Treating Patient, Not Disease: People-Centered Approach

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Adverse events of interest and serious adverse events: endTB cohort

Dr. Nino Lomtadze M.D. MSc

Head of Surveillance and Strategic Planning Department

National Centre for Tuberculosis and Lung Diseases (NCTLD), Tbilisi, Georgia

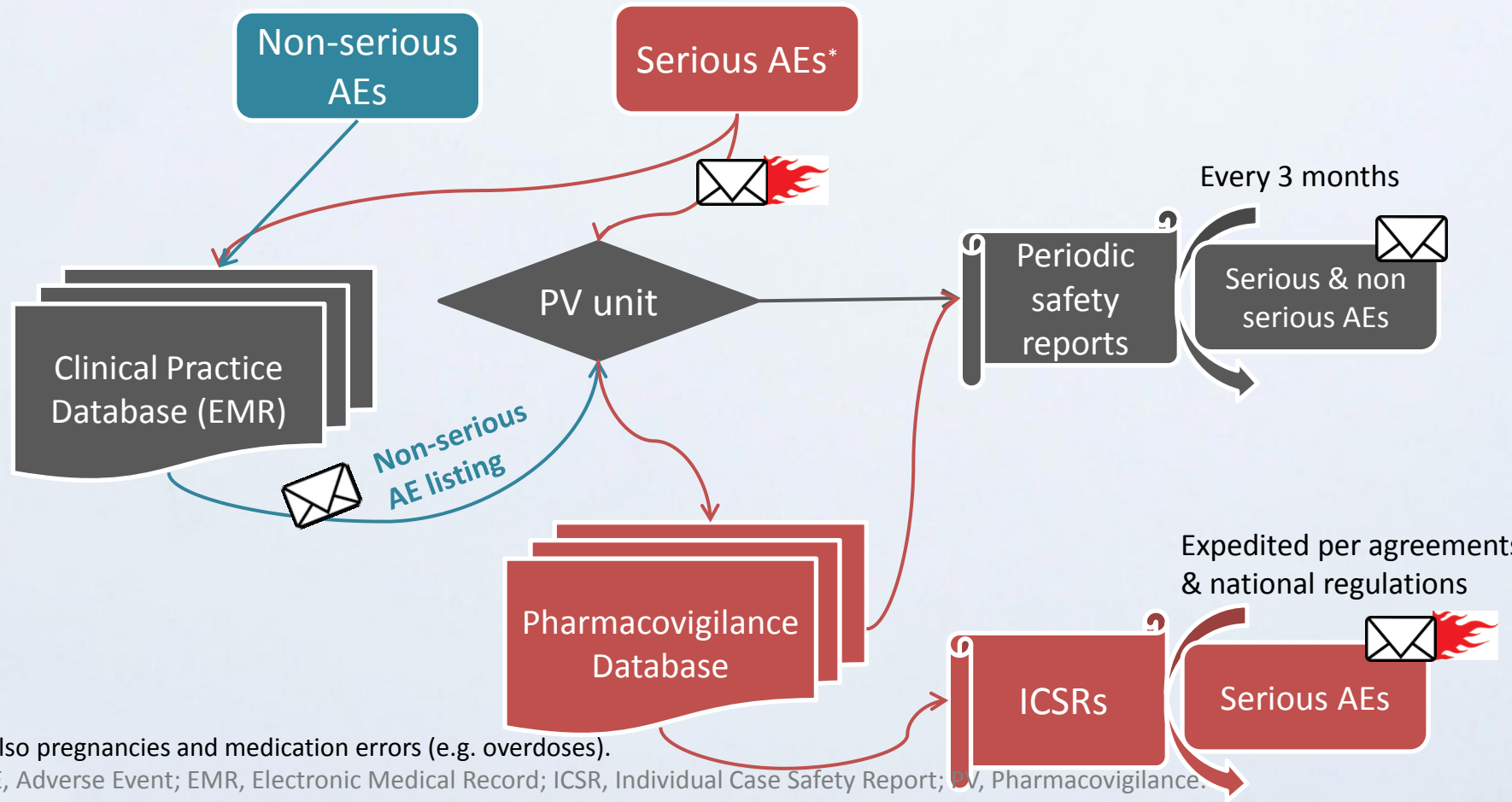
MEDECINS SANS FRONTIERES

Methods

- The endTB pharmacolvigilance:
  - All SAEs reported within 24 hours to the pharmacovigilance unit (PV unit) in Geneva
  - Non serious adverse events reported monthly
    - ✓ Adverse events of interest (pre-defined list)
    - ✓ Any adverse event leading to a change in TB drugs
    - ✓ Any other adverse event considered worthy of reporting by clinician
- Causality assessment is conservative: drug considered related to adverse events unless a causality is excluded
- Other assessment include outcome, other causal factors and final action on TB drugs
- Training of all sites by PV unit

Flow of safety data

Post-marketing and observational study



*Also pregnancies and medication errors (e.g. overdoses).

AE, Adverse Event; EMR, Electronic Medical Record; ICSR, Individual Case Safety Report; PV, Pharmacovigilance.

Methods …

We describe:

- **All SAEs** - any untoward medical occurrence that resulted in:
  - ✓ Death
  - ✓ Was life-threatening
  - ✓ Required hospitalization
  - ✓ Significant disability
  - ✓ Congenital defect

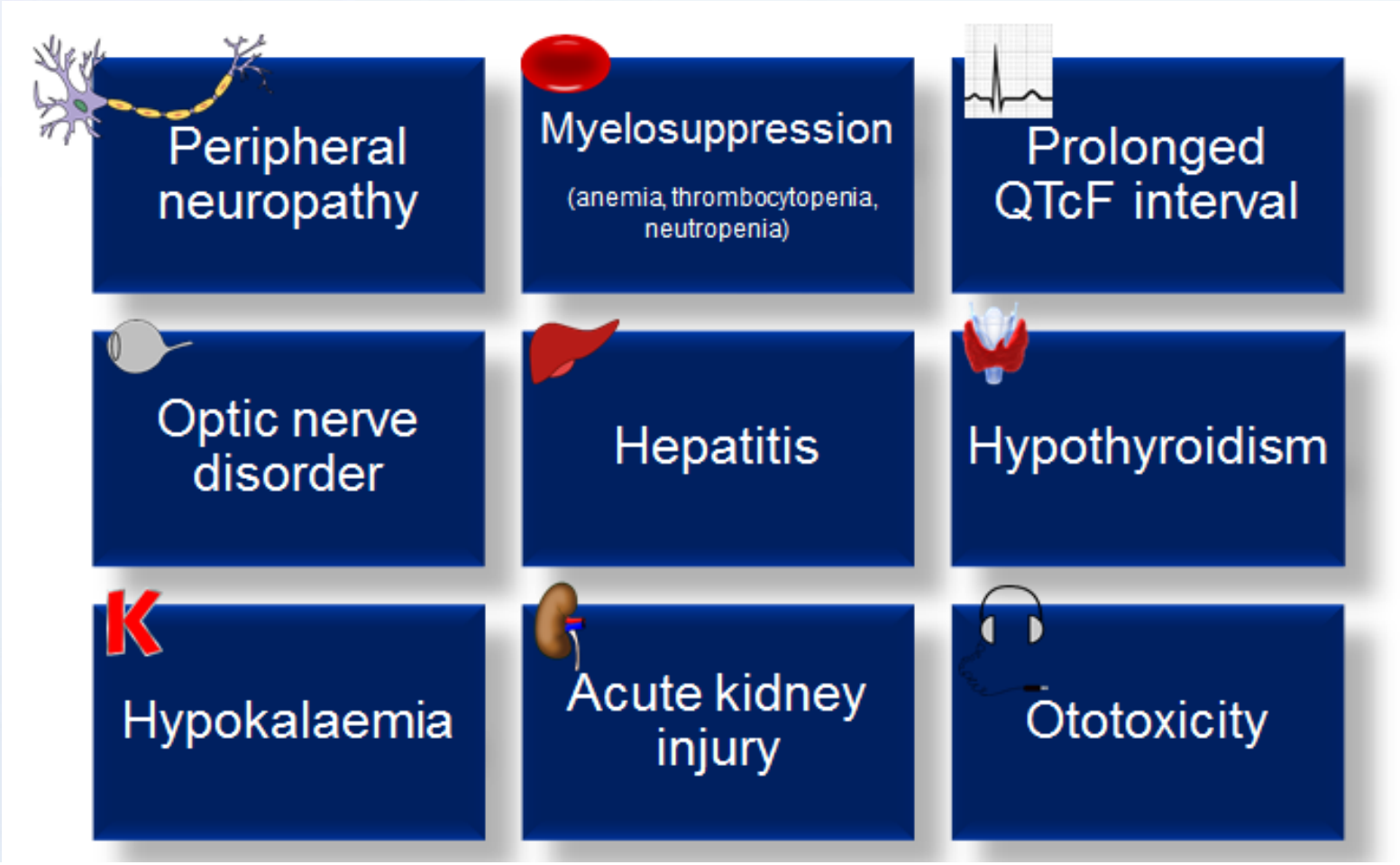


    - ❖ Data entry into PV database centrally

- Non serious Adverse Events of Interest (AEI)

    - ❖ Data entry into the custom local electonic medical record (EMR)

Non serious adverse events of interest



Methods

- **Study population**
  - Patients starting Bedaquiline (BDQ) and/or Delamanid (DLM) between 1st April 2015 and 31st October 2016

- **Start date of AEI or SAE within the first 6 months of treatment with BDQ and/or DLM**

Patient characteristics, N= 687

Characteristic	N (%)
Male	481 (70.0)
Median age [IQR]	38 [30-49]
Body mass index <18.5	248 (36.1)
Extensive disease (bilateral +/or cavities) Xray (N=610)	489 (80.2)
Resistance	
MDR or Rifampicin resistant	167 (24.3)
Pre-XDR (SLI-R)	70 (10.2)
Pre-XDR (FQ-R)	179 (26.1)
XDR	264 (38.4)
Other	7 (1.0)
HIV (N=683)	79 (11.6)
Hepatitis C (N=671)	112 (16.7)
Diabetes (N=649)	64 (9.9)
Previous use of SLD	477 (69.4)

Adverse Events of Interest: N= 687

- 503/687 (73.2%) patients had at least 1 AEI
- For those experiencing AEI:
  - Median number of AEI per patients was 2 [IQR 1 – 3]
  - Range number of AEI per patients [1 – 14]

Adverse Events of Interest: N= 687

AEI term	N (%) of patients with at least one AEI	N (%) of patients with at least one grade 3/4 AEI	N (%) of patients with AEI outcome not resolved or resolved with sequelae
Elevated liver enzymes (ALT or AST ≥ 1.1 x ULN)	210 (30.6)	25 (3.6)	10 (1.5)
Prolonged QTcF interval	164 (23.9)	8 (1.2)	1 (0.1)
Anemia (Hb < 10.5 g/dL)	125 (18.2)	14 (2.0)	5 (0.5)
Acute renal failure	114 (16.6)	2 (0.2)	3 (0.3)
Peripheral neuropathy	112 (16.3)	13 (1.9)	8 (1.2)
Hypokalemia (K ≤ 3.4 mEq/L)	96 (14.0)	9 (1.3)	3 (0.3)
Hearing impairment (hearing loss)	81 (11.8)	20 (2.9)	13 (1.9)
Low platelets (< 75,000/mm3)	53 (7.7)	0	1 (0.1)
Hypothyroidism	50 (7.3)	1 (0.1)	2 (0.2)
Optic neuritis	8 (1.2)	2 (0.2)	3 (0.3)
Low white blood cell	5 (0.7)	0	0
Total		84 (7.9)	45 (6.5)

Severity grading, relatedness to TB drugs and outcomes AEIs	n (%)
All anti-TB drug suspended due to this AE (n = 1,130)	38 (3.4)
AE Grade (severity) (n = 1,200)	
1	864 (72.0)
2	238 (19.8)
3	88 (7.3)
4	10 (0.8)
AE outcome (n = 939)	
Resolved	858 (93.9)
Not resolved	35 (3.8)
Resolved with sequelae	14 (1.5)
Resolving	7 (0.8)
AEI possibly related to TB drug (n = 830)	
Yes	680 (81.6)
Final action taken by drug: AEs possibly related to TB drug (N=680)	
Dose maintained	1076 (89.4)
Dose reduced	44 (3.7)
Drug permanently withdrawn	82 (6.8)

Serious Adverse Events

- **136 SAEs** were reported in this period for this cohort

- **109/687 (15.9%)** patients had **at least 1 SAE** in the first 6 months of new drug
  - 86 (12.5%) had 1 SAE
  - 19 (2.8%) had 2 SAEs
  - 4 (0.6%) had 3 SAEs

- **Incidence of SAEs was 3.50 / 100 PM (95%CI 2.93 – 4.13)**

10 Most Common SAEs

Term	N (%) of patients with at least one SAE	N (%) of patients with at least one grade ¾ SAE	N (%) of patients with fatal SAE outcome
Increased liver enzymes	23 (3.3)	19 (2.8)	0
QTcF Interval	12 (1.7)	10 (1.4)	0
Respiratory failure	7 (1.0)	7 (1.0)	4 (0.6)
Anemia	7 (1.0)	5 (0.7)	2 (0.2)
Cardiac failure	7 (1.0)	7 (1.0)	5 (0.5)
Infections	6 (0.9)	6 (0.9)	3 (0.3)
TB disease progression	5 (0.5)	5 (0.5)	5 (0.5)
Death	4 (0.5)	4 (0.5)	4 (0.5)
Myocardial infarction	4 (0.5)	4 (0.5)	4 (0.5)
Vomiting	4 (0.5)	1 (0.1)	0

10 Most Common SAEs

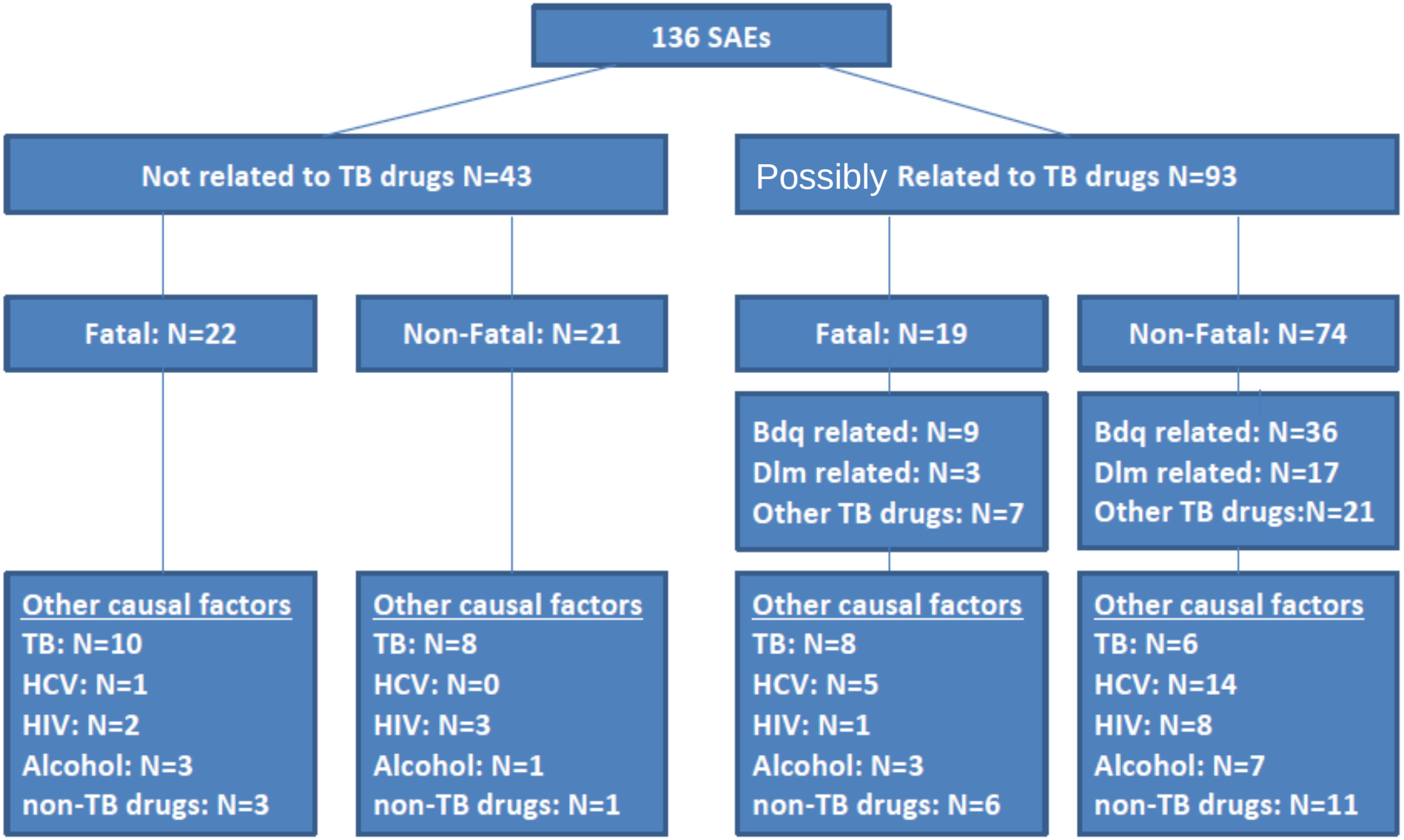
Term	N (%)	% fatal per SAE group	Median [IQR] time to SAE
Increased liver enzymes	26 (19.1)	0	1.5 [1.0-3.7]
QTcF Interval	12 (8.8)	0	2.2 [0.8-3.1]
Respiratory failure	8 (5.9)	5 (62.5)	1.7 [1.0-2.6]
Anemia	7 (5.1)	2 (28.6)	2.1 [0.6-3.3]
Cardiac failure	7 (5.1)	5 (71.4)	2.8 [0.3-4.8]
Infections	6 (4.4)	3 (50.0)	3.4 [0.7-5.1]
TB disease progression	5 (3.7)	5 (100)	2.1 [1.5-2.3]
Death	4 (2.9)	4 (100)	3.5 [2.9-4.0]
Myocardial infarction	4 (2.9)	4 (100)	1.3 [0.3-3.8]
Vomiting	4 (2.9)	0	2.8 [1.9-3.3]

SAE outcomes

Outcomes of Serious Adverse Events	N (%)
Fatal	41 (30.1)
Not recovered not resolved	6 (4.4)
Recovered/resolved	64 (47.1)
Recovering/resolving	15 (11.0)
Recovered/resolved with sequelae	7 (5.5)
TOTAL	133*

➢**41 fatal SAEs, concerning 36 patients**

*NOTE: Outcome unknown for 3 SAEs



Beta blockers related to fatal SAE: not recommended to treat QT prolongation or bradycardia
Other Non TB drugs include anti-retroviral drugs and polypharmacy

QTcF prolongation >500 msec

	AEI	SAE	Total= 15
QTcF prolongation with symptoms	0	2	2
QTcF prolongation without symptoms	7	6	13
Outcome			
Fatal	0	0	0
Resolved	7	7	14
Not recovered/not resolved /ongoing		1	1
Possible relation to TB drugs	5	8	13*
Final action taken on Bdq/Dlm			
Dose maintained	5	5	10
Drug withdrawn		2	2
Not applicable/unknown	2	1	3

Conclusions

- Good reporting on SAEs and AEIs
- AEIs common but most of low severity related to both new, re-purposed and conventional TB drugs such as linezolid and injectables
- Fatal SAEs often have other contributing factors such as comorbidites, tuberculosis and other non TB drugs such as betablockers
- QtcF prolongation was reported frequently but very few over 500msec and no fatality
- Raised liver enzymes are common AEI and SAE: attention to comorbidities and more analysis needed

THANK YOU!