Operational research on modified shorter treatment regimens for MDR/RR-TB in the WHO European region: results and programmatic impact on the burden of DR-TB

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World Health Organization

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Outline of the presentation:

- Background

- Cohort characteristics

- Findings on effectiveness of mSTR

- Independent predictors of unsuccessful study outcomes

- Frequency and type Adverse Events of Interest (AEI) during treatment

- Factors associated with development AEI

- Opportunities for improved programmatic decision making

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We extend our deepest gratitude to:
patients, nurses, doctors, national study teams, mSTR task force members, GFATM and other donors, partners and all those involved in OR implementation in countries and at the regional level

We are especially thankful to the colleagues primarily working on the analysis: Dr Jay ACHAR and Dr Arax HOVHANNESYAN for their determination, attention to details and hard work

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Part 1.
Background of mSTR OR

2020 WHO Guidelines
Shorter all-oral bedaquiline-containing regimen for MDR/RR-TB

4-6 Bdq (6m) – Lfx – Cfz – Eto – Z – E - Hh / 5 Lfx – Cfz – Z - E

2.1   A shorter all-oral bedaquiline-containing regimen of 9-12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant TB (MDR/RR-TB) who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded (*Conditional recommendation, very low certainty in the evidence*).

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WHO
consolidated
guidelines on
tuberculosis

Module 4: Treatment

Drug-resistant
tuberculosis treatment

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WHO Consolidated Guidelines on Tuberculosis, Module 4: Drug-Resistant Tuberculosis Treatment

Secondary analyses determined that a bedaquiline-containing shorter regimen was comparable to an all-oral longer regimen containing both bedaquiline and linezolid, in terms of death and failure outcomes; however, the shorter regimen seemed to have significantly less loss to follow-up. Further sensitivity analyses (albeit in the longer regimens containing bedaquiline–linezolid versus longer regimens containing bedaquiline only) determined that the addition of linezolid to bedaquiline-containing regimens would, overall, improve outcomes. Nevertheless, the GDG concurred that, because of the lack of direct data for shorter regimens, no general conclusions could be drawn at the time.

Until new evidence is forthcoming and available to WHO, the shorter all-oral bedaquiline-containing regimen advised to be used does not include linezolid. In settings with a high probability of resistance to, or confirmed resistance to, ethionamide, ethambutol, pyrazinamide, clofazimine and high-dose isoniazid, further modifications of the regimen using priority grouping of second-line oral medicines may be implemented; however, the efficacy, safety and tolerability of additionally modified shorter regimens are unknown and should be evaluated under operational research conditions.

WHO
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tuberculosis

Module 4: Treatment
Drug-resistant
tuberculosis treatment

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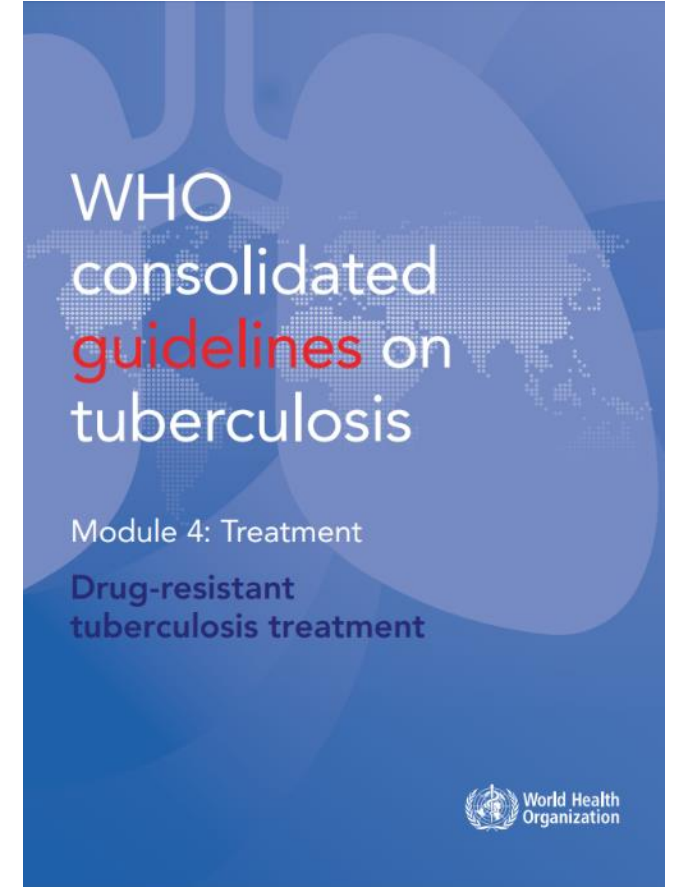
Introduction of modified fully-oral shorter regimens for MDR/RR-TB under operational research conditions (ERI-TB initiative)

13 countries joined the initiative:

ARM, AZE, BLR, GEO, KAZ, KGZ, LVA, LTA, MDA,TJK, TKM, UKR, UZB

Objectives:

- To facilitate introduction of all-oral mSTR for MDR-TB under OR;

- To foster good clinical care for MDR-TB through OR;

- To build and strengthen the research capacity in countries;

- To contribute to global knowledge for generation of new policy guidance for DR-TB.

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List of mSTR TF members:

Jay Achar	Elmira Gurbanova	Liga Kuksa
Ana Ciobanu	Arax Hovhannesyan	Nino Lomtadze
Gunta Dravniece	Naira Khachatryan	Michael Rich
		Alena Skrahina

Treatment regimens

In this study, three all-oral shorter RR-TB treatment regimens are proposed, based on knowledge of their safety and efficacy as of 2020.

Regimen 1: 39 weeks Lfx + Bdq + Lzd + Cfz + Cs

Regimen 2: 39 weeks Lfx + Bdq + Lzd + Cfz + Dlm

Treatment regimen 1 is preferred as it includes all Group A and Group B anti-TB drugs. In patients with suspected resistance or intolerance of Cs, regimen 2 should be considered as primary choice of therapy.

For children under 6 years of age:

Regimen 3: 39 weeks Lfx + Dlm + Lzd + Cfz

Table 3.1. Grouping of medicines recommended for use in longer MDR-TB regimens[a]

Groups and steps	Medicine	Abbreviation
Group A: Include all three medicines	Levofloxacin or moxifloxacin	Lfx Mfx
	Bedaquiline[b,c]	Bdq
	Linezolid[d]	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cycloserine or terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[e]	Dlm
	Pyrazinamide[f]	Z
	Imipenem–cilastatin or meropenem[g]	Ipm–Cln Mpm
	Amikacin (or streptomycin)[h]	Am (S)
	Ethionamide or prothionamide[i]	Eto Pto
	P-aminosalicylic acid[j]	PAS

Operational research objectives

- **Primary objective:**
  - To determine the treatment outcomes of patients who are treated with novel (modified) shorter MDR-TB regimen

- **Secondary objectives:**
  - To assess the safety of a novel (modified) shorter MDR-TB regimen through rates of adverse events
  - To determine the proportion of patients with recurrence during 12 months after successful treatment with a novel (modified) shorter MDR-TB regimen

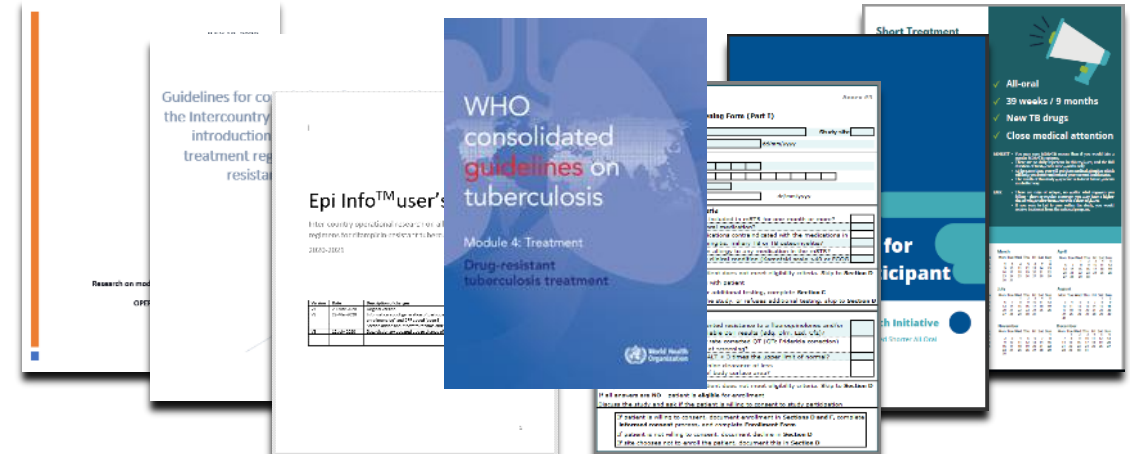Photo: First patient starting mSTR in Republic on Moldova, September 2020

Regional OR on mSTR implementation: highlights

13 high-priority countries of WHO European Region

Regional Operational Research Package in line with WHO guidelines on DR-TB

Ensuring people-centeredness of service delivery

- 9 months
- All-oral
- 6 times lower pill burden

Progress in the implementation of the new Regional initiative

- **2813 patients** were initiated on mSTR as the Regional cohort in 13 countries
- National mSTR cohorts have been established in all 13 countries; as of 31 December 2023, **over 5800 more patients** were enrolled
- The WHO Regional Office for Europe advised countries to continue enrollment in the mSTR national cohorts of children under 14 years of age and pregnant women who don't meet eligibility criteria for BPaL(M)

Treatment and follow-up monitoring schedule

	Baseline Visit	Week 2	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Until end of treatment	End of treatment	3 months post-end-of-treatment	6 months post-end-of-treatment	9 months post-end-of-treatment	12 months post-end-of-treatment
Clinical evaluation														
Vital signs	✗		✗	✗	✗	✗	✗	✗	Monthly	✗	✗	✗	✗	✗
Brief peripheral neuropathy screen	✗		✗	✗	✗	✗	✗	✗	Monthly	✗				✗
Visual acuity and colorblindness screen	✗		✗	✗	✗	✗	✗	✗	Monthly	✗				✗
Post-end-of- treatment consultation										✗	✗	✗	✗	✗
Assessment and follow-up of adverse events	✗	✗	✗	✗	✗	✗	✗	✗	At each scheduled /unscheduled visit	✗	✗	✗	✗	✗
Weight	✗	✗	✗	✗	✗	✗	✗	✗	Monthly	✗	✗	✗	✗	✗
Bacteriological testing														
Smear	✗		✗	✗	✗	✗	✗	✗	Monthly	✗		✗		✗
Culture	✗		✗	✗	✗	✗	✗	✗	Monthly	✗		✗		✗
Freeze baseline culture	✗													
Xpert MTB/RIF	✗													
LPA (Hain GenoType MTBDRsl)	✗		If smear- or culture-positive check for amplification of resistance											
Culture-based first-line DST	✗		If smear- or culture-positive check for amplification of resistance											
Culture-based second-line DST	✗		If smear- or culture-positive check for amplification of resistance											

	Baseline Visit	Week 2	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Until end of treatment	End of treatment	3 months post-end-of-treatment	6 months post-end-of-treatment	9 months post-end-of-treatment	12 months post-end-of-treatment
Laboratory testing														
ECG	✗	✗	✗	✗	✗	✗	✗	✗	Monthly	✗	✗	✗		
Full blood count (hemoglobin, red blood cells. white blood cells and platelets) if on Lzd	✗		✗	✗	✗	✗	✗	✗	Monthly (if on Lzd)	✗				
Liver function tests (AST, ALT)	✗		✗	✗	✗	✗	✗	✗	Monthly	✗				
Serum creatinine	✗		✗	✗	✗	✗	✗	✗	Monthly	✗				
Serum potassium	✗		✗	✗	✗	✗	✗	✗	Monthly	✗				
Hepatitis Bs Antigen	✗													
Hepatitis C Antibody	✗													
HbA1c	✗		Repeated every 3 months if elevated											
COVID-19 PCR	✗		At baseline and then only if clinically indicated											
Pregnancy test (females)	✗													
HIV testing	✗													
CD4 (repeated every 6 months if HIV+)	✗								✗					
HIV Viral load (repeated every 6 months if HIV +)	✗								✗					
Chest X-Ray	✗								✗	✗				

- Implementation of all-oral mSTR is not complicated and very similar to the standard conditions of good PMDT;
- Ensure effectiveness and safety of new regimens;
- Improve good clinical care of patients;
- Increase capacity of clinicians.

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Adverse Events of Interest monitored within mSTR OR
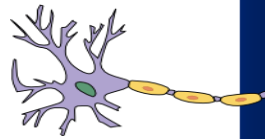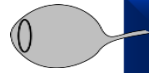
Peripheral neuropathy

Myelosuppression

(anemia, thrombocytopenia, neutropenia)

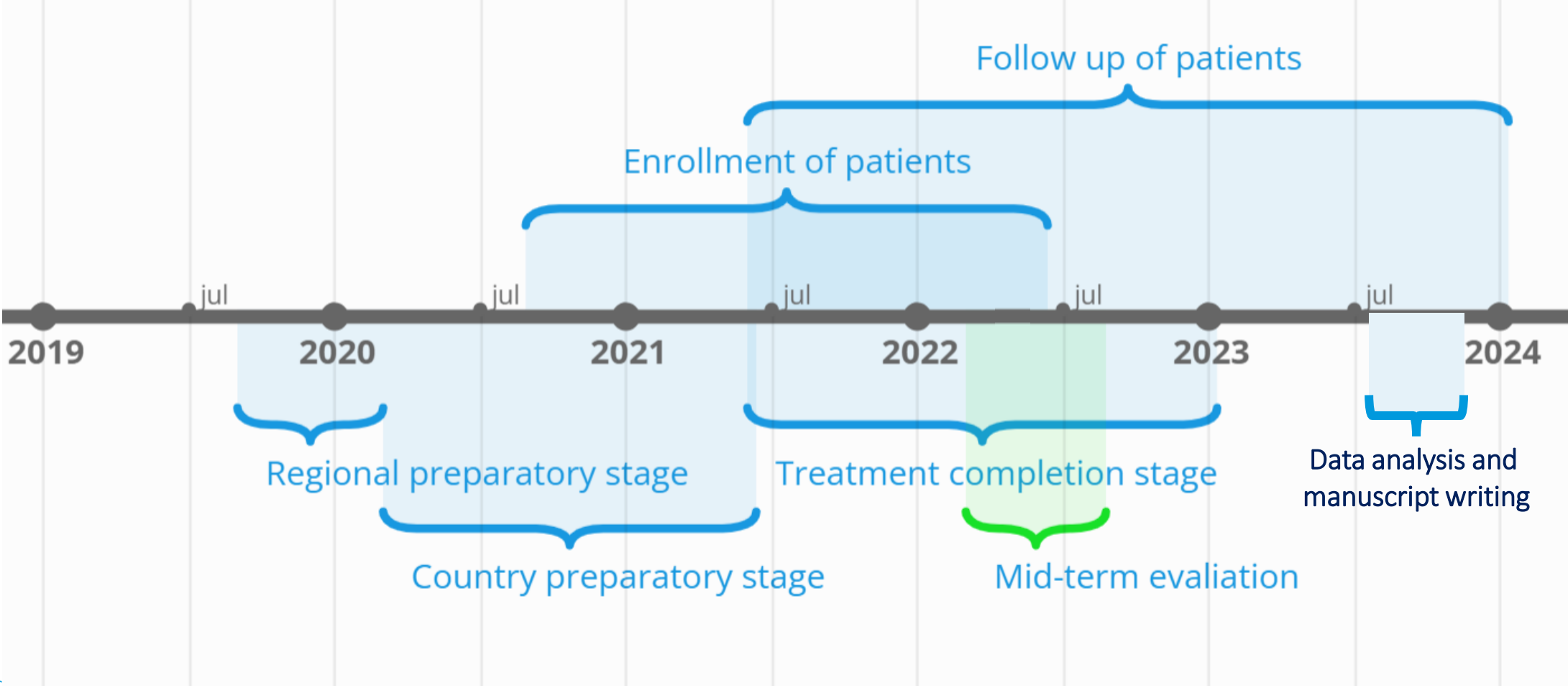Prolonged QTcF interval

Optic nerve disorder

Hepatitis

Hypokalaemia

Acute kidney injury
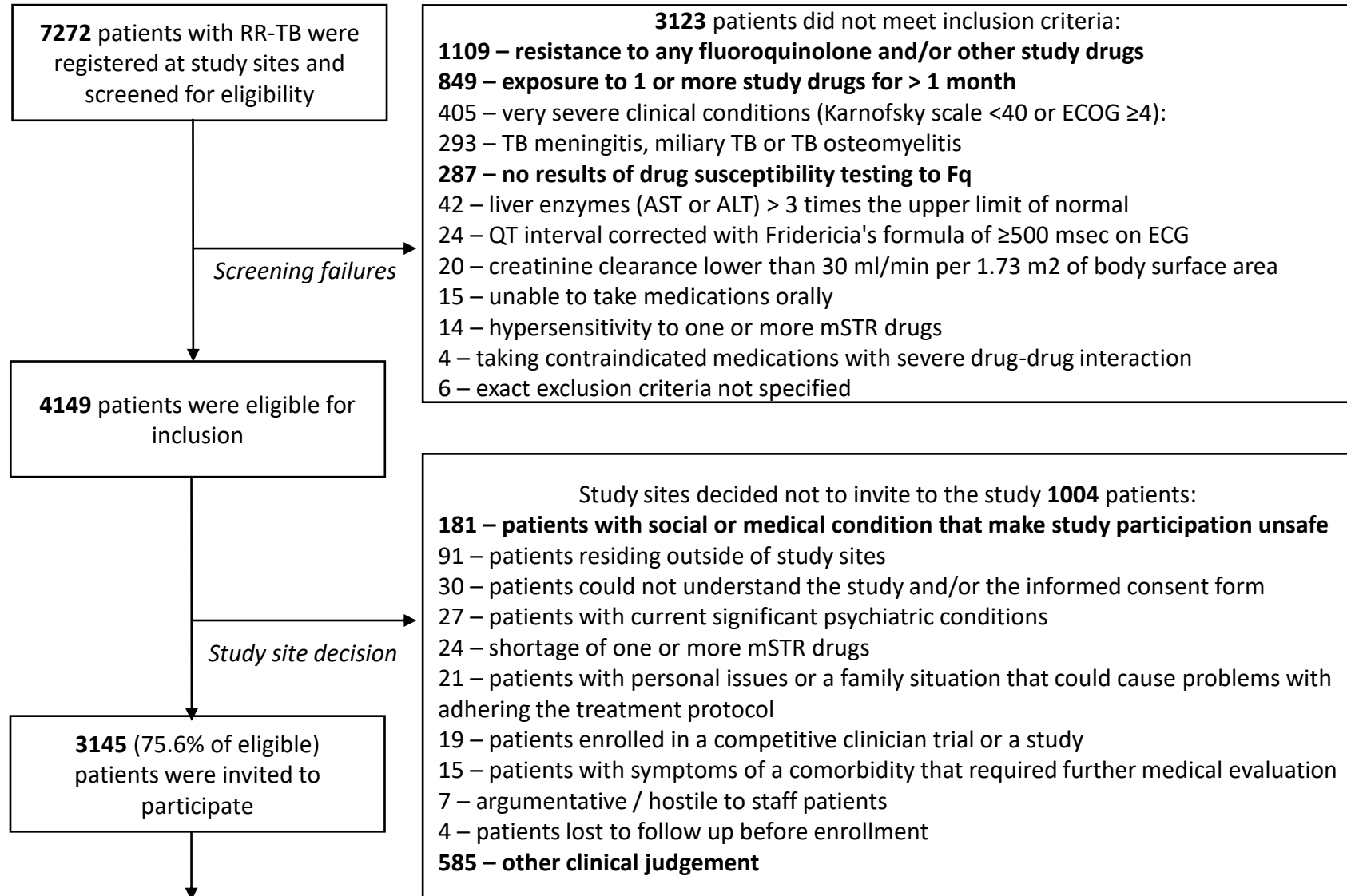
Regional cohort timeline

Follow up of patients

Enrollment of patients

Regional preparatory stage

Country preparatory stage

Treatment completion stage

Mid-term evaliation

Data analysis and manuscript writing

2019   jul   2020   jul   2021   jul   2022   jul   2023   jul   2024

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Part 2.
Cohort characteristics

Reasons for non-enrollment (1 part)

7272 patients with RR-TB were registered at study sites and screened for eligibility

Screening failures

4149 patients were eligible for inclusion

Study site decision

3145 (75.6% of eligible) patients were invited to participate
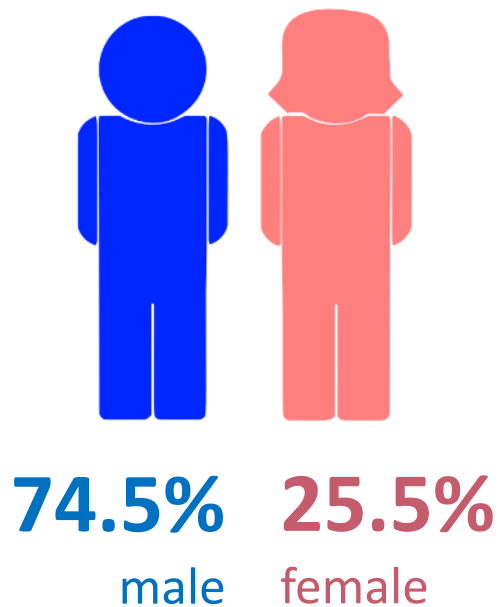
3123 patients did not meet inclusion criteria:
1109 – resistance to any fluoroquinolone and/or other study drugs
849 – exposure to 1 or more study drugs for > 1 month
405 – very severe clinical conditions (Karnofsky scale <40 or ECOG ≥4):
293 – TB meningitis, miliary TB or TB osteomyelitis
287 – no results of drug susceptibility testing to Fq
42 – liver enzymes (AST or ALT) > 3 times the upper limit of normal
24 – QT interval corrected with Fridericia's formula of ≥500 msec on ECG
20 – creatinine clearance lower than 30 ml/min per 1.73 m2 of body surface area
15 – unable to take medications orally
14 – hypersensitivity to one or more mSTR drugs
4 – taking contraindicated medications with severe drug-drug interaction
6 – exact exclusion criteria not specified

Study sites decided not to invite to the study **1004** patients:
181 – patients with social or medical condition that make study participation unsafe
91 – patients residing outside of study sites
30 – patients could not understand the study and/or the informed consent form
27 – patients with current significant psychiatric conditions
24 – shortage of one or more mSTR drugs
21 – patients with personal issues or a family situation that could cause problems with adhering the treatment protocol
19 – patients enrolled in a competitive clinician trial or a study
15 – patients with symptoms of a comorbidity that required further medical evaluation
7 – argumentative / hostile to staff patients
4 – patients lost to follow up before enrollment
585 – other clinical judgement

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Reasons for non-enrollment (2 part)

332 patients refused participation:
246 – patients unwilling to sign the informed consent
59 – patients unwilling to discuss the study
16 – patients fearful of research
4 – patients refusing invasive testing
2 – patients fearful of adverse drug reactions
5 – other

Patient decision

Safety cohort
2813 (67.8% of eligible) patients were enrolled and started on treatment

177 patients were withdrawn after enrollment:
94 – participants with MTB resistant to at least one study drug at baseline
53 – participants determined ineligible after enrollment
24 – participant withdrew consent
3 – physician decision
3 – other

Withdrawals

Treatment cohort
2636 patients were assessed for treatment outcomes

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Characteristics of study population

Total number of patients include into the regional cohort across 13 participating countries was 2813

74.5% male **25.5%** female

STUDY POPULATION BY AGE GROUPS

24.8% previously treated

STUDY POPULATION BY REGIMEN

Regimen 1 (Lfx + Bdq + Lzd + Cfz + Cs): **95.8%**

Regimen 2 (Lfx + Bdq + Lzd + Cfz + Dlm): **3.1%**

Regimen 3 (Lfx + Dlm + Lzd + Cfz, for children under 6 years): **1.1%**

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Geographic distribution

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19
0.7%

11
0.4%

550
19.6%

1194
42.4%

111
3.9%

170
6%

107
3.8%

30
1.1%

106
3.8%

193
6.9%

114
4.1%

101
3.6%

107
3.8%
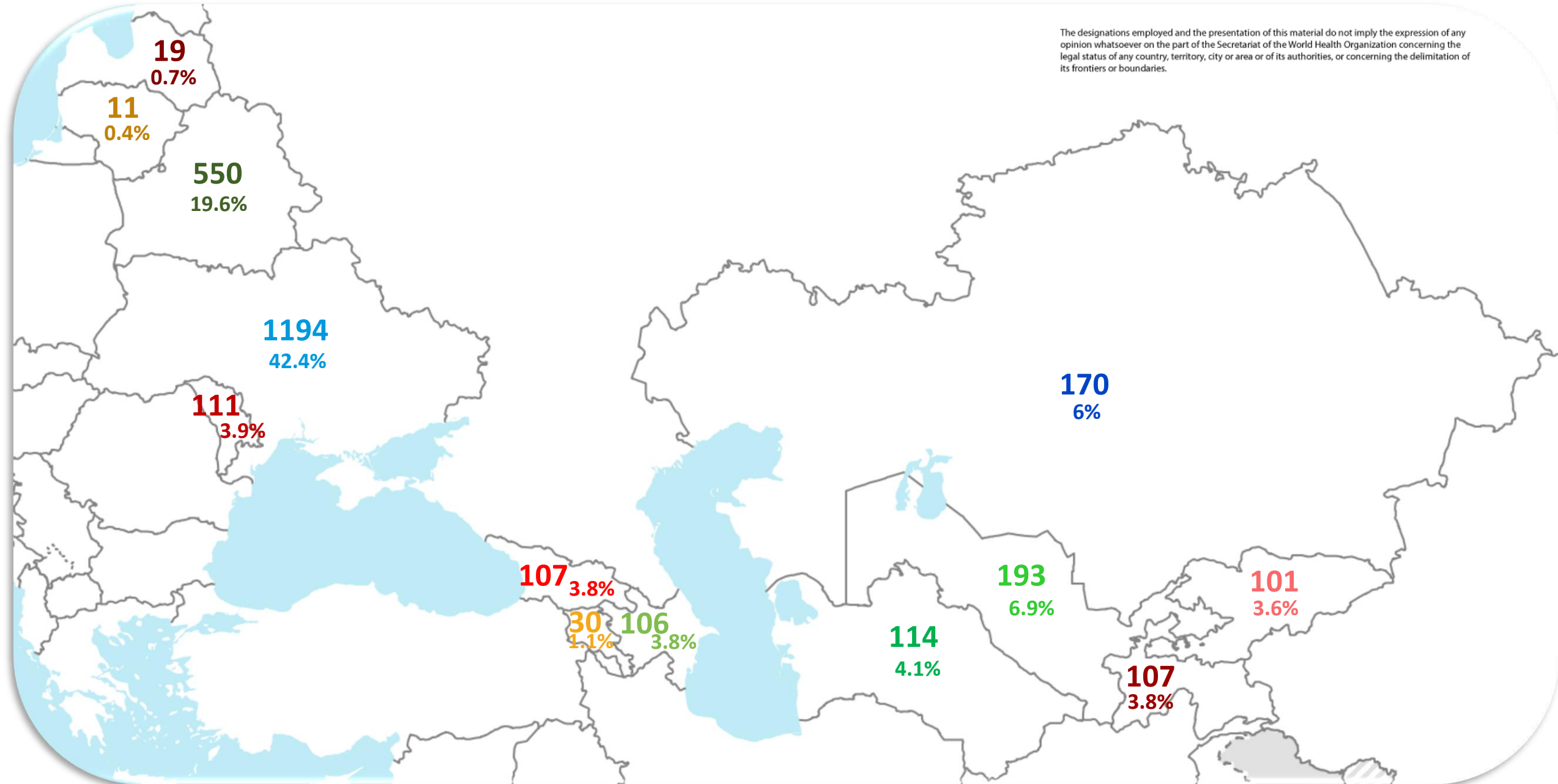
Concomitant diseases

n=2813, 5% of patients had unknown HCV status, 4.5% - HBV and 0.1% - HIV

10.4%
HIV positive
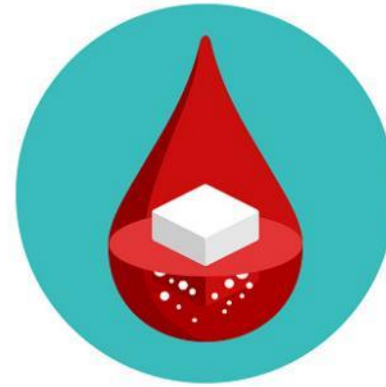
8.6%
Diabetes mellitus

11.1%
HCV positive

2.5%
HBV positive

HEPATITIS B

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Concomitant diseases

n=2813, 19.1% were not tested for COVID-19
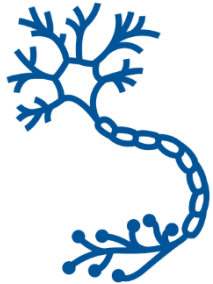
3.7%
History of peripheral neuropathy
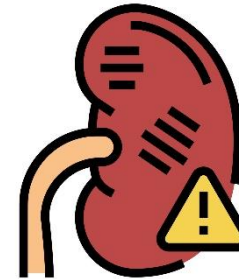
0.8%
History of kidney injury
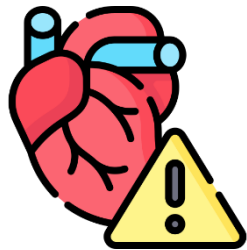
4.5%
History of heart disease

3.1%
COVID-19 at baseline

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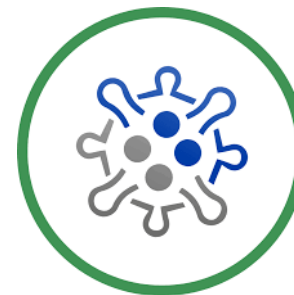
Social and behavioral characteristics

n=2813

61.5%
Were unemployed of able-bodied age

89.9%
Had secondary education or lower

2.7%
Were homeless

9.7%
Had incarceration experience

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Social and behavioral characteristics

n=2813

15.7%
Experienced problematic alcohol use

53.5%
Were current smokers
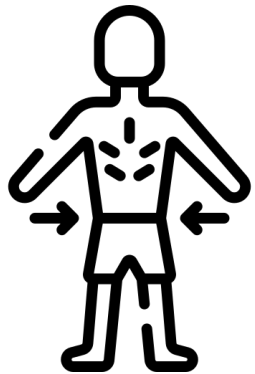
22.1%
Were malnourished (BMI<18.5)

2.7%
Were PWIDs

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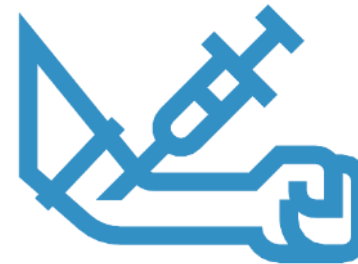
Baseline characteristics

n=2813

Study population by presence of lung cavities

0.1%

42.0%

41.0%

16.9%
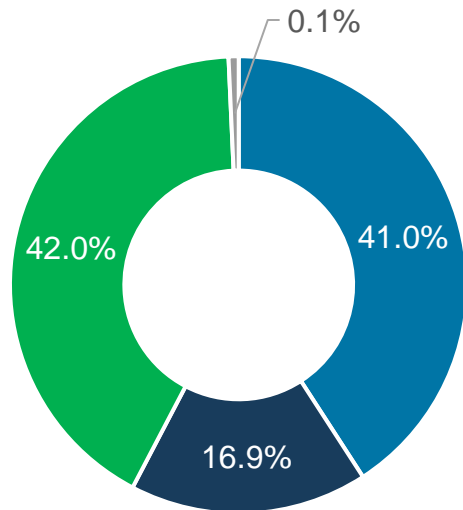
- One-sided
- Two-sided
- No cavity
- Unkown (or missing data)

Study population by lung radiographic changes

0.7%

50.1%

49.2%
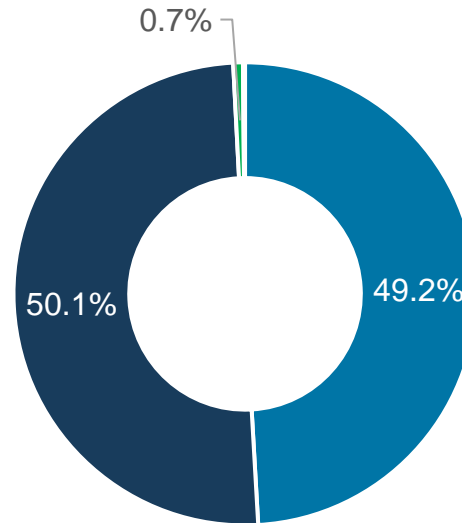
- Abnormal one-sided
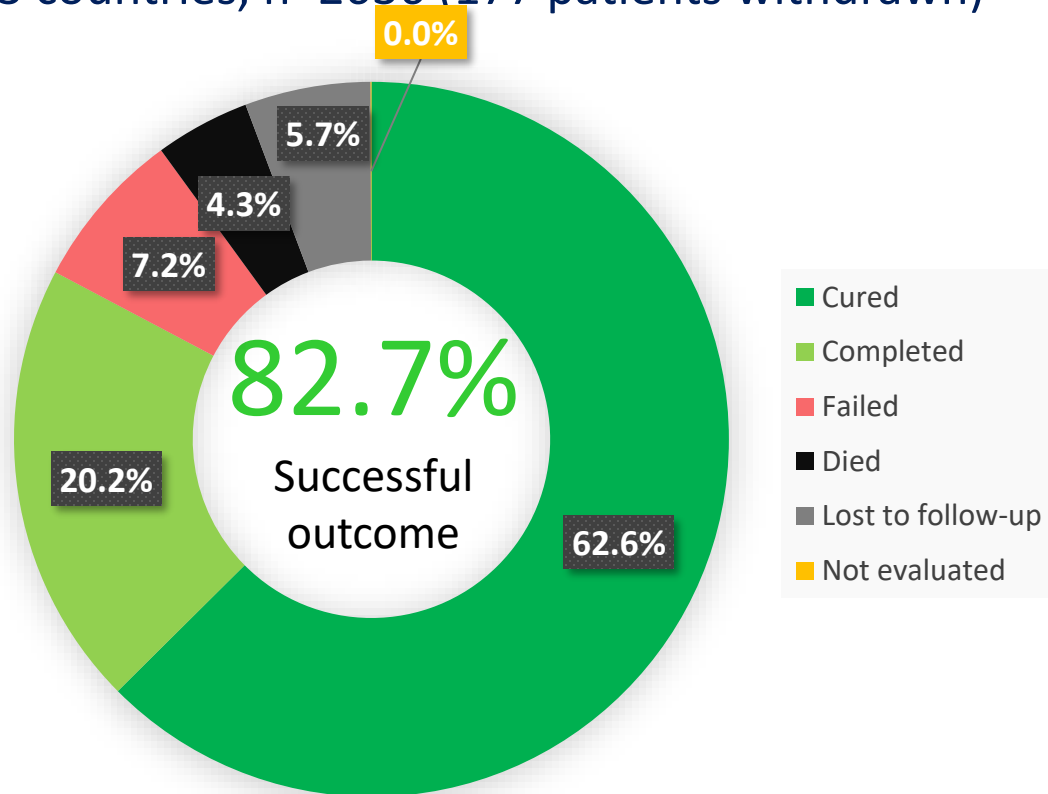- Abnormal two-sided
- Normal

Study population by microscopy results

0.8%

41.4%

57.8%
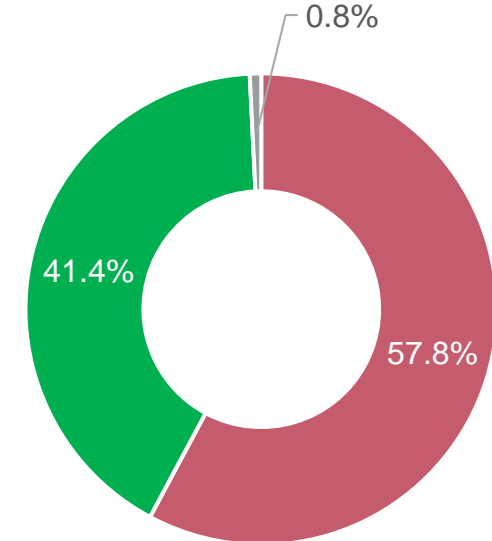
- Smear positive
- Smear negative
- Unknown/not done

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Part 3. Effectivness

Outcomes upon treatment completion

13 countries, n=2636 (177 patients withdrawn)

82.7% Successful outcome

- Cured
- Completed
- Failed
- Died
- Lost to follow-up
- Not evaluated

0.0%
5.7%
4.3%
7.2%
20.2%
62.6%

MDR/RR-TB outcomes

12 countries*; 2019 cohort; n=20145**

68.6% Successful outcome

2.6% Not evaluated
7.6% Failed
11.5% Died
9.7% LFU
Successful treatment

n=2636: out of 2813 patients included in the Regional cohort;
1 subject was missing final treatment outcome;
177 (6%) patients were withdrawn from the study without fulfilling treatment failed definition;
Patients that failed to receive at least 246, but no more than 300 doses, of mSTR regimen within 245 to 301 days regardless of the reason were classified as failure, though programmatically could have satisfied the definition of cured or treatment completed
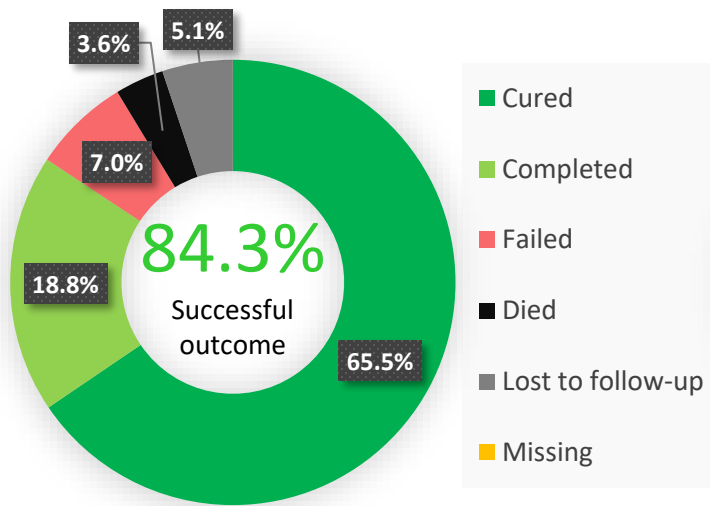
Source: WHO Global TB database

*Latvia did not report data
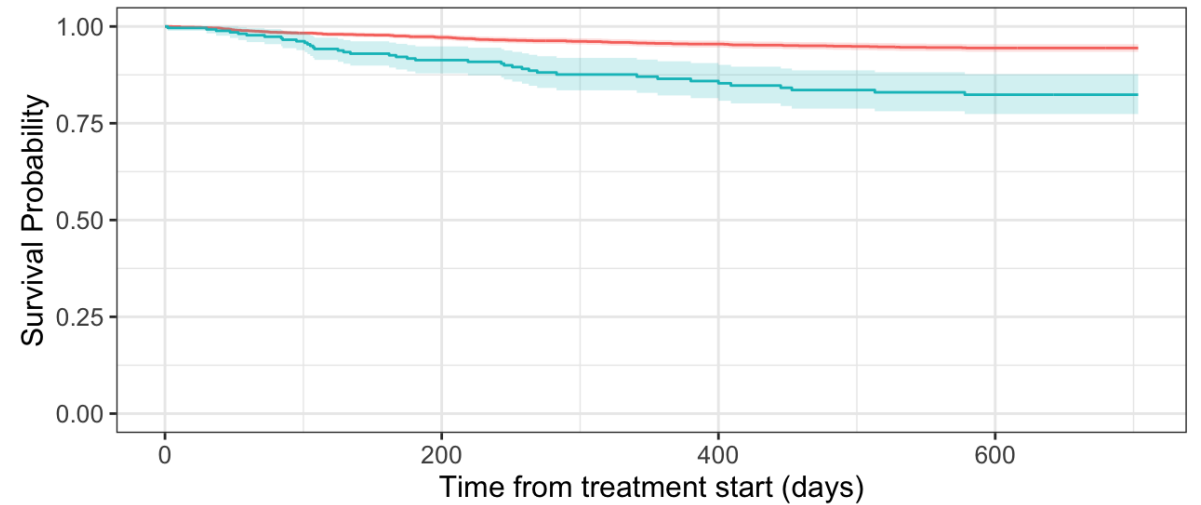**Patients with an outcome 'Not evaluated' were excluded

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End of treatment outcomes by HIV status

HIV-negative, n=2363

5.1%
3.6%
7.0%
18.8%
84.3%
Successful outcome
65.5%

HIV-positive, n=270

0.4%
10.7%
10.7%
8.9%
69.2%
Successful outcome
37.0%
32.2%

Legend:
- Cured
- Completed
- Failed
- Died
- Lost to follow-up
- Missing
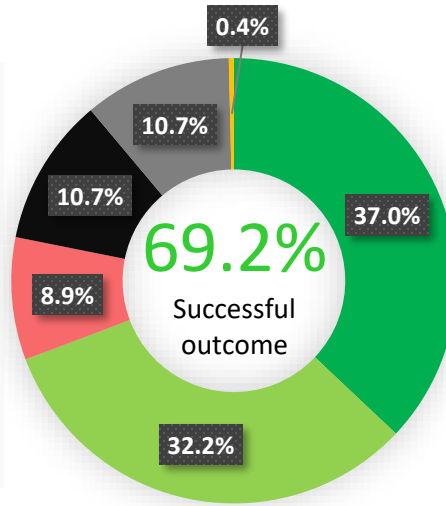
Kaplan Meier estimates for time to death by HIV status

Survival Probability
Time from treatment start (days)

No — Yes

	No			
At Risk	2363	2136	1731	1521
Events	0	65	100	118
	Yes			
At Risk	269	216	148	134
Events	0	22	34	39

Preliminary results of 12-month post-treatment follow-up (mSTR)

n=2636, as of 30 June 2023 in total 25 cases of recurrence and 44 deaths were registered; 460 patients were LTFU after achieving treatment success; this was a reason for censoring in Kaplan-Meier estimates, but we did not account it as unsuccessful study outcome

Cumulative probability of not experiencing an unsuccessful study outcome*
9, 15 and 21 months after treatment initiation in the treatment cohort

	Time from treatment initiation (months)		
	9	15	21
Overall	82% (81%, 84%)	80% (79%, 82%)	79% (77%, 81%)
Lfx+Bdq+Lzd+Cfz+Cs	82% (81%, 84%)	80% (79%, 82%)	79% (77%, 81%)
Lfx+Bdq+Lzd+Cfz+Dlm	81% (72%, 90%)	75% (65%, 86%)	75% (65%, 86%)
Lfx+Dlm+Lzd+Cfz	93% (84%, 100%)	93% (84%, 100%)	93% (84%, 100%)

Kaplan Meier estimates for time to unsuccessful study outcome

At Risk	2635	2354	1880	1655
Events	0	281	479	519
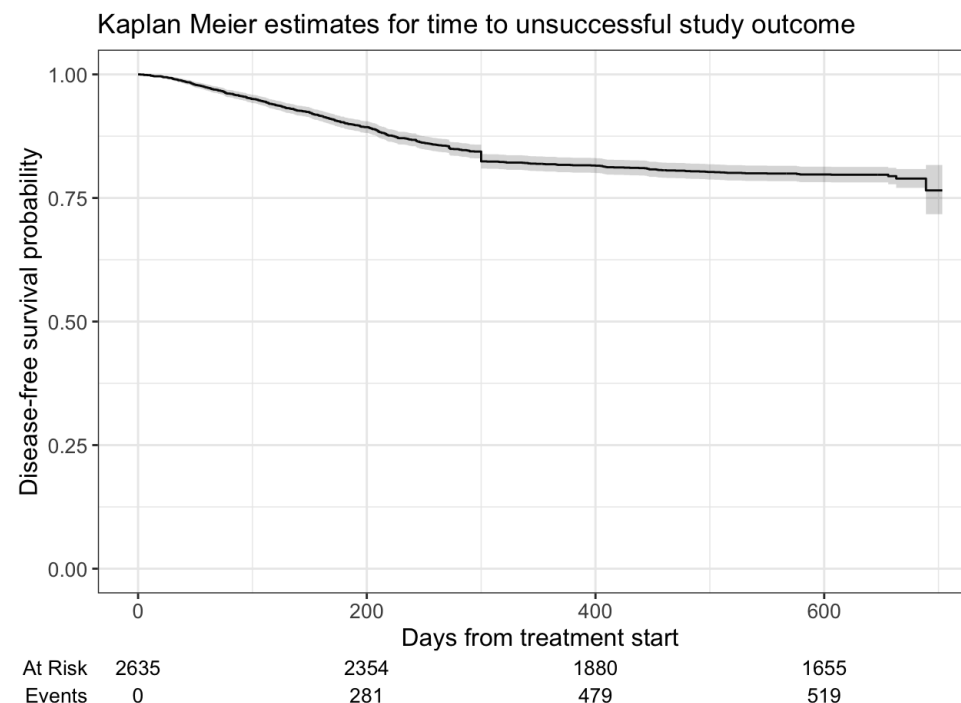
*Unsuccessful study outcomes included: death (during treatment and follow-up), failure, LTFU during treatment, recurrence

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Independent predictors of unsuccessful study outcomes: adjusted analysis resume

Unemployed patients:
45% higher hazard

Compared with 35-44 age group:
Patients aged 55-64: 37% higher hazard;
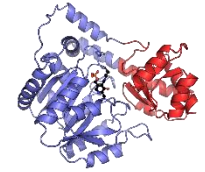Patients aged 64 and older:
2.5 times higher hazard

Unsuccessful study outcome: death (during treatment and follow-up), failure, LTFU during treatment, recurrence
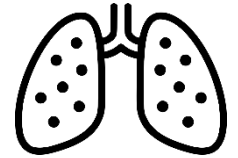
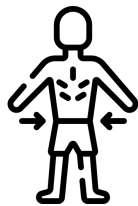Patients with two-sided cavities:
64% higher hazard

Patients with baseline elevated ALT/AST:
39% higher hazard

Patients with excess alcohol use:
46% higher hazard

Patients with BMI over 18.5:
22% lower hazard

Current smokers:
37% higher hazard

HIV positive patients:
57% higher hazard

Patients with baseline anemia:
45% higher hazard

Part 4.
# Safety

Secondary outcomes of interest

Adverse Events developed at any time while on treatment and 12-months follow-up period presented by incidence of:

- Serious Adverse Events;

- Adverse Events of Interest of grade 3 and greater by the severity grading scale;

- Adverse Events resulting in discontinuation (temporary or permanent) of any study drug(s);

- Outcomes of all recorded Adverse Events (resolved, not resolved, resolved with sequelae and fatal);

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Safety: Occurrence of AEI of grade 3 and higher by months and types

301 AEIs were observed during study treatment among 252 participants (9%), reaching the rate of 1.32 per 100 person-months;
7.5% patients had one incidence of AEI, 1.3% - two or more

Incidence rate of adverse events of interest by calendar month following RR-TB treatment initiation
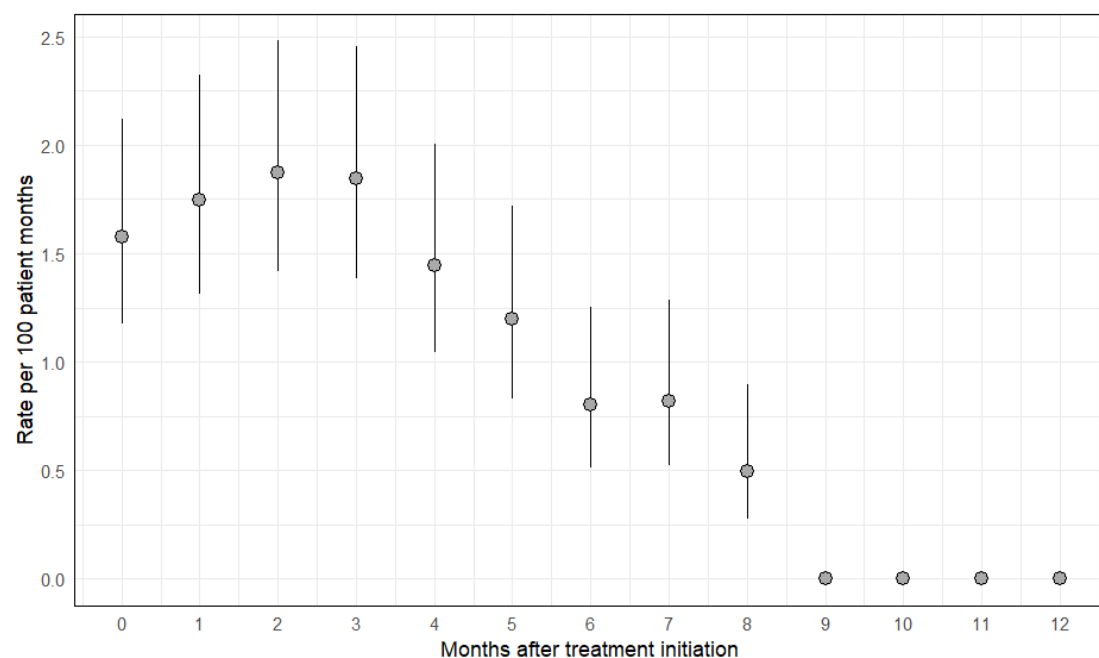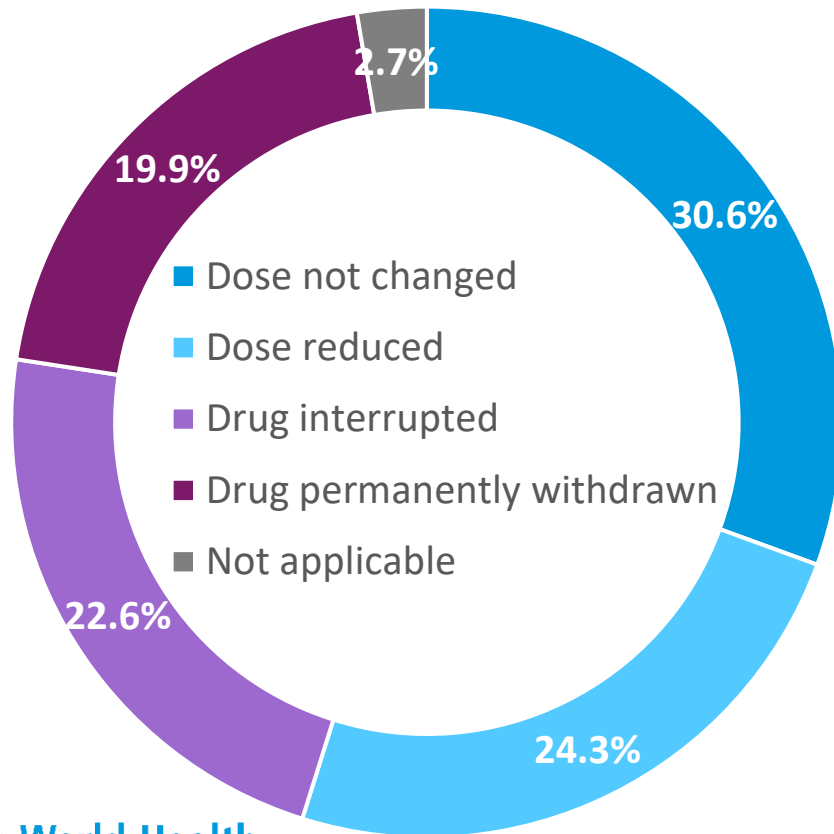
Frequency and type of AEI during treatment (in % of all and in per person-month)

AEI term	Number	%	Rate	95% CI
Peripheral neuropathy	32	10.6	0.14	(0.10-0.20)
Myelosuppression	157	52.2	0.69	(0.59-0.80)
QT interval prolongation	49	16.3	0.21	(0.16-0.28)
Hepatitis	25	8.3	0.11	(0.74-0.16)
Optic neuritis	16	5.3	0.07	(0.04-0.11)
Hypokalemia	7	2.3	0.03	(0.01-0.06)
Acute kidney inj.	15	5.0	0.07	(0.04-0.11)
Total	**301**	**100**	**1.32**	**(1.18-1.48)**

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Safety: Actions taken and outcomes of AEI of grade 3 and higher

Actions taken in response to AEI

Dose not changed — 30.6%
Dose reduced — 24.3%
Drug interrupted — 22.6%
Drug permanently withdrawn — 19.9%
Not applicable — 2.7%

Outcomes of AEI

Resolved — 46.5%
Resolving — 38.2%
Resolved with sequelae — 4%
Not resolved — 8%
Died — 2.3%
Unknown — 1%

World Health Organization

European Region
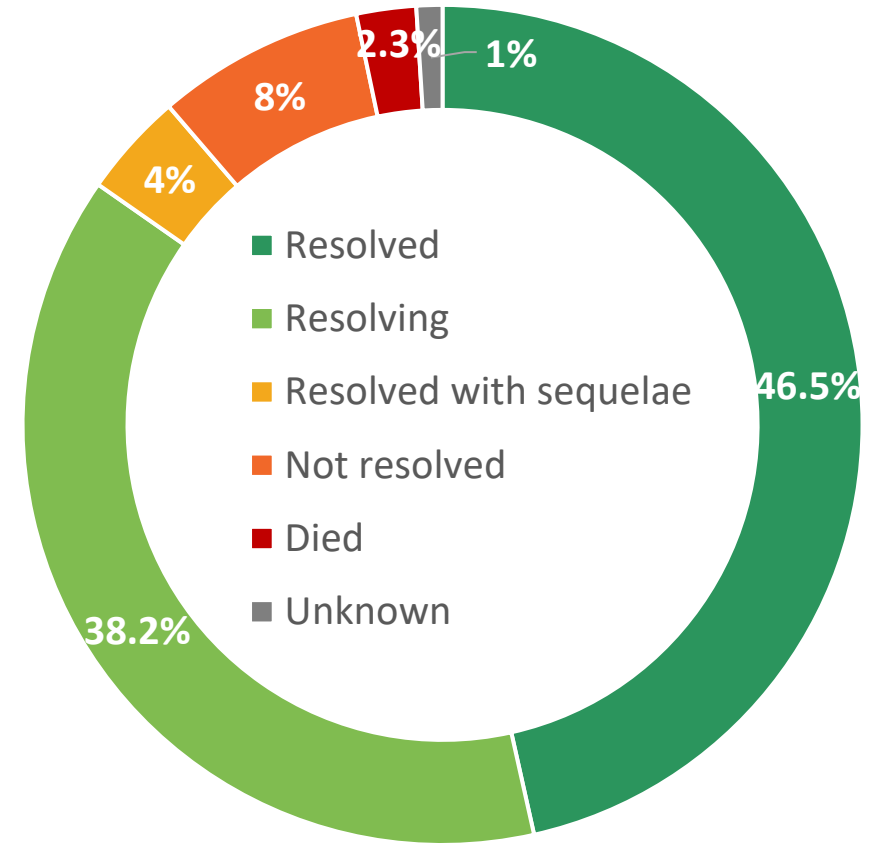
Safety: Factors associated with development of AEI of grade 3 and higher during treatment (adjusted analysis)

Male patients had **28% lower hazard** of AEIs vs female

Every 10 years increase in age was associated with **30% of increased AEIs hazard**

Lfx+Bdq+Lzd+Cfz+Dlm was associated over **2.5-fold increased hazard** of AEIs

Malnutrition (BMI below 18.5) **increased hazard for AEIs by 40%**

AEIs of grade 3 and higher

People with history of heart disease had **37% higher hazard of development of AEIs**

HIV positive patients had **a 21% increased hazard**

People with HCV had **64% elevated hazard of development of AEIs**

Baseline disturbances

Every **grade increase in severity** of the following baselines disturbances was associated with increased AEIs hazard:

Increased creatine: **64%**

Peripheral neuropathy: **40%**

Increased bilirubin: **55%**

Anemia: **76%**

Conclusions

# Impact of mSTR OR on the burden of DR-TB

- Increased coverage of patients with safer and more effective regimens

- Increased treatment success rate and decreases LTFU rates and rates of other unfavorable outcomes

- Promotion of good clinical care and simplifies treatment monitoring schedule

- Health system strengthening through reduction of hospitalization costs, promotion of patient-centered models of care and capacity building

- Decreased risk for nosocomial transmission of infection

- Contribution to the reduction of stigma and the decrease of household costs due to disability

- Faster impact on TB epidemic in the Region by reducing reservoir of infection

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Conclusions

- mSTR regimens show promising results and have a potential to facilitate achieving the regional target of 80% success rate for MDR/RR-TB by 2025

- 12-month post-treatment recurrence rate is low (1.1%)

- Analysis of predictors of unsuccessful outcomes suggest that DR-TB outcomes can be improved further, if specific attention is given to **reducing alcohol dependence and smoking**, ensuring **proper nutrition and management of anemia**, providing **social support and patient-centred care to elderly and unemployed**; providing **enhanced care and treatment monitoring to patients with HIV and elevated liver enzymes**; ensuring **early diagnosis of TB**

- Proportion of patients experiencing SAE or AEI is generally low, however it is important to **prioritize clinical monitoring and care** for patients with pre-existing conditions, as well as to ensure **adequate management** of those conditions to prevent SAE and AEI, particularly: **HIV, viral Hepatitis C, heart diseases, anemia, peripheral neuropathy, increased creatinine and liver enzymes, malnutrition**

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Geographic distribution – regional + national cohorts

19
+34

11
+9

550
+436

1194
+2121

111
+306

170
+1456

107 +59

30
+57

106
+251

193
+408

114
+407

101
+73

107
+205

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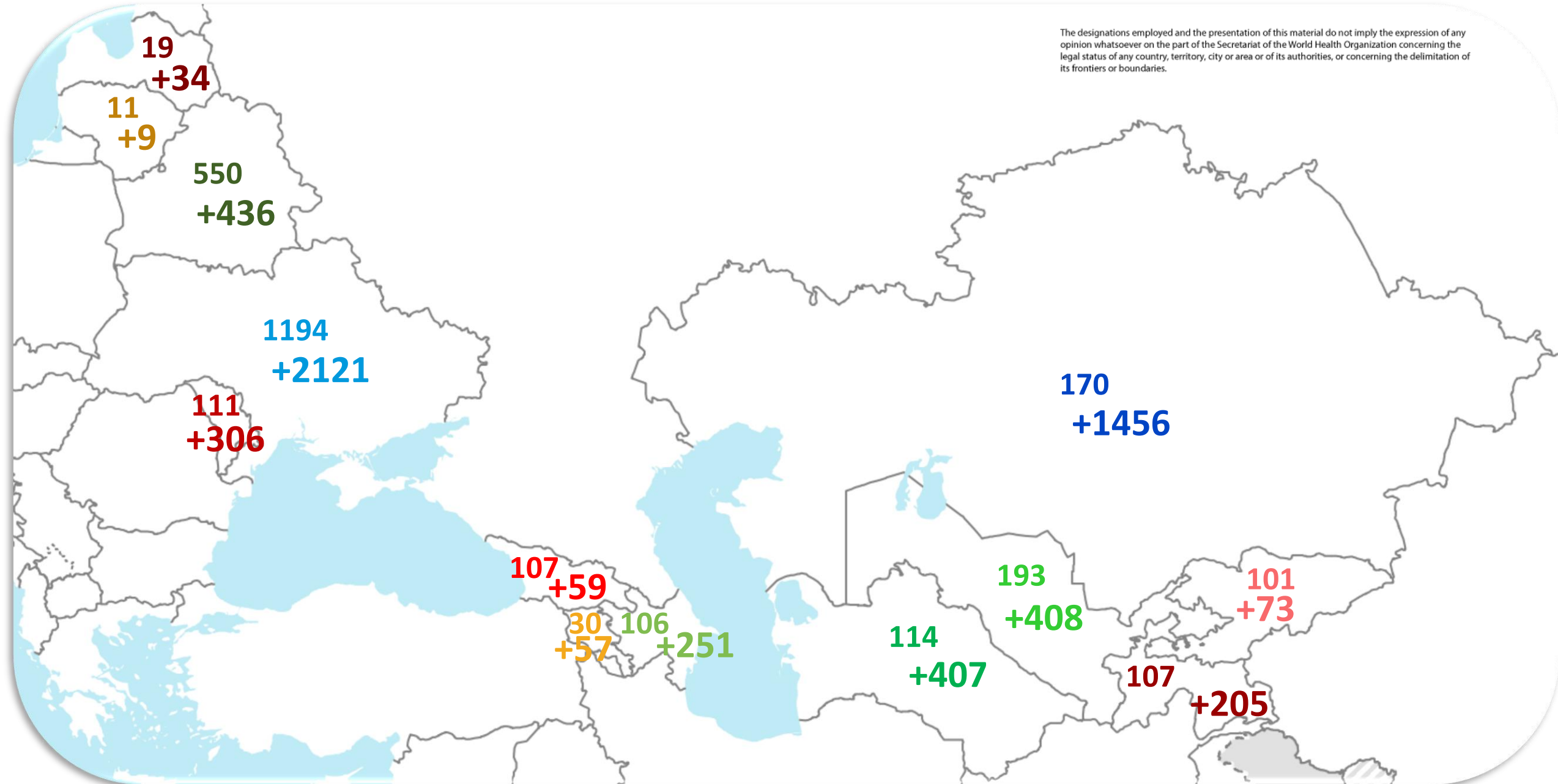
Once again, we thank everyone involved!

In case of questions, please contact:
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