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

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Compassionate use of Bedaquiline in Armenia and Georgia: end of treatment results

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MEDECINS SANS FRONTIERES

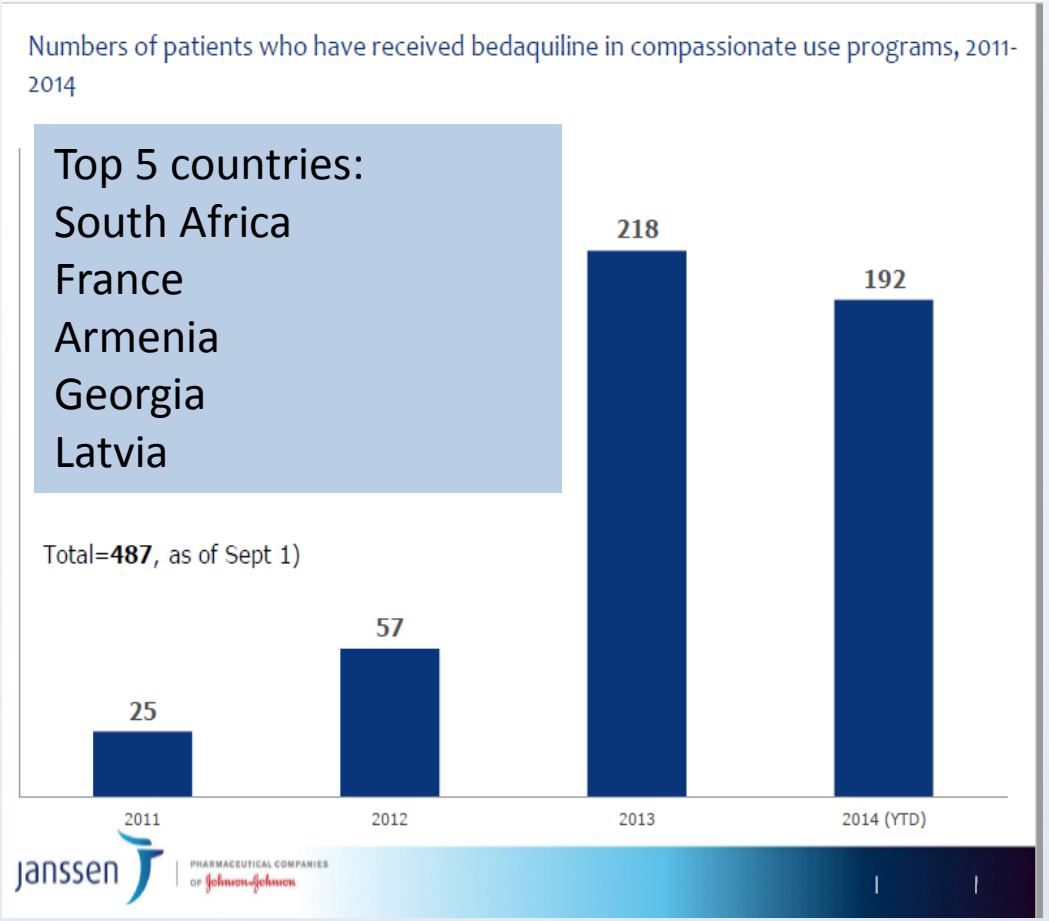
МІНІСТЭРСТВА АХОВЫ ЗДАРОЎЯ РЭСПУБЛІКА БЕЛАРУСЬ

Compassionate use

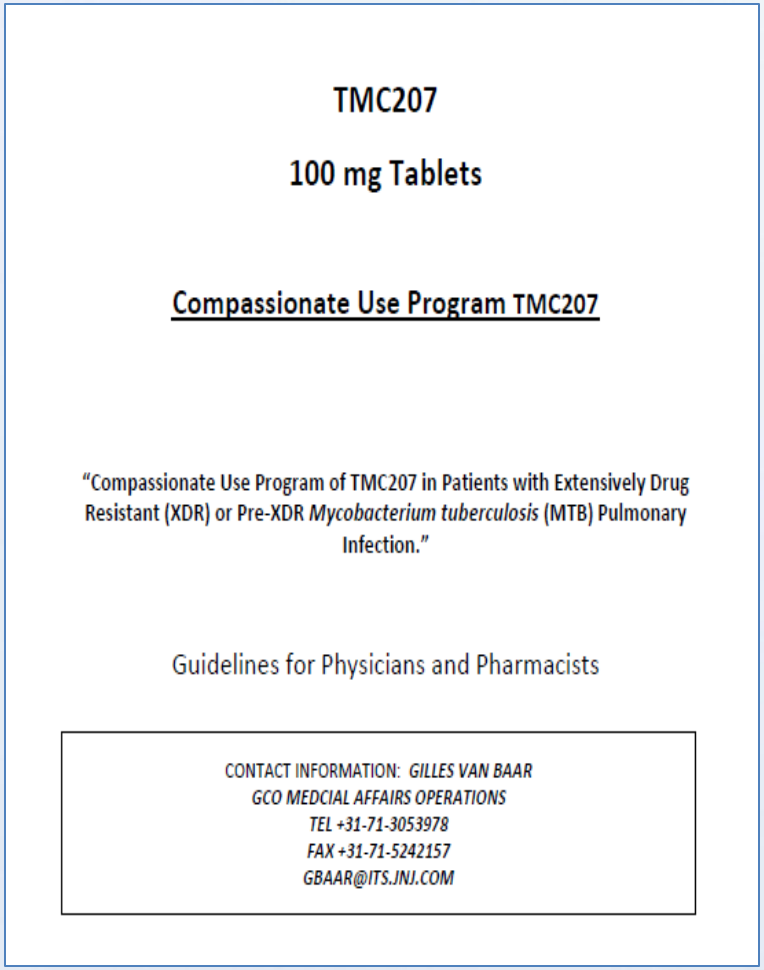
Allows individual use of unauthorized medicines for patients with limited treatment options within a legal framework

Janssen program

- 2011-2015
- 700 patients
- 45 countries



Compassionate use of Bedaquiline



TMC207

100 mg Tablets

Compassionate Use Program TMC207

"Compassionate Use Program of TMC207 in Patients with Extensively Drug Resistant (XDR) or Pre-XDR *Mycobacterium tuberculosis* (MTB) Pulmonary Infection."

Guidelines for Physicians and Pharmacists

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- Individual patient applications
- Supply of 24 weeks only of bdq
- Serious adverse event reporting within 24 hours whilst on Bdq (or any death up to 2 years after start of bdq)

Georgia: 2011-April 2015

- Rationale:
  - High burden of MDR TB
    - ~40% with unfavorable outcomes (death, defaulter, failure)
    - increasing number of pre-XDR and MDR patients
- Steps to introduction
  - MSF pharmacist visit and introduction of CU principal in 2010
  - Agreement at State Regulation Agency of Medical Activities
  - CU agreement with Janssen in 2011 (updated in 2014)
  - Bdq CU importation done by TB center

Georgia: 2011-April 2015

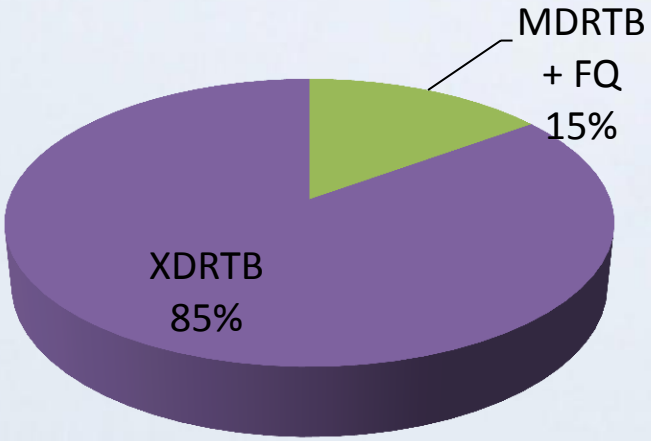
- Challenges
  - Started Bdq CU in 2011 (12 pts before MSF July 2014)
  - Initially not all patients accepted due to lack of repurposed drugs availability
    - July 2014 – MSF technical support (trainings, MSF medical committee recommendations) re-purposed drugs, medical materials for Ipm infusion
    - In 2014 GF also started provision of re-purposed drugs.
  - New I/V component introduction (challenge mainly in out-patient phase of treatment)
  - New clinical skills – different monitoring, new tools to use, awareness of drug to drug interactions, knowledge of long term I/V treatment options (insertion of PAC by surgeons, maintenance/infusions by nurses, etc..)

Georgia: cohort description

Total cohort: 20 patients	n (%)
Age years (median, IQR)	39.5 [30.5 – 50.5]
Sex, male	13 (65.0)
Site: Pulmonary	20 (100)
Previously treated: second line drugs	20 (100)
HIV Postive (n=19)	0
Hepatitis C Antibody positive (n=16)	5/16 (31.2)
Bilateral disease	13 (65.0)
Cavities	16 (80.0)
BMI kg/m^2 (median, IQR) BMI < 18.5 kg/m^2	17.9 [16.6 – 20.6] 12 (60.0)

Georgia: cohort description

DRTB subgroup	
MDRTB + FQ	3 (15.0 %)
XDRTB	17 (85.0 %)



Previous drug use	
FQ	20 (100 %)
Inj	19 (95.0 %)
Cfz	17 (85.0 %)

Drugs used at Bdq initiation (not exhaustive)	
Cfz	17 (85.0%)
Lzd	20 (100 %)
Imipenem	18 (90.0 %)
Mfx	0 (0 %)

Georgia: CU cohort results

Culture status at Bdq/MDRTB treatment start N= 20	n (%)
Culture positive	14 (70.0)
Culture negative	6 (30.0)
Culture conversion rate amongst culture positive	12/14 (85.7)
Time to culture conversion in months (median,[IQR])	3.0 [1.5-3.5]
Reversion	2/12 (16.7)

End of treatment results	n (%)
Cured or treatment complete	11 (55.0)
Failure	0
Death	4 (20.0)
Lost to followup*	5 (25.0)

*80% of LTFU after 9 months

Georgia: serious adverse events reported

5 serious adverse events reported in 5 patients, all fatal
No QTcF > 500 msec reported

Fatal Adverse event term	Related factors	Timing	Related to Bdq?
1. Respiratory failure	Severe XDRTB	During Bdq treatment	No
2. Nephrotic syndome	Severe TB, ? Amyloidosis	During Bdq treatment	possible
3. Suicide	Drug use	After Bdq treatment	No
4. Respiratory failure	Severe XDRTB	After Bdq treatment	No
5. Suicide	Psychiatric illness	After MDRTB treatment	No

Armenia: CU March 2013-April 2015

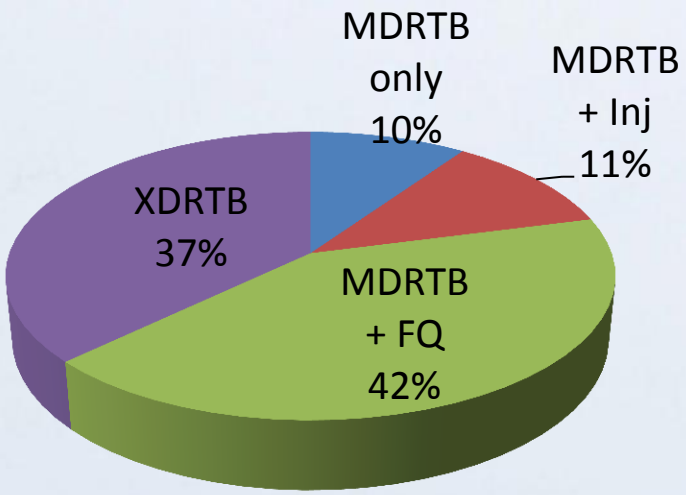
- Rationale:
  - in 2013: high burden MDRTB, 15% failure of MDRTB treatment, 30 patients with no treatment options
- Challenges
  - No CU mechanism, no pharmacovigilance
  - No experience of drugs Lzd, Imp (twice daily IV, portacath)
  - New clinical skills for clinicians (ECG, neurological)
- Steps to introduction
  - Strong williness from NTCC, Ethics board approval, programmatic set up favorable to implemenation of additional monitoring

Armenia: cohort description

Total cohort: 62 patients	N (%)
Age years (median, max-min or IQR)	40.5 [31 – 52]
Sex, male	55 (88.7)
Site: Pulmonary (n=61)	61 (98.4)
Previously treated: Second line drugs	62 (100)
HIV Postive (if CD4 or ARV)	4 (6.5)
Hepatitis C Antibody positive	12 (19.4)
Bilateral disease	40 (64.5)
Cavities	55 (88.7)
BMI kg/m^2 (median, IQR) BMI < 18.5	20.0 [18.4 – 22.9] 16 (25.8)

Armenia: cohort description

DRTB subgroup	
MDRTB only	6 (9.7)
MDRTB + Inj	7 (11.3)
MDRTB + FQ	26 (41.9)
XDRTB	23 (37.1)



Previous drug use	
FQ	61 (98.4)
Inj	62 (100)
Cfz	15 (24.2)

Drugs used at Bdq initiation (not exhaustive)	
Cfz	51 (82.3)
Lzd	62 (100)
Imipenem	44 (71.0)

Armenia: CU cohort results

Culture status at Bdq/MDRTB treatment start N= 62	
Culture positive	49 (79.0)
Culture negative	13 (21.0)
Culture conversion rate amongst culture positive N=	41/49 (83.7)
Time to culture conversion in months (median [IQR])	2.5 [1.5-4.0]
Reversion	8/41 (19.5)

End of treatment results	n (%)
Cured or treatment complete	37 (59.7)
Failure	6 (9.7)
Death	6 (9.7)
Lost to followup*	13 (21.0)

*10/13 LTFU after 9 months, median time to LTFU 17.6months [IQR 12.6 – 23.7]

Armenia: Serious adverse events reported

13 serious adverse events reported in 11 patients, 6 fatal			
1 case QTcF > 500 msec: related to Cfz (stopped) and Bdq (completed)			
Fatal Adverse event terms	**Related factors**	**Timing**	**Related to Bdq?**
1. Myocardial infarction, cardiac failure	Anaemia, extensive TB	During Bdq	Unlikely
2. Respiratory failure	Severe TB, Cor pulmonale	During Bdq	Unrelated
3. Sudden death		During Bdq	Possible
4. Acute respiratory insufficiency	Drug overdose	During Bdq	Unrelated
5. Respiratory failure	Severe TB, Cor pulmonale	During Bdq	Unrelated
6 .Tuberculosis	No response to treatment	20 months of MDRTB	Unrelated

Discussion

- Excellent results in difficult to treat patients:
  - 6 month culture conversion > 80%
    - O'Donnell et al,EID 2013: 36.8% in XDR-TB patients, Pietersen et al 9.3%
  - end of treatment success 55-60 %
    - (WHO Global report 2016, 28% success in XDRTB)

BUT

- High reversion rates after stopping Bdq (17-20%)
  - ➢ more than 24 weeks of Bdq may reduce this
    - ➢ (Guglielmetti et al, ERJ, 2016: 80 success %, no reversion, average 361 days of Bdq)
- ➢ High lost to followup (21-25%, 80% > 9 months)
  - ➢ MDRTB treatment is still 20-24 months long

Discussion

- Introduction of Bdq (CU) improved TB care
  - Early access to Bdq, rapid implemenation of routine use
  - Improved clinician skills
  - Improved detection, management, reporting of AEs
  - Improved access to ambulatory care, home based care
  - Access to and experience of repurposed drugs Imp and Lzd
- Limitations of CU
  - only 24 weeks of Bdq
  - only pulmonary MDR TB cases (EP case in Georgia refused)
  - some very severe cases refused (HIV case from Armenia)

Conclusion and perspectives

- Compassionate use is a useful tool for early access
  - More new drugs coming…get ready with CU mechanism!
- Bdq well tolerated and effective
  - What about < 18 year olds, more than 24 weeks duration ?
- Good results but they could be improved with
  - longer Bdq => WHO guidelines without a maximum duration but case by case assessment?
  - Shorter MDRTB treatment => clinical trials..endTB Georgia

THANK YOU

- All patients
- All Doctors and health staff from:
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  - Helena Huerga (Epidemiologist)
- MSF
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  - MSF medical team Armenia
  - MSF medical team Georgia