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Programmatic management of patients with pre-extensively drug-resistant tuberculosis in Peru, 2011-2014

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1 **Programmatic management of patients with pre-extensively drug-**
2 **resistant tuberculosis in Peru, 2011-2014**

3 Valentina Alarcón Guizado¹, Edith Alarcón Arrascue², Alberto Mendoza-Ticona^{1,3}, George Obregón Boltan⁴, José
4 Cornejo García^{1,5}, Dante Vargas^{1,6}, Jorge de los Ríos^{1,7}, David AJ Moore⁸ and Einar Helda⁹

5 1: Estrategia Sanitaria Nacional de Prevención y Control de la Tuberculosis, Ministerio de Salud, Peru

6 2: The International Union against Tuberculosis and Lung Disease, Peru

7 3: Hospital de Emergencias Villa El Salvador, Ministerio de Salud, Peru

8 4: Instituto Nacional de Salud de Perú

9 5: Hospital Nacional Arzobispo Loayza, Ministerio de Salud, Peru

10 6: Hospital Nacional Hipólito Unanue, Ministerio de Salud, Peru

11 7: Hospital María Auxiliadora, Ministerio de Salud, Peru

12 8: The London School of Hygiene and Tropical Diseases, UK

13 9: The International Union against Tuberculosis and Lung Disease, Norway

14

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23

24 **Corresponding author:** Valentina Alarcón Guizado

25

26 Address: Av. Cesar Vallejo, cuadra 13 s/n, El Agustino

27 Telephone: +51-99079882; +5113620765

28 Email: antonieta_alarcong@hotmail.com

29

30

31 **ABSTRACT:**

32 **Background:** In Peru, a treatment approach for XDR-TB that incorporated WHO group
33 5 drugs and a patient-centered care, has achieved 65% success. To expand this
34 approach for pre-XDR-TB, we have evaluated this population separately.

35 **Objective:** To assess programmatic management of pre-XDR-TB.

36 **Method:** Retrospective study using official registry from 2011 to 2014. Cases were
37 separately evaluated according to resistance to fluoroquinolones (pre-XDR-F) or 2nd
38 line injectable drugs (SLIs) (pre-XDR-I).

39 **Results:** From 610 pre-XDR-TB patients, 120 (20%) had pre-XDR-F and 490 (80%) had
40 pre-XDR-I. The pre-XDR-F cases were older (34 vs 28 years, $p < 0,001$) and a higher
41 proportion had previously received two or more regimens (70% vs 38%, $p < 0,001$). In
42 the 452 cases who started treatment in 2011-2013, treatment success was 43.3%,
43 26.5% were lost to follow-up, 12.1% died and 13.7% failed treatment. Success was
44 higher in pre-XDR-I (48.5%) than pre-XDR-F (21.4%). History of previous treatment (OR
45 2.23, CI 1.52-3.38) and pre-XDR-F (OR 2.39, CI 1.18 - 4.83) were associated with
46 unsuccessful outcome.

47 **Conclusion:** Programmatic management of pre-XDR-TB has not been successful,
48 especially in pre-XDR-F, with lower rates of success than have been achieved in the
49 same setting for XDR-TB. The strategy used for XDR-TB should be expanded to pre-
50 XDR-TB in Peru.

51 INTRODUCTION

52 Drug-resistant tuberculosis (TB) poses a challenge for TB elimination, with 660,000
53 estimated new cases resistant to rifampicin (RR-TB), of which 490,000 had multidrug-
54 resistant TB (MDR-TB) with resistance to at least isoniazid (H) and rifampicin (R) in
55 2016 worldwide. ¹ Among MDR-TB cases, 6.2% fulfil the criteria for XDR-TB with
56 additional resistance to a fluoroquinolone and a second line injectable drug (SLI)
57 [kanamycin (Km), capreomycin (Cm) or amikacin (Am)]. ¹ Pre-XDR-TB is defined as
58 MDR-TB with resistance to either a fluoroquinolone (pre-XDR-F) or a SLI (pre-XDR-I),
59 but not both. ² The burden of pre-XDR-TB is considerable and represents a threat to
60 MDR-TB control; the proportion of MDR-TB with resistance to any fluoroquinolone was
61 estimated at 21% worldwide in 2015, with an overall 51% with resistance to a
62 fluoroquinolone or a SLI. ³

63 In 2015, Peru reported 1,366 cases of MDR-TB and 104 cases of XDR-TB. ⁴ Since 2011,
64 Peru has provided individualized treatment for MDR-TB based on drug susceptibility
65 testing (DST) of first and second-line agents, as per WHO recommendations, with at
66 least 4 effective drugs delivered through the primary health care system ⁵. MDR-TB
67 treatment success rate in 2013 was 55%, with 29% of patients lost to follow-up, data
68 that included pre-XDR TB. During the same period, a more aggressive and multi-
69 faceted approach to the treatment of XDR-TB entailed: i) the additional use of drugs
70 from Group 5 of the former WHO classification and thioridazine (not used for non-XDR
71 MDR-TB), ii) a comprehensive care package starting in hospital, with follow-up at home
72 and ending in primary care, iii) direct observation of treatment, iv) additional social
73 support, v) improved monthly food baskets and vi) infection control measures in the
74 home. ⁴ With this package of interventions, the treatment success for XDR-TB rose
75 from 30% in 2011 to 66% in 2013 (higher than for programmatic management of MDR-
76 TB), while loss to follow-up decreased from 27% to 2%. ⁶

77 Resistance to fluoroquinolones and SLIs reduces the success rate for MDR-TB therapy,
78 and though there are a growing number of studies on XDR-TB treatment ⁷⁻⁹ there is a
79 scarcity of data on the much more common pre-XDR-TB. ^{2,10} The National Tuberculosis
80 Programme (NTP) in Peru suspected that the low success rate in MDR-TB might be due
81 to poor treatment outcomes amongst pre-XDR-TB cases, which are normally included

82 in the MDR-TB cohort. The objective of this study was to assess retrospectively the
83 programmatic management of pre-XDR-TB cases who started treatment between 2011
84 and 2014, evaluate time between diagnosis and treatment initiation, drugs used,
85 culture conversion and treatment outcome among those who started treatment in
86 2011-2013, disaggregated into cases with pre-XDR-F and pre-XDR-I.

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87 METHODS

88 The operational study to compare retrospective cohorts of pre-XDR-TB cases.

89 **Context:** Since 2013, the NTP has required DST to R and H for all diagnosed TB cases in
90 the country using direct rapid assays validated in the country, either nitrate reductase
91 (Griess) assay ¹¹, direct microscopic-observation drug-susceptibility (MODS) assay ^{12, 13}
92 or molecular line probe assay (LPA). ¹⁴. On detection of H or R resistance, indirect
93 culture-based DST **for first and second line drugs** using Middlebrook 7H10 agar plates
94 proportion (APP) assay is performed at the National Mycobacterial Reference
95 Laboratory, with annual external quality evaluation by the Supranational Laboratory of
96 WHO. Among fluoroquinolones, ciprofloxacin was tested, and for SLI kanamycin (Km)
97 and capreomycin (Cm). Before and even after the 2013 national standard was issued,
98 DST continued to be performed using the indirect proportion method in APP or
99 Lowenstein Jensen (LJ) medium. Due to delays in results of indirect DST, many patients
100 started standardized treatment with second-line drugs after having failed first-line
101 treatment, or because they were contacts of MDR-TB, before obtaining indirect DST
102 results.

103 Evaluation Committees on Retreatment approved regimens for MDR-TB cases, and
104 treatment was administered on an outpatient basis at the first level of care, at the
105 clinic nearest to the patient's home. MDR-TB regimens based on rapid H and R assays
106 were later adjusted to individualized regimens when the APP became available,
107 according to Peruvian guidelines ^{15, 16}. In some cases, the regimen was maintained if
108 the clinical course was favorable. The best available drugs were selected, based on the
109 previous WHO classification into five groups, including at least four effective drugs ⁵. In
110 cases of pre-XDR-TB, a fluoroquinolone or an SLI was included; in case of
111 fluoroquinolone resistance, moxifloxacin (Mfx) was added, and in case of SLI
112 resistance, Cm or amikacin (Am) were added, in both cases these drugs were not
113 counted as one of the four required effective drugs. Ethionamide (Eto), cycloserine (Cs)
114 and ethambutol (E) were added if the strain was still susceptible to these drugs, usually
115 maintaining pyrazinamide (Z). In cases with resistance to Eto, the drugs E, Z and/or
116 para-aminosalicylic acid (PAS) were always added with the goal to get four effective
117 drugs.

118 The **elevated** cost of group 5 drugs plus hospitalization, insertion of a central line for
119 carbapenems, and DOT in the household had a high cost for the government; these
120 drugs were therefore limited to XDR-TB cases. For pre-XDR-TB a supposedly adequate
121 individualized regimen could be designed based on either a fluoroquinolone or a SLI,
122 plus Eto, E, Z, Amx-Clv, Cs and PAS in line with WHO guidelines of 2011. ⁵ Confirmed
123 cases of XDR-TB were treated also with linezolid (Lzd), carbapenems plus amoxicillin
124 clavulanate (Amx-Clv), as well as thioridazine ⁴. Bacteriological conversion was
125 monitored by monthly sputum cultures. ¹⁵

126

127 **Study population:** Pulmonary pre-XDR-TB patients who started treatment from
128 January 2011 to December 2014 were included. Patients were classified in two cohorts
129 based on fluoroquinolone (ciprofloxacin) resistance (pre-XDR-F TB), or resistance to
130 one or both SLIs (Km, Cm) (pre-XDR-I TB), as assessed by APP. Patients of all ages and
131 from all over the country were included. For treatment outcome, the subgroup of
132 patients who started treatment in 2011-2013 was assessed. Treatment outcomes
133 were: cured, treatment completed, failure, lost to follow-up, deceased, and not
134 evaluated, in accordance with WHO Guidelines. ¹⁷ Two authors examined the clinical
135 records of all patients to determine treatment outcome. For evaluating monthly
136 culture results and treatment outcome, the group of pre-XDR-I was subdivided in
137 three: pre-XDR-Km, pre-XDR-Cm and pre-XDR-Km-Cm.

138 **Data collection:** The National Resistant Tuberculosis Registry was used, which is
139 updated daily with quarterly reports of each resistant TB case in the country. The
140 result of the DST was checked with the computerized NETLAB database. ¹⁸
141 Demographic variables, treatment history, comorbidities, monthly culture results, DST
142 results, treatment regimens, and outcomes were evaluated in accordance with WHO
143 guidelines. **The outcomes were re-categorized in successful (cure and completed
144 treatment) and unsuccessful (failure, death, lost to follow-up and not evaluated).**

145 **Statistical analysis:** The database was analyzed using STATA version 14.2 (Stata corp,
146 Texas, USA). Clinical and epidemiological characteristics were compared between pre-
147 XDR-F and pre-XDR-I patients. A Chi-squared test (X^2) was used to assess the
148 association between categorical variables, while a Wilcoxon test was used for

149 continuous variables. In the subgroup of patients registered in 2011-2013, treatment
150 outcome was compared between pre-XDR-F and pre-XDR-I cases and injectable
151 subgroups. A p-value <0.05 was considered to define a significant difference.
152 Multivariate analysis was performed to identify factors significantly associated with
153 unsuccessful treatment outcome.

154 **Ethical considerations:** The protocol was approved by the Ethics Committees at the
155 Hospital Nacional Hipólito Unanue, and from The Union.

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156 RESULTS

157 A total of 610 pre-XDR-TB patients who started treatment in 2011-2014 were included:
158 120 (19.7%) with pre-XDR-F and 490 (80.3%) with pre-XDR-I. Among pre-XDR-I, 213
159 (43.5%) were resistant to Km only, 102 (20.8%) were resistant to Cm only, and 175
160 (35.7%) were resistant to both injectable drugs.

161 Male gender was more common in both cohorts, median age was 29 years old.
162 Diabetes mellitus was recorded for 8% of patients and HIV in 4%. Among pre-XDR-TB
163 patients, 67% had undergone two or more previous courses of TB treatment. Pre-XDR-
164 F patients were significantly older (median 34 vs 28 years, $p<0.001$), more commonly
165 reported both diabetes and previous treatment episodes: 70% had received two or
166 more prior courses of treatment vs. 38% of pre-XDR-I patients ($p<0.001$) and most of
167 them received their treatment after previous loss to follow-up (Table 1).

168 Treatment for drug-resistant TB was started in 29% of patients pending bacteriological
169 confirmation with an indirect DST. Treatment was started in 39% of patients less than
170 two weeks after diagnosis, and 32% after more than 3 weeks, with no significant
171 differences between the groups (Table 2).

172 The drugs from the individualized regimens that were used in more than 50% of the
173 patients, were grouped based on the resistance pattern: i) for pre-XDR-F: Cm, Z, Mfx,
174 Cs, Eto and Amx-Clv, ii) for pre-XDR-I Km-resistant: Z, Cm, Lfx, PAS, Cs and Eto, iii) for
175 pre-XDR-I Cm-resistant: Z, Lfx, PAS, Cs, Eto and Amx-Clv and iv) for pre-XDR-I Km+Cm-
176 resistant: Z, Lfx, PAS, Cs, Eto and Amx-Clv. Drugs from previous Group 5 and
177 thioridazine were very rarely used (Table 3).

178 Of the 610 patients, 342 (56%) had achieved bacteriological conversion by the sixth
179 month; this was higher in the pre-XDR-I group (60.6%) than in pre-XDR-F group
180 (42.5%), $p<0.001$. The proportion with positive culture by month of treatment was
181 higher in the pre-XDR-F group, followed by the pre-XDR Km+Cm (Figure 1). The
182 number not assessed for conversion (because of death, loss to follow-up or missing
183 information) were in total 157 (26%): 41 (34%) pre-XDR-F, 53 (25%) pre-XDR-Km, 25
184 (25%) pre-XDR-Cm and 38 (22%) pre-XDR-Km+Cm.

185 Among the 452 patients who started treatment in 2011-2013, 43.4% were successfully
186 treated, 26.5% were lost to follow-up, 13.7% had treatment failure, 12.2% were
187 deceased, and in 4.2% treatment outcome was not evaluated. A successful treatment
188 outcome was significantly less likely in patients with pre-XDR-F (21.4%) vs. pre-XDR-I
189 (48.5%), $p < 0.001$. Among pre-XDR-I patients, the lowest success rate was seen in
190 patients with resistance to both Km and Cm (Table 4). Among patients with lost to
191 follow result, 48% occurred during first to six month, 34% at seven to 12 month, and
192 18% after 12 months. Treatment failure and death rates were lower in pre-XDR-I with
193 Cm resistance. The highest proportion of death (22.6%) was in the pre-XDR-F type. In a
194 multivariate model, the only variables independently associated with unsuccessful
195 outcome were a history of previous treatment and resistance to fluoroquinolones (pre-
196 XDR-F), OR 2.23 (1.52 - 3.38), $p < 0.001$ and OR 2.39 (1.18 - 4.83), $p < 0.015$, respectively
197 (Table 5).

198

199 **DISCUSSION**

200 The study is one of few published on programmatic management of pre-XDR-TB and
201 the first nationwide study in Peru. The overall success rate in pre-XDR was low, even
202 surprisingly lower than XDR-TB but this reflects the intensive attention² paid to
203 treating XDR-TB patients in Peru, with particularly strengthened treatment regimens,
204 patient-centralized DOT, and social support.⁴ The study confirmed significantly lower
205 treatment success in pre-XDR-TB with resistance to fluoroquinolones than to SLI, **as**
206 **also found in previous reports.**^{2, 10}

207 Even though pre-XDR-TB patients were diagnosed quickly and treated in line with WHO
208 recommendations,⁵ the majority of cases had unfavorable outcomes. **The most**
209 **frequent unfavorable outcome was lost to follow up with 26.4%, which were more**
210 **frequent in the first six months, and probably due to long and weak treatment**
211 **regimens, clinic-centered DOT, adverse reactions, inadequate social support, and**
212 **limitations of the health system to follow up timely patients who take their treatment**
213 **irregularly.** The high death rate was likely due in the early years to a delay in DST
214 results for second-line drugs (with conventional method) and late treatment initiation,
215 although it subsequently remained high even though rapid DST coverage was
216 increased. Comorbidities or coinfections may have contributed to the increased
217 mortality as well. The death rate was higher in pre-XDR-F than pre-XDR-I, possibly
218 because these patients were older and had received more previous treatments.
219 Acquired resistance may explain the high failure rate as patient already with pre-XDR
220 were started on standardized MDR-TB treatment because DST results came late.
221 Fluoroquinolone resistance was only tested to ciprofloxacin. Probably a considerable
222 proportion of strains with resistance to ciprofloxacin maintained susceptibility to
223 levofloxacin or moxifloxacin with which they were treated, but still ciprofloxacin
224 resistance was associated with poor outcome in a multivariable model. There was no
225 DST for Am so the use of this injectable may not have been optimal.

226 Our study is unusual in finding higher success rate in XDR-TB than pre-XDR-TB; lower
227 treatment success rate in pre-XDR-F than pre-XDR-I has also been found in other
228 studies. Data from 6724 MDR-TB patients with personalized treatment in 26 sites
229 worldwide showed a 64% success rate in cases with no resistance to injectable or

230 fluoroquinolones, 56% in pre-XDR-I, 48% in pre-XDR-F and 40% in XDR. Failure/relapse
231 rate increased with increasing resistance (from 4% in MDR-TB to 22% in XDR-TB), as
232 did deaths (from 8 to 15%), but not the proportion lost to follow-up (18-16-12-16%,
233 respectively)¹⁰. In 1407 MDR-TB patients from Korea, similar data were observed, with
234 a 47% success rate in cases with no fluoroquinolone and injectable resistance, the
235 same success rate (47%) in patients with pre-XDR-I, but lower in pre-XDR-F (36%) and
236 in XDR (29%). Failure and death rates increased with increased resistance, while
237 patients lost to follow-up decreased with increasing resistance.²

238 A strength was that the study was nation-wide, with DST done centralized in an
239 externally quality assured reference laboratory. One limitation was that
240 fluoroquinolone susceptibility was only tested for ciprofloxacin, while treatment
241 included levofloxacin or moxifloxacin. Another limitation was incomplete culture
242 conversion data because data were missing or many patients lost or died. Instead, the
243 proportion of all cases with positive culture by month was shown for each subgroup,
244 but such grouped data must be interpreted with caution. Recording of adverse drug
245 reactions was incomplete at central level, so that the relationship with loss to follow-
246 up could not be assessed.

247 The recommendations arising from our findings are that: i) pre-XDR-TB cases should be
248 handled similarly to XDR TB cases, incorporating new effective drugs (current WHO
249 Groups C & D) with special care for patients resistant to fluoroquinolones, ii) all MDR-
250 TB patients (and not just XDR-TB patients) need patient-centered strategies to prevent
251 and reduce loss to follow-up, with strictly supervised home treatment (intensive
252 phase) and then as outpatients at the health facility (continuation phase), iii) rapid DST
253 for fluoroquinolone and SLI should be implemented in MDR-TB high burden countries,
254 iv) surveillance for adverse events should be improved, and v) patient cohort outcomes
255 should be evaluated separately for MDR-TB, pre-XDR-F TB, pre-XDR-I TB and XDR-TB.

256 Our results suggest that the current definition of pre-XDR-TB as a distinct entity may
257 not be a very useful concept since it consists of two very different groups with
258 different treatment success rates. As of January 2016, pre-XDR-TB patients have been
259 managed under the same conditions as XDR-TB patients in Peru and in line with other
260 reports¹⁹ and WHO guidelines from 2016.²⁰

261 In conclusion, previous programmatic management of pre-XDR-TB, treated as other
262 MDR-TB patients, had too low success rate, especially in cases of pre-XDR-F. Rapid
263 drug susceptibility testing for fluoroquinolones and SLIs, patient-centered strategies
264 and regimens including new drugs are needed.

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338 **Table 1. General characteristics of the study population of pre-XDR-TB patients**
 339 **who started treatment, Peru: 2011-2014**
 340

Characteristics	Pre-XDR-F (N=120)	Pre-XDR-I (N=490)	Total (N=610)	p-value
	n (%)	n (%)	n (%)	
Male	90 (75)	325 (63)	415 (68)	0.07
Age groups				
0 - 14 years	1 (1)	5 (1)	6 (1)	
15 - 34 years	62 (52)	332 (68)	394 (65)	
35 - 54 years	42 (35)	123 (25)	165 (27)	
55 years or more	15 (13)	30 (6)	45 (7)	
Age - median (IQR)	34 (27 - 45)	28 (22 - 38)	29 (22 - 40)	<0.001
HIV-positive	5 (4)	18 (4)	23 (4)	0.71
Diabetes mellitus	17 (14)	29 (6)	46 (8)	0.002
Place of origin				
Lima and Callao	86 (72)	393 (80)	479 (79)	0.041
Number of previous treatments				
No previous treatments	20 (17)	183 (37)	203 (33)	<0.001
1 previous treatment	16 (13)	121 (25)	137 (22)	
2 or more previous treatments	84 (70)	186 (38)	270 (44)	
Treatment history				
New	20 (17)	183 (37)	203 (33)	<0.001
Relapse	12 (10)	53 (11)	65 (11)	
Treatment after loss to follow-up	65 (54)	169 (34)	234 (38)	
Treatment after failure	23 (19)	85 (17)	108 (18)	
Year of treatment initiation				
2011	33 (28)	133 (27)	166 (27)	0.136
2012	19 (16)	125 (26)	144 (24)	
2013	32 (27)	111 (23)	143 (23)	
2014	36 (30)	121 (25)	157 (26)	

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343 **Table 2. Days from diagnosis to treatment initiation for pre-XDR-TB, Peru: 2011-**
 344 **2014**
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Treatment initiation	Pre-XDR-F (N=120)	Pre-XDR-I (N=490)	Total (N=610)	p-value
Before diagnosis, n (%)	33 (28)	143 (29)	176 (29)	0.80
After diagnosis, n (%)	87 (72)	347 (71)	434 (71)	
Before diagnosis, median (IQR)	-30 (-66, -7)	-22 (-58, -8)	-225 (-61, -8)	0.79
After diagnosis, median (IQR)	14.5 (7, 28)	14 (6, 23)	14 (6, 24)	0.23
After diagnosis:				
Less than 2 weeks, n (%)	50 (42)	187 (38)	237 (39)	0.54
3-4 weeks, n (%)	20 (17)	101 (21)	121 (20)	0.40
Over 4 weeks, n (%)	17 (14)	59 (12)	76 (12)	0.63

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347 IQR: Interquartile range

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350**Table 3. Drugs used according to resistance pattern in pre-XDR-TB patients, Peru: 2011-2014**

Resistance pattern	Pre-XDR-F		Pre-XDR-Km		Pre-XDR-Cm		Pre -XDR-Km+Cm		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total	120		213		102		175		610	
E	43	(36)	89	(42)	34	(3)	52	(30)	218	(36)
Z	77	(64)	148	(70)	70	(69)	137	(78)	432	(71)
S	3	(3)	8	(4)	2	(2)	16	(9)	29	(5)
Km	22	(18)	18	(9)	34	(33)	56	(32)	130	(2)
Cm	57	(48)	164	(77)	5	(5)	71	(41)	297	(49)
Am	22	(18)	18	(9)	34	(33)	56	(32)	130	(21)
Cfz	0	(0)	3	(1)	0	(0)	1	(1)	4	(1)
Lfx	33	(28)	140	(66)	81	(80)	89	(51)	343	(56)
Mfx	77	(64)	66	(31)	17	(17)	81	(46)	241	(40)
PAS	61	(51)	118	(55)	57	(56)	105	(60)	341	(56)
Cs	105	(88)	203	(95)	100	(98)	168	(96)	576	(94)
Thz	4	(3)	3	(1)	0	(0)	6	(3)	13	(2)
Eto	76	(63)	127	(60)	83	(81)	98	(56)	384	(63)
Lzd	4	(3)	4	(1)	0	(0)	6	(3)	14	(2)
Amx-Clv	61	(51)	90	(42)	36	(35)	100	(57)	287	(47)
Imp	3	(3)	0	(0)	0	(0)	3	(2)	6	(1)

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354 **Table 4. Clinical outcomes for pre-XDR-TB cases according to baseline**
 355 **resistance pattern, Peru: 2011-2013**

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Treatment outcomes	Pre-XDR-F	Pre-XDR-Km	Pre-XDR-Cm	Pre-XDR-Km-Cm	Total	P Value
	(n=83)	(n=155)	(n=73)	(n=141)	(n=452)	
Success	18 (21.7)	81 (52.3)	37 (50.7)	60 (42.6)	196 (43.4)	<0.001
Lost to follow-up	25 (30.1)	35 (22.6)	28 (38.4)	32 (22.7)	120 (26.5)	0.043
Failure	15 (18.1)	18 (11.6)	3 (4.1)	26 (18.4)	62 (13.7)	0.018
Death	19 (22.9)	16 (10.3)	2 (2.7)	18 (12.8)	55 (12.2)	0.0016
Not evaluated	6 (7.2)	5 (3.2)	3 (4.1)	5 (3.5)	19 (4.2)	0.276

357 Values are n (%)

358 Statistical analyses were performed using chi-squared test

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For Review Only

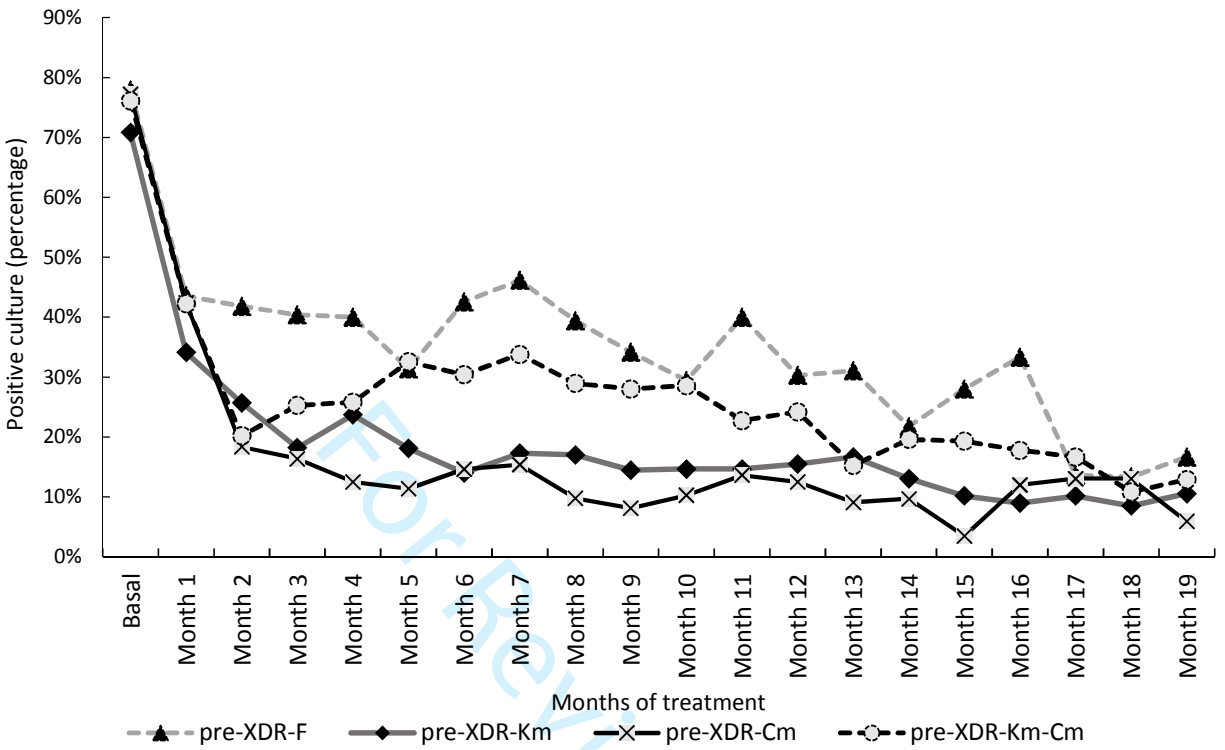
360 **Table 5. Factors associated with unsuccessful treatment outcome in pre-XDR-TB**
 361 **patients, Peru: 2011-2013**

Variables	Univariate analysis			Multivariate analysis		
	OR	CI	p-value	OR	CI	p-value
Age	1.02	1.003 - 1.03	<0.016	1.01	0.99 - 1.03	0.20
Male sex	1.42	0.97-2.1	<0.071	1.32	0.89 - 1.97	0.17
HIV+	0.87	0.32-2.29	0.774			
Diabetes	1.64	0.81-3.34	0.17	1.29	0.58 - 2.88	0.53
Previously treated	2.54	1.73-3.74	<0.001	2.23	1.52 - 3.38	<0.001
Pre-XDR-F	3.07	1.78-5.3	<0.001	2.39	1.18 - 4.83	<0.015
Pre-XDR-I (Km-resistant)	0.61	0.41-0.89	<0.012	0.94	0.57 - 1.58	0.84
Pre-XDR-I (Cm-resistant)	0.91	0.64-1.31	0.613			
Pre-XDR (Km+Cm-resistant)	1.06	0.72-1.57	0.77			
Origin: Lima	0.97	0.63-1.5	0.91			

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Figure 1. Proportion of all pre-XDR patients with positive culture according to month of treatment and pre-XDR types



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		Basal	Mes 1	Mes 2	Mes 3	Mes 4	Mes 5	Mes 6	Mes 7	Mes 8	Mes 9	Mes 10	Mes 11	Mes 12	Mes 13	Mes 14	Mes 15	Mes 16	Mes 17	Mes 18	Mes 19	Mes 20
pre-XDR-F	Positivo	81	27	23	21	18	16	20	18	13	14	10	14	10	9	5	7	7	3	2	2	3
	Negativo	23	35	32	31	27	35	27	21	20	27	24	21	23	20	18	18	14	19	13	10	7
	No evaluado	16	58	65	68	75	69	73	81	87	79	86	85	87	91	97	95	99	98	105	108	110
pre-XDR-Km	Positivo	131	44	28	20	23	19	14	14	16	13	11	11	11	11	9	6	6	6	4	4	3
	Negativo	54	85	81	90	74	86	86	67	78	77	64	64	60	55	60	53	61	53	43	34	30
	No evaluado	28	84	104	103	116	108	113	132	119	123	138	138	142	147	144	154	146	154	166	175	180
pre-XDR-Cm	Positivo	71	28	11	9	6	5	6	6	4	3	4	3	4	3	3	1	3	3	3	1	0
	Negativo	21	38	49	46	42	39	35	33	37	34	35	19	28	30	28	28	22	20	20	16	13
	No evaluado	10	36	42	47	54	58	61	63	61	65	63	80	70	69	71	73	77	79	79	85	89
pre-XDR-Km-Cm	Positivo	121	41	19	24	24	28	24	25	22	21	20	15	15	9	10	11	8	6	4	4	5
	Negativo	38	56	75	71	69	58	55	49	54	54	50	51	47	50	41	46	37	30	33	27	33
	No evaluado	16	78	81	80	82	89	96	101	99	100	105	109	113	116	124	118	130	139	138	144	148

	Basal	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12	Month 13	Month 14	Month 15	Month 16	Month 17	Month 18	Month 19	Mes 20
<u>pre-XDR-F</u>	78%	44%	42%	40%	40%	31%	43%	46%	39%	34%	29%	40%	30%	31%	22%	28%	33%	14%	13%	17%	
<u>pre-XDR-Km</u>	71%	34%	26%	18%	24%	18%	14%	17%	17%	14%	15%	15%	15%	17%	13%	10%	9%	10%	9%	11%	
<u>pre-XDR-Cm</u>	77%	42%	18%	16%	13%	11%	15%	15%	10%	8%	10%	14%	13%	9%	10%	3%	12%	13%	13%	6%	
<u>pre-XDR-Km-Crr</u>	76%	42%	20%	25%	26%	33%	30%	34%	29%	28%	29%	23%	24%	15%	20%	19%	18%	17%	11%	13%	