

**Electronic Annex 3. Severe Adverse Events of anti-tuberculosis drugs by organ/apparatus in 658 patients (of whom 55 reported 57 episodes)**

Severe Adverse Events		Episodes n=57	Comments	Outcome
Gastrointestinal	Diarrhoea/ enterocolitis <i>Clostridium difficile</i>	1	<u>MDR-PULM</u> Diarrhoea, grade 3 AE occurred 81 days after starting treatment with new drugs. Adverse event duration: 100 days (27 <sup>th</sup> April – 5 <sup>th</sup> August 2018) requiring prolonged hospitalization. AE attributed to all anti-TB drugs. Anti-TB drugs stopped and then re-challenged after recovery. Toxigenic <i>Clostridium difficile</i> was identified (laboratory test performed on 5 April 2018).	Resolved
		1	<u>XDR-PULM</u> . <i>Clostridium difficile</i> infection required prolonged hospitalization. Grade 3 AE occurred 17 days before starting treatment with new drugs (25 <sup>th</sup> April 2018). AE attributed to all anti-TB drugs. AE duration: 244 days (8 <sup>th</sup> April – 8 <sup>th</sup> December 2018). Anti-TB drugs stopped and re-challenged after recovery.	Resolved
Nervous system	Optic neuritis	1	<u>XDR-PULM</u> . Sudden appearance of visual blurring with associated retro-ocular pain, grade 3. AE occurred 643 days after starting treatment with new drugs. Adverse event duration: 20 days (30 <sup>th</sup> June-20 <sup>th</sup> July 2014). AE attributed to linezolid (dosage 600 mg daily) administered for 643 days (25 <sup>th</sup> Sept. 2012 – 30 <sup>th</sup> June 2014) then stopped and not re-administered.	Resolved
	Visual impairment	1	<u>XDR-PULM</u> . Diplopia, visual acuity impaired, threat of losing visual function, grade 3 AE occurred 117 days after start of treatment with new drugs. Adverse event duration: 2 days (13 <sup>th</sup> -15 <sup>th</sup> Nov. 2017). AE attributed to linezolid (dosage 600 mg daily) administered for 117 days (19 <sup>th</sup> July – 13 <sup>th</sup> November 2017) then stopped and not re-administered.	Resolved
	Peripheral neuropathy	<u>Pt.1</u> : 1 <u>Pt.2</u> : 1 <u>Pt.3</u> : 1 <u>Pt.4</u> : 1	<u>Pt 1 Pre-XDR-PULM</u> : Tingling numbness with risk of crippling neuropathy, serious AE. AE occurred 93 days after starting treatment with new drugs and still ongoing (20 <sup>th</sup> December 2018). AE attributed to linezolid (dosage 600 mg daily) administered for 104 days (19 <sup>th</sup> July – 13 <sup>th</sup> November 2017) then stopped and not re-administered. <u>Pt.2 MDR-PULM</u> : Polyneuropathy, grade 3. Severity due to marked clinical signs, all drugs were withdrawn since 28 <sup>th</sup> November 2016; after re-challenge linezolid dose was reduced from 1,200 mg daily to 600 mg daily. AE occurred 145 days after starting treatment with new drugs. Adverse event duration: 179 days (16 <sup>th</sup> November 2016-22 <sup>nd</sup> August 2017). End of anti-TB treatment: 22 <sup>nd</sup> August 2017 (total anti-TB treatment duration: 426 days, 22 <sup>nd</sup> June 2016 – 22 <sup>nd</sup> Aug 2017). Linezolid was administered for a total of 424 days (24 <sup>th</sup> June 2016	Pt1: Resolving Pt2: Resolved with sequelae Pt.3: Resolved with sequelae Pt4: Not resolved

			<p>– 22<sup>nd</sup> August 2017) with dose reduction.</p> <p><u>Pt.3 XDR-PULM</u>: Polyneuropathy, grade 3 AE; episode occurred on 16<sup>th</sup> Nov 2017, 64 days after starting treatment with new drugs. AE attributed to linezolid (dosage 600 mg daily) administered for 64 days (13<sup>th</sup> September– 16<sup>th</sup> November 2017) then stopped and not re-administered. Recovery with persistent disability.</p> <p><u>Pt4 MDR-PULM+EXTRAPULM</u>: Severe peripheral neuropathy, grade 3 AE occurred on 18<sup>th</sup> September 2017, 255 days after start of treatment with new drugs and still ongoing.</p> <p>AE attributed to linezolid (dosage 600 mg daily) administered for 257 days (13<sup>th</sup> January – 27<sup>th</sup> September 2017) then stopped and not re-administered.</p>	
	Headache	1	<p><u>Pre-XDR-PULM</u>: Severe headache requiring hospitalization, grade 3 AE occurring 145 days after starting treatment with new drugs. Adverse event duration: 9 days (7 -16<sup>th</sup> February 2018). AE attributed to cycloserine (dosage 750 mg daily) administered for 146 days (15<sup>th</sup> Sept 2017- 08<sup>th</sup> Feb 2018); its dosage was not changed .</p>	Resolved
Skin / Subcutaneous	Rash	1	<p><u>Pre-XDR-PULM</u>: Extensive papulo-vesicular lesions, grade 3. AE occurred 438 days after starting treatment with new drugs. Adverse event duration: 21 days (16<sup>th</sup> December 2014-06 January 2015). AE attributed to clofazimine (dosage 100 mg daily) administered for 439 days (4<sup>th</sup> October 2013-17<sup>th</sup> December 2014) then stopped and, after recovery, drug re-challenge causing a new AE and drug finally discontinued.</p>	Resolved
	Other skin allergy	<p><u>Pt1</u>: 1</p> <p><u>Pt.2</u>: 1</p> <p><u>Pt.3</u>: 1</p>	<p><u>Pt.1 Pre-XDR-PULM</u>: Severe urticaria requiring hospitalization, grade 3 AE occurred 1 day after starting treatment with new drugs. AE duration: 6 days (4-10<sup>th</sup> April 2018). AE due to clarithromycin (dosage 500 mg daily), administered for 1 day (4<sup>th</sup> Apr 2018) as AE occurred immediately after first drug dose. Drug not re-administered after recovery.</p> <p><u>Pt.2 XDR-PULM</u>: Severe urticaria grade 3 with important hyperaemia and oedema of the face, but not Quinke oedema. AE occurred 21 days after starting treatment with new drugs. AE duration: 8 days (7-15<sup>th</sup> February 2018). All drugs (bedaquiline, linezolid, moxifloxacin, terizidone, prothionamide, PAS, amikacin) withdrawn on 7<sup>th</sup> February 2018.</p> <p>On February 22<sup>nd</sup>, linezolid was re-challenged but immediately after its first infusion severe face hyperaemia occurred, grade 3, occurred again due to linezolid (dosage 600 mg daily). AE duration 4 days (22-26 Feb 2018). Linezolid was withdrawn on the same day (administered for 1 day only on 22<sup>nd</sup> February 2018). Drug not re-challenged after recovery. From 27<sup>th</sup> February</p>	<p>Pt.1: Resolved</p> <p>Pt.2: Resolved</p> <p>Pt.3: Resolving</p>

			<p>2018 anti-TB treatment re-started (bedaquiline, moxifloxacin, terizidone, pyrazinamide, ethambutol, azithromycin).</p> <p><u>Pt.3 MDR-PULM</u>: Toxic allergic dermatitis, grade 3 AE occurred at start of treatment with new drugs (19<sup>th</sup> March 2019) and still ongoing. AE attributed to terizidone* (dosage 600 mg daily), administered for 6 days (13-19<sup>th</sup> March 2019). Drug not re-challenged</p>	
<b>Hearing</b>	Hearing problems	<p><u>Pt.1</u>: 1</p> <p><u>Pt.2</u>: 1</p> <p><u>Pt.3</u>: 1</p> <p><u>Pt.4</u>: 1</p> <p><u>Pt.5</u>: 1</p> <p><u>Pt.6</u>: 1</p> <p><u>Pt.7</u>: 1</p> <p><u>Pt.8</u>: 1</p> <p><u>Pt.9</u>: 1</p> <p><u>Pt.10</u>: 1</p> <p><u>Pt.11</u>: 1</p>	<p><u>Pt.1 Pre-XDR-PULM</u>: Tinnitus potentially leading to hearing loss, serious AE. AE occurred on 20<sup>th</sup> Feb 2018, 32 days after start of treatment with new drugs and still ongoing. AE attributed to amikacin** (dosage 750 mg, 5 days/week) administered for 156 days (18<sup>th</sup> September 2017 – 21<sup>th</sup> February 2018) then stopped and not re-challenged.</p> <p><u>Pt.2 Pre-XDR-PULM</u>: severe hearing problems leading to hospitalization, serious AE. AE occurred 145 days after start of treatment with new drugs. Adverse event duration: 9 days (7<sup>th</sup> -16<sup>th</sup> February 2018). AE attributed to cycloserine (dosage 750 mg daily) administered for 146 days (15<sup>th</sup> September 2017- 8<sup>th</sup> February 2018), not re-challenged after de-challenge.</p> <p><u>Pt.3 MDR-PULM+EXTRAPULM</u>: severe hearing problems, serious AE. AE occurred 80 days after starting treatment with new drugs. Adverse event duration: 1 day (7 -8<sup>th</sup> December 2018) attributed to amikacin. Drug withdrawn.</p> <p><u>Pt.4 Pre-XDR-PULM</u>: Important hearing loss, serious AE. AE occurred on 20<sup>th</sup> March 2013, 89 days after starting treatment with new drugs and not resolved. AE attributed to amikacin (dosage 1 g daily) administered for 182 days (21<sup>st</sup> December 2012-21<sup>st</sup> June 2013), drug not withdrawn but dosage reduced.</p> <p><u>Pt.5 Pre-XDR-PULM</u>: Severe hearing loss, serious AE. AE occurred on 8<sup>th</sup> Sept. 2015, 214 days after starting treatment with new drugs and recovered with sequelae. AE attributed to amikacin (dosage 1 g daily) administered for 214 days (6<sup>th</sup> February 2015- 8<sup>th</sup> September 2015), drug not withdrawn but dosage reduced.</p> <p><u>Pt.6 RR+FQ-PULM</u>: Serious vertigo. Patient unable to stand up, serious AE. AE occurred 103 days after starting treatment with new drugs. AE duration 6 days (30<sup>th</sup> March-05<sup>th</sup> April 2018). AE attributed to amikacin (dosage 1 g daily) administered for 109 days (17<sup>th</sup> December 2017- 5<sup>th</sup> April 2018), drug withdrawn and not re-challenged.</p> <p><u>Pt.7 Pre-XDR-PULM</u>: Severe hearing loss, serious AE. AE occurred on 23<sup>rd</sup> May 2018, 61 days after starting treatment with new drugs and recovered with sequelae. AE attributed to amikacin (dosage 1 g daily) administered for 66</p>	<p>Pt.1: Resolving</p> <p>Pt. 2: Resolved</p> <p>Pt.3: Resolved with sequelae</p> <p>Pt.4: Not resolved</p> <p>Pt.5: Resolved with sequelae</p> <p>Pt. 6: Resolved</p> <p>Pt. 7: Resolved with sequelae</p> <p>Pt. 8: Resolved</p> <p>Pt. 9: Resolved</p> <p>Pt. 10: Resolved</p> <p>Pt. 11: Resolved</p>

			<p>days (23<sup>rd</sup> March -28<sup>rd</sup> May 2018). Drug withdrawn and not re-challenged.</p> <p><u>Pt.8 XDR-PULM</u>: Tinnitus, threat of function loss, grade 3 AE occurred 6 days after starting treatment with new drugs. AE duration 2 days (23<sup>rd</sup>-25<sup>th</sup> January 2018) attributed to amikacin (dosage 1 g daily) administered for 26 days (29<sup>th</sup> December 2017-24<sup>th</sup> January 2018). Drug not re-challenged after withdrawn.</p> <p><u>Pt.9 MDR-PULM</u>: Bilateral hearing loss, tinnitus, threat of function loss, grade 3. AE occurred 2 days after starting treatment with new drugs. AE duration 14 days (6<sup>th</sup>-20<sup>th</sup> April 2018) attributed to capreomycin (dosage 1 g daily) administered for 5 days (4<sup>th</sup>-9<sup>th</sup> April 2018). Drug not re-challenged after withdrawn.</p> <p><u>Pt.10 MDR-PULM</u>: Tinnitus, threat of function loss, grade 3 AE occurred on 22<sup>nd</sup> March 2018, 93 days after starting treatment with new drugs and resolved. AE attributed to amikacin (dosage 1 g daily) administered for 93 days (19<sup>th</sup> December 2017 – 22<sup>nd</sup> March 2018). Drug not re-challenged after withdrawn.</p> <p><u>Pt.11 MDR-PULM</u>: Hearing problems, dizziness, grade 3 AE occurred 9 days after starting treatment with new drugs and resolved. AE duration: 2 days (24<sup>th</sup>-25<sup>th</sup> August 2018) attributed to cycloserine (dosage 750 mg daily) administered for 9 days (16<sup>th</sup>-25<sup>th</sup> August 2018). Drug not re-challenged after withdrawn.</p>	
Psychiatric	Hallucinations	1	<p><u>XDR-PULM</u> Nightmares, fear, auditory hallucination with significant disability, grade 3 AE occurring 179 days after starting treatment with new drugs and resolved. AE duration: 2 days (14<sup>th</sup>-16<sup>th</sup> Jan 2018) attributed to cycloserine (dosage 750 mg daily) administered for 179 days (19<sup>th</sup> July 2017-14<sup>th</sup> January 2018). Drug not re-challenged after withdrawn.</p>	Resolved
	Mental disorders	1	<p><u>Pre-XDR-PULM</u>: Permanent intense anxiety, fear, inner tremor, grade 3 AE occurred on 26<sup>th</sup> March 2018, 10 days after starting treatment with new drugs. AE not resolved but stable. AE attributed to cycloserine<sup>s</sup> (dosage 500 mg daily) administered for 193 (14<sup>th</sup> September 2017-26<sup>th</sup> March 18). Drug re-challenged after being withdrawn.</p>	Not resolved
	Depression	<p><u>Pt.1</u>: 1  <u>Pt.2</u>: 1  <u>Pt.3</u>: 1</p>	<p><u>Pt.1 XDR-PULM</u>: depression and suicidal thoughts, grade 4 AE occurred on 1<sup>st</sup> September 2017, 14 days after starting treatment with new drugs. AE resolving. AE attributed to cycloserine<sup>l</sup> (dosage 750 mg daily) administered for 183 days (2<sup>nd</sup> March-1<sup>st</sup> September 2017). Drug not re-challenged but dose reduced.</p> <p><u>Pt.2 Pre-XDR-PULM</u>: patient already on treatment for depression prescribed by a psychiatrist. Patient admitted to undergo new psychiatric evaluation, after reporting symptoms worsening and suicide thoughts. Grade 3 AE occurring 20 days after starting treatment with new drugs. AE duration: 9 days (1<sup>st</sup>-10<sup>th</sup></p>	<p>Pt.1: Resolving  Pt.2: Resolving  Pt.3: Unknown (lost to follow-up).</p>

			<p>December 2018) attributed to cycloserine# (dosage 1000 mg daily) administered for 56 days (10<sup>th</sup> October – 5<sup>th</sup> December 2018). Drug stopped and then re-challenged after recovery.</p> <p><u>Pt.3 Pre-XDR-PULM:</u> The patient had taken tranquilizers in potentially lethal dose, grade 4.AE occurring on 4<sup>th</sup> November 2017, 43 days after starting treatment with new drugs. AE duration: unknown as the patient was lost to follow-up. AE attributed to cycloserine<sup>¶</sup> (dosage 750 mg daily) administered for 56 days (9<sup>th</sup> September-4<sup>th</sup> November 2017). Drug stopped and not re-challenged (patient lost to follow-up at 43 days after starting treatment with new drugs.</p>	
<b>Blood / Lymph nodes</b>	Anaemia	<p><u>Pt.1:</u> 1 <u>Pt.2:</u> 1 <u>Pt.3:</u> 1 <u>Pt.4:</u> 1 <u>Pt.5:</u> 1 <u>Pt.6:</u> 1 <u>Pt.7:</u> 1</p>	<p><u>Pt.1 XDR-PULM:</u> Hb level 48 g/l, patient received urgent haematology consultation and blood transfusion of packed red blood cells. Grade 3. AE occurred 69 days after starting treatment with new drugs. AE duration: 133 days (19<sup>th</sup> September 2015-30<sup>th</sup> January 2016). AE attributed to linezolid (dosage 1,200 mg daily) administered for 115 days (12<sup>th</sup> July-4<sup>th</sup> November 2015). On 4<sup>th</sup> November 2015 all anti-TB drugs were stopped and then re-challenged after recovery.</p> <p><u>Pt.2 Pre-XDR-PULM:</u> Hb level 65 g/l, grade 3 AE occurring 145 days after starting treatment with new drugs. AE duration: 62 days (16<sup>th</sup> November 2016-17<sup>th</sup> January 2017). AE attributed to linezolid (dosage 1,200 mg daily) administered for 424 days (24<sup>th</sup> June -22<sup>nd</sup> August 2017). Drug stopped and then re-challenged after recovery.</p> <p><u>Pt.3 Pre-XDR-PULM:</u> Hb 69 g/l, serious AE. AE occurring on 10<sup>th</sup> December 2018, 85 days after starting treatment with new drugs, resolving. AE attributed to linezolid (dosage 600 mg daily) administered from 16<sup>th</sup> September 2018. Drug stopped and re-challenged.</p> <p><u>Pt.4 MDR-PULM+EXTRAPULM:</u> Hb decrease, prolongation of hospitalization and erythropoietin administered for 2 months, grade 3 AE occurring 188 days after starting treatment with new drugs. AE duration: 68 days (6<sup>th</sup> December 2017-12<sup>th</sup> February 2018). AE attributed to linezolid (dosage 600 mg daily) administered for 188 days (1<sup>st</sup> June-6<sup>th</sup> December 2017). Drug stopped and not re-challenged.</p> <p><u>Pt.5 XDR-PULM:</u> Anaemia till Hb 48 g/l, erythrocytes 1.2 10<sup>12</sup>/l, serious AE, grade 3. AE occurred 41 days after starting treatment with new drugs. AE duration: 90 days (20<sup>th</sup> September – 19<sup>th</sup> December 2017). AE attributed to linezolid (dosage 600 mg daily) administered for 104 days (10<sup>th</sup> August-22<sup>nd</sup> November 2017). Drug stopped and not re-challenged.</p>	<p>Pt.1: Resolved Pt.2: Resolved Pt.3: Resolving Pt.4: Resolved Pt.5: Resolving Pt.6: Resolving Pt.7: Resolving</p>

			<p><u>Pt.6 Pre-XDR-PULM:</u> Hb decrease (Hb 35 g/l); serious AE grade 4. AE occurred 297 days after starting treatment with new drugs. AE duration 19 days (24<sup>th</sup> April-13<sup>th</sup> May 2019). AE attributed to linezolid (dosage 600 mg daily) administered for 311 days (1<sup>st</sup> July 2018 - 8<sup>th</sup> May 2019). Drug stopped and not re-challenged.</p> <p><u>Pt.7 MDR-PULM:</u> Hb decrease (Hb 69 g/l, Er 2,1 10<sup>12</sup>/l), serious AE grade 3. AE occurred 100 days after start of treatment with new drugs. AE resolving. AE attributed to linezolid (dosage 600 mg daily) administered for 40 days (28<sup>th</sup> November 2018- 7<sup>th</sup> January 2019). Drug finally withdrawn.</p>	
	Bone marrow depression	<p><u>Pt.1:</u> 1 <u>Pt.2:</u> 1</p>	<p><u>Pt.1 RR+FQ-PULM:</u> Severe sudden anaemia; grade 3 AE occurring 31 days after starting treatment with new drugs. AE duration: 30 days (17<sup>th</sup> January-16<sup>th</sup> February 2018). AE attributed to linezolid (dosage 600 mg daily) administered for 61 days (17<sup>th</sup> December 2017-16<sup>th</sup> February 2018). Drug stopped and then re-challenged.</p> <p><u>Pt.2 Pre-XDR-PULM:</u> Severe sudden anaemia; grade 3.AE occurring 61 days after starting treatment with new drugs. AE duration: 30 days (23<sup>rd</sup> May -22<sup>nd</sup> June 2018). AE attributed to linezolid (dosage 600 mg daily) administered from the start of treatment with new drugs (23<sup>rd</sup> March 2018), stopped and, after recovery, re-challenged.</p>	<p>Pt.1: Resolved Pt.2: Resolved</p>
<b>Cardiac</b>	Arrhythmia	1	See Table 4 for details	See Table 4 for details
	QT prolongation	8	See Table 4 for details	See Table 4 for details
<b>Hepatic</b>	Hepatitis	<p><u>Pt.1:</u> 1 <u>Pt.2:</u> 1 <u>Pt.3:</u> 1</p>	<p><u>Pt.1 XDR-PULM:</u> transaminases increased 10 times, severe AE with progressive increase of transaminases after bedaquiline introduction. AE occurred on 22<sup>nd</sup> August 2018, 20 days after starting treatment with new drugs. On 24<sup>th</sup> September 2018 all drugs were stopped. On 5<sup>th</sup> October 2018 anti-TB drugs were reintroduced except bedaquiline and the transaminases level continued to slowly go down (not yet normal on 18<sup>th</sup> January 2019, probably because of the long bedaquiline half-life). AE attributed to bedaquiline (dosage 200 mg 3 days/week) administered for 53 days (2<sup>nd</sup> August -24<sup>th</sup> September 2018).</p> <p><u>Pt.2 XDR-PULM:</u> hepatitis, serious AE. AE occurred 9 days after starting treatment with new drugs. AE duration: 20 days (20<sup>th</sup> September-10<sup>th</sup> October 2017). AE attributed to ethionamide (dosage 750 mg daily) administered for 9 days (11<sup>th</sup>-20<sup>th</sup> September 2017), stopped and not re-challenged after recovery.</p> <p><u>Pt.3 XDR-PULM:</u> Severe hepatotoxic reaction, due to concomitant Hepatitis C</p>	<p>Pt.1: Resolving Pt.2: Resolved Pt.3: Unknown (lost to follow-up)</p>

			and anti-TB treatment, grade 3 AE occurring 15 days after starting treatment with new drugs. AE duration: 197 days (21 <sup>st</sup> December 2016-6 <sup>th</sup> July 2017). AE attributed to bedaquiline (dosage 200 mg 3 days/week) stopped on 6 <sup>th</sup> July 2017 and then re-challenged when stable but severe hepatotoxic reaction grade 3 occurred again on 25 <sup>th</sup> July 2017. All TB drugs were stopped on 25 <sup>th</sup> July and not re-challenged as the patient was lost to follow-up. Bedaquiline administered for 227 days (6 <sup>th</sup> December 2016-25 <sup>th</sup> July 2017).	
<b>Renal</b>	Renal problems	<u>Pt.1:</u> 1 <u>Pt.2:</u> 1 <u>Pt.3:</u> 1 <u>Pt.4:</u> 1 <u>Pt.5:</u> 1 <u>Pt.6:</u> 1 <u>Pt.7:</u> 1	<u>Pt. 1 MDR-PULM:</u> low glomerular filtration rate, severe AE. AE occurring on 25 <sup>th</sup> August 2017, 60 days after starting treatment with new drugs. AE duration 94 days (25 <sup>th</sup> August -27 <sup>th</sup> November 2017). AE attributed to capreomycin (dosage: 1 g 6 days/week) administered for 78 days (26 <sup>th</sup> June – 12 <sup>th</sup> September 2017) not stopped but dose reduced. <u>Pt.2 MDR-PULM:</u> Renal problems, severe AE. AE occurred on 10 <sup>th</sup> July 2017, 18 days after starting treatment with new drugs. AE attributed to amikacin administered for 35 days (5 <sup>th</sup> June-10 <sup>th</sup> July 2017) and then stopped.. <u>Pt.3 Pre-XDR-PULM:</u> Loss of renal function requiring prolongation of hospital admission, severe AE. AE occurred 138 days before starting treatment with new drugs (22 <sup>nd</sup> November 2017). AE duration: 249 days (7 <sup>th</sup> July 2017-13 March 2018). AE attributed to capreomycin (dose 1000 mg lowered from 7 to 3 times/ week) administered for 276 days (10 <sup>th</sup> May 2017-10 <sup>th</sup> February 2018), drug not stopped but dose reduced. <u>Pt.4 MDR-PULM:</u> Renal biopsy showed tubulo-interstitial nephritis, severe AE requiring prolonged hospitalisation and prednisone at high dosage. AE occurred 2 days before starting treatment with new drugs. AE duration: 68 days (25 <sup>th</sup> June- 1 <sup>st</sup> September 2016). AE attributed to capreomycin (dose 1000 mg 5 times/week) administered for 94 days (15 <sup>th</sup> April-18 <sup>th</sup> July 2016), drug stopped and not re-challenged. <u>Pt.5 XDR-PULM+EXTRAPULM:</u> low glomerular filtration rate and concomitant kidney tuberculosis; grade 3 AE occurred 30 days after starting treatment with new drugs. AE duration: 99 days (26 <sup>th</sup> October 2015-2 <sup>nd</sup> February 2016). AE attributed to capreomycin (dose 1000 mg 7 times/ week) administered for 192 days (26 <sup>th</sup> September 2015-5 <sup>th</sup> April 2016). Capreomycin stopped with all TB drugs from 6 <sup>th</sup> November to 30 <sup>th</sup> December 2015 and then re-challenged. <u>Pt. 6 XDR-PULM:</u> acute renal failure occurred on the second day after right lower lobectomy in a patient with diabetic nephropathy of the single kidney (for previous nephrectomy due to the cancer, 1995). Grade 4 AE occurring 47	Pt.1 : Resolved Pt.2: Unknown Pt.3: Resolved Pt.4: Resolved with sequelae Pt.5: Resolving Pt.6: Resolving Pt.7 : Resolved

			<p>days after start of treatment with new drugs. AE duration: 2 days (19<sup>th</sup>-20<sup>th</sup> July 2017). Anti-TB drugs' doses were not reduced.</p> <p><u>Pt. 7 XDR-PULM</u>: Nephropathy, glomerulonephritis, Grade 3</p> <p>AE occurring 57 days after starting treatment with new drugs. AE duration: 21 days (15<sup>th</sup> September – 6<sup>th</sup> October 2017). The AE was attributed to pyrazinamide (dose 1.5g 7 times/ week) which was stopped and after recovery, re-challenged. The AE occurred again and pyrazinamide was finally withdrawn. Pyrazinamide was administered for 58 days.</p>	
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\* Terizidone started 5 days before anti-TB treatment with new drugs.

\*\* Amikacin started 123 days before anti-TB treatment with new drugs.

§ Cycloserine started 183 days before anti-TB treatment with new drugs.

¶ Cycloserine started 169 days before anti-TB treatment with new drugs

# Cycloserine started 32 days before anti-TB treatment with new drugs

¶¶ Cycloserine started 13 days before anti-TB treatment with new drugs

Legend: TB: tuberculosis; MDR: multidrug-resistant; XDR: extensively drug-resistant; TB: tuberculosis; PULM: pulmonary; EXTRAPULM: extra- pulmonary; AE: adverse event; Pt: patient; PAS: para-aminosalicylic acid; Hb: haemoglobin.