Bedaquiline and delamanid: expanded indications

Patient needs and evidence based medicine

Cathy Hewison: Médecins Sans Frontières

DRTB STAT

November 30th 2017

What are expanded indications for Bdq/Dlm?

- Optimal use of new drugs
- Patient by patient decision by clinicians based on patient treatment needs
- Is not always off label
- Includes:
  - > 24 weeks Bdq and Dlm
  - Combination Bdq and Dlm
  - Bdq and Dlm in children and adolescents
  - Bdq in Pregnant women

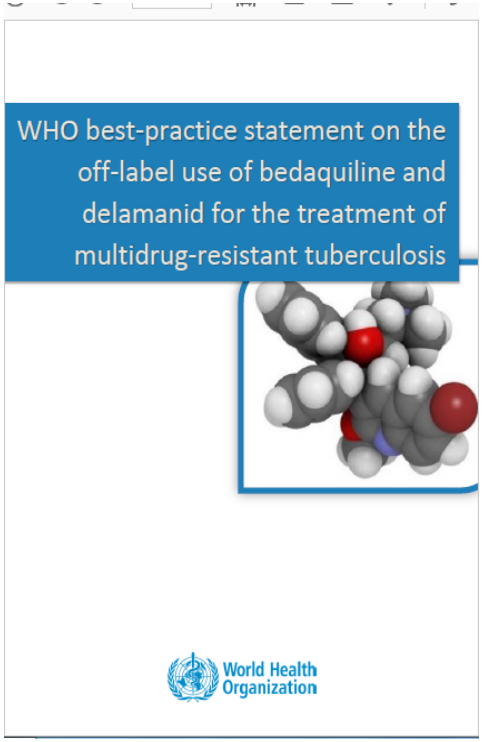
WHO best practice on expanded indications (« off-label » use)

"Off-label use" is legal

"Off label" is common (especially in special populations)

"Off-label use" falls under the purview of national regulatory agencies

"Off-label use" is usually case by case



MDR-TB: an off-label disease

All re-purposed drugs do NOT have the indication for the treatment of TB

- Linezolid
- Clofazimine
- Carbapenems
- Amoxicilline/Clavulanate
- …. but also Fluoroquinolones and Second-line Injectables

MSF and endTB experience

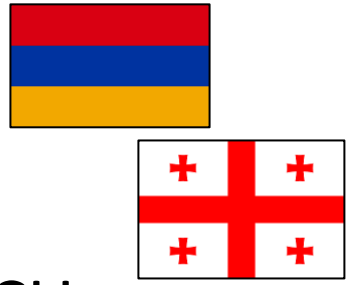
- Early experience of new drug use through compassionate use
- Role of the endTB medical committee
- Patient needs based decision making by clinicians
- Following WHO recommendations on sufficient number of effective drugs

=> how to make best use of Bdq and Dlm

MORE THAN 24 WEEKS

Prolonged Bdq/Dlm use: why?

Georgia and Armenia CU cohort[1]



82 MDR-TB patients receiving Bdq through CU

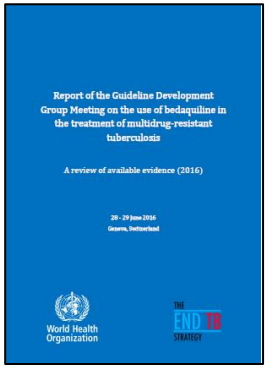
- 6 month culture conversion > 80%
- High reversion rates after stopping Bdq (19%)
- End of treatment success rate: 55-60 %

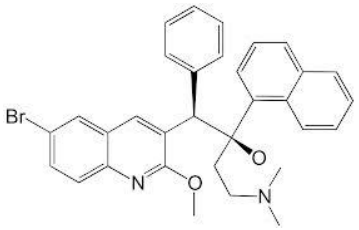
1: Hewison et al. Union World Conference on Lung Health, Guadalajara: OA-188-13 - Culture conversion and reversion of multidrug resistant tuberculosis patients receiving bedaquiline in a compassionate use programme in Armenia and Georgia

Prolonged Bdq use: recommendations

- NOT off-label
- Manufacturer: 24 weeks of treatment (based on clinical trial data - Bdq) but with possibility of > 24
- WHO: max 24 weeks of treatment, but…2017 no negative recommenations

Data seemed to indicate an absence of effect of duration of bedaquiline exposure [higher than six months] on QTc prolongation >480 ms. However, the very limited sample size needs to be noted.
There is limited evidence, so far, to warrant its use beyond 6 months.



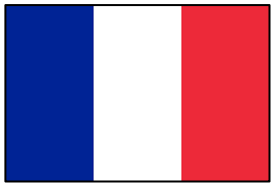


Bedaquiline extension beyond 24 weeks

Evidence overview

N=1

N=33/45

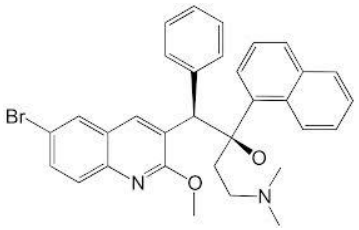


N=76

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

endTB symposium
Union conference
Mexico 2017

1. Lewis et al, Eur Resp J 2016.
2. Guglielmetti et al, Eur Resp J 2017.
3. Sinha A. Liverpool, Union Congress 2016, MSF Satellite Symposium.
4. endTB symposium, Union World Conference on Lung Health, Guadalajara, 2017, Accelerating TB elimination through access to bedaquiline and delamanid



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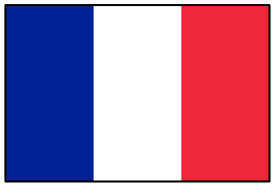
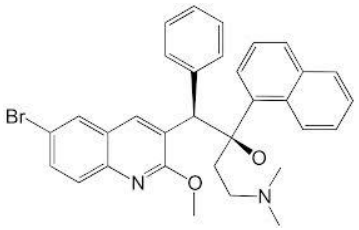


N=76

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

Patient cured, no severe adverse events

1. Lewis et al, Eur Resp J 2016.
2. Guglielmetti et al, Eur Resp J 2017.
3. Sinha A. Liverpool, Union Congress 2016, MSF Satellite Symposium.



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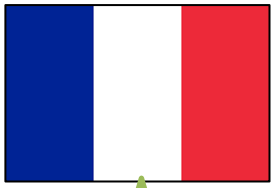

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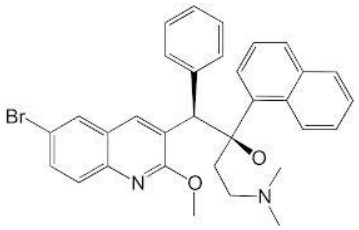
MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

- 33/45 pts >6 mts Bdq, 15 for full treatment
- 80% favorable outcomes, no difference between the two groups
- No difference in tolerability between standard and prolonged Bdq

1. Lewis et al, Eur Resp J 2016.
2. Guglielmetti et al, Eur Resp J 2017.
3. Sinha A. Liverpool, Union Congress 2016, MSF Satellite Symposium.



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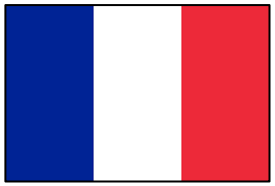


N=76

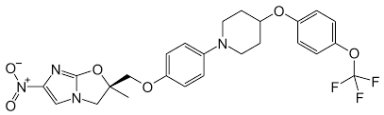
MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

- Different duration of Bdq treatment, few pts until the end of ttt
- 6-month culture conversion: 82%
- Low rate of SAE
- Outcomes pending

1. Lewis et al, Eur Resp J 2016.
2. Guglielmetti et al, Eur Resp J 2017.
3. Sinha A. Liverpool, Union Congress 2016, MSF Satellite Symposium.

Prolonged Dlm use: recommendations

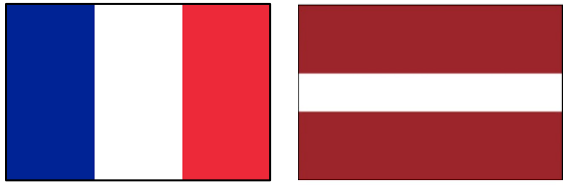
- EMA: 24 weeks
- Clinical trial more than 24 weeks in many patients
- WHO: No maximum but standard duration of 6 months



Delamanid extension beyond 24 weeks

Evidence overview

N=19/30



N=9

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

endTB

endTB symposium
Union conference
Mexico 2017

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2. Sinha A. Liverpool, Union Congress 2016, MSF Satellite Symposium.
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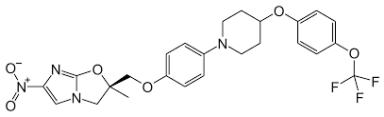
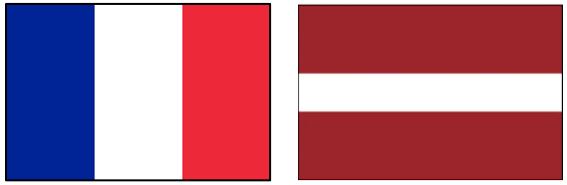


Delamanid extension beyond 24 weeks

Evidence overview

N=19/30

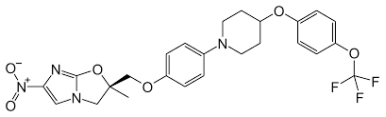


N=9

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

- Different treatment durations
  - 1 SAE
  - Treatment ongoing

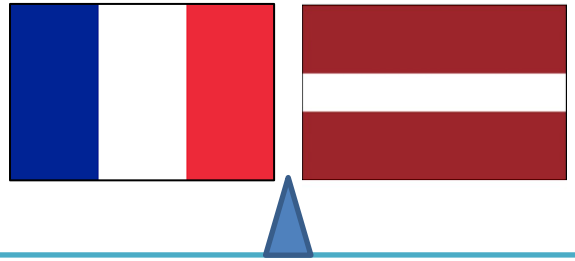
1. Guglielmetti et al, Union Congress 2017; accepted abstract.
2. Sinha A. Liverpool, Union Congress 2016, MSF Satellite Symposium.



Delamanid extension beyond 24 weeks

Evidence overview

N=19/30



N=9

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

- 19/30 > 24 weeks of delamanid; median duration 275 days
- SAE in 7 (23%) patients; QTcF>500ms in 2 patients (7%); no arrhythmias / symptomatic cardiac AE
- 6-month culture conversion: 86%
- Outcomes (24 pts): 20 (83%) cured and 4 (17%) lost to follow-up

1. Guglielmetti et al, Union Congress 2017; accepted abstract.
2. Sinha A. Liverpool, Union Congress 2016, MSF Satellite Symposium.

endTB Extended use of Bdq or Dlm

- 223 of 687 (32%) patients received more than 24 weeks of treatment:
  - 157 (70%) received Bdq extension alone
  - 38 (17%) received Dlm extension alone
  - 28 (13%) received extension of both Bdq and Dlm

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Union conference
Mexico 2017

endTB symposium, Union World Conference on Lung Health, Guadalajara, 2017, Accelerating TB elimination through access to bedaquiline and delamanid

Extended use of Bdq or Dlm: safety

AEI (N=91)	0 to 6 months of treatment			6 to 12 months of treatment		
	N events	% of pts	% in grade 3 or 4	N events	% of pts	% in grade 3 or 4
Increased liver enzymes (ALT increased or AST increased (≥ 1.1 x ULN))	55	24.4	5.4	32	23.0	0
Prolonged(corrected) QT interval	38	16.9	2.6	25	18.0	8.0
Peripheral neuropathy	26	11.6	15.4	9	6.5	11.1
Acute kidney injury	22	9.8	0.0	17	12.2	0

AEI = Adverse Event of Interest

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Extended use of Bdq or Dlm: safety

SAE (=91)	0 to 6 months of treatment		6 to 12 months of treatment	
	N	%	N	%
Patients with ≥ 1 SAE	14	15.4	13	14.3
Total number of SAE	17		20	
Electrocardiogram QT Corrected Interval	3	17.7	1	5.0
Increased liver enzymes	1	5.9	1	5.0
Acute kidney injury	1	5.9	0	0

SAE = Serious Adverse Event

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Prolonged Bdq/Dlm use: criteria (endTB guide)

Criteria for Bdq or Dlm extension	Definition
Late treatment response	Sputum culture-positive after 3 months (not treatment failure) AND positive bacteriologic / clinical evolution
Insufficient number of effective drugs in the treatment regimen	< 3 effective drugs in the regimen if Bdq or Dlm is stopped. If an injectable drug is given and it is planned to discontinue it, it should not be counted.

Prolonged Bdq/Dlm use: pre-requisites (endTB guide)

Pre-requisite	Comments
Good adherence	Good treatment adherence during the first 24 weeks of treatment.
Good tolerability	No SAE linked to Bdq / Dlm during the first 24 wks, or SAE is resolved.
No treatment interruption	Bdq or Dlm should be prolonged without interrupting it
Informed consent	Additional informed consent for treatment extension should be signed
Closely monitored treatment	Specific monitoring should be extended for the entire duration of Dlm / Bdq exposure.

DLM AND BDQ COMBINATION

Combination of Bdq and Dlm use: recommendations

- No evidence
- No recommendation
- Was possible with Otsuka compassionate use program
- Accepted by drug companies in clinical trials
- Ongoing Drug-Drug Interaction study (DELIBERATE)

Bdq-Dlm combination: why?

ANTIBIOGRAMME		
date : 18/11/2013		
	Géno	Phéno
INH	Kat G **S315T** InhA **-15C>T**	**R**
RIF	rpoB **S531L**	**R**
EMB	EmbB **M306V**	**R**
PZA	pncA **G97D**	**R**
SM		**R**
AMK	rrs **1401A>G**	**R**
KAN		**R**
CAP		**R**
OFX	GyrA **D94G** GyrB S	**R**

	Géno	Phéno
MXF	GyrA **D94G** GyrB S	**R**
ETH	ethA **Q254** ethR S	**R**
PAS		**R**
CYC		**R**
LNZ	rplC **T460C** rrl S	**R**
TMC207	atpE S Rv0678 **ins g140**	**R?**
CFZ		
IPM/AMX		

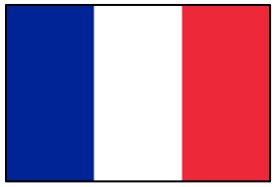
Bdq-Dlm combination

Evidence overview

N=1

N=5

N=11/30



N=28

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DOCTORS WITHOUT BORDERS

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1. Tadolini et al, Eur Resp J 2016
2. Maryandyshev A et al.
3. Guglielmetti et al, Union Congress 2017; accepted abstract.
4. Lachatre et al, Lancet Inf Dis 2015
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Bdq-Dlm combination

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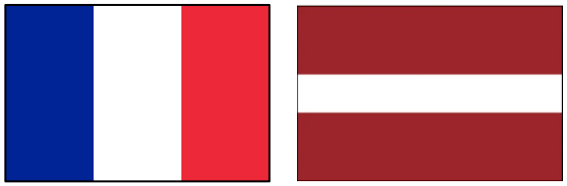

N=28

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

- Good initial treatment response
- QTc prolongation (<500 ms)
- Treatment ongoing

1. Tadolini et al, Eur Resp J 2016
2. Maryandyshev A et al.
3. Guglielmetti et al, Union Congress 2017; accepted abstract.
4. Lachatre et al, Lancet Inf Dis 2015
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Bdq-Dlm combination

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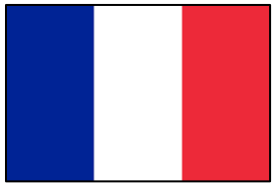

2 patients with QT > 500 msec
- not requiring stopping of combination, resolved
- no arrythmia

1. Tadolini et al, Eur Resp J 2016
2. Maryandyshev A et al.
3. Guglielmetti et al, Union Congress 2017; accepted abstract.
4. Lachatre et al, Lancet Inf Dis 2015
5. Ferlazzo G. Liverpool, Union Congress 2016, MSF Satellite Symposium

Bdq-Dlm combination

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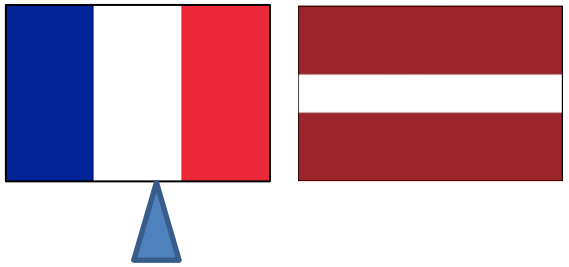
N=1 N=5 N=11/30 N=28






- 11/30 received the Bdq/Dlm combination: 6 as concomitant treatment, 5 as sequential treatment but without wash-out
- SAE in 4 patients; QTcF>500ms in 2 patients; no arrhythmias nor symptomatic cardiac side effects occurred.
- 6-month culture conversion: 100%; Outcomes: 5 ongoing, 5 cure, 1 LTFU

1. Tadolini et al, Eur Resp J 2016Maryandyshev A et al.
2. Guglielmetti et al, Union Congress 2017;
3. Lachatre et al, Lancet Inf Dis 2015
4. Ferlazzo G et al , Union Congress 2017; accepted abstract.

Bdq-Dlm combination

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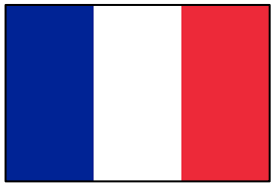

- 28 patients (40% HIV Positive), 86% resistant to FQ
- 16 SAE in 7 patients;
- NO QTcF>500ms. 6 episodes of > 60 msec in 4 patients. No arrhythmias nor symptomatic cardiac side effects occurred.
- 6-month culture conversion: 74%; Outcomes: 27 ongoing, 1 death

1. Tadolini et al, Eur Resp J 2016
2. Maryandyshev A et al.
3. Guglielmetti et al, Union Congress 2017;
4. Lachatre et al, Lancet Inf Dis 2015
5. Ferlazzo G et al , Union Congress 2017;

endTB combined Bdq / Dlm Use

- 46 patients ever received Dlm and Bdq in combination
- 22 (48%) started Dlm and Bdq combination within 7 days of each other
- 24 (52%) started Dlm and Bdq sequentially
  - Dlm added to Bdq: 18 (75%)
  - Bdq added to Dlm: 6 (25%)
- 8/11 (73%) culture +ve culture converted

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Efficacy and safety of combined use with Bdq and Dlm

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Includes 22 patients who started Bdq and Dlm together

AEI term (37 Aes of interest in the first 6 mos)	N	%	Number in grade 3 or 4	Median [IQR] time to AEI
Prolonged (corrected) QT interval	9	24	1	3.0 [1.5-4.6]
Increased liver enzymes (ALT increased or AST increased (≥ 1.1 x ULN))	8	22	0	2.1 [1.0-2.9]
Peripheral Neuropathy	8	22	0	3.5 [1.3-5.0]

- No SAEs were reported in the first 6 months of treatment

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Bdq/Dlm combination: recommendations

- NOT off-label
- Manufacturer: ok (currently tested in trials)
- WHO: (concomitant treatment or sequential treatment without washout (Bdq->Dlm: 5.5 mts; Dlm->Bdq: 5 days) in selected patients

Safety of use together is not established. Until more data is available, no recommendation for or against simultaneous use can be made. Concomitant use of bedaquiline and delamanid is the responsibility of individual expert clinicians and should only be considered for individual patients (…)

PAEDIATRIC AND ADOLESCENT USE

Pediatric use: evidence

Delamanid

- 19 patients (8-17 y.o.)
- 13/16 (81.2%) converted
- 18/19 good tolerance

N=19

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DOCTORS WITHOUT BORDERS

- 5 adolescents
- Good tolerance/efficacy

N=5

Bedaquiline

- 27 children and adolescents
- Median age was 16 (range 10–17) years
- Good tolerance/efficacy

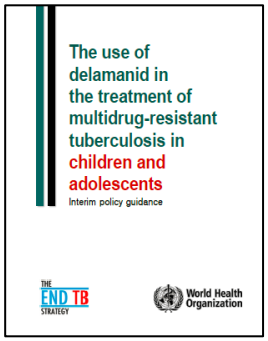
1. Tadolini et al, Eur Resp J 2016.
2. Sharipov B. Presented at the MSF TB Symposium 2016, Minsk, Belarus.
3. Achar et al, EID, 2017

Pediatric use: recommendations

Delamanid

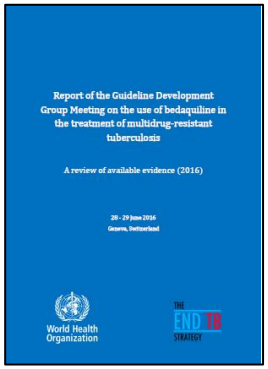
Children 6-17 years old, MDR-TB or RR-TB, not eligible for the WHO-recommended shorter MDR-TB regimen:

- Previous treatment with second-line drugs
- Additional resistance to Fq/SLI
- Contraindication shorter MDR-TB regimen drugs
- Pregnancy and extrapulmonary TB



Bedaquiline

(…) in some instances, bedaquiline has been used in adolescents. However, data are insufficient to make any recommendation.



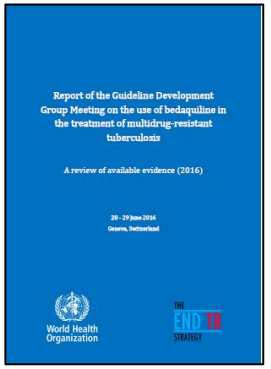
Pediatric use: dosage

Delamanid

- >35kg: 100mg twice daily
- 20-35kg: 50mg twice daily
- <20 kg and <6 y.o.: right dose unknown, in general 3-4 mg/kg
- No pediatric formulation available

Bedaquiline

- Adolescents (≥33 kg and >12 y.o.): standard dose
- Children <33kg: 6 mg/kg loading, then 3 mg/kg
- No pediatric formulation available



Pregnant women

Table 1. FDA Drug Risk Classification

Category	Description
A	Controlled studies in humans show no risk to the fetus
B	No controlled studies have been conducted in humans; animal studies show no risk to the fetus
C	No controlled studies have been conducted in animals or humans
D	Evidence of human risk to the fetus exists; however, benefits may outweigh risks in certain situations
X	Controlled studies in both animals and humans demonstrate fetal abnormalities; the risk in pregnant women outweighs any possible benefit

Source: References 4-7.

Pregnant women

Safety of anti-TB drugs in pregnancy

Medication	Safety class*	Comments
First-line anti-TB drugs		
Isoniazid (H)	C	Experience in gravid patients suggests safety. Pyridoxine (vitamin B6) should be used during pregnancy.
Rifampin (R)	C	Experience in gravid patients suggests safety.
Ethambutol (E)	B	Experience in gravid patients suggests safety.
Pyrazinamide (Z)	C	Experience in gravid patients suggests safety; however, there is less data than other first-line anti-TB drugs. WHO recommends its routine use.
Streptomycin (S)	D	Documented toxicity to developing fetal ear. Risks and benefits must be carefully considered. Avoid use when possible.

CONDITIONS AND SITUATIONS

Pregnant women

Second-line anti-TB drugs		
Kanamycin (Km) Amikacin (Am)	D	Documented toxicity to developing fetal ear. Risks and benefits must be carefully considered. Avoid use when possible.
Capreomycin (Cm)	C	Avoidance strongly recommended. Less ototoxicity reported in adults with capreomycin than with aminoglycosides; unknown if these data can be extrapolated to the developing fetal ear. Generally, injectables are avoided in the gravid patient, but in life-threatening situations when an injectable is needed capreomycin could be considered. (Wavy ribs were reported in studies with rodents.)
Fluoroquinolones	C	Use with caution when essential. No teratogenic effects seen in humans when used for short periods of time (two to four weeks). Long-term use in gravid patients is limited, but given bactericidal activity, benefits may outweigh risks.
Ethionamide (Eto)	C	Avoid if possible. Teratogenic effects observed in animal studies; significantly worsens nausea associated with pregnancy.
Cycloserine (Cs)	C	No significant experience in gravid patients; animal studies have not documented toxicity.
PAS	C	Use with caution when essential. Not considered to be teratogenic.

New drugs in pregnant women

Delamanid

- Teratogenic in reproductive toxicity studies in animals
- No data in humans.
- Passage in breast milk: ***unknown.*** Breastfeeding not recommended

Bedaquiline

- Animal reproduction studies: no fetal risk
- No data in humans (FDA pregnancy category B)
- Drug concentrated in breast milk. ***Breastfeeding not recommended***

Pregnant women

- Bedaquiline is FDA Pregnancy Category B, however, there are no adequate and well-controlled studies of Bdq and pregnancy.

- Both clofazimine and linezolid are FDA Pregnancy Category C - Risk cannot be ruled out.

- 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.

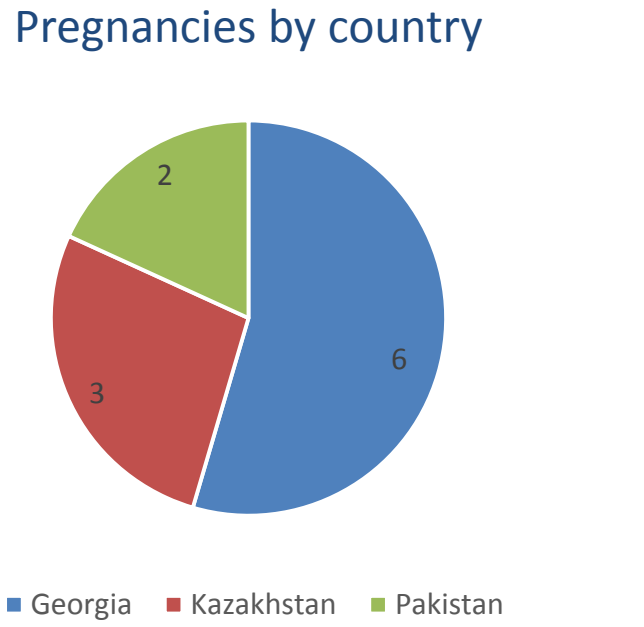
Pregnant women

Bedaquiline (Bdq)	B	Not recommended due to limited data. This drug should only be used in pregnancy when there are clearly no other options.
Linezolid (Lzd)	C	Not recommended due to limited data.
Clofazimine (Cfz)	C	Use with caution when essential; drug appears to be safe during pregnancy when used at lower doses for leprosy, but experience is limited.
Clarithromycin (Clr)	C	Avoid if possible. May be teratogenic.
Rifabutin (Rfb)	B	Experience in gravid patients suggests safety.
Amoxicillin/ Clavulanic acid (Amx/Clv)	B	Experience in gravid patients suggests safety.

*A=Safety established using human studies; B=Presumed safety based on animal studies; C=Uncertain safety, no human studies and animal studies show an adverse effect; D=Unsafe, evidence of risk that may be justifiable under certain clinical circumstances.

end TB Pregnancy: patient characteristics

- 11 pregnancies in patient (N=8) or patient's partner (N=3)
- Mother's median age (yrs): 24 (range: 21 - 33)
- Timing of new drug treatment initiation
  - Prior to pregnancy: 11
    - Median time on Tx (mos): 9.46 (range: 0.83 – 19.8)

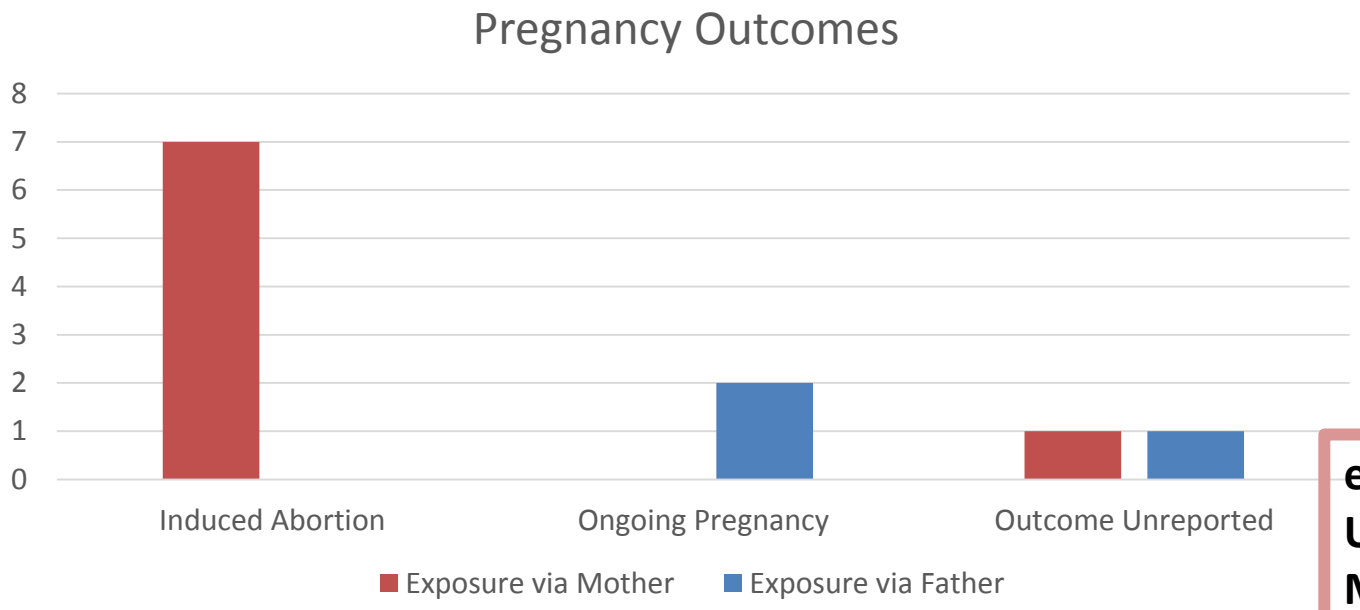


endTB symposium
Union conference
Mexico 2017

endTB symposium, Union World Conference on Lung Health, Guadalajara, 2017, Accelerating TB elimination through access to bedaquiline and delamanid

endTB Pregnancy: outcomes

	Exposure via mother (N=8)	Exposure via father (N=3)
TB regimen maintained	6	N/A
TB treatment modified	1	N/A
Unknown	1	3



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