New treatments and approaches to Tuberculosis

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Armenia Experience on Treatment of XDR and pre-XDR Patients with New drugs under Compassionate Use program

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Challenges to Introduce CU program in Armenia

- There was no legal framework for compassionate use in general
- No previous use of other group 5 drugs for XDRTB treatments (other than Cfz, Amox-Clav and Clr)
- No use of Investigational New Drugs for other diseases (e.g., cancer, Alzheimer's , AIDS) when other treatment options are exhausted!

Chronology, introduction of CU program for the treatment of DR TB (New /re-purposed anti TB medication)

- **October 2012:** NTP Armenia signed the 'Confidentiality Agreement' with J&J
- **Nov 2012:** NTP formed an Ethic Committee to review bedaquiline use for TB patient
- **Jan 2013:** Ethic Committee and MOH approved Bedaquiline importation for humanitarian reasons (life saving treatment whilst CU legislation is in the process of development)
- **25th January:** first patient sent to MSF-PIH committee – first cases across MSF and PIH
- **Feb 2013:** 1st case sent to J&J
- **March 2013:** Janssen approved 1st 4 cases
- **April 2013:** Bedaquiline received (6-month drugs/patient)
- **Introduction** of Delamanide still under discussion !

Process , Submission & Approval for Treatment under CU Program

1. Treating doctors (MSF/MOH) select patients based on the CU eligibility criteria
2. Present the cases to the DR TB Committee for endorsement
3. Submit the cases to MSF-PIH Medical Committee for endorsement and clinical advices
4. Obtain the written informed consent from the patients
5. Submit the patients clinical dossier to Janssen for the final approval
6. Importation procedure (4-6 weeks)

Eligibility for CU access to new drugs

Criteria for inclusion :

- **XDR**
- **Pre-XDR (FQ)**
- **MDR who have failed all treatment options**
- **Age ≥ 18 yrs,**

Criteria for caution:

- **Laboratory abnormalities (renal and liver function)**
- **Long QT interval or other ECG abnormalities**
- **Family history of long QT syndrome**

Consequences of CU Initiative…

Use of other Repurposed group 5 drugs in the Treatment regimen (Linezolid /Imp)

Challenges :

- **Less known on safety of drugs on long run use.**
- **High Cost (Lzd), now generic is available!**
- **Rout of administration (Imp), Ambulatory ,HBC , Port-a-Cat (Now Possible!)**

Approach :

- Clinical Protocol developed / MOH and MSF staff trained.
- Comprehensive initial clinical assessment, Crucial.
- More frequent medical follow-up , Mandatory.
- Pharmachovigilance reporting system at patient care level established .
- Need to revive clinical skills that traditionally TB doctors/nurses do not practice (e.g, ECG, IV drugs use)

Current Situation, Evaluated cases for New treatment under CU program as of 15.01.2015 (Slide 1)

Total cases evaluated for new treatment with MSF-PIH Expert Committee	**73**	
Approved by MSF-PIH Expert Committee	**69**	96%
Rejected by MSF-PIH Expert Committee	4	4%
Approved by MSF-PIH but died before submission to J&J (n.69)	3	2%
Total cases Submitted to J&J	**66**	
Approved by J&J	**63**	95%
Rejected by J&J	3	5%

Current Situation, Evaluated cases for New treatment under CU program as of 15.01.2015 (Slide 2)

J&J Approved Cases to Started Treatment with Bdq	**63**	%
Patients Started treatment with Bdq	**53**	83%
Patients refused to start treatment with Bdq	6	9%
Lost on follow up before starting treatment with Bdq	2	4%
Died Before starting Treatment with Bdq	1	2%
Approved but not started yet	1	2%

Patients started on Bdq (n=53)

Distribution by Sex (started on Bdq)

- Male : 46 (87%)
- Female: 7 (13%)

DST pattern (started on Bdq)

- XDR : 24 (45%)
- Pre-XDR Flourquinolone (r): 26 (49%)
- Pre-XDR Injectable (r): 3 (6%)

DOT Points (including Failure cases who still continue the background regimen)

- IPD Structures : 15 (36%)
- Ambulatory points (TB cabinets): 19 (45%)
- Home based care : 8 (19%)

Started on Imp: 40 (75%)

- With Port-a-Cat: 13 (33%)
- Without Port-a-Cat: 27(68%)

Bacteriological Status After completion of 6 Months Bdq Course (April 2013 –Jan 2015)

Cases completed Bdq Course (C+,C- at treatment initiation)	**32**	%
1. Culture positive at the treatment initiation	**26**	100 %
Culture converted by 6 months (2 cons Neg culture)	**22**	**84 %**
Culture not converted by 6 months	3	12 %
Culture results Pending	1	4 %
Reverted back to culture positive after conversion (n=22)	4	**18%**
2.Culture Negative at treatment initiation	**6**	%
Remained Culture Negative by end of Bdq Course	**6**	**100 %**

Bacteriological Status, Culture conversion by Months (continue ..)

Culture Convention by Completion of 6 Month Bdq Course (for 26 C+ cases)						
	1st Month	2nd Month	3rd Month	4th Month	5th Month	6th Month
Number of patients cumulative	6	14	15	20	21	22
Proportion Cumulative	23%	54%	58%	77%	81%	85%

-3 cases remained culture positive after 6 Months of Bdq course
-4 Culture converted cases reverted back to Positive later on .

Interim Outcome/status (n.53)

53 Patients Started on Treatment (April 2013-Jan 2015)	N (%)
Still on treatment (excluding failure cases)	36(68%)
Treatment completed	2(4%)
Failure cases (including, non converted and reverted cases)	7(13%)
Lost to Follow up (75% labour migrants)	4(8%)
Died	4(8%)
Completed Bdq Course	32(60%)

- The 7 failure cases continue taking treatment with Background regimen **(total still on Rx = 43)**
- Between March 2013-april 2014 , 12 out of 18 cases who completed the 6 months of Bdq Tx ,presented an increase in QTcF, (mean increase 36 milliseconds, range: 4-75 milliseconds), 83% (10/12) of whom were taking clofazimine concomitantly

Conclusions

DESPITE …

- New drugs giving hope to desperate DR TB cases.

BUT ……

- Still Adherence with or without New drugs is a BIG CHALLENGE.
  There is a NEED to offer SHORTER and LESS TOXIC TREATMENT REGIMENES !
- Extend access to other new anti TB drugs (Delamanide).
- Effective Pharmachovigilance reporting system.
- Many ongoing questions to find answer for :
  - How best to use the drugs?
  - How to avoid development of resistance to new Drugs ?
  - …..

Thank You !