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**Effectiveness and cardiovascular safety of delamanid-containing regimens in adults with multidrug-resistant or extensively drug-resistant tuberculosis: A nationwide cohort study from Belarus, 2016-18**

Vera Auchynka<sup>1</sup>, Ajay M.V. Kumar<sup>2,3,4</sup>, Hennadz Hurevich<sup>1</sup>, Yuliia Sereda<sup>5</sup>, Varvara Solodovnikova<sup>1</sup>, Dzmitry Katovich<sup>6</sup>, Svetlana Setkina<sup>7</sup>, Askar Yedilbayev<sup>5</sup>, Aliaksandr Skrahin<sup>8</sup>, Alena Skrahina<sup>1</sup>

<sup>1</sup>Republican Scientific and Practical Centre for Pulmonology and Tuberculosis, Minsk, Belarus; <sup>2</sup>International Union Against Tuberculosis and Lung Disease, Paris, France; <sup>3</sup>International Union Against Tuberculosis and Lung Disease, South-East Asia Office, New Delhi, India; <sup>4</sup>Yenepoya Medical College, Yenepoya (Deemed to be University), Mangaluru, India; <sup>5</sup>World Health Organization, Regional Office for Europe, Copenhagen, Denmark; <sup>6</sup>Pulmonary Centre Klinikum Mittelbaden GmbH, Baden-Baden, Germany; <sup>7</sup>Center for Examination and Tests in Health Service, Minsk, Belarus; <sup>8</sup>Belarusian State Medical University, Minsk, Belarus

**Corresponding author:** Vera Auchynka, Republican Scientific and Practical Centre for Pulmonology and Tuberculosis, 157, Dolginovsky trakt, 220053 Minsk, Belarus. Tel. +375.29.6521152. E-mail: [veraavchinko@mail.ru](mailto:veraavchinko@mail.ru)

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**Supplementary Table 1.** Drugs and dosage used for the treatment of M/XDR-TB patients in Belarus, 2016-18.

Drug	Drug doses by weight group				
	30-35 kg	36-45 kg	46-55 kg	56-70 kg	> 70 kg
Moxifloxacin (Mfx)	400 mg	400 mg	400 mg	400 mg	400 mg
Moxifloxacin (Mfx)*	800 mg	800 mg	800 mg	800 mg	800 mg
Levofloxacin (Lx)	500 mg	750 mg	1000 mg	1000 mg	1000 mg
Bedaquiline (Bdq)	400 mg for first 2 weeks; then 200 mg 3 times a week				
Linezolid (Lzd)	300 mg	300 mg	600 mg	600 mg	600 mg
Clofazimine (Cfz)	50 mg	100 mg	100 mg	100 mg	100 mg
Cycloserine (Cs) OR Terizidone (Trd)	500 mg	500 mg	500 mg	750 mg	750 mg
Delamanid (Dlm)	200 mg	200 mg	200 mg	200 mg	200 mg
Pyrazinamide (Z)	800 mg	1200 mg	1600 mg	2000 mg	2000 mg
Imipenem/cilastatin (Imp)	2000 mg	2000 mg	2000 mg	2000 mg	2000 mg
Amikacyn (Am)	500 mg	750 mg	750 g	1 g	1 g
Capreomycin (Cm)	500 mg	750 mg	750 mg	1 g	1 g
Prothionamide (Pto) OR Ethionamide (Eto)	500 mg	500 mg	750 mg	750 mg	1000 mg
Amoxicillin/Clavulanic acid (Amx/Clv)	2000 mg/ 500 mg	2000 mg/ 500 mg	2000 mg/ 500 mg	2000 mg/ 500 mg	2000 mg/ 500 mg

\*The dosage of Mfx 800 mg is prescribed to patients with resistance to Mfx 0.25, but sensitivity to Mfx 1.0 on liquid culture drug susceptibility testing.

**Supplementary Table 2.** Types of adverse drug events and their grading among patients with M/XDR-TB treated with delamanid-containing regimens in Belarus, 2016-18.

Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
QTcF prolongation	450-480ms	481-500ms	≥500 ms; >60 ms change from baseline	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	-
Atrioventricular block complete	-	Non-urgent intervention indicated	Symptomatic and incompletely controlled with device (e.g., pacemaker); new onset	Life-threatening consequences; urgent intervention indicated	Death
Atrioventricular block first degree	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	-	-	-
Chest pain	Mild pain	Moderate pain; pain on exertion; limiting instrumental ADL; hemodynamically stable	Pain at rest; limiting self-care ADL; cardiac catheterization; new onset cardiac chest pain; unstable angina	-	-
Heart failure	Asymptomatic with laboratory or cardiac imaging abnormalities	Symptoms with moderate activity or exertion	Symptoms at rest or with minimal activities or exertion; hospitalization; new onset of symptoms	Life-threatening consequences; urgent intervention indicated	Death
Myocardial infarction	-	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction	Life-threatening consequences; hemodynamically unstable	Death
Sinus bradycardia	Asymptomatic, intervention not indicated	Symptomatic, intervention not indicated, change in medication initiated	Symptomatic, intervention required	Life-threatening consequences; urgent intervention indicated	Death
Sinus tachycardia	Asymptomatic, intervention not indicated	Symptomatic, intervention not indicated, change in	Urgent medical intervention indicated	-	-

		medication initiated			
Supraventricular tachycardia	Asymptomatic, intervention not indicated	Not-urgent medical intervention indicated	Symptomatic, urgent intervention indicated	Life-threatening consequences	Death
Ventricular arrhythmia	Asymptomatic, intervention not indicated	Not-urgent medical intervention indicated	Urgent medical intervention indicated	Life-threatening consequences	Death
Ventricular tachycardia	-	Not-urgent medical intervention indicated	Symptomatic, urgent intervention indicated	Life-threatening consequences; hemodynamic compromise	Death
Cardiac disorders-other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or existing hospitalization indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Hypertension	Systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg	Systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg if previously WNL; change in baseline medical intervention indicated; recurrent or persistent ( $\geq 24$ hrs); symptomatic increase by $>20$ mm Hg (diastolic) or to $>140/90$ mmHg	Systolic BP $\geq 160$ mm Hg or diastolic BP $\geq 100$ mm Hg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated;	Adult: Life threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Death
Hypoalbuminemia	$<LLN$ 30 g/l	$<30-20$ g/l	$<20$ g/l	Life-threatening consequences; urgent intervention indicated	Death
Hypocalcemia	Corrected serum calcium of $<LLN$ - 2.0 mmol/L; Ionized calcium	Corrected serum calcium of $<2.0$ - 1.75 mmol/L; Ionized calcium	Corrected serum calcium of $<1.75$ - 1.5 mmol/L; Ionized calcium	Corrected serum calcium of $<1.5$ mmol/L;	Death

	<LLN - 1.0 mmol/L	<1.0 - 0.9 mmol/L; symptomatic	<0.9 - 0.8 mmol/L; hospitalization indicated	Ionized calcium <0.8 mmol/L; life-threatening consequences	
Hypokalaemia	<LLN - 3.0 mmol/L	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Hypomagnesemia	<LLN - 0.5 mmol/L	<0.5 - 0.4 mmol/L	<0.4 - 0.3 mmol/L	<0.3 mmol/L; life-threatening consequences	Death
Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L asymptomatic;	125-129 mmol/L symptomatic; <120-124 mmol/L regardless of symptoms	<120 mmol/L; life-threatening consequences	Death
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; intervention initiated	> 7.0 mmol/L; life-threatening consequences	Death
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>ULN - 3.0-8.0 mg/dL; > 1.23-3.30 mmol/L	>8.0.mg/gl;3/30 mmol/L life-threatening consequences	Death
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 – 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death

ADL, activities of daily living; BP, blood pressure; WNL, within normal limits; LLN, lower limit of normal; ULN, upper limit of normal; QTcF, adjusted QT interval using Fredericia formula.

**Supplementary Table 3.** Management, outcomes and timing of cardiovascular adverse drug events in M/XDR-TB patients treated with delamanid-containing regimens in Belarus, from June 2016 to February 2018 (N=125).

	Total, n	Management, n				Resolved outcome		Time to AE, days			Duration <sup>o</sup> of AE, days		
		Drug withdrawal	Drug interruption	Dose reduced	None	n	%	Median [Q1-Q3]	Min	Max	Median [Q1-Q3]	Min	Max
QTcF prolongation	64	-	-	-	64	60	93.8	186 [75-313]	20	607	66 [30-124]	2	760
ECG abnormalities	40	1	-	-	39	33	82.5	101 [36-274]	1	530	91 [46-180]	1	685
Sinus tachycardia	28	-	-	-	28	27	96.4	153 [40-342]	1	637	64 [31-101]	4	157
Sinus bradycardia	23	1	-	-	22	21	91.3	149 [49-358]	21	635	36 [27-101]	7	430
Ventricular extrasystoles	5	-	-	-	5	4	80.0	333 [123-435]	24	568	31 [30-101]	1	155
Bundle branch block	5	-	-	-	5	5	100	345 [252-427]	57	641	73 [72-88]	27	145
Atrioventricular block	3	1	-	-	2	2	66.7	71 [14-352]	14	352	141 [96-365]	96	365
Supraventricular extrasystoles	2	-	-	-	2	2	100	414 [217-611]	217	611	51 [45-57]	45	57
Hypertension arterial	2	-	-	-	2	2	100	167 [140-194]	140	194	63 [61-65]	61	65
Heart rate irregular	1	-	-	-	1	1	100	181 [181-181]	181	181	86 [86-86]	86	86
Other disorders	2	2	-	-	-	0	0	241 [45-436]	45	436	0 [0-0]	0	0
Other investigations	2	-	-	-	2	2	100	202 [87-317]	87	317	52 [32-71]	32	71
Total	177	5	-	-	172	159	89.8	155 [60-333]	1	641	72 [30-122]	0	760

<sup>o</sup>If AE was not resolved, we considered its duration as time period between AE onset and final treatment outcome; AE, adverse events; MDR, multidrug-resistant; QTcF, adjusted QT interval using Fredericia formula; Q1, 25<sup>th</sup> percentile; Q2, 75<sup>th</sup> percentile; TB, tuberculosis; XDR, extensively drug-resistant; ECG, electrocardiogram.

**Supplementary Table 4.** Factors associated with cardiovascular adverse drug events in M/XDR-TB patients treated with delamanid-containing regimens in Belarus, from June 2016 to February 2018 (N=125).

Characteristics	Events, n	Person-months	IR per 100 pm	Crude HR (95% CI)	Adjusted HR (95% CI)
<b>Demographic characteristics</b>					
Age groups					
18-35	48	736	6.52	ref.	ref.
36-55	95	1327	7.16	1.09 (0.79-1.51)	1.14 (0.83-1.57)
56-72	34	479	7.10	1.04 (0.68-1.61)	0.98 (0.62-1.56)
Sex					
Male	116	1811	6.41	<b>0.71 (0.53-0.95)</b>	<b>0.72 (0.51-0.998)</b>
Female	61	731	8.34	ref.	ref.
Type of residence <sup>o</sup>					
Urban	118	1613	7.32	1.16 (0.86-1.57)	-
Rural	53	851	6.22	ref.	-
Homelessness					
Yes	6	78	7.74	1.18 (0.50-2.81)	-
No / Not recorded	171	2464	6.94	ref.	-
Employment					
Yes	42	698	6.02	0.85 (0.63-1.15)	-
No / Not recorded	135	1844	7.32	ref.	-
<b>Behaviour characteristics</b>					
Current tobacco smoker					
Yes	99	1600	6.19	<b>0.74 (0.56-0.98)</b>	0.79 (0.57-1.08)
No	78	942	8.28	ref.	ref.
Alcohol abuse					
Yes	63	882	7.14	0.99 (0.72-1.37)	-
No	114	1660	6.87	ref.	-
Drug use					
Yes	4	128	3.12	0.47 (0.20-1.07)	-
No	173	2414	7.17	ref.	-
<b>Clinical characteristics</b>					
Body mass index					
Underweight (<18.5)	29	322	9.02	1.20 (0.87-1.65)	-
Normal weight (18.5-24.9)	118	1699	6.95	ref.	-
Overweight / obese (>24.9)	30	522	5.75	0.86 (0.59-1.26)	-
HIV status					
Positive	23	384	5.98	0.80 (0.54-1.20)	-
Negative	154	2157	7.14	ref.	-
Diabetes mellitus					
Yes	14	303	4.61	0.70 (0.43-1.15)	-
No	163	2239	7.28	ref.	-
Hypertension					
Yes	23	274	8.39	1.14 (0.71-1.82)	-
No	154	2268	6.79	ref.	-
Hepatitis B					
Yes	15	222	6.77	1.05 (0.67-1.65)	-
No	162	2320	6.98	ref.	-
Hepatitis C					
Yes	22	368	5.98	0.81 (0.53-1.24)	-
No	155	2174	7.13	ref.	-
Baseline cardiovascular disorders					
Yes	53	567	9.35	<b>1.49 (1.09-2.04)</b>	-
No	124	1975	6.28	ref.	-
Baseline ECG abnormalities					

Characteristics	Events, n	Person- months	IR per 100 pm	Crude HR (95% CI)	Adjusted HR (95% CI)
Yes	74	764	9.68	<b>1.62 (1.16-2.26)</b>	<b>1.68 (1.19-2.36)</b>
No	103	1778	5.79	ref.	ref.
Type of drug resistance					
MDR	49	753	6.51	ref.	-
XDR	128	1789	7.16	1.20 (0.89-1.63)	-
TB localization					
Pulmonary	169	2451	6.90	ref.	-
Extrapulmonary / both	8	91	8.76	1.31 (0.74-2.31)	-
Cavity					
Yes	110	1524	7.22	1.09 (0.81-1.47)	-
No	67	1018	6.58	ref.	-
<b>Treatment of tuberculosis</b>					
History of treatment					
New	72	1046	6.89	1.00 (0.75-1.33)	-
Previously treated	105	1496	7.02	ref.	-
Bedaquiline in Delamanid- containing regimen					
Yes	29	379	7.66	1.08 (0.71-1.65)	-
No	148	2163	6.84	ref.	-

Missing data excluded (type of residence, n=4); Bold indicates statistically significant associations ( $p < 0.05$ ); CI, confidence interval; HR, hazard ratio; IR, incidence rate; TB, tuberculosis; MDR, multidrug-resistant; XDR, extensively drug-resistant.



**Supplementary Table 5.** Factors associated with unsuccessful treatment outcomes in M/XDR-TB patients treated with delamanid-containing regimens in Belarus, from June 2016 to February 2018 (N=125).

Characteristics	Unsuccessful outcomes, n/N (%)	Person-time	IR per 1000 pm	Crude HR (95% CI)	Adjusted HR (95% CI)
<b>Demographic characteristics</b>					
Age groups					
18-35	5/37 (13.5)	736	6.79	ref.	ref.
36-55	7/65 (10.8)	1327	5.28	0.82 (0.26-2.58)	0.66 (0.20-2.14)
56-72	3/22 (13.0)	479	6.27	1.04 (0.24-4.43)	1.28 (0.27-6.08)
Sex					
Male	13/90 (14.4)	1811	7.18	2.40 (0.54-10.73)	2.56 (0.48-10.50)
Female	2/35 (5.7)	731	2.73	ref.	ref.
Type of residence					
Urban	7/79 (8.9)	1613	4.34	0.55 (0.19-1.59)	-
Rural	7/42 (16.7)	851	8.22	ref.	-
Homelessness					
Yes	1/4 (25.0)	78	12.90	2.72 (0.36-20.78)	-
No / Not recorded	14/121(11.6)	2464	5.68	ref.	-
Employment					
Yes	1/34 (2.9)	698	1.43	0.20 (0.03-1.53)	-
No / Not recorded	14/91 (15.4)	1844	7.59	ref.	-
<b>Behaviour characteristics</b>					
Current tobacco smoker					
Yes	11/79 (13.9)	1600	6.87	1.71 (0.54-5.40)	-
No	4/46 (8.7)	942	4.25	ref.	-
Alcohol abuse					
Yes	8/44 (18.1)	882	9.07	1.84 (0.65-5.26)	-
No	7/81 (8.6)	1660	4.22	ref.	-
Drug use					
Yes	0/6 (0)	128	0.00	Not applicable (zero cases in 1 group)	-
No	15/119 (12.6)	2414	6.21	ref.	-
<b>Clinical characteristics</b>					
Body mass index					
Underweight (<18.5)	3/17 (17.6)	322	9.33	1.43 (0.40-5.14)	-
Normal weight (18.5-24.9)	12/84 (14.3)	1699	7.06	ref.	-
Overweight / Obese (>24.9)	0/24 (0)	522	0.00	Not applicable (zero cases in the group)	-
HIV status					
Positive	2/19 (10.5)	384	5.20	0.73 (0.16-3.38)	-
Negative	13/106 (12.3)	2157	6.03	ref.	-
Diabetes Mellitus					
Yes	2/14 (14.3)	303	6.59	0.93 (0.20-4.38)	-
No	13/111 (11.7)	2239	5.81	ref.	-
Hypertension					
Yes	2/14 (14.3)	274	7.29	1.34 (0.30-5.98)	-
No	13/111 (11.7)	2268	5.73	ref.	-

Hepatitis B					
Yes	0/10 (0)	222	0.00	Not applicable (zero cases in 1 group)	-
No	15/115 (13.0)	2320	0.65	ref.	-
Hepatitis C					
Yes	5/19 (26.3)	368	13.60	<b>3.32 (1.11-9.91)</b>	<b>3.61 (1.09-11.95)</b>
No	10/106 (9.4)	2174	4.60	ref.	ref.
Baseline cardiovascular disorders					
Yes	4/28 (14.3)	567	7.06	1.35 (0.42-4.29)	-
No	11/97 (11.3)	1975	5.57	ref.	-
Baseline ECG abnormalities					
Yes	4/37 (10.8)	764	5.23	0.92 (0.29-2.95)	-
No	11/88 (12.5)	1778	6.19	ref.	-
Type of drug resistance					
MDR	7/40 (17.5)	753	9.30	2.30 (0.81-6.57)	-
XDR	8/85 (9.4)	1789	4.47	ref.	-
TB localization					
Pulmonary	15/121 (12.4)	2451	6.12	ref.	-
Extrapulmonary / both	0/4 (0)	91	0.00	Not applicable (zero cases in 1 group)	-
Cavity					
Yes	12/75 (16.0)	1524	7.88	2.52 (0.70-9.04)	-
No	3/50 (6.0)	1018	2.95	ref.	-
<b>Treatment of tuberculosis</b>					
History of treatment					
New	4/52 (7.7)	1046	3.83	0.56 (0.18-1.79)	-
Previously treated	11/73 (15.1)	1496	7.35	ref.	-
Bedaquiline in Delamanid-containing regimen					
Yes	4/20 (20.0)	379	10.60	2.33 (0.73-7.44)	-
No	11/105 (10.5)	2163	5.08	ref.	-