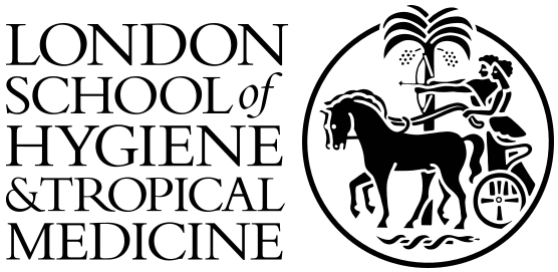


The International Journal of Tuberculosis and Lung Disease

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

Journal:	*The International Journal of Tuberculosis and Lung Disease*
Manuscript ID	IJTLD-12-17-0900.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	29-Apr-2018
Complete List of Authors:	Alarcon, Antonieta; Ministerio de Salud, Estrategia Sanitaria Nacional de Prevención y Control de la Tuberculosis Alarcon, Edith; Pan-American Health Organisation, US office Mendoza-Ticona, Alberto; Hospital de Emergencias Villa El Salvador, Infectious Diseases Division Obregon, George; Instituto Nacional de Salud, Laboratorio de Referencia Nacional de Micobacterias Cornejo, José; Hospital Nacional Arzobispo Loayza, Service of Neumology Vargas, Dante; Hospital Nacional Hipolito Unanue, Department of Medicine de los Ríos, Jorge; Hospital Maria Auxiliadora, Service of Neumology Moore, David; The London School of Hygiene and Tropical Diseases, Department of Clinical Research Heldal, Einar; Nasjonalt folkehelseinstitutt, Public Health
Key Words:	pre-XDR TB, culture conversion, treatment outcome, Peru

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

Valentina Alarcón Guizado[1], Edith Alarcón Arrascue[2], Alberto Mendoza-Ticona[1,3], George Obregón Boltan[4], José Cornejo García[1,5], Dante Vargas[1,6], Jorge de los Ríos[1,7], David AJ Moore[8] and Einar Heldal[9]

1: Estrategia Sanitaria Nacional de Prevención y Control de la Tuberculosis, Ministerio de Salud, Peru
2: The International Union against Tuberculosis and Lung Disease, Peru
3: Hospital de Emergencias Villa El Salvador, Ministerio de Salud, Peru
4: Instituto Nacional de Salud de Perú
5: Hospital Nacional Arzobispo Loayza, Ministerio de Salud, Peru
6: Hospital Nacional Hipólito Unanue, Ministerio de Salud, Peru
7: Hospital María Auxiliadora, Ministerio de Salud, Peru
8: The London School of Hygiene and Tropical Diseases, UK
9: The International Union against Tuberculosis and Lung Disease, Norway

Running head: Pre-extensively drug-resistant tuberculosis in Peru

Summary: 200 (Max 200)
Text: 2495 (Max 2500)
Number of references: 20
Number of tables and figures: 6

Keywords: Pre-XDR TB, culture conversion, treatment outcome, Peru

Corresponding author: Valentina Alarcón Guizado

Address: Av. Cesar Vallejo, cuadra 13 s/n, El Agustino
Telephone: +51-99079882; +5113620765
Email: antonieta_alarcong@hotmail.com

ABSTRACT:

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

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

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

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

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

INTRODUCTION

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

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

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

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

METHODS

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

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

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

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

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

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

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

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

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

RESULTS

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

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

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

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

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

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

DISCUSSION

The study is one of few published on programmatic management of pre-XDR-TB and the first nationwide study in Peru. The overall success rate in pre-XDR was low, even surprisingly lower than XDR-TB but this reflects the intensive attentio[2]n paid to treating XDR-TB patients in Peru, with particularly strengthened treatment regimens, patient-centralized DOT, and social support. [4] The study confirmed significantly lower treatment success in pre-XDR-TB with resistance to fluoroquinolones than to SLI, as also found in previous reports. [2, 10]

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

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

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

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

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

Our results suggest that the current definition of pre-XDR-TB as a distinct entity may not be a very useful concept since it consists of two very different groups with different treatment success rates. As of January 2016, pre-XDR-TB patients have been managed under the same conditions as XDR-TB patients in Peru and in line with other reports [19] and WHO guidelines from 2016. [20]

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

ACKNOWLEDGEMENTS

This research was made possible with support from the United States Agency for International Development (USAID) through the TREAT TB Cooperative Agreement (AID-GHN-A-00-08-00004). The contents are the responsibility of the authors and do not necessarily reflect the views of USAID or the United States Government. Additional support was provided through the Structured Operational Research and Training Initiative (SORT IT), a global partnership led by UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) based at the World Health Organization.

REFERENCES:

1. World Health Organization. Global Tuberculosis Report 2017. Geneva: Licence: CC BY-NCSA 3.0 IGO. WHO/HTM/TB/2017.23 2017.
2. Kim DH, Kim HJ, Park SK, et al. Treatment outcomes and survival based on drug resistance patterns in multidrug-resistant tuberculosis. American journal of respiratory and critical care medicine. 2010;182(1):113-119.
3. World Health Organization. Global Tuberculosis Report 2016. Geneva: WHO/HTM/TB/2016.13 2016.
4. Alarcon V, Alarcon E, Figueroa C, et al. [Tuberculosis in Peru: epidemiological situation, progress and challenges for its control]. Revista peruana de medicina experimental y salud publica. 2017;34(2):299-310.
5. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis – 2011 update. WHO Document Production Services, Geneva, Switzerland. WHO/HTM/TB/2011.6 2011.
6. Alarcon A. La experiencia en el manejo programático de la TB-XDR en Perú Available: http://www.tuberculosis.minsa.gob.pe/Archivos/RecursoInformacion/201609200407.pdf.
7. Johnston JC, Shahidi NC, Sadatsafavi M, et al. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. PloS one. 2009;4(9):e6914.
8. Orenstein EW, Basu S, Shah NS, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. The Lancet Infectious diseases. 2009;9(3):153-161.
9. Javaid A, Ullah I, Masud H, et al. Predictors of poor treatment outcomes in multidrug-resistant tuberculosis patients: a retrospective cohort study. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2017.
10. Falzon D, Gandhi N, Migliori GB, et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. The European respiratory journal. 2013;42(1):156-168.
11. Solis LA, Shin SS, Han LL, et al. Validation of a rapid method for detection of M. tuberculosis resistance to isoniazid and rifampin in Lima, Peru. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2005;9(7):760-764.
12. Caviedes L, Lee TS, Gilman RH, et al. Rapid, efficient detection and drug susceptibility testing of Mycobacterium tuberculosis in sputum by microscopic observation of broth cultures. The Tuberculosis Working Group in Peru. Journal of clinical microbiology. 2000;38(3):1203-1208.
13. Moore DA, Evans CA, Gilman RH, et al. Microscopic-observation drug-susceptibility assay for the diagnosis of TB. The New England journal of medicine. 2006;355(15):1539-1550.
14. Asencios L, Galarza M, Quispe N, et al. [Molecular test Genotype(R) MTBDRplus, an alternative to rapid detection of multidrug resistance tuberculosis]. Revista peruana de medicina experimental y salud publica. 2012;29(1):92-98.
15. Ministerio de Salud. Norma técnica de salud para la atención integral de las personas afectadas por tuberculosis. Lima - Perú. Available: http://www.tuberculosis.minsa.gob.pe/Archivos/norma_tecnica.pdf.
16. Mendoza-Ticona A, Moore DA, Alarcon V, et al. [Proposal of anti-tuberculosis regimens based on susceptibility to isoniazid and rifampicin]. Revista peruana de medicina experimental y salud publica. 2013;30(2):197-204.
17. World Health Organization. Definiciones y marco de trabajo para la notificación de tuberculosis - revisión 2013. Available:

http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&gid=22984&Itemid=270&lang=en.

18. Vargas-Herrera J, Segovia-Juarez J, Garro Nunez GM. [Information system of the national network of public health laboratories in Peru (Netlab)]. Revista peruana de medicina experimental y salud publica. 2015;32(2):378-384.

19. Palmero D, Gonzalez Montaner P, Cufre M, et al. First series of patients with XDR and pre-XDR TB treated with regimens that included meropenen-clavulanate in Argentina. Archivos de bronconeumologia. 2015;51(10):e49-52.

20. World Health Organization. WHO Treatment guidelines for drug-resistant tuberculosis – 2016 update. Geneva: WHO/HTM/TB/2016.04 2016.

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

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)	

Table 2. Days from diagnosis to treatment initiation for pre-XDR-TB, Peru: 2011-2014

Treatment initiation	Pre-XDR-F	Pre-XDR-I	Total	p-value
	(N=120)	(N=490)	(N=610)	
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

IQR: Interquartile range

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)

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

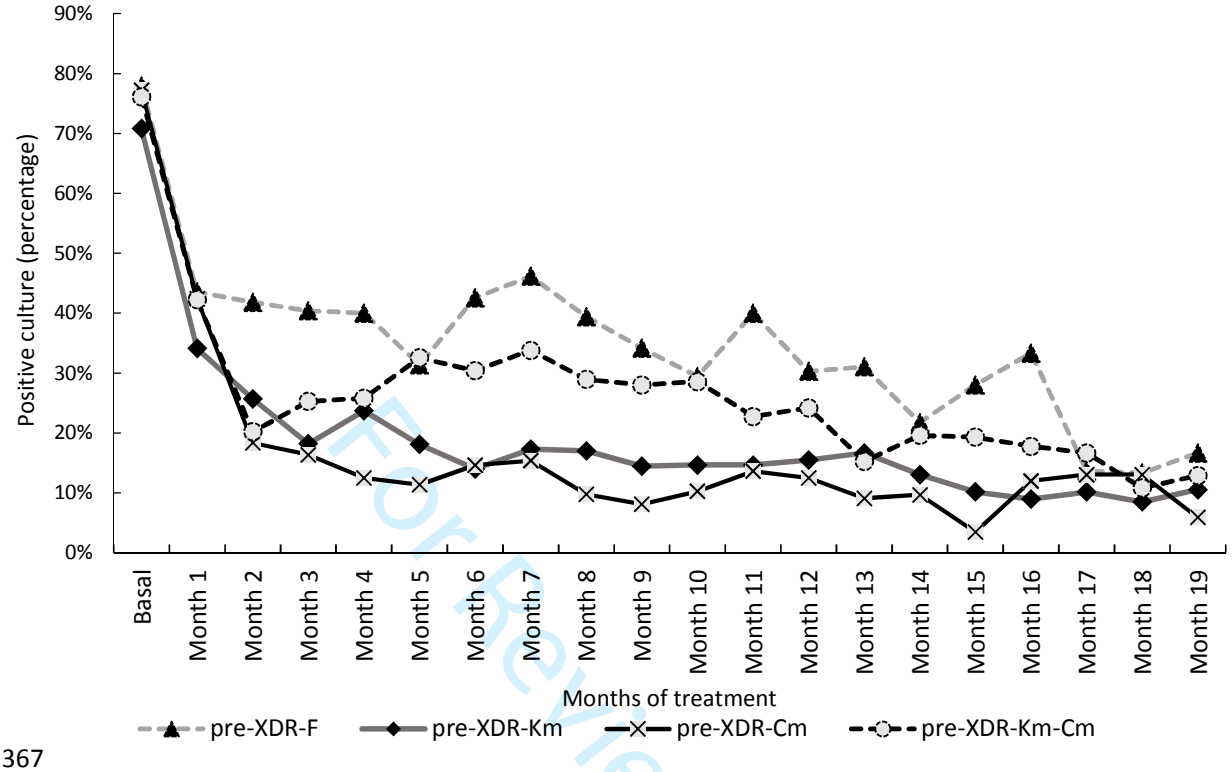
Treatment outcomes	Pre-XDR-F (n=83)	Pre-XDR-Km (n=155)	Pre-XDR-Cm (n=73)	Pre-XDR Km-Cm (n=141)	Total (n=452)	P Value
Success	18 (21.7)	81 (52.3)	37 (50.7)	60 (42.6)	196 (43.4)	<0.001
Lost to follow-up	25 (30.1)	35 (22.6)	28 (38.4)	32 (22.7)	120 (26.5)	0.043
Failure	15 (18.1)	18 (11.6)	3 (4.1)	26 (18.4)	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

Values are n (%)
Statistical analyses were performed using chi-squared test

Table 5. Factors associated with unsuccessful treatment outcome in pre-XDR-TB 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			

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



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