aDSM – safety of new and repurposed drugs
Experience in the endTB project

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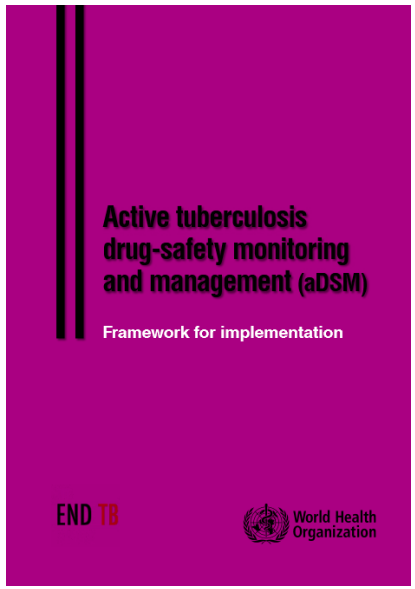
Global Consultation on Transition towards new and better treatments of DRTB and LTBI

Introduction

- Concerns about safety of bedaquiline and delamanid - particularly regarding cardiotoxicity
- Phase II trials revealed a risk of prolonged QT interval
- Bedaquiline has been used widely in selected populations without additional safety concerns
- endTB observational study looks at the safety in patients receiving MDR-TB regimens containing bedaquiline or delamanid

Active TB drug safety monitoring & management (aDSM)

- Part of routine patients' monitoring and care for MDRTB
- Patients undergo active and systematic clinical and laboratory assessment to detect drug toxicity and adverse events (AEs)
- All AEs detected are managed in a timely manner
- Standardized data are systematically collected and reported for any detected Serious Adverse Event (SAE)



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											

Safety data collected and reported

- **Data collection:**
  - SAEs (    )
  - AEs of special interest
  - AEs of clinical significance (drug stopped)

- **Reporting:**
  - Only SAEs
  - To the National aDSM coordination / National Authorities & PV Unit (Geneva)

Safety Question in endTB Interim Analyses

What types of adverse events are observed in patients receiving multidrug regimens that include bedaquiline and/or delamanid?

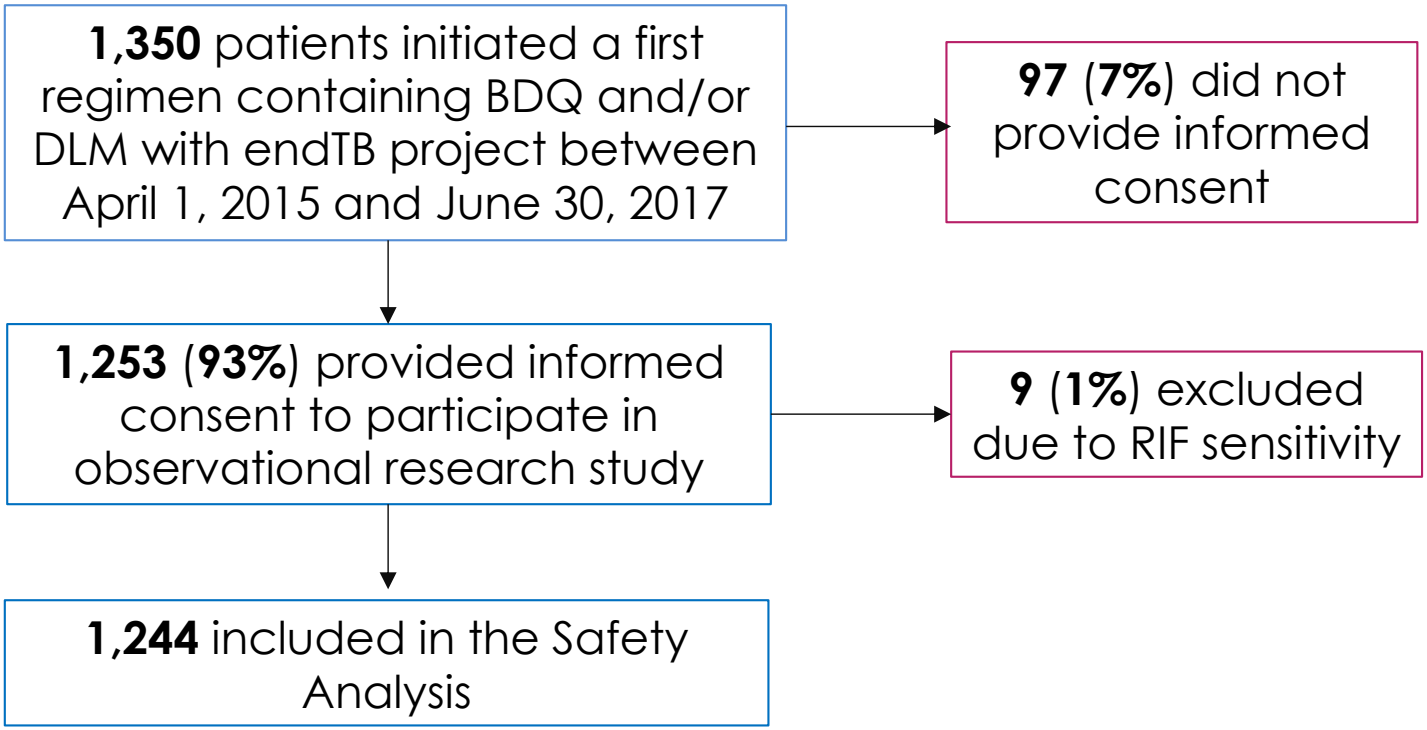
1. Frequency of patients experiencing at least one clinically relevant AEs
2. Incidence of clinically relevant AEs
3. Incidence of specific clinically relevant AEs in patients receiving an injectable drug and in patients receiving linezolid at initiation of Bdq and/or Dlm

Methods

Patients started Bdq and/or Dlm between April 2015 - June 2017

AE of special interest	Threshold grade for clinically relevant AEs and definitions	
QT prolongation	≥3	3: QTcF >= 501 msec no symptoms 4: QTcF > 501 or 60msec increase AND symptoms
Peripheral neuropathy	≥2	2: Moderate discomfort, BPNS sensory score 4-6
Optic neuritis	≥1	1: Clinical diagnosis, no symptoms, 2, 3, 4: reduction in VA
Myelosuppression		Anemia grade 3 (< 7.9g/dl); Platelets grade 3 (<50,000/mm3); WBC grade 3 (<2000/mm3); Lymphocyte grade 3(<500/mm3); Neutrophil grade 2 (<750/mm3)
Hearing loss	≥1	1: Shift of 15-25dB at 2 frequencies
Acute renal failure	≥2	2: Creatinine 2-3 times above baseline
Hypokalemia/ hypomagnesemia	≥1	K: < 3.4 mmol/l requiring K replacement Mg: < 1.4 mmol/l requiring Mg replacement
Hepatotoxicity	≥3	3: > 5 times the upper limit of normal
Hypothyroidism	≥2	2: Symptomatic requiring thyroxin replacement

Results


1,350 patients initiated a first regimen containing BDQ and/or DLM with endTB project between April 1, 2015 and June 30, 2017
97 (**7%**) did not provide informed consent
1,253 (**93%**) provided informed consent to participate in observational research study
9 (**1%**) excluded due to RIF sensitivity
1,244 included in the Safety Analysis

Characteristics of endTB Study Cohort

	Total n (%) N=1244	BDQ only n (%) N=848	DLM only n (%) N=354	BDQ & DLM n (%) N=42
Median age [IQR]	35 [27-46]	35 [27-45]	37 [29-48]	37 [29-45]
Female	415 (33)	298 (35)	107 (30)	10 (24)
BMI <18.5 (N=968)	283 (29)	188 (30)	80 (28)	15 (37)
Diabetes mellitus(N=1187)	135 (11)	85 (10)	43 (13)	7 (1)
HIV infection (N=1223)	143 (12)	69 (8)	72 (20)	2 (5)
Hepatitis B (N=1227)	49 (4)	31 (4)	16 (5)	2 (5)
Hepatitis C (N=1231)	167 (14)	95 (11)	61 (17)	11 (26)

Characteristics of endTB Study Cohort

	Total n (%)	BDQ only n (%)	DLM only n (%)	BDQ & DLM n (%)
Past TB 2nd-line drugs (N=1063)	964 (78)	694 (82)	229 (65)	41 (98)
Radiographic findings				
Bilateral (N=1111)	733 (66)	489 (65)	210 (67)	34 (83)
Cavitary (N=1061)	622 (59)	410 (57)	177 (59)	35 (85)
Resistance profile				
MDR-TB (no FQ or inject)	313 (25)	163 (19)	147 (42)	3 (7)
MDR-TB + inject resistance	161 (13)	100 (12)	60 (17)	1 (2)
MDR-TB + FQ resistance	316 (25)	255 (30)	58 (16)	3 (7)
XDR-TB	419 (34)	310 (37)	79 (22)	30 (71)
Not tested for RR/MDR	35 (3)	20 (2)	10 (3)	5 (12)

Baseline Regimen Characteristics

	Total n (%)	BDQ only n (%)	DLM only n (%)	BDQ & DLM n (%)
Prothio/Ethionamide	446 (36)	292 (34)	153 (43)	1 (2)
PAS	462 (37)	340 (40)	116 (33)	6 (14)
Moxi/Levofloxacin	778 (63)	491 (58)	278 (79)	9 (21)
Linezolid	1020 (82)	728 (86)	251 (71)	41 (98)
2nd-line injectable	643 (52)	491 (58)	145 (41)	7 (17)
Imipenem or Meropenem/Cilastatin	232 (19)	154 (18)	58 (16)	20 (48)
Clofazimine	839 (67)	601 (71)	200 (57)	38 (91)
Cycloserine	851 (68)	569 (67)	270 (76)	12 (29)
Pyrazinamide	690 (56)	486 (57)	191 (54)	13 (31)

Frequency and Incidence of clinically relevant AEs

AE term and grade	Patients N (%)	Time to first AE Median [IQR]	Incidence /100 person-months (95% CI)
Hypokalemia/ hypomagnesia	327 (26.3)	3.0 [1.0-8.0]	2.15 (1.93-2.40)
Hearing loss	211 (17.0)	3.7 [2.0-6.9]	1.29 (1.13-1.47)
Peripheral neuropathy	107 (8.6)	4.1 [2.0-7.5]	0.60 (0.50-0.73)
Hepatotoxicity	71 (5.7)	2.1 [1.0-7.0]	0.38 (0.30-0.49)
Hypothryoidism	59 (4.7)	4.0 [2.9-7.3]	0.32 (0.25-0.42)
Acute renal failure	52 (4.2)	1.9 [0.9-5.2]	0.28 (0.22-0.37)
Myelosupression	49 (3.9)	1.9 [0.6-4.9]	0.27 (0.20-0.35)
QT prolongation	34 (2.7)	2.0 [0.7-6.4]	0.18 (0.13-0.26)
Optic neuritis	30 (2.4)	7.2 [3.6-13-1]	0.16 (0.11-0.23)

Clinically Relevant AEs while on Drug of Interest

AEs	Patients with ≥ 1 N, % (95% CI)	Person time exposure (months)	Incidence per 100 person-months (95% CI)
QT prolongation ≥ grade 3 (bedaquiline and/or delamanid)	34/1244 **2.7 (1.5-4.8)**	BDQ only: 12,968 DLM only: 4916 Combined: 620	**0.18 (0.13-0.26)**
Hearing loss all grade (injectable)	128/643 **19.9 (12.5-30.1)**	3803	**3.36 (2.83-4.00)**
Hearing loss all grade; Acute renal failure ≥ grade 2; or Hypokalemia, hypomagnesemia (injectable)	229/643 **35.6 (28.0-44.0)**	4236	**6.16 (5.46-6.93)**
Peripheral neuropathy ≥ grade 2; Myelosuppression; or optic neuritis all grades (linezolid)	112/1020 **11.0 (7.9-15.0)**	12,685	**0.94 (0.78-1.13)**

Discussion

1. Most frequent clinically relevant AEs associated with injectables and linezolid:

- Hearing loss (17%), hypokalemia/hypomagnesemia (9%)
  - Only 50% of patients received injectables
- Peripheral neuropathy (9%)
  - Frequent, less than in other cohorts
  - 82% patients received linezolid, 70% received cycloserine
  - Other risk factors such as HIV, diabetes, alcohol, other treatment such as ARVs
  - Other linezolid-related AEs also important but less common
- Hepatotoxicity (5.7%, 0.38/100 person months)
  - Alcohol, viral hepatitis risk factors, common in endTB
  - Multiple drugs potentially responsible

Discussion

2. QTc prolongation least common clinically relevant AE (< 3%)

- ALL patients received bedaquiline or delamanid
- 70% clofazimine, 60% fluoroquinolone

3. Toxicity monitoring should reflect risk:

- Audiometry, electrolytes, BPNS, and ECG

Conclusion

- Injectable toxicity was the most common in the endTB patients.
- Linezolid toxicity was also common but less than seen in other cohorts.
- No evidence of any major safety issue with delamanid or bedaquiline.

Interim report would not be possible without the involvement of thousands!

Patients, endTB Teams, National TB Programs, and other collaborators in 15 countries:

1. Armenia
2. Bangladesh
3. Belarus
4. DPR Korea
5. Ethiopia
6. Georgia
7. Indonesia
8. Kazakhstan
9. Kenya
10. Kyrgyzstan
11. Myanmar
12. Lesotho
13. Pakistan
14. Peru
15. S. Africa

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9. Uzma Khan (co-PI)
10. Sarah McAnaw
11. Carole Mitnick
12. Michael Rich
13. KJ Seung (co-PI)
14. Francis Varaine

Hearing loss grades

Grade	Patients N (%)
1	124 (59.9)
2	46 (22.2)
3	31 (15.0)
4	6 (2.9)
Total	207 (100)

* 4 patients with hearing loss and missing grade