Effectiveness of BPaL regimens : analysis of the first country cohort of operational research

NTP, Republic of Uzbekistan

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Operational study SMARRTT

- Goals
  - Determine **the effectiveness and safety** of the (BPaIM /C) regimen in programmatic conditions
- Place of the study
  - Tashkent city
  - Republic of Karakalpakstan
- The study protocol was approved by the Ethical Review Committee of the Republic of Uzbekistan and Karakalpakstan.
- Written **informed consent form** is signed by all patients included in the study.

Operational study SMARRTT

Treatment regimens:

- ❖Bdq -Pa- Lzd - Mfx for 24 weeks
- ❖Bdq -Pa- Lzd - Cfz for 24 weeks

Duration of observation:

- ❖24 weeks of treatment
- ❖12 months follow-up

Investigation/Observation	Baseline assessment & Screening	Treatment Phase (W=Week)						Follo (M=M
		W_T 4	W_T 8	W_T 12	W_T 16	W_T 20	W_T 24	M_F 6
Written informed consent	X							
Demographics, Medical History	X							
Clinical Examination[1]	X	X	X	X	X	X	X	X
Treatment adherence		X	X	X	X	X	X	
Concomitant treatment		X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X

Operational study SMARRTT

Inclusion criteria for the study:

- 18 years or older
- Tuberculosis, bacteriologically confirmed, with proven resistance to at least rifampicin or with a clinical diagnosis with a close history of contact with a patient with RR/MDR-TB)

Exclusion criteria for the study:

- Inability to take medications orally
- Resistance to BPaL regimen drugs or previous BPaL use for >1 month.
- There is a known allergy to any of the drugs in the BPaL treatment regimen .
- QTcF interval ≥ 500 m/sec at baseline
- TB meningoencephalitis , osteoarthritis, osteomyelitis, septic arthritis or brain abscess
- Pregnant women

May – June 2022

- Approval from the Ethical Council of the Ministries of Health of the Republic of Uzbekistan and Karakalpakstan

June - November 2022

- Training of health workers
  - 63 phthisiologists
  - 341 general practitioners
  - 469 nurses

June 2022

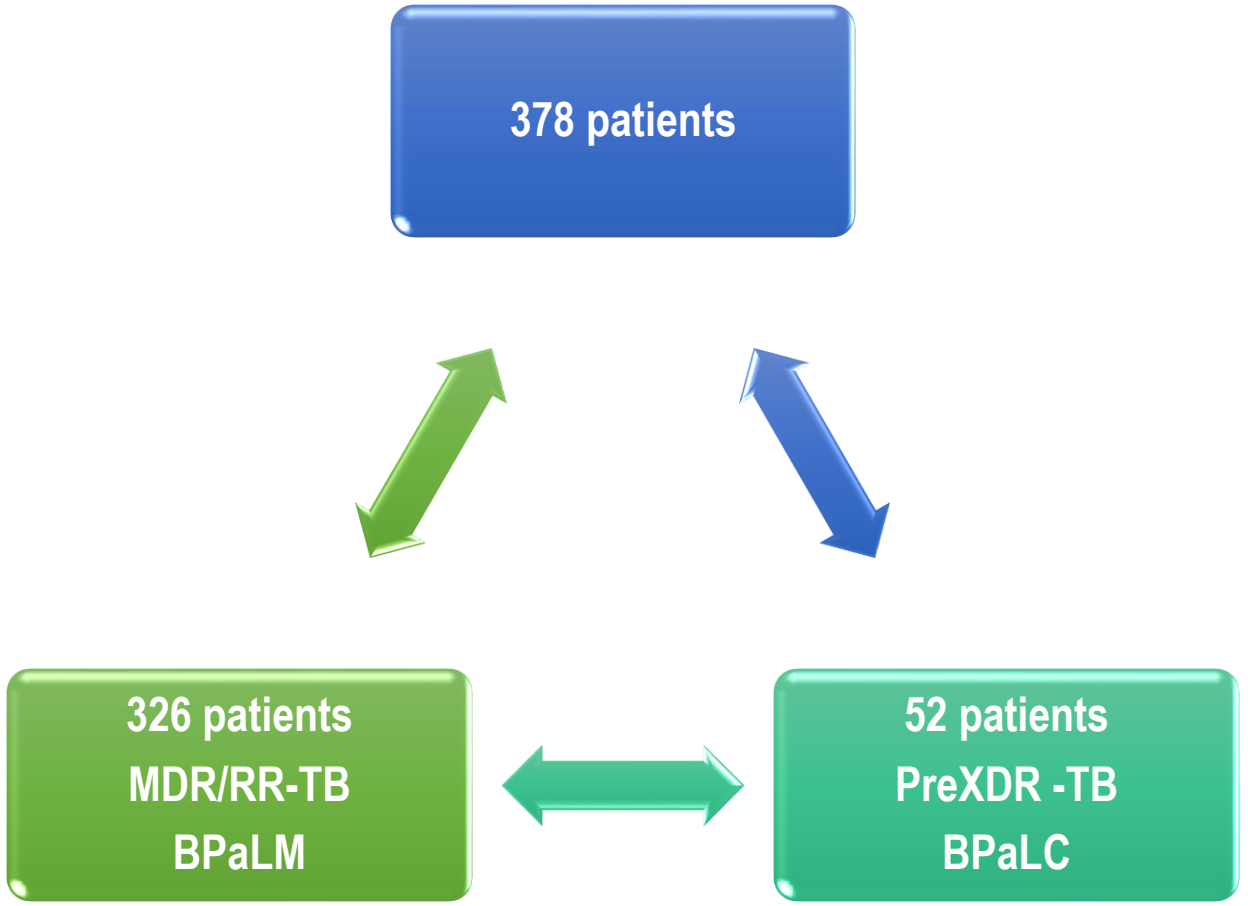
- Start of patient recruitment

December 2023

- Patient recruitment end date

Operational study SMARRTT

Recruitment of patients for OI



Operational study SMARRTT

Characteristics of the study population

Characteristic	N	Overall, n=378	DR category		p-value
			MDR/RR, n=326	Pre-XDR, n=52	
Age (years)	378				0.019
Median (IQR)		40 (29, 58)	43 (29, 61)	34 (26, 50)	
Range		18, 86	18, 86	18, 76	
Geographic distribution	378				0.16
Nukus / Nukus		308 (81.5%)	262 (80.4%)	46 (88.5%)	
Tashkent		70 (18.5%)	64 (19.6%)	6 (11.5%)	
Female gender	378	174 (46.0%)	153 (46.9%)	21 (40.4%)	0.38
Body mass index	378				0.46
Median (IQR)		20.1 (18.4, 23.2)	20.2 (18.4, 23.2)	19.7 (17.9, 24.1)	
Range		11.6, 40.4	11.6, 40.4	13.8, 35.4	

Operational study SMARRTT

Characteristics of the study population

Characteristic	N	Overall, n=378	DR category		p-value
			MDR/RR, n=326	Pre-XDR, n=5 2	
Confirmed Hepatitis B	378	10 (2.6%)	7 (2.1%)	3 (5.8%)	0.093
Confirmed Hepatitis C	378	20 (5.3%)	16 (4.9%)	4 (7.7%)	0.29
Confirmed diabetes mellitus	378	58 (15.3%)	52 (16.0%)	6 (11.5%)	0.65
Confirmed HIV	378	6 (1.6%)	5 (1.5%)	1 (1.9%)	0.41
Alcohol abuse	378				0.28
Yes		13 (3.4%)	10 (3.1%)	3 (5.8%)	
No		361 (95.5%)	313 (96.0%)	48 (92.3%)	
Unknown		4 (1.1%)	3 (0.9%)	1 (1.9%)	

Operational study SMARRTT

Characteristics of the study population

Characteristic	N	Overall, n=378	DR category		p-value
			MDR/RR, n=326	Pre-XDR, n=52	
Disease site	378				>0.99
Pulmonary		374 (98.9%)	322 (98.8%)	52 (100.0%)	
Extra -pulmonary		4 (1.1%)	4 (1.2%)	0 (0.0%)	
Previously treated	378	117 (31.0%)	100 (30.7%)	17 (32.7%)	0.77
Treatment regimen	378				<0.001
BPaLC		53 (14.0%)	5 (1.5%)	48 (92.3%)	
BPaLM		325 (86.0%)	321 (98.5%)	4 (7.7%)	
Underweight, BMI < 18.5 kg/m2	378	100 (26.5%)	83 (25.5%)	17 (32.7%)	0.27

Operational study SMARRTT

Characteristics of the TB process

Characteristic	N	Overall, n=378	DR category		p-value
			MDR/RR, n=326	Pre-XDR, n=5 2	
Abnormal Chest X-ray	375	375 (100.0%)	323 (100.0%)	52 (100.0%)	
Unknown		3	3	0	
Cavitary lesion	375	231 (61.6%)	192 (59.4%)	39 (75.0%)	0.032
Unknown		3	3	0	
Sputum smear positive	378	185 (48.9%)	154 (47.2%)	31 (59.6%)	0.10
Rifampicin resistance	356				0.20
Detected		342 (96.1%)	294 (95.8%)	48 (98.0%)	
Indeterminate		11 (3.1%)	11 (3.6%)	0 (0.0%)	
Not detected		3 (0.8%)	2 (0.7%)	1 (2.0%)	
Unknown		22	19	3	

Operational study SMARRTT

Determination of susceptibility to fluoroquinolones

Characteristic	N	Overall, n=378
FQ test result	378	
FQNA		23 (6.1%)
FQ not done		27 (7.1%)
FQ resistant		52 (13.8%)
FQ susceptible		276 (73.0%)

Operational study SMARRTT

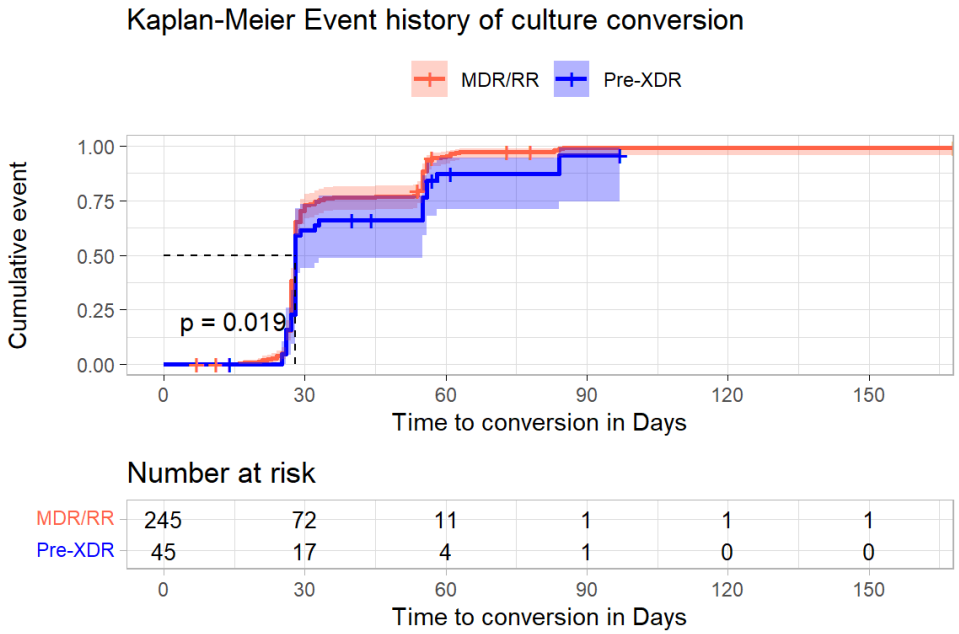
Culture conversion

Characteristic	N	Overall, n=378	DR category		p-value
			MDR/RR, n=326	Pre-XDR, n=52	
Baseline Culture Results	340				0.074
With the growth of MBT complex		290 (85.3%)	245 (83.9%)	45 (93.8%)	
No growth		50 (14.7%)	47 (16.1%)	3 (6.3%)	
Unknown		38	34	4	
Time to conversion (days)	277				0.36
Median (IQR)		28 (27, 32)	28 (27, 32)	28 (28, 44)	
Range		16, 85	16, 85	25, 84	

Operational study SMARRTT

Culture conversion

Characteristic	N	Overall, n=378	DR category		p-value
			MDR/RR, n=326	Pre-XDR, n=5 2	
Month of conversion	277				0.24
1		216 (78.0%)	187 (78.6%)	29 (74.4%)	
2		56 (20.2%)	48 (20.2%)	8 (20.5%)	
3		5 (1.8%)	3 (1.3%)	2 (5.1%)	



Operational research SMARRTT

Safety profile

Characteristic	N	Overall, n=378	DR category		p-value
			MDR/RR, n=326	Pre-XDR, n=5 2	
Serious adverse events, grade 3 and above	378	18 (4.8 %)	13 (4.0 %)	5 (9.6 %)	0.45
Type	18				0.55
Death		3 (16.7%)	3 (23.1%)	0 (0.0%)	
Life - threatening experience		2 (11.1%)	1 (7.7%)	1 (20.0%)	
Hospitalization or prolongation of hospitalization		13 (72.2%)	9 (69.2%)	4 (80.0%)	
Signs / Symptoms	18				0.55
Cardiovascular disorders: Cardiac rhythm		1 (5.6%)	1 (7.7%)	0 (0.0%)	
Prolonged (corrected) QT interval		2 (11.1%)	2 (15.4%)	0 (0.0%)	
Increased liver enzymes (ALT or AST increased)		4 (22.2%)	3 (23.1%)	1 (20.0%)	
Gastrointestinal disorders: Dyspepsia		1 (5.6%)	1 (7.7%)	0 (0.0%)	
Gastrointestinal disorders: Nausea		1 (5.6%)	1 (7.7%)	0 (0.0%)	
Immune disorders: Allergic reaction		1 (5.6%)	1 (7.7%)	0 (0.0%)	
Skin disorders: Mucocutaneous symptoms (includes rash)		2 (11.1%)	0 (0.0%)	2 (40.0%)	
Other if not listed in the most common list		6 (33.3%)	4 (30.8%)	2 (40.0%	

Operational research SMARRTT

Safety profile

Characteristic	N	Overall, n=378	DR category		p-value
			MDR/RR, n=326	Pre-XDR, n=5 2	
Clinician action taken with regard to treatment	18				0.24
Dose not changed		1 (5.6%)	0 (0.0%)	1 (20.0%)	
Drug interrupted		11 (61.1%)	7 (53.8%)	4 (80.0%)	
Drug withdrawn		4 (22.2%)	4 (30.8%)	0 (0.0%)	
Not applicable		2 (11.1%)	2 (15.4%)	0 (0.0%)	
Outcome (Status of the AE):	18				0.41
Resolved		13 (72.4 %)	8 (61.5 %)	5 (100.0%)	
Death / Fatal		4 (22.2%)	4 (30.8%)	0 (0.0%)	
Not resolved		1 (5.6%)	1 (7.7%)	0 (0.0%)	

Operational study SMARRTT

Treatment outcomes

Characteristic	N	Overall, n=378	DR category		p-value
			MDR/RR, n=326	Pre-XDR, n=5 2	
Total with outcome	**375**				**<0.001** [2]
Cured		336 (89.6%)	294 (91.0%)	42 (80.8%)	
Treatment completed		19 (5.1%)	18 (5.6%)	1 (1.9%)	
Died		9 (2.4%)	7 (2.2%)	2 (3.8%)	
Lost for further medical attention observations		1 (0.3%)	0 (0.0%)	1 (1.9%)	
Unsuccessful treatment		2 (0.5%)	1 (0.3%)	1 (1.9%)	
Refusal of treatment		2 (0.5%)	1 (0.3%)	1 (1.9%)	
The result is not evaluated		6 (1.6%)	2 (0.6%)	4 (7.7%)	
Continues treatment	**3**	**3**	**3**	**0**	

Operational study SMARRTT

Observation period after treatment

Characteristic	N	Overall, n= 181	DR category		p-value
			MDR/RR, n= 156	Pre-XDR, n= 25	
12 months follow - up period completed	149	149 (82.3%)	128 (82.1%)	21 (84.0%)	
Unknown		32	28	4	
Is the patient alive?	149				>0.99
Yes		148 (99.3%)	127 (99.2%)	21 (100.0%)	
No		1 (0.7%)	1 (0.8%)	0 (0.0%)	
Unknown		32	28	4	
Patient suffered from TB recurrence?	143				
No		143 (100.0%)	122 (100.0%)	21 (100.0%)	
Unknown		38	34	4	

Operational study SMARRTT

Conclusion

- ✓ The presence of comorbidities can complicate the treatment of TB;
- ✓ The BPaL-based regimen is effective in patients with rifampicin-resistant tuberculosis in programmatic settings, with a treatment success rate of 94.7%;
- ✓ The treatment regimen based on BPaL drugs is safe. Only **4.8 %** patients experienced serious adverse events of grade 3 or higher . Most serious adverse events resolved without sequelae.

Operational study SMARRTT

Restrictions:

- Safety and eficacy of BPaLM /C -based regimens in children and pregnant women cannot be determined.

Difficulties:

- Recruitment at the start of the SMARRTT operational study was slow due to hesitancy on the part of patients, families and healthcare professionals
- Lack of reliable DST for pretomanid in the country

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