions. Collection of these data during programmatic implementation of MDR-TB regimens is important for future evidence-based recommendations, especially given the lack of randomized control studies on the management of DR-TB. If patient records are already digital, changes may be needed in the electronic recording and reporting system to allow individuals belonging to MDR-TB regimen cohorts of interest (e.g. shorter regimens, bedaquiline-containing regimens and operational research subgroups) to be identifiable, and for certain options to be included in the monitoring framework. It is crucial for programmes to maintain such data diligently and prospectively, so that they can contribute to programme evaluation and to global policy-making (the development of the WHO Consolidated Guidelines benefited hugely from experience of patient treatment within programmes). Moreover, electronic tools can enhance the quantification of consumables; for example, volumes of medicine can be calculated automatically using QuanTB – an application that is available for download free of charge.

As AE prevalence in DR-TB treatment varies from 13–17% to 62–65%, these events are common reasons why patients interrupt treatment. Laboratory aDSM plans have to include include essential tests, such as full blood count, liver function tests (AST, ALT, bilirubin), serum electrolytes, urea, creatinine, thyroid hormones, lipase, amylase, pregnancy tests, etc.

Currently, the role of laboratories in aDSM is underestimated and needs empowerment, especially in view of the implementation of the shorter regimens, which creates new demands for laboratory monitoring of drug safety.

**15. Laboratory requirements for implementation of the shorter DR-TB treatment regimens/Dr Vladimir Antonenka, Programme Lead, International Institute of Microbiology and Laboratory Medicine, WHO Supranational Reference Laboratory, Germany**

Laboratory requirements include not only laboratory infrastructure, personnel, diagnostic algorithms and spectrum of tests provided. Pre-analytical and post-analytical stages are also crucial including specimen collection, storage, transportation and documentation flow.



Currently, both phenotypic and genotypic test play an important role in TB diagnostics. Phenotypic tests are based on critical concentrations able to inhibit bacterial growth, require high laboratory biosafety level and take time for bacterial cultivation. Although genotyping is usually faster and requires fewer biosafety measures, its effective implementation need good evidence of genetic resistance mechanisms, which must be obtained at population level. As yet, there are no genotype techniques for the new drugs for DR-TB treatment. In addition, WHO has identified critical concentrations for all new drugs and revisited the data for the existing ones. These concentrations have been added to the *Technical manual for drug susceptibility testing of medicines used in the treatment of tuberculosis*; this is the basis, from which National Reference Laboratories and regional diagnostic laboratories can develop specific diagnostic algorithms.

Use of liquid and especially solid media cultures for further genetic tests significantly prolongs the time to treatment start, and delays up to 2 months, which usually occurs if solid media isolates are use, is unacceptable. Therefore, development of direct genetic tests is a priority. Xpert MTB/RIF is widely used to detect MTB and rifampicin resistance with high sensitivity and specificity. Xpert MTB/RIF Ultra increases overall diagnostic accuracy, and is recommended for initial TB diagnosis.

If rifampicin resistance is detected, according to the European algorithm, isoniazid resistance detection is needed, and this can be done with LPA, which has slightly lower sensitivity (90%), but has good specificity. As high isoniazid doses are widely used for DR-TB treatment, identification of Inh A-based and Kat G-based isoniazid-resistant mechanisms by molecular tests is essential. Among LPA for second-line drugs, the focus will be on fluoroquinolone and bedaquiline resistance. Abbot real time MTB and Abbot real time INH/RIF resistance assays provide similar sensitivities to Xpert MTB/RIF Ultra and specificities close to MTBDRPlus. In March 2020, the GF working group approved the Abbot and BD Max platforms for procurement through GF mechanisms. This also is a step towards WHO approval, which could occur in early 2021. Xpert cartridges for simultaneous testing of isoniazid, rifampicin and fluoquinoline and injectables resistance are also expected in 2021. There are some complications related to the use of upgraded Xpert instruments, which needs the replacement of existing machines. Satellite stations for existing Xpert instruments is an optimal solution. Upgraded instruments are completely compatible with the rest of Xpert diagnostics.

The main strategies for laboratory testing adaptation for new regimens use include: focus on rapid TB diagnosis and DST; access to genotype and/or phenotype DST; and validation of new centralized platforms with a high throughput. Quality of DST, development of DST for the new and repurposed drugs, in particular, BDQ, DLM, CFZ, LZD and availability of critical concentration and clinical critical concentration methods for MFX are among the priority tasks.

Effective specimen transportation and electronic data transfer can significantly improve quality of pre-analytical and post-analytical phases.

**16. Mechanisms of resistance to the new and repurposed TB drugs/Dr Vladzimir Antonenka, Programme Lead, International Institute of Microbiology and Laboratory Medicine, WHO Supranational Reference Laboratory, Germany**

In 2014, the first publication appeared on a simultaneous BDQ and DLM resistance case, which, in fact, is the first pan-resistant case including the new drugs. The study indicates that emergence of drug resistance to bedaquiline is already an ongoing threat and provided in vivo evidence of acquired resistance due to a mutation in an efflux pump-related gene Rv0678, and its association with clofazimine and bedaquiline cross-resistance in the *M. tuberculosis* isolate from a patient with MDR-TB.

As yet, only phenotypic tests are available for resistance testing to the new drugs, unless whole genome sequencing (WGS) is done. The Rv0678 is a long gene; therefore, the potential rapid “hotspot” diagnostic is not expected shortly. The gene responsible for ATP-synthase can also input to clofazimine resistance. Although the first publication on BDQ and CFZ resistance described an inappropriate treatment regimen, some evidence suggests that in treatment-naive populations such resistance also is expressed. The involvement of Rv0678 in other cell functions is the possible explanation.

As DLM is a pro-drug which needs activation inside the cell, drug resistance can be due to mutations in the genes responsible for such activation. The genes catalogue is to be updated.

The genetic mechanisms of LZD resistance are still unclear. As LZD is blocking protein biosynthesis, RNK genes could be responsible for these. Efflux pumps can also be involved.

Drug resistance among treatment-naive populations presents a serious risk of transmission of resistant strains if the drug are administered without DST. Currently, phenotypic test are the most reliable methods of DST for the new drugs; however, the mutations catalogue is constantly being updated.

**17. Interpreting difficult cases of discrepancies in laboratory tests results. Case studies/ Dr Eugene Sahalchyk, the Project Lead, International Institute of Microbiology and Laboratory medicine, WHO Supranational Reference Laboratory, Germany**

Overall the laboratory tests discrepancies are related to:

- Human factors:
  - errors of pre-analytical stage including specimen collection and transportation;
  - laboratory cross-contamination;
  - misinterpretation;
  - result recording and transfer from paper to electronic media.
- Natural limitation of the tests principles, sensitivity and specificity:
  - For genotype tests – mainly related to DNA concentration; sometimes the existing methods do not include all relevant mutations (known and unknown); therefore, a case described as “no resistance” on a genotype test may be associated with phenotypic resistance;
  - In contrast, silent mutations (detected on genotypic tests) do not leading to gene expression and, later, phenotypic resistance;

- Heteroresistance could be due to superinfection and/or segregation of one strain. The detection threshold on LPA is 5%, but WGS is the most accurate;
- Because of higher sensitivity on Xpert Ultra, a new grade has appeared – namely the “traces”, which specifies an indeterminate result which needs further clarification;
- Discordance between no resistance on LPA and phenotypic resistance allows the presumption of new, less common mutation;
- Different resistance grades for isoniazid (Inh A and Kat G-related) and MFX can be detected on LPA, whereas for rifampicin, LFX, Pto/Eto and injectables, just two variants exist: mutation detected or mutation not detected. Overall, the WHO recommendation suggests considering LFX and MFX resistance separately;
- Non-tuberculosis mycobacteria:
  - Smear-positive, specific culture tests results (rapid growth, pigments, colonies feature);
  - PCR and LPA – negative;
  - Xpert – negative (in a case of extremely high concentration, a false positive result can occur; if Xpert Ultra, is used such probability is very low).

The European Laboratory Initiative (ELI) provides different standard operational procedures in the case of any discrepancies between laboratory tests. The key requirements include the involvement of all available tests and use of one or two specimens consequently collected within a narrow time frame.

Internal data validation and quality assurance are reasonable measures to avoid technical errors and time-consuming clarification of each particular discrepancy case.

In conclusion, the participants discussed two case studies and identified the possible reasons for the discordant results.

### **Summary of questions, comments and clarifications**

- WGS is a far more accurate genetic technique than the rapid genetic tests. In addition, it requires a sophisticated and expensive supply chain, prepared premises and data interpretation including the bioinformatics approach. Unclear relationships between genetic mutations and drug resistance hamper interpretation. In Kyrgyzstan, the data are being interpreted in supranational reference laboratories. In terms of data quality, it is reasonable to do WGS in one national reference laboratory. In the near future, WGS will provide the most accurate results, and target sequencing will allow identification of mutations from sputum rather than from culture which will accelerate the testing process. Automatic database searching is also a promising approach.
- Interpretation of the false positive Xpert results is associated with the low-discriminative nature of Xpert. Overall, it only in 1–5% case depending of the setting. In addition, MGIT has difficulty detecting some rifampicin resistance mutations, which leads to so-called low-dose mutations; Xpert effectively detects such mutations which explains its wide use in diagnostics. In spite of the difficulties in data interpretation, Xpert results should be recorded and reported correspondingly.

- ELI developed the online course on laboratory result interpretation for clinicians. Currently, this is available in English; the Russian translation is being finalized. The course will take about 5 hours and certificates will be provided upon completion. In addition, WHO Regional Office for Europe will prepare a specific course with in-person involvement of the experts from the supranational reference laboratories. ELI also developed a specific dashboard, which can accelerate the evaluation of laboratories, especially if the consultant is a clinician rather than laboratory specialist. The tool will be available shortly.
- Genotype tests for the new drugs are not available yet. WGS is the only solution. Preliminary critical concentrations for phenotypic tests are available, and test accuracy is a matter of quality assurance and standard operational procedures. Nevertheless, as more data are accumulated, both critical concentrations and standard operational procedures will be updated.
- Mycobacteriosis prevalence is growing, but the American Thoracic society recommendation is the only regulating document worldwide. Environmental contamination can lead to false positive results; therefore, only repeating the result in smear-negative cases should be considered. In addition, in advanced TB cases, superinfection with non-TB mycobacteria could be the case. Xpert Ultra uses two insertion sequences, and if these are present in *M. avium*, false positive results are possible.

**18. Decreasing the risk of TB transmission. Implementation of infection control programmes/ Dr Grigoriy Volchenkov, Director of the Specialized TB and Respiratory Care Centre, Vladimir, Russian Federation**

Each NTP should consider IC as a key component. Many experts perceive the spread of hyperresistance in eastern Europe as a “perfect storm” of over-hospitalization, delayed diagnosis/ineffective treatment, and cold climate-limited ventilation. These led to a dramatic rising of DR-TB in eastern Europe in comparison with central European and Asian countries. WGS has explained the genetic composition and evolution of MDR- and XDR-TB in the Region. Between 2010 and 2013, the genomes of 138 *M. tuberculosis* isolates from 97 patients were sampled in Minsk, Belarus. MDR and XDR-TB isolates were significantly more likely to belong to the Beijing lineage than to the Euro-American lineage, and known resistance-conferring loci accounted for the majority of phenotypic resistance to first- and second-line drugs in MDR and XDR-TB. Using a phylogenomic approach, the majority of MDR-TB were estimated to be due to the recent transmission of already-resistant *M. tuberculosis* strains rather than repeated *de novo* evolution of resistance within patients, while XDR-TB was acquired through both routes. Longitudinal sampling of *M. tuberculosis* from 34 patients with treatment failure showed that most strains persisted genetically unchanged during treatment, or acquired resistance to fluoroquinolones. HIV-positive patients were significantly more likely to have multiple infections over time than HIV-negative patients, highlighting a specific need for careful infection control in these patients.

COVID-19 draw attention to airborne transmission, which is one of the transmission pathways for COVID-19 and the only pathway for TB. Bio-aerosols are expectorating while the source of

infection is coughing, sneezing or speaking. Larger droplets are rapidly sedimenting whereas those of <10 µm in diameter stay suspended for a longer time, and *M. tuberculosis* remains viable after insiccation (droplet nuclei). The smaller droplet can penetrate deeper into the respiratory tract, and the nuclei of 1–5 µm can immediately reach alveoli and alveolar macrophages and lead to infection.

The airborne transmission challenge requires specific measures, which are complicated enough. Therefore, implementation of the all-oral regimen is a good chance to move away from over-hospitalization practices in eastern Europe and improve the treatment safety.

Administrative control is the first priority of TB infection control (TB IC). The administrative measures presume: triage of people with TB signs and symptoms, or with TB disease, is recommended to reduce *M. tuberculosis* transmission to health workers (including community health workers), persons attending health care facilities or other persons in settings with a high risk of transmission; respiratory separation/isolation of people with presumed or demonstrated infectious TB is recommended to reduce *M. tuberculosis* transmission to health workers or other persons attending health care facilities; prompt initiation of effective TB treatment of people with TB disease; and respiratory hygiene (including cough etiquette) in people with presumed or confirmed TB.

Environmental control is based on two main approaches. These are upper-room germicidal ultraviolet (GUV) systems and ventilation systems (including natural, mixed-mode, mechanical ventilation and recirculated air through high-efficiency particulate air (HEPA) filters).

The third priority of infection control can only be effectively implemented if previous two are in place, and includes particulate respirators of at least FFP2 and FFP3, within the framework of a respiratory protection programme.

The classic Wells-Riley experiments (1952–1956), later supported by WGS in E Nardell experiments (2014), confirmed that rapid treatment starts with consideration for drug-resistance patterns decrease the patient contagiousness within 2 weeks. Loudon's experiments (1968) explained this by the exponential increase of drug concentration after droplet insiccation into the droplet nuclei. This concept laid the foundation for E Nardell's FAST strategy (Find cases actively, separate and treat). Rapid case detection and DST are essential for such an approach. Such tests are accessible for TB, unlike COVID-19 which has no reliable rapid tests and uses time-consuming conventional genetic tests, the results of which can be seriously affected by the pre-analytical stage, equipment and personnel expertise. In Vladimir TB hospital, where effective TB IC measures are in place, no COVID-19 transmission occurred.

### **Summary of questions, comments and clarifications**

- In terms of COVID-19, respirators without valves could be a better choice to provide both inhaling and exhaling air filtration. Screening thermometry on the shift start is an effective measure to decrease the risk of the disease transmission from health care workers to patients.

- “14-days isolation after patients’ admission” is not exercised in Vladimir TB hospital, and only symptom-based isolation is done. In contrast, In Arhangelsk such isolation is widely used and no hospital transmission has been registered yet.
- Each certified type of shielded UV-radiator has its own benefits and limitations, including the premises volume, floor-to-ceiling height and other factors. Effective radiators provide at least 200 watt/cm<sup>3</sup>, and no ozone smell.
- There is no limitations of a respirator use term as long as they are fully functional.

**19. Stop TB Partnership’s Global Drug Facility: Procurement and supply of TB products/ Dr Natavan Alikhanova, GDF Regional Technical Advisor for Eastern Europe and Central Asia, rGLC/Europe member**

The Global Drug Facility (GDF) was established in 2001 as an initiative within the Stop TB Partnership, hosted by United Nations Office for Project Services (UNOPS) and largely funded by USAID. GDF has been providing an online ordering system since 2005 as the one-stop shop for all TB products. All countries are eligible to procure from GDF, in line with national regulations, including the private sector. All drugs for TB including FDC and paediatric formulations are available, except CFZ (dissolving tabs, which are easier for dividing, are available).

FDC of isoniazid and rifapentine (3HP) for 12 doses LTBI treatment became available recently.

More than 500 TB diagnostic products and laboratory supplies are in the GDF Catalogue to equip and maintain all levels of laboratories, including molecular tests, rapid antigen detection tests, culture and DST, in particular, pure drug substances for DST (including bedaquiline and delamanid), consumables for microscopy, general laboratory supplies, including biosafety and waste management. Recently, IGRA-tests have become available.

COVID-19 seriously affected the supply chain primarily due to the decline of production of pure substances, as many manufacturers are located in China and India. Further, the lockdown affected the stockpiles in the GDF rotational warehouse in the Netherlands. Turkmenistan and Tajikistan are the countries most affected by such shortages. Custom procedures have also slowed down. In such circumstances, GDF is striving to minimize the negative impact of COVID-19 by splitting the delivery batches, prioritizing needs and working with the vendors. Under these circumstances, the role of QuanTB, as an electronic quantification and early warning system, increased dramatically. If maintained correctly, this is a powerful tool, which allows countries to make forecasts for at least 1–2 months and manage stock expiries/wastage.

Paediatric formulations are in the focus of GDF, as, currently, the UN target of 115 000 children being enrolled into DR-TB treatment is far from being achieved. GDF has identified 60 countries that need paediatric formulations and all 11 eastern Europe and central Asia countries are among them. To date, 47 countries, including the 11 eastern European ones, have received grants for procurement of paediatric formulations. The Government of Japan and USAID are funding these activities. GDF, through Sentinel Project on TB Care, provides technical consultation on this. The grants are being provided for 1 year. Countries should ensure the availability of funds for the procurement of second-line paediatric medicines in the post-donation period.

While countries are developing the procurement plan, they should consider that GDF procurement takes from 4 to 6 months after money has been wired to the manufacturer's account. The GDF procurement cycle includes the responsibility of the rGLC consultant, as only after receipt of approval on regimens from rGLC, can the GDF Regional Technical Advisors, who verify the quantification of the order, raise the Order Management System. Faults in the regimens design and calculation, order corrections after submission, and custom procedures can significantly affect the delivery terms.

In addition, GDF provides technical assistance for procurement and supply planning preparedness and developing and monitoring of procurement and supply management transition plans. Additional GDF services include virtual stocks for emergency order in small batches; online management system and technical assistance through a system of regional technical advisers.

The GDF package of comprehensive technical assistance and capacity-building includes:

- facilitation of the uptake of new tools: procurement and supply planning preparedness, developing and monitoring of procurement transition plans;
- quantification and supply planning for all TB medicines;
- support in the procurement process: optimized procurement frequency, procurement of quality-assured products using domestic funding, monitoring order placement by countries and review of procurement requests, review and validation of quantification files;
- prevention/minimization of stock-outs in countries: facilitation of regular and accurate country data collection and analysis, apply the early warning system, inform global demand;
- ongoing tailored technical assistance and capacity-building for procurement systems strengthening: GDF is a designated lead partner managing the component of procurement and supply plans of all joint missions and joint reviews;
- support to develop funding requests, concept notes, and GF/domestic procurement and supply plans.

GDF is working on improvement of its tools, mainly to get more flexible mechanisms, implement more stringent criteria of quality and implementing new regimens. Procurement gets more complicated because of new trends in treatment. As vendors are not so interested in small batches, GDF consolidated ordering is a solution to provide small size batches to the countries. Institutionalization of this experience at a country level is vital to prevent the loss of the new achievement. COVID-19 creates new requirements for accurate order quantification.

The good news is that BDQ costs are expected to decrease shortly, mainly due to optimistic procurement forecasts and consolidated procurement.

### **Summary of questions, comments and clarifications**

- WHO has a procurement project of Xpert consumables for the north-western part of Syria. Currently, it is complicated because of US sanctions. UN-organizations are

successfully procuring consumables through GDF; therefore, some algorithms could be developed for WHO as well.

## **20. Procurement needs assessment using the QuanTB platform/ Dr Natavan Alikhanova, GDF Regional Technical Advisor for Eastern Europe and Central Asia, rGLC/Europe member**

QuanTB, an electronic quantification and early warning system, being updated regularly is a powerful tool, which allows countries to develop the different scenarios of transition plans, to forecast the needs for any type of TB medicines, manage stock-out and expiries/wastage, schedule regular and emergency orders, and monitor patients enrollment. Countries are requested to share updated files with GDF on a regular basis. Involvement of MDR consiliums in the regular review and requantification is essential, especially during the transition to the new regimens. At the global level, consolidated QuanTB country information allows GDF to produce accurate forecasts for suppliers to smoothen production planning; to ensure that GDF medicines are provided at lowest possible, sustainable prices; and to maintain and improve software. It is essential that rGLC provides expertise to countries on the projected number of cases to start treatment, the breakdown per medicine/regimen based on country drug-resistance survey (DRS) profiles, coverage, etc. GDF is preparing generic recommendations on the drugs stocks and buffer size in the context of COVID-19.

During the session, the consultants were offered the practical exercises, had an opportunity to see the main processes inside the QuanTB interface and worked with the data exports into Excel files. Each consultant had a chance to make a calculation on their own, including the drugs buffer formulation, which appeared to be of the most importance in terms of COVID-19.

### **Summary of questions, comments and clarifications**

- As the majority of consultants including the new ones, experience difficulties in QuanTB data interpretation, the participants agreed to schedule a specific training session for the consultants on QuanTB use.

## **21. aDSM and safety management. aDSM in concurrent conditions/Ms Svitlana Setkina, National Centre of Pharmacovigilance, Belarus**

Key challenges with implementation and ensuring an effective aDSM system at the programmatic level include:

### **1. Adaptation of the safety monitoring and management system:**

- Difficulties in changing the established routine practices;
- Need to raise additional resources to provide equipment for missing components of clinical, functional and laboratory monitoring;
- Limited capacities to ensure monitoring at the outpatient stage of patient management;
- Adaptation of the safety monitoring and management after the start of new treatment regimens;
- Difficulties in ensuring systematic and continuous monitoring and safety management (limited availability of personnel, interrupted supply of reagents, medicines to manage ADRs).

### **2. Establishment of the adverse events reporting system:**

- Suboptimal support from national PV centres;



- Legislative barriers to reporting serious adverse events;
- Uneven compliance with the requirement to report serious adverse events;
- Quality of submitted data is not adequate to enough for causality assessment and signal detection;
- Limitations in detection of important safety issues (signals) at the country level.

3. Consistent operation of PV mechanism requires the following measures:

- Appropriate individualized safety monitoring;
- Monitoring of personnel availability and consumables stocks;
- Supervision and assessment of ADR/AE management;
- Regular reporting of SAEs and AE of special interest.

National PV systems submit information to the WHO database (VigiBase, aDSM database), which is an effective pathway to generating evidence. According to VigiBase, in the WHO European Region, Armenia is reporting the largest number of AEs (about 15%) and the reports for Kazakhstan, Lavia and Georgia are close to zero. QTcF prolongation is the most frequently reported ADR (exceeds 30%).

Safety concerns from safety monitoring, which need further analysis:

- BDQ, DLM, CFZ, MFX cardiotoxicity (QT prolongation, cardiac rhythm disorders) and potentially ischaemic myocardial changes, myocardial hypertrophy, acute coronary syndromes, acute heart failure, cardiac failure progression and other cardiotoxic effects (in particular, BDQ);
- BDQ hepatotoxicity;
- LZD neurotoxicity (peripheral nervous system disorders, optic nerve disorders), haematotoxicity (anaemia, thrombocytopenia, leukopenia) and ability to provoke lactic acidosis.

Areas for improvement of the safety monitoring and management systems:

- For NTPs: introduction of a tool for monitoring and sustainable implementation of aDSM components (knowledge, practice, resources); pro-active aDSM non-compliance risk identification mechanism; patients education in safety monitoring and management;
- For national PV centres: safety data assessment, detection of signals, evaluation of risk minimization measures; setting up a mechanism to support the reporting of SAE.

aDSM performance in the National TB programme is based on:

- Clinical MDR-TB guideline – full scope of safety monitoring and management requirement, ADR reporting;
- Availability of clinical, diagnostic and laboratory facilities for regular safety monitoring in line with WHO recommendations in hospital and outpatient settings;
- TB practitioners safety monitoring and management knowledge and practical performance: systematic clinical and laboratory assessment, ADR prevention and management;
- ADR recording and reporting practice: TB register, availability and quality of ADR reporting tool, reporting to the National PV Centre;
- Performance of individual benefit–risk assessment and reassessment mechanisms;

- Integrated performance M&E tool;
- Availability of intrinsic pro-active non-performance risk detection and management tool;
- aDSM performance sustainability (knowledge, practice, resources);
- Involvement of patients and caregivers in risk minimization and safety monitoring.

The role of the national PV system includes:

- Statutory provision of the national PV legislative framework, political commitment, mitigation the obstacles for ADR reporting activity;
- National ADR reporting form, national ADR database (E2B compatibility, integrated MedDRA, VigiBase compatibility, safety assessment and signal detection tools);
- Availability of PV training for care providers, integration of PV training in curricula and post-graduate education;
- Performance indicators: ADR collection and analysis, signal management;
- Sharing of updated safety information with care providers and patients;
- Risk mitigation measures, implementation of effective, integrated performance monitoring tool;
- Capacity-building and monitoring signal management;
- ADR reporting to WHO VigiBase and aDSM database.

At the end of each working day, the trainees were asked to evaluate each using five possible rating. The majority receive “5” and “4” scoring.

### **Annex 1. Supporting documents**

1. WHO. Rapid Communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.
2. WHO. WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020.
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15. WHO. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization; 2014.
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18. WHO. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. Geneva: World Health Organization; 2017.
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## Annex 2. Training agenda

15–18 June 2020

<b>15 June 2020</b>		
08:15–08:45 (CET)/09:15–09:45 (EEST)	<b>Registration</b>	
08:45–09:00 (CET)/09:45–10:00 (EEST)	<b>Introduction:</b> <ul style="list-style-type: none"> <li>✓ Opening and welcome speech</li> <li>✓ Adoption of agenda and programme</li> <li>✓ Briefing on background, purpose and expected outcomes</li> </ul>	Dr Gennady Gurevich Dr Alena Skrahina Dr Masoud Dara Dr Askar Yedilbayev Dr Fuad Mirzaev Dr Ogtay Gozalov
<b>Session 1. DR-TB clinical and practical aspects</b>		
09:00–10:00 (CET)/10:00–11:00 (EEST)	Presentation of WHO consolidated guidelines on tuberculosis	Dr Fuad Mirzayev
10:00–10:30 (CET)/11:00–11:30 (EEST)	Tuberculosis programme and the COVID-19 pandemic	Dr Masoud Dara
10:30–11:00 (CET)/11:30–12:00 (EEST)	Practical consideration of Green Light Committee activities	Dr Ogtay Gozalov
11:00–11:30 (CET)/12:00–12:30 (EEST)	<b>Coffee break</b>	
11:30–12:10 (CET)/12:30–13:10 (EEST)	Implementation of the new modified DR-TB treatment regimen in Belarus	Dr Alena Skrahina
12:10–12:50 (CET)/13:10–13:50 (EEST)	Modified shorter DR-TB treatment regimens	Dr Askar Yedilbayev
12:50–13:30 (CET)/13:50–14:30 (EEST)	Implementation of modified shorter all-oral regimen. Belarus experience	Dr Elmira Gurbanova

<b>16 June 2020</b>		
08:30– 09:00(CET)/09:30– 10:00 (EEST)	<b>Registration</b>	
09:00– 09:40(CET)/10:00– 10:40 (EEST)	Piloting the video-supported treatment. An operational research in Belarus	Dr Alena Skrahina
09:40– 10:20(CET)/10:40– 11:20 (EEST)	TB and pregnancy	Dr Alena Skrahina
10:20– 11:00(CET)/11:20– 12:00 (EEST)	New drugs in treatment in DR-TB treatment in children. Case studies	Dr Alena Skrahina
11:00–11:30 (CET)/12:00–12:30 (EEST)	<b>Coffee break</b>	
11:30–12:10 (CET)/12:30–13:10 (EEST)	LTBI prevalence worldwide, diagnosis and treatment according to WHO recommendation	Dr Aleksander Skrahin
12:10–12:50 (CET)/13:10–13:50 (EEST)	New WHO recommendation on TB/HIV management	Dr Aleksander Skrahin
12:50– 13:30(CET)/13:50– 14:30 (EEST)	Drug–drug interaction in TB/HIV treatment and design of TB regimen	Dr Aleksander Skrahin

<b>17 June 2020</b>		
08:30– 09:00(CET)/09:30– 10:00 (EEST)	<b>Registration</b>	
<b>Session 2. MDR-TB Consilium</b>		
09:00– 11:00(CET)/10:00– 12:00 (EEST)	MDR-TB Consilium role during the transition to the new WHO-recommended DR-TB treatment regimens. Case presentations: longer and shorter treatment regimens; TB associated with HIV, hepatitis C and COVID-19	Dr Alena Skrahina, Dr Dmitryy Vetushko Dr Varvara Solodovnikova, Dr Elena Nikolenko, Dr Dmitryy Klimuk
11:00–11:30 (CET)/12:00–12:30 (EEST)	<b>Coffee break</b>	
<b>Session 3. Laboratory diagnosis</b>		
11:30–12:00 (CET)/12:30–13:00 (EEST)	Laboratory tests role in the monitoring of AE of DR-TB treatment including shorter treatment regimens	Dr Gulmira Kalmambetova
12:00–12:30 (CET)/13:00–13:30 (EEST)	Laboratory requirements for implementation of the shorter DR-TB treatment regimens	Dr Vladzimir Antonenka
12:30–13:00 (CET)/13:30–14:00 (EEST)	Mechanisms of resistance to the new and repurposed TB drugs	Dr Vladzimir Antonenka
13:00– 13:30(CET)/14:00– 14:30 (EEST)	Interpreting the difficult cases of discrepancies in laboratory tests results. Case studies	Dr Eugene Sahalchik



<b>18 June 2020</b>		
08:30– 09:00(CET)/09:30– 10:00 (EEST)	<b>Registration</b>	
<b>Session 4. Infection Control</b>		
09:00– 10:30(CET)/10:00– 11:30 (EEST)	Decreasing the risk of TB transmission. Implementation of Infection Control programmes	Dr Grigoriy Volchenkov
<b>Session 5. Drug management and pharmacovigilance</b>		
10:30– 11:00(CET)/11:30– 12:00 (EEST)	Stop TB Partnership’s Global Drug Facility: procurement and supply of TB products	Dr Natavan Alikhanova
11:00–11:30 (CET)/12:00–12:30 (EEST)	<b>Coffee break</b>	
11:30– 12:30(CET)/12:30– 13:30 (EEST)	Procurement needs assessment using the QuanTB platform	Dr Natavan Alikhanova
12:30– 13:30(CET)/13:30– 14:30 (EEST)	aDSM and safety management. aDSM in concurrent conditions	Ms Svitlana Setkina
13:30– 13:40(CET)/14:30– 14:40 (EEST)	<b>Closure of the training</b>	Dr Gennadyy Gurevich Dr Alena Skrahina Dr Masoud Dara Dr Askar Yedilbayev Dr Fuad Mirzaev Dr Ogtay Gozalov

### **Annex 3. List of participants**

#### **A. rGLC/Europe members/consultants**

1. Dr Alena Skrahina, Chair
2. Dr Andrei Mariandyshev
3. Dr Elmira Gurbanova
4. Dr Gunta Dravniece
5. Dr Liga Kuksa
6. Dr Sergii Filippovych
7. Ms Svetlana Setkina
8. Dr Nino Lomtadze
9. Dr Inna Motrich
10. Dr. Linda Barkane
11. Dr Lali Mikeashvil
12. Dr Rais Mazitov
13. Dr Iana Terleeva
14. Dr Naira Khachatryan
15. Dr Ana Ciobanu
16. Dr Aysel Aslanova
17. Dr Sevinj Tagiyeva
18. Dr Lesia Tyлина

#### **B. Stop TB Partnership / Global Drugs Facility (GDF)**

19. Dr Natavan Alikhanova

#### **C. WHO Regional Office for Europe**

20. Dr Masoud Dara, Coordinator
21. Dr Askar Yedilbayev, TB Team lead
22. Dr Ogtay Gozalov, Medical officer
23. Dr Andrei Dadu, Medical Officer
24. Dr Elena Vovc, Technical officer
25. Dr. Maria Dolynska, Rapporteur

#### **D. WHO HQ**

26. Dr Fuad Mirzaev

#### **E. European Laboratory Initiative**

27. Dr. Vladzimir Antonenka
28. Dr. Eugene Sahalchyk

#### **F. National Institute of TB and Respiratory Diseases, WHO Collaborating Centre, Minsk, Belarus**

29. Dr Gennady Gurevich
30. Dr Aleksander Skrahin
31. Dr Dmitryy Vetushko
32. Dr. Varvara Solodovnikova
33. Dr. Elena Nikolenko
34. Dr. Dmitryy Klimuk

#### **National Reference Laboratory, Kyrgyzstan NTP**

Dr Gulmira Kalmambetova

#### **Specialized TB and Respiratory Care Centre, Vladimir, Russian Federation**

Dr Grigoriy Volchenkov

## **The WHO Regional Office for Europe**

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