Tuberculosis in 2017: Searching for new solutions in the face of new challenges

6th TB Symposium – Ministry of Health of the Republic of Belarus, Republican Scientific and Practical Center for Pulmonology and Tuberculosis, and Médecins Sans Frontières

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Interim results of MSF endTB projects in Belarus, Georgia, Armenia focusing on safety profiles and aDSM

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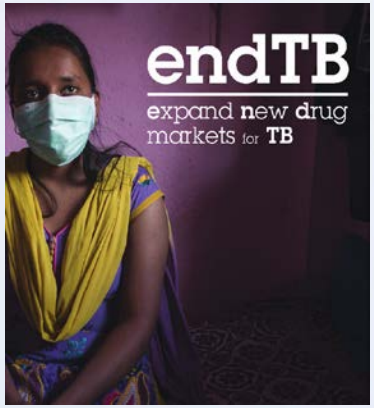
What is endTB?



www.endtb.org

- Partnership between National TB Program and endTB consortium partner in each country
  - Partners In Health (PIH)
  - Médecins Sans Frontiéres (MSF)
  - Interactive Research and Development (IRD)
- Funding partner: UNITAID
- Expand access to bedaquiline and delamanid
- Produce evidence on new TB drugs (inform clinical decision and policy)

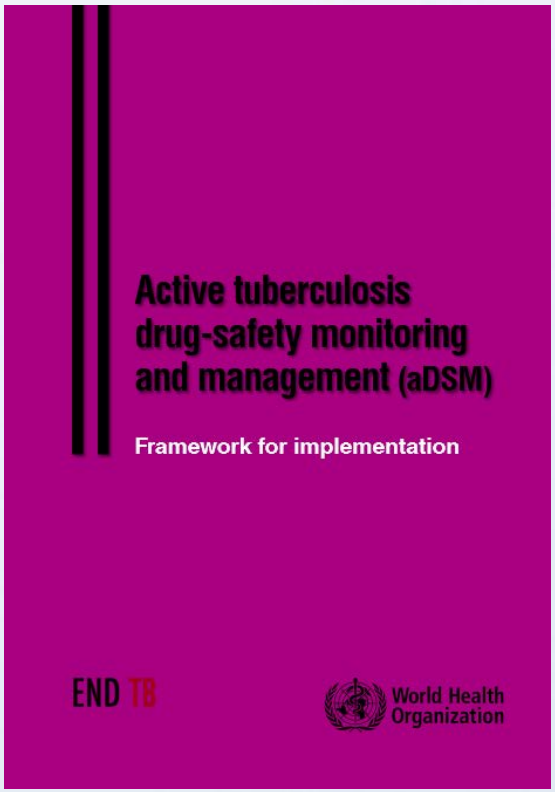
endTB implementation

Active TB drug safety monitoring & management (aDSM)

- aDSM refers to active & systematic clinical and laboratory assessment of patients while on TB treatment.

- aDSM applies to **patients** treated with:
    1. new anti-TB drugs,
    2. novel MDR-TB treatment regimens, or
    3. XDR-TB treatment regimens.

- aDSM aims to detect, manage & report suspected or confirmed drug toxicities.



WHO/HTM/TB/2015.28

Active detection
endTB monitoring schedule

	D1	W2	M1	M2	M3	M4	M5	M6	Inj	FU	End	After 6m
Peripheral neuropathy screen	X		X	X	X	X	X	X	Monthly		X	X
Audiometry	X		X	X	X	X	X	X	M		X	
Visual acuity /colorblindness	X		X	X	X	X	X	X	Monthly		X	X
Assessment adverse events	X	X	X	X	X	X	X	X	At each visit		X	X
ECG	X	X	X	X	X	X	X	X			X	X
Full Blood Count	X	X	X	X	X	X	X	X	Monthly		X	
Urea, creatinine	X		X	X	X	X	X	X	M		X	
Serum electrolytes	X		X	X	X	X	X	X	M		X	
Liver function tests (AST, ALT)	X		X	X	X	X	X	X	Monthly		X	
TSH	X				X				3 months			
Serum albumin	X											
Hep B Ag, Hep C Ab, HIV	X											
Pregnancy test	X											

aDSM Safety Data Collection

- **Serious Adverse Events (SAE) -** all events causing:
  - Death,
  - Immediately life threatening (e.g. anaphylaxis),
  - Hospitalisation or prolongation of hospitalisation,
  - Congenital malformation or birth defect,
  - Permanent disability/significant incapacity
  - Otherwise medically significant

- **Reporting**: PV Unit (Geneva) & National aDSM coordination / National Authorities

- Data collection on non serious AEs of clinical significance

Preliminary results

Cohort: patients on Bdq or Dlm within endTB project

Period: April 2015- December 2016

	Belarus n (%)	Armenia n (%)	Georgia n (%)
No. patients	**50**	**89**	**300**
- Bedaquiline at start	32 (64.0)	41 (46.1)	176 (58.7)
- Delamanid at start	16 (32.0)	32 (35.9)	62 (20.7)
- Both combined at start	2 (4.0)	8 (9.0)	0
- Bdq or Dlm added	0	8 (9.0)	62 (20.7)

Patients' characteristics

	Belarus n (%) N=50	Armenia n (%) N=89	Georgia n (%) N=300
Men	33 (66.0)	71 (79.8)	240 (80.0)
Age (median, IQR)	42.5 [34.9-49.9]	43.5 [32.5-52.6]	35.9 [27.7-46.7]
Under 18 years			
- Children (6-14)	0	1 (1.1)	1 (0.3)
- Adolescents (15-17)	0	1 (1.1)	7 (2.3)
Prisoners			
In the past	17 (34.0)	17 (19.3)	61 (20.3)
Currently	0	0	19 (6.3)
HIV positive	3 (6.0)	9 (10.1)	17 (5.8)
Hepatitis C positive	8/45 (17.8)	22 (24.7)	66 (22.6)
Culture positive (baseline)	27/39 (69.2)	66/81 (81.5)	153/238 (64.3)

Adverse Events (Armenia)

Patients with at least 1 AE: 74/89 (83.1%)

	Frequency (N=425) n (%)	Time to AE Median (IQR)
Gastrointestinal symptoms	48 (20.1)	1.2 [0.3-7.0]
Hepatotoxicity	39 (16.3)	3.1 [1.2-9.4]
Metabolic disorders (Mg, K)	28 (11.7)	3.6 [1.5-6.4]
Neuropathy peripheral	26 (10.9)	2.1 [0.9-5.8]
Electrocardiogram QT prolonged	20 (8.4)	2.3 [0.6-7.8]
Hearing disorder	20 (8.4)	2.1 [1.1-5.1]
Neurological disorder/headache	16 (6.7)	2.4 [0.6-4.2]
Injection site reaction	15 (6.3)	2.2 [0.4-10.6]
Renal disorder	14 (5.9)	3.2 [1.6-9.1]
Blood disorder (anaemia, leukopenia)	13 (5.4)	1.1 [0.5-3.6]

Serious Adverse Events (3 countries)

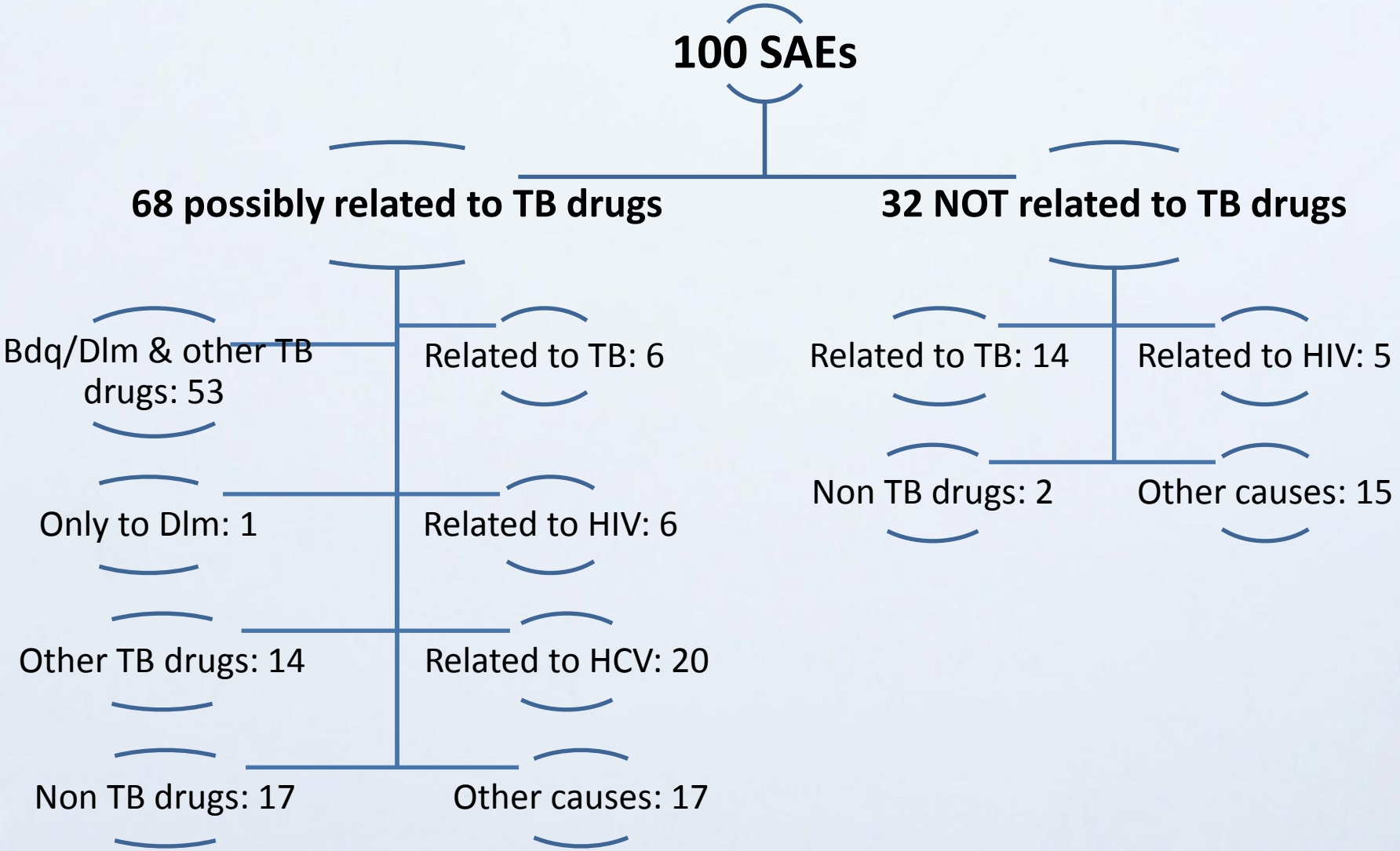
Patients with at least 1 SAE: 75/439 (17.1%)

	Frequency SAE (N=100)	Frequency Fatal SAE (N=27)
Hepatotoxicity	32	4
Respiratory disorders (includes TB)	14	9
Cardiac disorders	8	6
Gastrointestinal symptoms	7	0
Electrocardiogram QT prolonged	7	0
Death (of unknown cause)	4	4
Neuropathy peripheral	4	0
Renal disorders	3	1
Road traffic accident	2	0
Sudden death	2	2

Serious Adverse Events (3 countries)

	Frequency SAE (N=100)	Frequency Fatal SAE (N=27)
Systemic inflammatory response syndrome	1	
Psychotic disorder	1	
Dyshidrotic eczema	1	
Appendicitis	1	
Encephalitis	1	1
Subclavian vein thrombosis	1	
Headache	1	
Dizziness	1	
Pancoast's tumour	1	
Concussion	1	
Pneumonia	1	
Anaemia	1	
Pruritus generalised	1	
Hypersensitivity (to flour)	1	
Infectious pleural effusion	1	
Delirium tremens	1	
Intestinal obstruction	1	

Causes of the SAEs



SAEs follow-up

	SAEs (N=100) n (%)
Favorable	
Recovered/Resolved	35 (35%)
Recovering/Resolving	9 (9%)
Recovered/Resolved with sequelae	4 (4%)
Unfavorable	
Fatal	27 (27%)
Not recovered/Not resolved	18 (18%)
Unknown	7 (7%)

Causality assessment / signal detection

- Safety findings (all endTB countries):
  - Most SAEs are expected
  - Risk factors in fatal SAEs that potentially involved cardiac arrhythmia:
    - **Low albumin, low electrolytes and/or high TSH**
    - **Polymedication -** other cardiotoxic medications
    - **Beta-blockers -** *Don't use for sinus tachycardia*
    - Contributing factors: *female gender* and *low body weight*
    - Potential risk factor: **Hypoglycemia** (reported as associated with QT interval prolongation) - *Drug-drug interaction causing hypoglycemia*

- The endTB PV unit – Medical Review Board issue case studies and recommendations and communicate on safety signals.

Conclusions

- Programmatic use of Bdq & Dlm: early patients the most sick
- aDSM/PV reporting require continuous efforts by doctors and national programs
- The active detection (schedule of assessment) allows early identification of abnormality
- Most frequent non serious conditions (as expected):
  - Gastrointestinal, hepatotoxicity, metabolic disorders
  - Observed in first 6 months of treatment
- SAEs most frequent:
  - Overall: hepatoxicity, respiratory disorders and cardiac disorders
  - Among fatal: respiratory disorders (consequence of TB)
- SAEs accurate documentation is a challenge that impacts on analyses:
  - Term, serious vs. non serious, severity grade, causality, etc.
- Causes of SAEs are multiple: drugs (TB and non-TB), advanced TB disease, co-morbidities (HIV, HCV)
- Half of the SAEs have a favourable follow-up

Acknowledgements

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- The National Center for Tuberculosis and Lung Disease, Georgia
- The National Centre for Tuberculosis Control, Armenia
- The Republican Scientific and Practical Centre of Pulmonology and Tuberculosis, Belarus

MSF field teams Armenia, Belarus and Georgia

Patients

Médecins Sans Frontières and Epicentre HQ endTB team

MSF Pharmacovigilance unit

endTB partners:

- UNITAID
- Thoughtworks (EMR)
- Partners In Health
- Interactive Research & Development
- Institute of Tropical Medicine in Antwerp