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17th European AIDS Conference
November 6-9, 2019
Basel, Switzerland

Comparison of TB drug susceptibility, treatment regimens and outcome among TB/HIV-patients in a setting with high prevalence of resistant TB: results from a national and supranational reference laboratories

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Background

- Eastern Europe (**EE**) is among regions with world highest prevalence of multi-drug resistant tuberculosis (**MDR-TB**). Inferior management and outcomes in EE compared to Western Europe have previously been documented.[1]
- In Belarus, MDR-TB rates among previously treated TB cases are app 70%
- Treatment of MDR-TB should be based on detailed information on resistance patterns of *Mycobacterium tuberculosis* (**Mtb**), and can be challenging in areas with limited access to drug-susceptibility testing (**DST**)

[1.] *Podlekareva D. & Efsen A. et al, Lancet HIV 2016*

Aims

- We aimed to compare the results of conventional phenotypic DST performed in **Minsk**, Belarus (high MDR-TB burden country) with extensive geno- and phenotypic DST analyses performed at the State Serum Institute (SSI) WHO TB Supranational Reference Laboratory (**SRL**) in Denmark
  - and relate DST results to treatment patterns and outcomes for TB/HIV patients

Definitions

- **DS-TB:** drug sensitive TB
- **H-resistant TB:** resistance to isoniazid only
- **MDR-TB**: multidrug resistant TB - resistance to at least both isoniazid **AND** rifampicin
- **Pre-XDR TB**: pre- extensive drug resistant TB – **MDR-TB** + resistance to **EITHER** any fluoroquinolone **OR** to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin)
- **XDR-TB:** Extensive drug resistant TB – **MDR-TB** + resistance to any fluoroquinolone **AND** to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin)

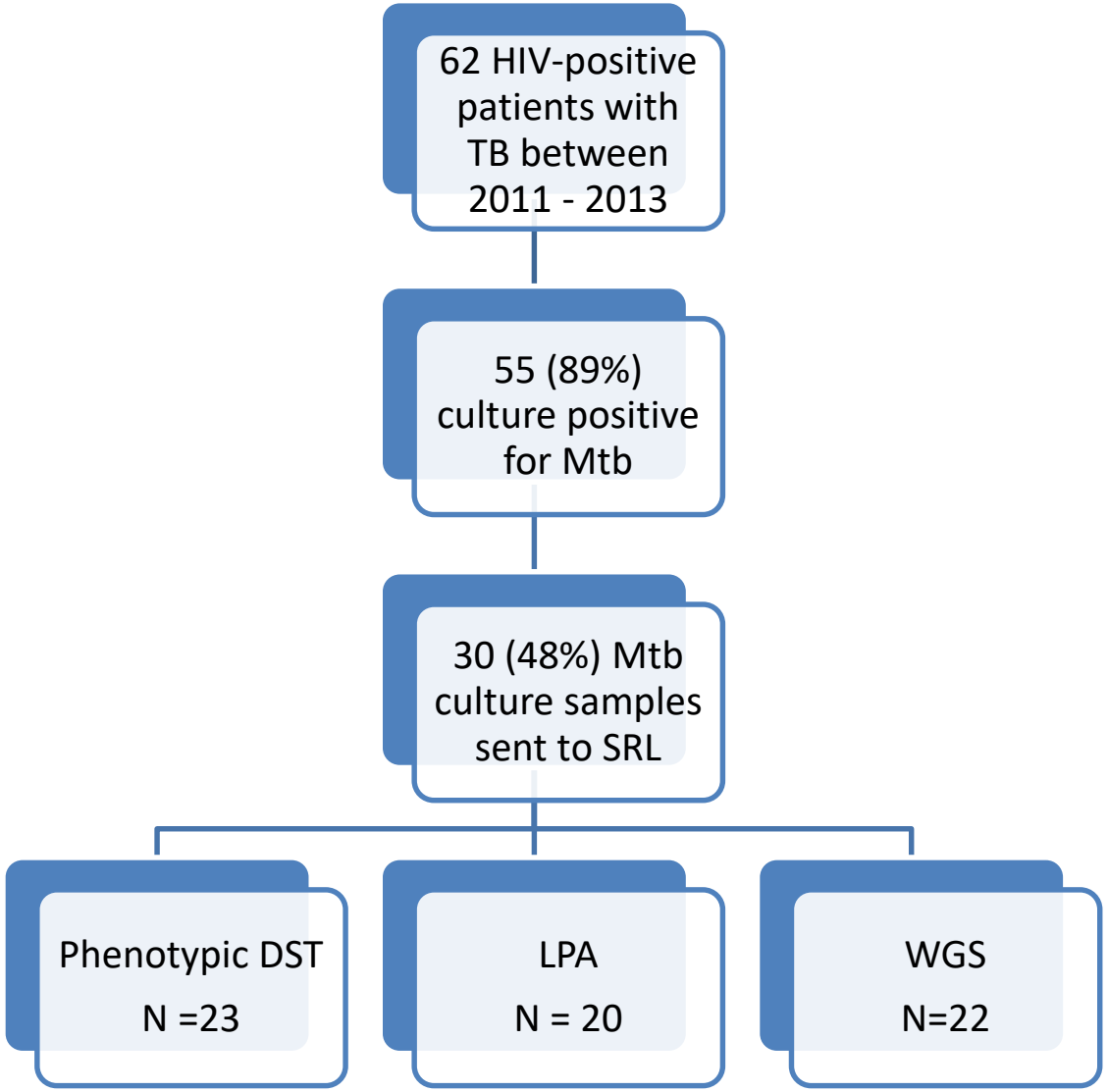
Methods I

- 30 HIV-patients from Minsk with TB-diagnosis between 2011-2013, and with Mtb-culture samples were included

- All samples were shipped to the SRL, phenotypically re-tested and genotypically tested by Line Probe Assays (**LPA**) and Whole Genome Sequencing (**WGS**)

- Descriptive statistics applied to compare DST results and analyze treatment regimens and outcome

Methods II



Phenotypic DST: 7 Mtb samples failed to grow at SRL

LPA: Performed if phenotypic resistance was detected (N=13) or culture failed to grow (N =7)

WGS: failed for 8 Mtb samples

Baseline characteristics of 62 TB/HIV patients from Minsk, Belarus

		Sample Yes, N (%)	Sample No, N (%)	P
Total		30	32	
Male Gender	Yes, N (%)	22 (73.3)	28 (87.5)	0.206
Age	Years, Median (IQR)	37.2 (30.4 – 41.0)	34.7 (31.5 - 42.3)	0.789
TB/HIV Risk Factors	Ever Injecting drug use, N (%)	19 (63.3)	24 (75.0)	0.319
	History of imprisonment, N (%)	5 (16.7)	12 (37.5)	0.090
	History of excess alcohol consumption, N (%)	19 (63.3)	15 (46.9)	0.213
Mtb Culture positive		30 (100.0)	25 (78.1)	0.011
MDR	Yes, N (%)	18 (60)	16 (50)	0.456
TB Disease	Disseminated, N (%)	12 (40.0)	6 (18.8)	0.094
Hepatitis C antibody +	Ever, N (%)	24 (80.0)	23 (72.0)	0.558
HIV duration	Months, Median (IQR)	87.5 (44.3-136.4)	67.0 (24.8-120.0)	0.535
ART at baseline	Yes, N (%)	15 (50.0)	14 (43.8)	0.799
CD4 cell count, mm^3/ml^1	Median (IQR)	85.5 (22.0-171.0)	126.5 (57.0-310.0)	0.097
Died	Yes, N (%)	16 (53.3)	10 (31.3)	0.122

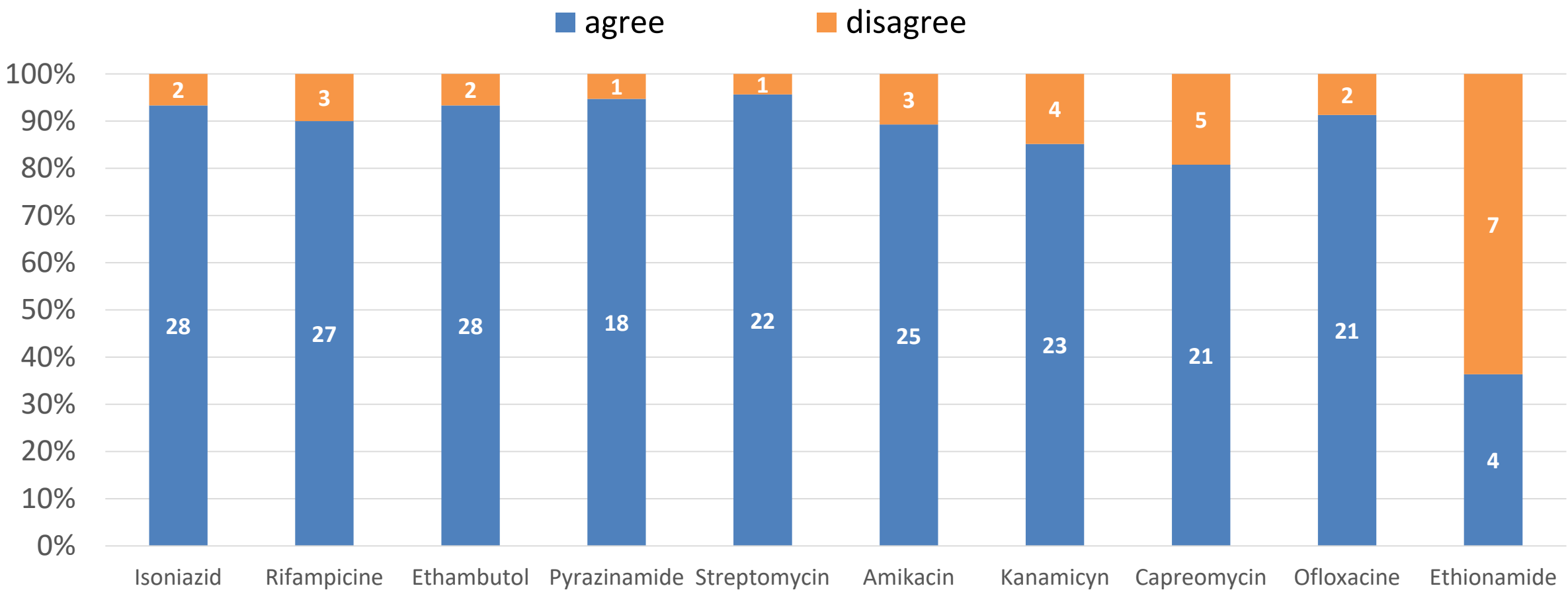
Type of TB in 30 TB/HIV patients from Minsk according to the DST performed in Belarus and in Denmark

Type of TB	Minsk* N (%)	SRL** N (%)	P-value	Note
Drug Sensitive TB	10 (33,3)	12 (40,0)	0,79	2 pts classified as MDR-TB in Minsk and as DS-TB at SRL
H-resistant TB	2 (6,7)	2 (6,6)	1,00	
MDR-TB	8 (26,7)	3 (10,0)	0,18	No discrepancies between DSTs for Rifampicin and isoniazid
Pre-XDR-TB	5 (16,7)	9 (30,0)	0,36	Discrepancies mainly observed for 2nd-line injectables
XDR-TB	5 (16,7)	4 (13,3)	1,00	

*As reported

** According to the results of combined phenotypic DST, LPA and WGS. In case of discrepancies, the worst (=resistant) result was considered

Agreement in DST results between two laboratories



N tested in both labs	Isoniazid	Rifampicine	Ethambutol	Pyrazinamide	Streptomycin	Amikacin	Kanamicyn	Capreomycin	Ofloxacine	Ethionamide
	30	30	30	19	23	28	27	26	23	11

Type of TB in 30 TB/HIV patients from Minsk according to the DST performed in Belarus and in Denmark, and number of active drugs in treatment regimens

Type of TB	Minsk* N (%)	SRL** N (%)	P-value	N Active drugs initially, median (range)		N Active drugs after 1st change, median (range)	
				Minsk	SRL	Minsk	SRL
Drug Sensitive TB	10 (33,3)	12 (40,0)	0,79	4 (4-4)	4 (4-4)	2 (2-3)	2 (2-3)
H-resistant TB	2 (6,7)	2 (6,6)	1,00	4 (3-4)	4 (3-4)	5 (4-5)	5 (4-5)
MDR-TB	8 (26,7)	3 (10,0)	0,18	0 (0-5)	0 (0-0)	5 (1-5)	4 (1-5)
Pre-XDR-TB	5 (16,7)	9 (30,0)	0,36	1 (0-1)	1 (0-1)	4 (1-5)	3 (1-4)
XDR-TB	5 (16,7)	4 (13,3)	1,00	0 (0-1)	0 (0-1)	3 (2-3)	3 (1-4)

*As reported

** According to the results of combined phenotypic DST, LPA and WGS. In case of discrepancies, the worst result was considered

Type of TB in 30 TB/HIV patients from Minsk according to the DST performed in Belarus and in Denmark, number of active drugs in treatment regimens **and outcomes at 24 months**

Type of TB	Minsk* N (%)	SRL** N (%)	P-value	N Active drugs initially, median (IQR)		N Active drugs after 1st change, median (IQR)		Died N (%)
				Minsk	SRL	Minsk	SRL	
Drug Sensitive TB	10 (33,3)	12 (40,0)	0,79	4 (4-4)	4 (4-4)	2 (2-2)	2 (2-2)	3 (30)
H-resistant TB	2 (6,7)	2 (6,6)	1,00	4 (3-4)	4 (3-4)	5 (5-5)	5 (5-5)	1 (50)
MDR-TB	8 (26,7)	3 (10,0)	0,18	0 (0-0)	0 (0-0)	5 (5-5)	4 (3-5)	
Pre-XDR-TB	5 (16,7)	9 (30,0)	0,36	1 (0-1)	1 (0-1)	4 (3-4)	3 (2-4)	12 (67)
XDR-TB	5 (16,7)	4 (13,3)	1,00	0 (0-0)	0 (0-0)	3 (3-3)	3 (2-3)	

*As reported

** According to the results of combined phenotypic DST, LPA and WGS. In case of discrepancies, the worst result was considered

Anti-TB drugs used and median treatment duration

- 29/30 patients started anti- TB treatment based on
  - Rifampicin + Isoniazid + pyrazinamide, which was an active regimen for 40% of patients only
- Majority of MDR-TB patients (N=13, 72%) switched to a standard 2nd line regimen at a median of 1,5 months (IQR 1-2m):
  - Pyrazinamide + Fluoroquinolone + Aminoglycoside (injectable) + Cycloserine + Ethionamide + PAS
- Treatment duration:
  - DS-TB: 9,5 months (IQR 7,3 -10)
  - MDR-TB treatment: after treatment adjustment: 8 months (IQR 2-11 months)
  - Of note, 6 (33%) patients, who stayed alive, received treatment for 11 – 26 months

Summary

- Good quality of local DSTs
- Standard treatment regimens used
  - Suboptimal number of active drugs and delay in initiating adequate regimens
  - High mortality rate
- Better accessibility to rapid molecular DSTs is required
- Individualized potent TB treatment regimens should be DST-tailored, ultimately improving outcome

Aknowledgement

- Minsk, Belarus:
  - Republican Scientific and Practical Center for Pulmonology and TB: Alena Skrahina, Aliaksandr Skrahin, Henadz Hurevich, Dzmitry Klimuk
  - Belarussian State Medical University: Igor Karpov, Anna Vassilenko
- Copenhagen, Denmark:
  - International Reference Laboratory of Mycobacteriology, Statens Serum Institut: Dorte Bek Folkvardsen, Troels Lillebaek
  - CHIP: Jens D. Lundgren, Dorthe Raben, Ole Kirk