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National Center for Tuberculosis and Lung Diseases

Implementing active drug safety monitoring and management (aDSM) of TB medicines: Georgia Experience

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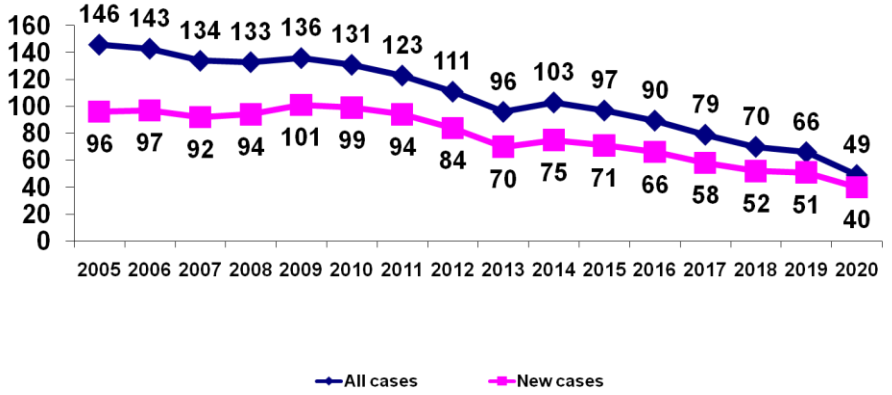
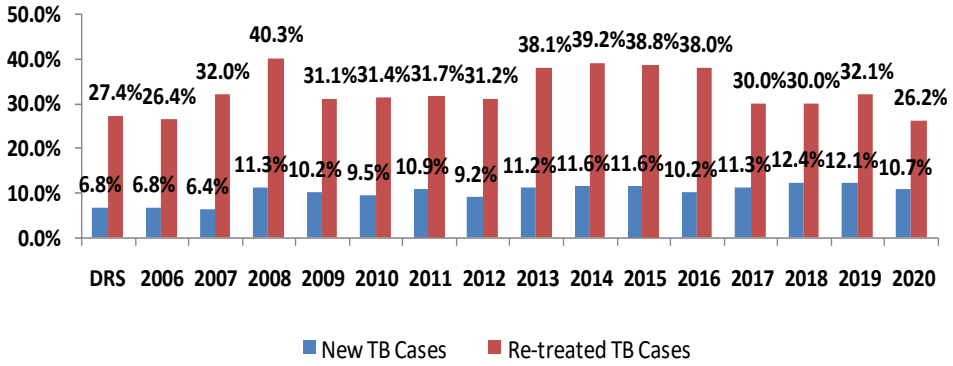
Georgia TB Profile: Case notification

TB case notifications, 2020

Total new and relapse	1 671
- % tested with rapid diagnostics at time of diagnosis	88%
- % with known HIV status	89%
- % pulmonary	79%
- % bacteriologically confirmed ^	92%
- % children aged 0-14 years	3%
- % women (aged ≥15 years)	32%
- % men (aged ≥15 years)	65%
Total cases notified	1 842

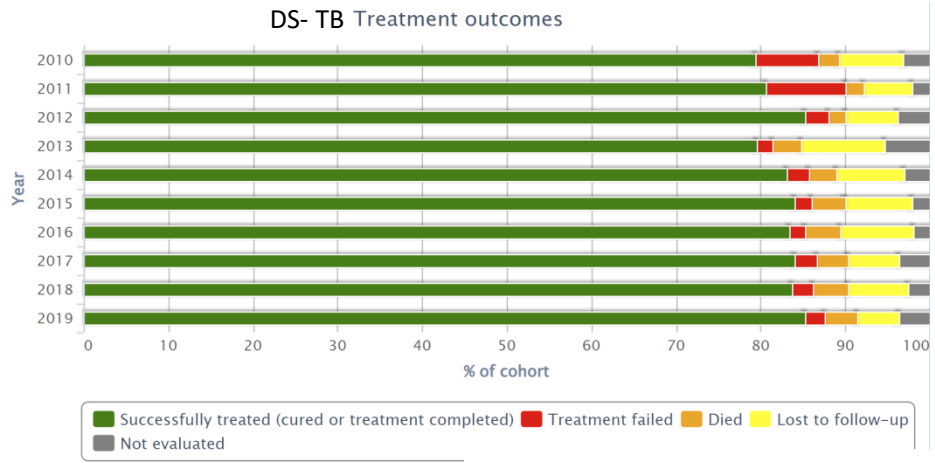


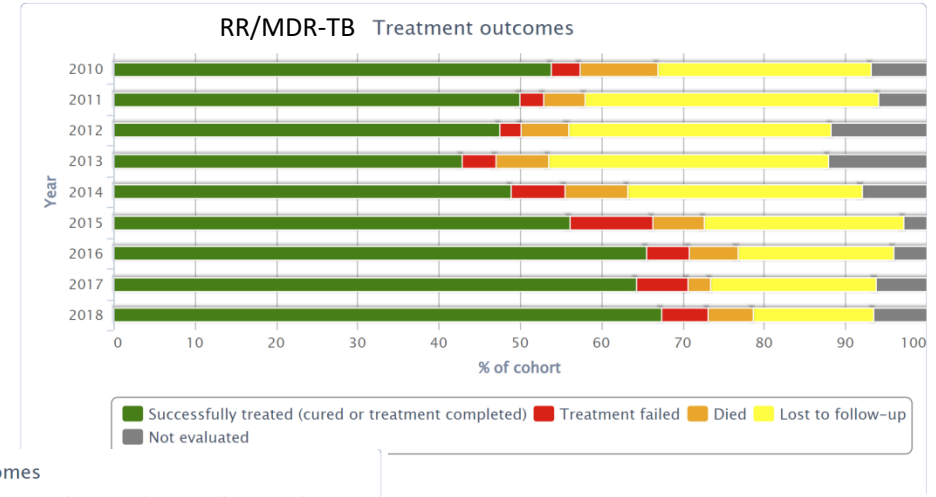


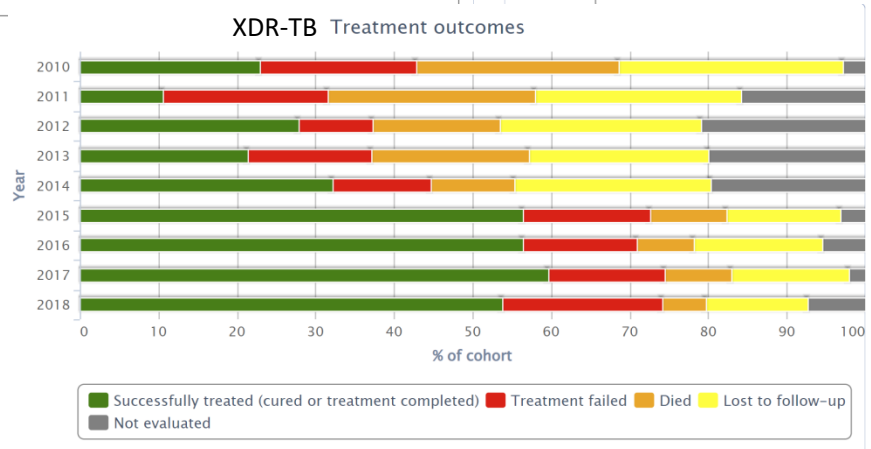
Drug-resistant TB care**, 2020

% of bacteriologically confirmed TB cases tested for rifampicin resistance - New cases ^	100%
% of bacteriologically confirmed TB cases tested for rifampicin resistance - Previously treated cases ^	95%
Laboratory-confirmed cases - MDR/RR-TB ^^	202
Patients started on treatment - MDR/RR-TB ^^^	217
Laboratory-confirmed cases - pre-XDR-TB or XDR-TB ^^	52
Patients started on treatment - pre-XDR-TB or XDR-TB ^^^	44
MDR/RR-TB cases tested for resistance to any fluoroquinolone	173

Georgia TB Profile: Treatment outcomes







Chronology of access to New TB Drugs

2013
- **Start** BDQ Compassionate Use (CU) Program

From 2014
MSF supported **scale up** of CU & programmatic use of BDQ and CU of Delamanid

Aug 2015
Programmatic use of BDQ through **USAID Donation Program** and Delamanid through **GDF**

Nov 2015
- **Universal access** to diagnosis/treatment for TB including 'pre-XDR'/ XDR-TB
- **National TB guidelines**: up to date, endorsed by MoH, include M/XDR treatment regimens and new drug safety monitoring schedule (WHO guidance)

Chronology of Practical Steps Taken

2014

- **National BDQ Implementation Plan** developed with the USAID project
- Approved by National TB Council chaired by the Minister of Health himself

Jan 2015

Technical Working Group created to coordinate new drug implementation, including PV, led by NCTLD

March 2015

MoH-approved **new voucher funding** for safety monitoring linked with new drug use, incl. ECG investigations, etc

Apr2015

- Georgia became a primary Candidate to receive BDQ through **USAID & Janssen Therapeutics' donation** program followed by the ceremony of BDQ handover in Oct 2015

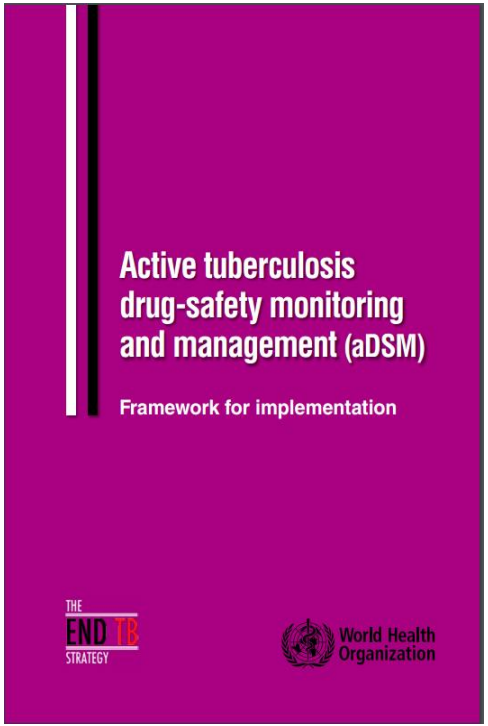
July 2015

- An innovative approach of **Mobile Consilium** was launched by the NCTLD with the support of the Global Fund TB Program

Current National DR-TB Treatment Guidelines

- Recommendations targeting adults and children include the following:
  - **Modified fully oral shorter regimen (mSTR) for pulmonary and non-severe EPTB RR-/MDR-TB within WHO European Region mSTR Operational Research**- 9 months BDQ/Lzd/Lfx/Cfz/Cs with DLM first drug to substitute in case of toxicity, 9 months BDQ/Lzd/Lfx/Cfz/Dlm and Dlm/Lzd/Lfx/Cfz – for children below 6years old.
  - **Longer 18-20 month regimens for all other patients**, e.g. quinolone resistance, extensive TB disease with a backbone of BDQ/Lzd/Lfx/Cfz, with additional drugs based on treatment history and drug resistance patterns
- Additional/updated guidance on:
  - **Post-treatment pulmonary/respiratory rehabilitation**;
  - **Expansion of the active TB screening groups**
  - **Expansion and revision LTBI treatment strategies with 3HP to be used for all close TB contacts of any age above 2 years and 6INH below 2 years, HIV, organ transplant patients, miners, dialysis and TNF therapy patients**
  - Surgical management, TB Meningitis, laboratory monitoring, DST to DR-TB drugs

Active Drug Safety Monitoring and Management (aDSM)



The overall *objective* of aDSM is to reduce risks from drug-related harms in patients on second line treatment for drug-resistant TB and to generate standardized aDSM data to inform future policy updates on the use of such medicines.

Three essential aDSM activities:

1. Patients targeted for aDSM should undergo active and systematic clinical and laboratory assessment during treatment to detect drug toxicity and AEs.
2. All AEs detected should be managed in a timely manner in order to deliver the best possible patient care.
3. Standardized data should be systematically collected and reported for any detected SAE.2 These will eventually be used to characterize the types of SAEs, assess the safety of the treatment, and inform future policy on the use of these medicines.

3 Levels of aDSM

1. **Core package**: requiring monitoring for and reporting of all Serious Adverse Events (**SAE**s);
2. **Intermediate package**: includes **SAE**s as well as Adverse Events (**AE**s) of special interest;
3. **Advanced package**: includes **all AEs** of clinical significance.

Post-*aDSM* PV Implementation

- Elaboration of the SAE/AEI reporting form, completion guidelines and adoption of the severity grading scale from endTB project for use at the National Level
- The NCTLD/NTP referred to the Minister of Health with a letter summarizing the need of the mandatory reporting rules and practices of SAEs for patients undergoing SLD TB treatment
- In May 2016 Permanent Ministerial Decree #01-18/ნ on mandatory recording and reporting of the SAEs for all DR-TB patients was issued that went into force since June 2016

aDSM Implementation: Training

June 2016

July 2016

Oct 2016

2017-2021

- To facilitate the effective implementation of the Ministerial Decree regarding mandatory SAE reporting, a training materials and lectures were developed with participation of the NCTLD, USAID/SIAPS and MSF experts/consultants for TB doctors and programmatic staff
- Within frames of the USAID/SIAPS program, implemented by MSH, the Phthisiologists and Pulmonologists Association of Georgia (GPPA), was engaged to conduct 3 days training of at least 200 Tuberculosis doctors and TB programmatic staff on active Drug Safety Monitoring and Management (aDSM)
- By October 17th 2016, the training mission has been accomplished in Tbilisi and regions and total of 275 TB doctors and PMDT staff have received the training covering the 100% of need;
- 100% of TB Doctors and programmatic staff have been retrained twice on differrent aspects of aDSM including the evaluation of AEs by assigning the Severity Grading scale, management of drug toxicities and R&R on adverse events in 2019 and just recently in November 2021 – trainings funded by the Global Fund project.

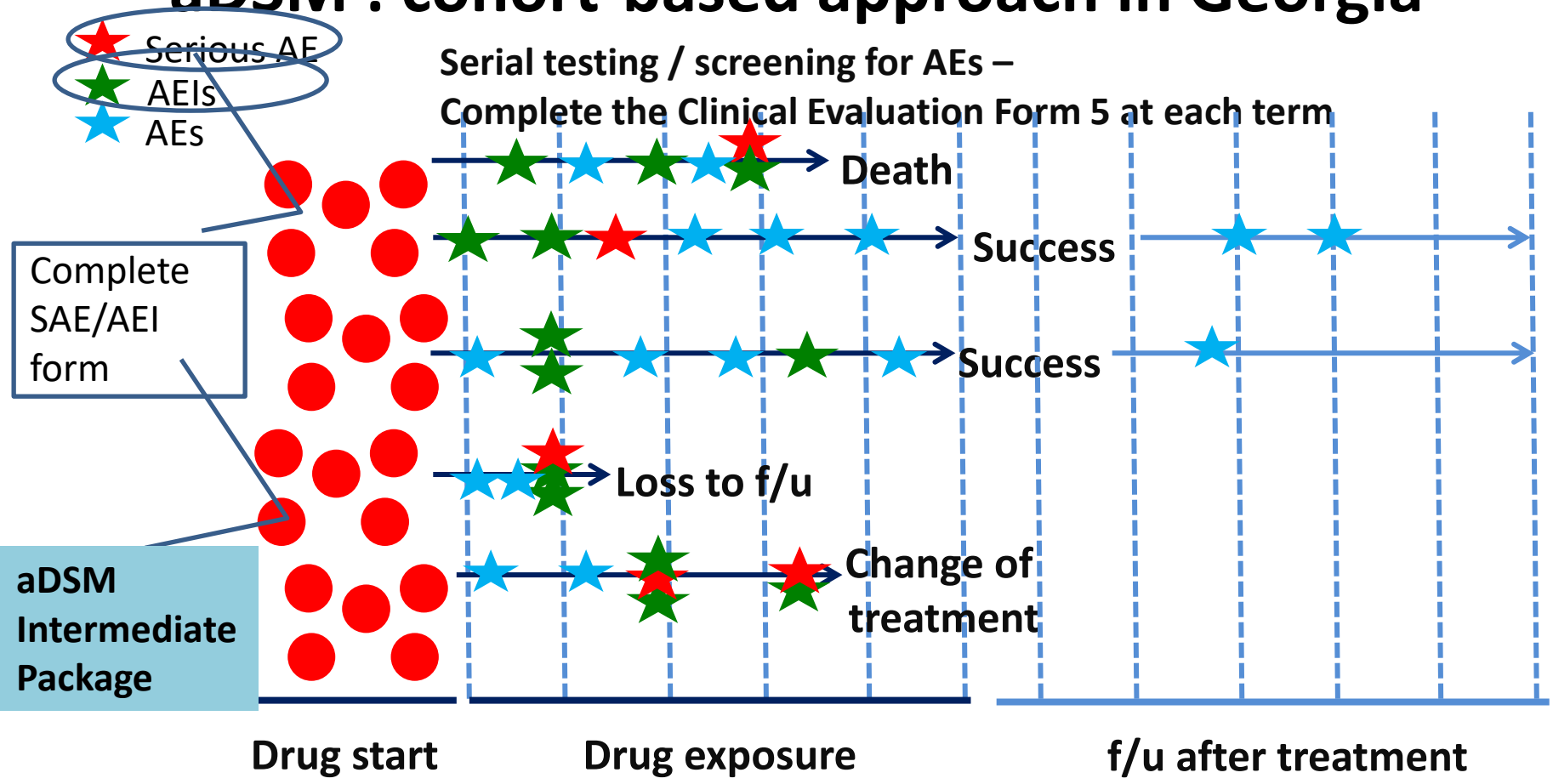
Reminder: Serious adverse event (SAE)

- Any un-favourable or unintended sign/ symptom/ disease (incl. lab abnormality) that at any dose is:

	Fatal
	Immediately life threatening
	Leading to hospitalisation or prolongation of hospitalisation
	Leading to a significant disability / incapacity
	Birth defect or congenital anomaly
	Otherwise medically important, necessitating an intervention to prevent one of the above listed outcomes

Adverse Events of Special Interest Targeted in Georgia

aDSM : cohort-based approach in Georgia



Monitoring Schedule (1)

	Baseline Visit	Week 2	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Until end of treatment	End of treatment	3 months post-end-of-treatment	6 months post-end-of-treatment	9 months post-end-of-treatment	12 months post-end-of-treatment
Clinical evaluation														
Vital signs	x		x	x	x	x	x	x	Monthly	x	x	x	x	x
Brief peripheral neuropathy screen	x		x	x	x	x	x	x	Monthly	x				x
Visual acuity and colorblindness screen	x		x	x	x	x	x	x	Monthly	x				x
Post-end-of- treatment consultation										x	x	x	x	x
Assessment and follow-up of adverse events	x	x	x	x	x	x	x	x	At each scheduled /unscheduled visit	x	x	x	x	x
Weight	x	x	x	x	x	x	x	x	Monthly	x	x	x	x	x
Bacteriological testing														
Smear	x		x	x	x	x	x	x	Monthly	x		x		x
Culture	x		x	x	x	x	x	x	Monthly	x		x		x
Freeze baseline culture	x													
Xpert MTB/RIF	x													
LPA (Hain GenoTypeMTBDRsl)	x			If smear- or culture-positive check for amplification of resistance										
Culture-based first-line DST	x			If smear- or culture-positive check for amplification of resistance										

Monitoring Schedule (2)

	Baseline Visit	Week 2	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Until end of treatment	End of treatment	3 months post-end-of-treatment	6 months post-end-of-treatment	9 months post-end-of-treatment	12 months post-end-of-treatment
Culture-based second-line DST	✕			If smear- or culture-positive check for amplification of resistance										
Laboratory testing														
ECG	✕	✕	✕	✕	✕	✕	✕	✕	Monthly	✕	✕	✕		
Full blood count (hemoglobin, red blood cells.white blood cells and platelets) if on Lzd	✕		✕	✕	✕	✕	✕	✕	Monthly (if on Lzd)	✕				
Liver function tests (AST, ALT)	✕		✕	✕	✕	✕	✕	✕	Monthly	✕				
Serum creatinine	✕		✕	✕	✕	✕	✕	✕	Monthly	✕				
Serum potassium	✕		✕	✕	✕	✕	✕	✕	Monthly	✕				
Hepatitis Bs Antigen	✕													
Hepatitis C Antibody	✕													
HbA1c	✕		Repeated every 3 months if elevated											
COVID-19 PCR	✕		At baseline and then only if clinically indicated											
Pregnancy test (females)	✕													
HIV testing	✕													
CD4 (repeated every 6 months if HIV+)	✕							✕						
HIV Viral load (repeated every 6 months if HIV +)	✕							✕						
Chest X-Ray	✕							✕		✕				

SAE/AEI reporting Form in Georgia

- **A 4 pages reporting form with checkboxes that capture the essential information to enable adequate causality assessment, including:**
- **Adverse event (AE)**
  - name/description
  - date of onset
  - Severity
  - Seriousness
  - response to de-challenge/re-challenge
  - AE outcome
  - date of outcome;
- **Drug(s) including the concomitant drugs**
  - treatment start/end dates
  - dose, route, frequency of administration
  - Indication
  - measures taken in response to AE
- **Relevant laboratory or Instrumental investigations**
- **Doctors decision on causality – related/not related**

aDSM management and Required Human Resources

- One AE reporting form is completed per one AE term that incorporates information on all suspected drugs. It is not encouraged to complete several AE forms for one AE term if more than one drug is suspected – this approach multiplies efforts and is discourages the AE reporting practices among doctors;
- Global Fund is supporting a salary of two Pharmacovigilance (PV) consultants who are Clinical pharmacologists by training at central level (NCTLD) in order to ensure continuous technical support to the reporting doctors countrywide, report screening for completeness and data entry of the aDSM reports in a home made excel spreadsheet;
- WHO-UMC causality categories are assigned to the reported AEs at the Pharm-Committee meetings at the NCTLD represented by a multidisciplinary team of TB Doctors, PV focal point (working in kind for the program) chairing the committee, PV consultants/clinical pharmacologist and chair of the clinical consilium.

Flow of aDSM Data

Any SAE, AEI or an AE requiring treatment change requires SAE/AEI form completion and reporting to the NCTLD from TB Doctor within 72 hours from awareness.

NCTLD

PV consultants:

- Acknowledge the receipt,
- Screen for Completeness and coherence;
- Enter data into the Excel database.

Pharm-Committee meetings 1x/month:

- Reviewing AE reports;
- Assessing Causality-WHO UMC;
- Providing feedback to the Doctor

Early Detection of Adverse events

- Prior to and during treatment, patients undergo regular, free of charge, laboratory and instrumental examinations in accordance with the established monitoring schedule to determine the toxicity of the drug in a timely manner and at the earlier stages of event severity;
- The treating physician is responsible for conducting or referring the patient to the scheduled examinations as defined in the guideline. They ensure that all MDR / RR-TB patients are screened for all parameters included in the schedule;
- In case of toxicity that requires treatment modification, the treating doctor presents the patient to the central clinical consilium along with the completed SAE/AEI form for discussion. A copy of the form is sent to the PV consultants (2 consultants) at the NCTLD, whose salary is covered within the Global Fund TB grant.
- Any SAE or AEI regardless the need of treatment modification should also be reported – weakness of the program.

NTP and DRA - State Regulation Agency for Medical Activities (RAMA)

RAMA is in the process of **building the PV analytic capacity**

- Currently RAMA ensures spontaneous ADR reporting form storing, filing, database support, regulatory decision making functions
- TB drug PV (aDSM) is implemented by the National TB Program, per delegated responsibilities from the MOH decree;
- RAMA preserves the oversight function of TB drug ADRs;
- RAMA representative is the invited member of the Pharm-committee under the NCTLD per internal NCTLD order of the Director.
- NCTLD supported RAMA to become the full member of the WHO Uppsala Monitoring Center by entering 20 quality reports into the Vigibase on their behalf in 2018 after being an associate member since 2001 with a plan to give access to NTP to the Vigibase for direct data entry – not accomplished.

PV Challenges Faced

- There is not a single dedicated person to PV related activities within RAMA
- PV is somewhat low on RAMA agenda
- Very low (almost no) ADR reporting to RAMA
- Despite becoming a full member of WHO collaborating Uppsala Monitoring Center (WHO-UMC), no data entry to Vigibase is taking place
- TB drug related safety reports are reported and analyzed only within NCTLD/NTP - no further sharing for proper regulatory interventions
- ADR Reporting level is satisfactory within TB program but very dependent on continuous training and coaching.

Some publications related aDSM in Georgia

Monaldi Archives for Chest Disease 2021; volume 91:1649

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Key words: Tuberculosis; drug resistance; new/repurposed anti-TB drugs; SAEs.

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Incidence rate and time to serious adverse events among rifampicin resistant tuberculosis patients in Georgia treated with new and repurposed anti-tuberculosis drugs, 2016-2018

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FOCUS ON BDQ

Setting up pharmacovigilance based on available endTB Project data for bedaquiline

N. Lachenal,[1] C. Hewison,[2] C. Mitnick,[3,4] N. Lomtadze,[5] S. Coutisson,[1] E. Osso,[4,6] S. Ahmed,[7] G. Leblanc,[8] S. Islam,[9] H. Atshemyan,[10] P. Nair,[11] B. Kholikulov,[11] S. Aiylchiev,[12] K. Zarli,[13] S. Adnan,[14] A. Krisnanda,[15] S. Padayachee,[16] A. Stambekova,[17] Y. Sahabutdinova,[17] S. de Guadalupe Perea Moreno,[18] A. Kumsa,[19] A. Reshid,[19] J. Makaka,[20] S. Abebe,[20] N. Melikyan,[2] K. J. Seung,[4,21] U. Khan,[22] P. Khan,[22] H. Huerga,[2] M. Rich,[4,21] F. Varaine[2]

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Compendium of good practices in the implementation of the Tuberculosis Action Plan for the WHO European Region 2016–2020

the MSF programme. In April 2015, Georgia became a prime global candidate to receive life-saving access to Bdq for programmatic use through the joint USAID/ Janssen Therapeutics donation programme and the programmatic use of Bdq (through the USAID Bedaquiline Donation Program) and Dlm (through the Global Fund to Fight AIDS, Tuberculosis and Malaria/ Global Drug Facility) started in August 2015. Prior to

Thank you!