Common practices of using new TB drugs in endTB project countries: prolongation, concomitant use and use in special populations

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overview

- Combination
- Prolongation
- Children
- Pregnant women
- Extrapulmonary TB

From new drugs to core drugs

- endTB experience comes from:
  - Clinical practice:
    - patient management with medical committee support when needed
    - endTB clinical guidelines
    - Monitoring of patients and reporting of adverse events
  - Programmatic implementation:
    - access to drugs
    - implementation of monitoring and reporting, support from PV unit for aDSM,
  - Operational research:
    - observational study

endTB Bdq and Dlm use summary

- From the cohort of **2241** patients enrolled on MDRTB treatment in the endTB study and starting Dlm or Bdq before May 2018
  - 923 (41%) patients had **more 24 weeks of Bdq**
    - Median duration of Bdq was **317 days**
  - 619 (28%) patients **had more than 24 weeks of Dlm**
    - Median duration of Dlm was **300 days**
  - 334 patients **had Dlm and Bdq concomittantly**
    - **219** started Dlm and Bdq together
    - **115** had one added to the other (Dlm added to a Bdq containing regimen, or Bdq added to Dlm containing regimen)
    - **238** had more than 24 weeks of Dlm and Bdq together in a MDRTB regimen

Use of bedaquiline or delamanid more than 24 weeks – specific analysis of QT prolongation

- Methods:
  - cohort of patients who started Bdq or Dlm before 1/1/2017
  - Who had at least 12 months of Bdq or Dlm
  - Clinically relevant QtcF prolongation: grade 3 and 4 events in **first 6 months** of treatment with Bdq or Dlm (0-6 months of Bdq or Dlm)and events in the **second 6 months** of treatment with Bdq or Dlm (6-12 months Bdq or Dlm) are reported

Clinically relevant QTcF prolongation

Table 18 Clinical management of prolonged QT interval according to severity grading

Severity grade*	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Electrocardiogram QT Corrected Interval Prolonged	QTcF 450 – 480 ms#	QTcF 481 – 500 ms#	QTcF >= 501 ms without signs/symptoms of serious arrhythmia#	QTcF >= 501 or >60 ms change from baseline and one of the following: Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia#
Action	Monitor more closely; at least weekly ECG until QTcF has returned to less than grade 1. Replete electrolytes as necessary.	Monitor more closely; at least weekly ECG until QTcF has returned to less than grade 1. Replete electrolytes as	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.

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)

Description of cohort at start of Dlm or Bdq of patients with at least 12 months of Bdq or Dlm from cohort of MDRTB patients starting Bdq or Dlm before 1/1/2017

Characteristic N=184	n (%)
Median age [range]	35 [15-67]
Male	116 (63.0)
Body mass index <18.5	78 (42.4)
Bilateral disease	128 (78.0)
Resistance	
MDR or Xpert RR	17 (9.2)
Pre-XDR (Inj)	23 (12.5)
Pre-XDR (FQ)	38 (20.6)
XDR	97 (52.7)
Other	9 (4.8)

Characteristic N=184	n (%)
Previously treated w/ SLDs	170 (92.4)
Comorbidities	
HIV	9 (5.3)
Hepatitis C	29 (16.8)
Diabetes	21 (12.6)

Other drugs in MDRTB regimen at Dlm or Bdq start	n (%)
Moxifloxacin	68 (37.0)
Levofloxacin	35 (19.0)
Clofazimine	141 (76.6)
Bedaquiline	142 (77.2)
Delamanid	60 (32.6)
Linezolid	172 (93.5)

Use of bedaquiline more than 24 weeks

Results: 146 patients with at least 12 months of Bdq from the cohort of MDRTB patients started Dlm or Bdq before 1/1/2017

	First 6 months of bedaquiline	Second 6 months of bedaquiline
Number of QtcF prolongation events of **clinical relevance** (grade 3 and 4)	6	0
Number of **patients** with QtcF prolongation events of **clinical relevance** (grade 3 and 4)	**6 (4.1%)**	**0**

Use of delamanid more than 24 weeks

- Results: 70 patients with at least 12 months of Dlm from the cohort of MDRTB patients started Dlm before 1/1/2017

	First 6 months of delamanid	Second 6 months of delamanid
Number of QtcF prolongation events of **clinical relevance** (grade 3 and 4)	4	1
Number of **patients** with QtcF prolongation events of **clinical relevance** (grade 3 and 4)	**4 (5.7%)**	**1 (1.4%)**

Use of bedaquiline and delamanid together – specific analysis of QT prolongation

- Methods:
  - Description of cohort of patients who started Bdq or Dlm at the same time before 1/5/2018
  - Specific analysis:
    - In the subgroup of patients who had had at least 6 months of Dlm and Bdq started at the **same** time **1/7/2017** (at least 6 months of followup and dataset complete for AE/SAE - used for interim report)
    - Clinically relevant QtcF prolongation: grade 3and 4 events in the **first 6 months** of treatment with Bdq AND Dlm together

Description of cohort at start of Dlm or Bdq for patients who received both Dlm and Bdq from the cohort of MDRTB patients starting Bdq or Dlm before May 2018

Characteristic N=219	n (%)
Median age [range]	35 [15-69]
Male	137 (62.5)
Body mass index <18.5	103 (47.3)
Bilateral disease	155 (73.5)
Resistance	
MDR or Xpert RR	25 (11.4)
Pre-XDR (Inj)	9 (4.1)
Pre-XDR (FQ)	33 (15.1)
XDR	131 (59.8)
Other	21 (9.6)

Characteristic N=219	n (%)
Previously treated w/ SLDs	207 (94.5)
Comorbidities	
HIV	15 (6.8)
Hepatitis C	42 (19.4)
Diabetes	32 (14.8)

Other drugs in MDRTB regimen at time of starting bedaquiline and delamanid together	n(%)
Moxifloxacin	20 (9.1)
Levofloxacin	17 (7.8)
Clofazamine	200 (91.3)
Linezolid	214 (97.7)

Combination of delamanid and bedaquiline

- How many had clinically relevant QT prolongation: only amongst those who **started** Dlm and Bdq together before 1/7/2017 and in the first 6 months of combination

N= 42	0-6 months of delamanid and bedaquiline together
Number of QtcF prolongation events of **clinical relevance** (grade 3 and 4)	1
Number of **patients** with QtcF prolongation events of **clinical relevance** (grade 3 and 4)	**1(2.4%)**

Pregnancy

- Principles of treating MDR-TB and pregnancy:
  - Important to **balance risk** of teratogenicity with risk of poor outcome for mother and baby due to inadequate regimen
  - Case by case decision: stage of pregnancy, mother clinical status, effective drugs
  - No clinical trials in women: important to collect data on outcomes of mothers and babies
  - Test for pregnancy (before and during treatment), offer contraception,

DRTB drugs in pregnancy

- Bedaquiline: FDA Pregnancy Category B, however, there are no adequate and well-controlled studies of Bdq and pregnancy
- Delamanid is teratogenic in reproductive toxicity studies in animals. No data in humans. It is not yet given a USA FDA pregnancy category but is best avoided in pregnancy unless no other options
- Both clofazimine and linezolid are FDA Pregnancy Category C - Risk cannot be ruled out but used if needed
- Most TB drugs are group C: except injectable drugs (D) and E (B)
- **Avoid** injectables and Eto
- FQ, E, Z commonly used
- Consider : Lzd risk of anemia, Cfz risk of skin coloration baby

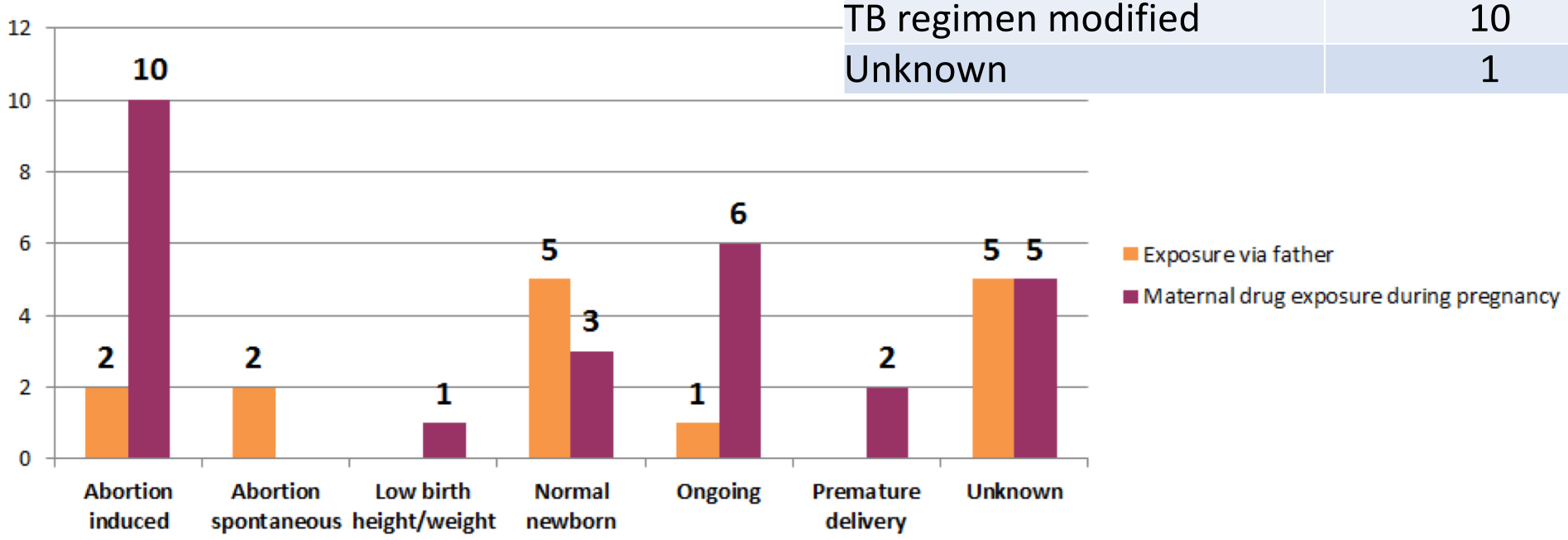
Pregnancy: patient characteristics

42 pregnancies in patient (N=27) or patient's partner (N=15)

- Mother's median age (yrs): 28 (range: 18-40)
- Timing of new drug treatment initiation:
  - –New drug started prior to pregnancy: 20
    - •Median time on treatment (months): 8.9 (range: 1.2-21.3)
  - –New drug started during pregnancy: 7
    - •Very difficult patients to treat, life or death decision
    - •1 patient was 23 weeks pregnant when pregnancy was found *(all false negative pregnancy tests before)*

Pregnancy outcomes

Action taken	Exposure via the mother (N=27)
TB regimen maintained	16
TB regimen modified	10
Unknown	1



Children and adolescents < 18 years old (N=38)

Characteristic	n (%)
Male	9 (24)
Median age [range]	16 [9 – 17]
Body mass index <18.5	25 (66)
Bilateral disease on x-ray (N=)	16 (47)
Resistance MDR Pre-XDR (FQ-R) Pre-XDR (SLI-R) XDR Other	 16 (42) 1 (3) 13 (34) 7 (18) 1 (3)
HIV	0 (0)
Culture positive at the start of new drug (N=34)	17 (50)

Extrapulmonary (EP) tuberculosis

- 67 patients with EP or EP and pulmonary TB
- Site of EP (may be multiple)
  - Bone or joint: 12
  - Brain: 11
  - Lymph node: 15
  - Abdominal:7
  - Pleura: 10
  - Pericarditis: 2
  - Other: 2

Other drugs in MDRTB regimen at time of starting Bdq or Dlm	n(%)
Moxifloxacin	12 (18)
Levofloxacin	34 (51)
Clofazamine	46 (69)
Bedaquiline	47 (70)
Delamanid	25 (37)
Linezolid	43 (64)

Conclusions

- endTB projects developed wide experience with Bdq, Dlm, Cfz and Lzd with support from medical committee
- Preliminary analyses: No QT prolongation concerns when prolonging Bdq/Dlm or using in combination
- Clinical practice, expert support and early evidence helps guide programmatic use
  - Clinicians quickly develop skills with increasing use
  - Programmes have included drugs with few difficulties
- All data collected will help contribute to the knowledge base
- Patients are waiting :)