Overcoming challenges in TB care: from policy to practice

Current status of the operational research on shorter modified all oral MDR-TB treatment regimens and BPaL in Belarus

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МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ

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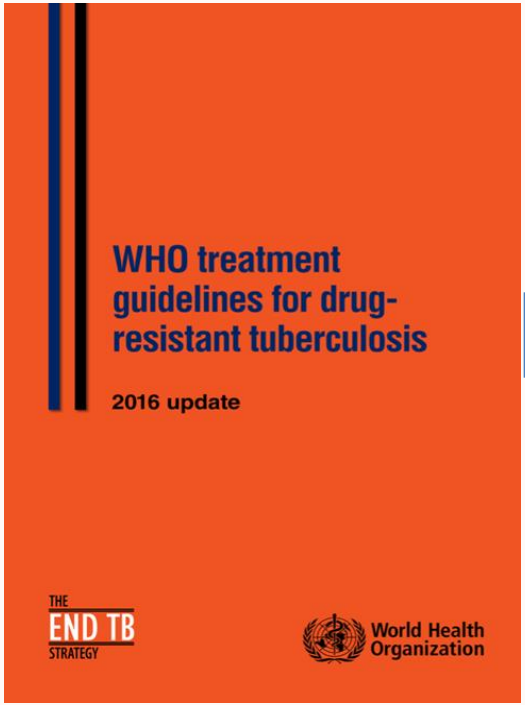
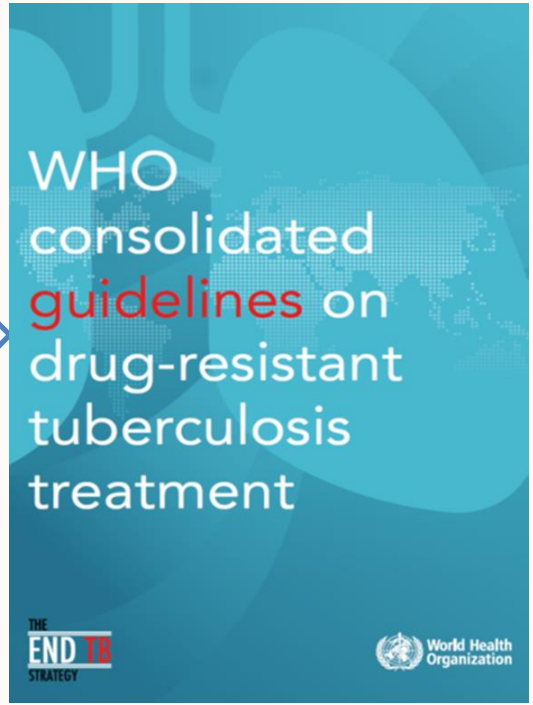
MEDECINS SANS FRONTIERES

WHO Shorter Treatment Standardized Regimen





Limitations for use in Belarus

1) High level of resistance to second line drugs
2) High level resistance to Z
3) Presence of SLI in regimen
4) New effective TB drugs have been already introduced

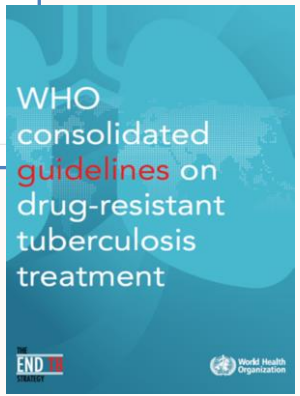
Modified Shorter All Oral Treatment Regimen

under operational research conditions

- Study protocol
  - eligibility criteria
  - regimen composition
  - monitoring schedules
  - other key elements
- Approval by a national ethics review committee,

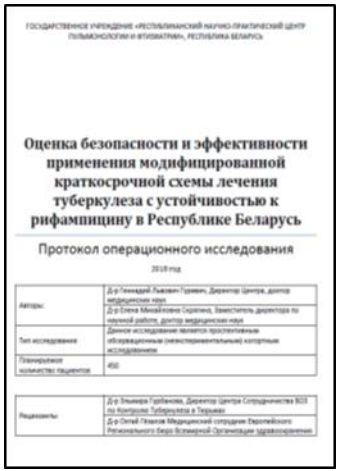
ahead of any patient enrolment

- Treatment delivery under WHO-recommended standards, including
  - informed consent
  - principles of good clinical practice
  - aDSM
  - Treatment monitoring to assess regimen effectiveness;



Operational Research Preparation

- Includes all required components such as generic protocol, actual (national) protocol, informational and educational material, patient's informed consent form, training for medical personnel, approval by local Ethics Committee etc.



Оценка безопасности и эффективности применения модифицированной краткосрочной схемы лечения туберкулеза с устойчивостью к рифампицину в Республике Беларусь

Протокол операционного исследования

Operational Research Objectives

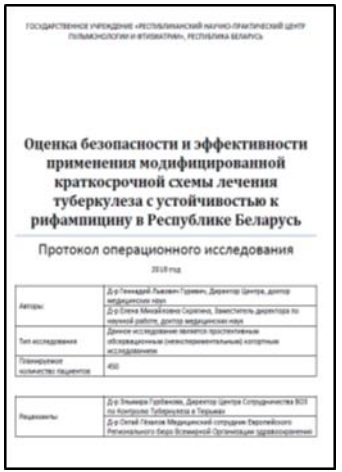
- **Primary objective:** Determine **treatment outcomes** of patients treated with novel modified shorter MDR-TB regimen
- **Secondary objectives:**

  a) Assess its **safety** through seriousness, severity and rates of adverse events

  b) Determine proportion of patients with **recurrence/relapse** during 12 and 24 months after successful treatment

Patient selection: Inclusion criteria

- willing and able to give informed consent
- bacteriologically confirmed TB with initial resistance to at least rifampicin
- willing to use effective contraception (if pre-menopausal woman)
- willing to adhere to follow-up schedule and study procedures



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Протокол операционного исследования

Patient selection: Exclusion criteria

- Strain resistant to any drug in the regimen
- Previous second-line drug treatment > 1 month
- QT > 500 msec, ALT/AST > 5 times, allergy to drug, severe comorbidity (e.g. renal failure)

To be decided (Generic protocol):

- Severe forms of TB (e.g. fibfro-cavernous lung lesions, Potts disease, meningitis)
- Pregnant women? (Just 1st trimester, but older drugs more toxic than some newer ones)
- Age limit of children? (children can be included: discuss with experts)

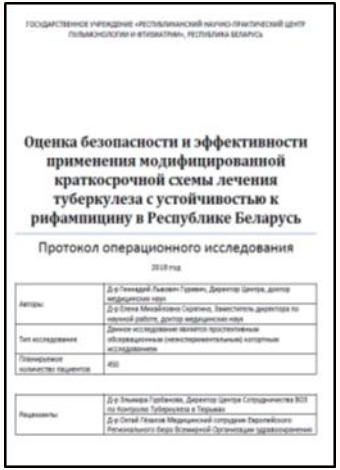
Excluded (Actual protocol)

Actual Protocol

Treatment: regimen selection and drug doses

Treatment 39 weeks → **Follow up (after treatment completion) 24 month**

Drug	Body weight	
	30-46 kg	46 kg and more
Bdq (tab., 100 mg)	400 mg/day - 2 weeks., then 200 mg 3/week	
Lzd (tab., 600 mg)	300 mg/day	600 mg/day
Lfx (tab., 250 mg or 500 mg)	750 mg/day	1000 mg /day
Cfz (caps., 100 mg)	100 mg/day	
Cs (caps., 250 mg)	500 mg/day	750 mg/day



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Протокол операционного исследования

Costs of regimen: Lfx-Bdq-Lzd-Cfz-Cs

Drug	Form	# units/pack	Price/pack (USD)	# units for 39 weeks	# packs for 39 weeks	Price for 39 weeks (USD)
Lfx 500 mg	Tablets	100	$6.34	546	5.5	$34.62
Bdq 100 mg	Tablets	188	$400.00	278	1.5	$591.49
Lzd 600 mg	Tablets	10	$13.39	192.5	19.3	$257.76
Cfz 100 mg	Capsules	100	$98.24	273	2.7	$268.20
Cs 250 mg	Capsules	100	$26.80	819	8.2	$219.49
TOTAL						**$1,479.34**

Duration: 39 weeks (273 days), weight >46 kg:

- Lfx: 1,000 mg/daily for 39 weeks
- Bdq: 400 mg/daily for 14 days followed by 200 mg thrice/weekly for 37 weeks
- Linezolid: 600 mg/daily for 39 weeks
- Cfz: 100 mg/daily for 39 weeks
- Cs: 750 mg/daily for 39 weeks

Protocol

Treatment monitoring and aDSM

Investigation / test	Month														
	-1 0	1	2	3	4	5	6	7	8	9		+6	+12	+18	+24
Sputum Smear X-pert LPA (1st & 2nd lines) Culture (BACTEC /L-J) DST (BACTEC /L-J)	 x x x x x	x x x	x x x	x x x	x x x	x x x	x x x	x x x	x x x	x x x	END OF TREATMENT	x x x	x x x	x x x	x x x
Chest X-ray / CT	x			x		x		x		x		x	x	x	x
Pregnancy test	x	On requirement													
HIV, HCV, HBV tests	x	On requirement										On requirement			
TB history, past illnesses	x														
Clinical examination	x	x	x	x	x	x	x	x	x	x		x	x	x	x
FBC	x	X	x	x	x	x	x	x	x	x		x	x	x	x
Creatinine (Cr. Cl)	x	x	x	x	x	x	x	x	x	x			x		x
ALT, AST	x	x	x	x	x	x	x	x	x	x			x		x
Bilirubin	x	x	x	x	x	x	x	x	x	x			x		x
Lipase	x	On requirement										On requirement			
Amilase	x	On requirement										On requirement			
ECG (QTcF)	x	X	x	x	x	x	x	x	x	x		once in 3 mo.			
K, Mg, Ca, Na	x	x	x	x	x	x	x	x	x	x		On requirement			
Albumine	x	x	x	x	x	x	x	x	x	x		On requirement			
Glycated hemoglobin (HbA1c)	x	On requirement										On requirement			
Glucose	x	x	x	x	x	x	x	x	x	x		On requirement			
TSH	x	On requirement										On requirement			
Ophthalmology examination	x	On requirement										On requirement			
Neurologist / Psychiatrist		On requirement										On requirement			

Short modified MDR-TB treatment regimen. Preliminary results

282 enrolled, 46 excluded (additional Q/I res.)

236 in OR

Sputum culture conversion	n
Total (Sep 2018 – Nov 2019)	136
1st mo.	90 (66 %)
2nd mo.	38 (28 %)
3rd mo.	5 (4 %)
4th mo.	3 (2 %)

28 – successfully treated, 4 – deaths, 2 - LTFU

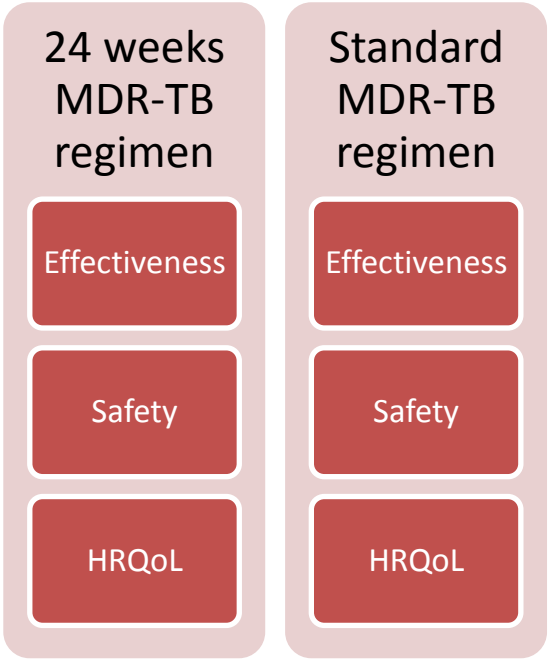
17 – DST from lung tissue

83 – recently started treatment

Short (6 months) Regimen: TB-REACH grant

Study Objectives:

- Determine treatment **effectiveness** and **safety** of all-oral short (24 weeks) MDR-TB regimens compared to standard MDR-TB regimen
- Investigate **HRQoL** among patients receiving all-oral short MDR-TB treatment regimen compared to standard MDR-TB regimen

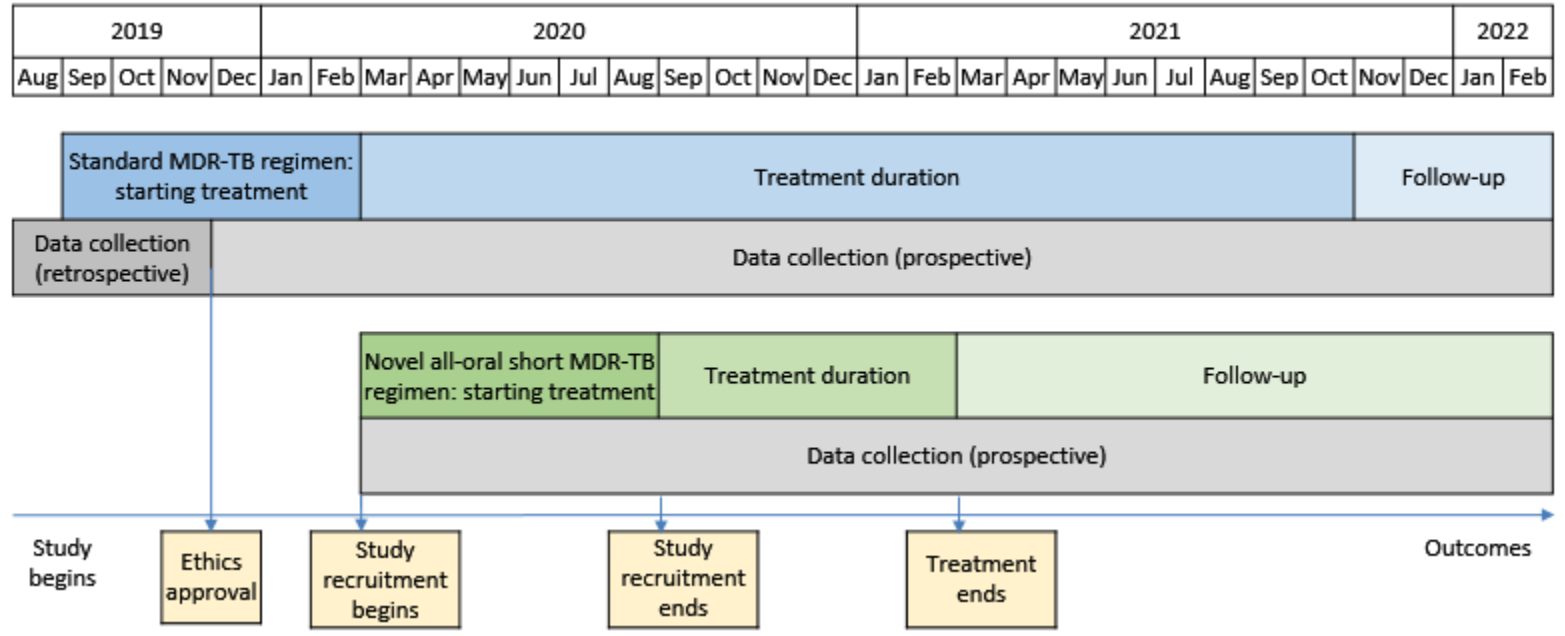


Study Design:

Longitudinal design with two concurrent cohorts:

- Intervention cohort: all-oral, short, 24 weeks
- Comparator cohort: standard 18-24 months

Study Design



Study Population

TB patients with evidence of resistance to rifampicin by conventional DST (culture-based) or rapid DST (Xpert MTB/RIF or LPA)

Inclusion Criteria

- Is willing and able to give informed consent to be enrolled in the research project and for follow-up
- Has bacteriological or molecular confirmed TB with evidence of resistance to at least rifampicin

Exclusion Criteria

Is unable to take oral medication

Is taking any medications contraindicated with the medicines in the MDR-TB regimen

Has a known allergy to any of the drugs in the MDR-TB regimen

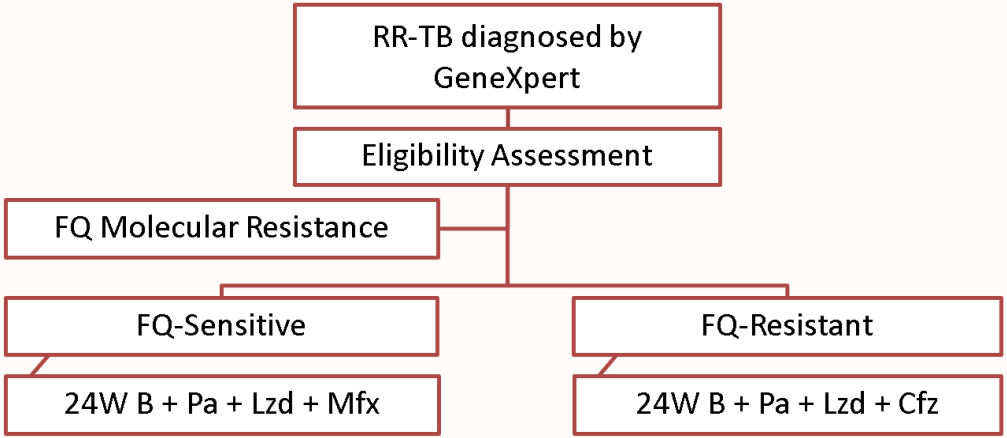
Has a QTcF interval of > 500 msec

Not willing to take effective contraception

Is a pregnant woman

A child under 18 years of age

Treatment Regimens



For FQ sensitive patients: 24 weeks of

- Bedaquiline
- Pretomanid
- Linezolid (600->300mg)
- Moxifloxacin

For FQ resistant patients: 24 weeks of

- Bedaquiline
- Pretomanid
- Linezolid (600->300mg)
- Clofazimine

Investigational Schedule

		Treatment						Follow-up				
Investigation/Observation	Screening	W 4	W 8	W 12	W 16	W 20	W 24	M 8	M 10	M 12	M 15	M 18
Written informed consent	X											
Demographics, Medical History	X											
Clinical Examination	X	X	X	X	X	X	X	X	X	X	X	X
Chest X-ray	X						X					
Sputum smear	X	X	X	X	X	X	X	X		X		X
Sputum culture	X	X	X	X	X	X	X	X		X		X
DST (FQ/Injectables)	X											
NGS (Illumina platform)	X											X
Haemoglobin/platelets count	X	X	X	X	X	X	X					
White blood and differential count	X	X	X	X	X	X	X					
Serum creatinine	X	X	X	X	X	X	X					
Serum potassium	X	X	X	X	X	X	X					
Serum liver enzymes	X	X	X	X	X	X	X					
TSH	X											
HIV, Hep B and Hep C	X						X					
Pregnancy test (female)	X						X					
ECG	X	X	X	X	X	X	X					
Visual acuity and Ishihara	X	X	X	X	X	X	X					
Treatment adherence		X	X	X	X	X	X					
Concomitant treatment		X	X	X	X	X	X					
Adverse events		X	X	X	X	X	X					
SF-12	x		x				x					

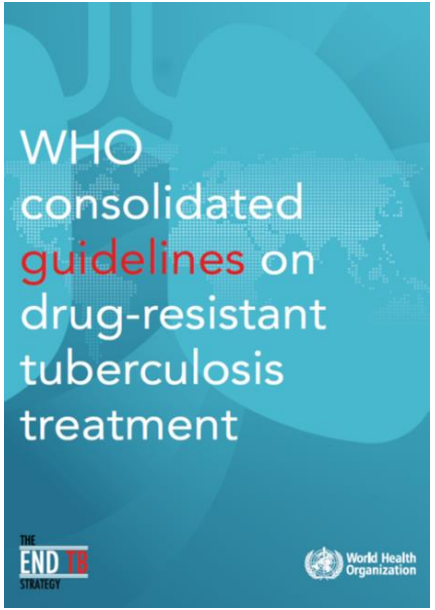
- Routine hematology/ biochemistry
- Next-Generation Sequencing
- SF-12 for HRQoL

Conclusion

Operational research on short modified all oral treatment MDR-TB regimens were **started** in Belarus

9 mo. Lfx-Bdq-Lzn-Cfz-Cs

6 mo. Pa-Bdq-Lzn-Mfx/Cfz



Thanks