TRATAMIENTO DE LA TUBERCULOSIS RESISTENTE A RIFAMPICINA

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AGENDA

- **EPIDEMIOLOGIA DE LA TUBERCULOSIS RESISTENTE**
- **FACTORES DE RIESGO PARA TUBERCULOSIS RESISTENTE**
- **CLASIFICACION DE LA TUBERCULOSIS RESISTENTE**
- **FARMACOS USADOS EN TUBERCULOSIS RESISTENTE**
- **RECOMENDACIONES DE LA OMS PARA EL USO DE LOS NUEVOS FARMACOS**
- **PRINCIPALES ESQUEMAS DE TRATAMIENTO PARA TUBERCULOSIS RESISTENTE**
- **TRABAJOS DE INVESTIGACION SOBRE FARMACORRESISTENCIA**
- **REACCIONES ADVERSAS COMUNES**

RIESGO DE TB. PERU.2022*

- Población: 33'245,895 hab.
- Densidad poblacional: 25 hab. x km²
- 25 Regiones geografías

- Morbilidad de casos de TB: 29,292
- Casos nuevos de TB: 28,125
- Casos nuevos de TBP FP: 16,432
- Casos TB-MDR: 1,149
- Casos TB-XDR por PS: 85
- Lima y Callao, representan:
  - **56.4%** (16,508) del total nacional de casos.
  - **78.2 %** (898) de TB-MDR.
  - **85.9 %** (73) de TB-XDR por PS

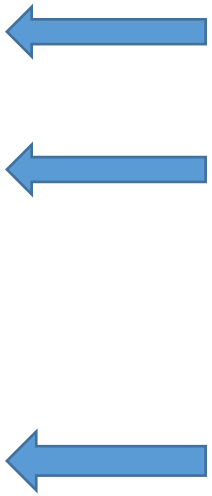
RIESGO DE TB EN REGIONES. PERU.2021.

TENDENCIA DEL RIESGO	MUY ALTO RIESGO	ALTO RIESGO	RIESGO MODERADO	RIESGO LEVE
	Ucayali	Loreto	Tacna	La Libertad
	Lima	Ica	Pasco	Arequipa
	Callao	San Martín	Cajamarca	Piura
	Madre de Dios	Huancavelica	Moquegua	Ayacucho
	Tumbes	Apurímac	Ancash	Junín
	Cusco	Puno	Lambayeque	Huánuco
	Amazonas			

*** El riesgo se sustenta en la media de 14 indicadores:** 05 epidemiológicos y 09 operacionales + tendencia de la curva de incidencia

Table 2. Countries with estimated high tuberculosis burdens, 2020

Country	Estimated cases	Percentage of cases in the Region	Estimated rate*
Brazil	96 000	33.0%	45.2
Peru	38 000	13.1%	115.2
Mexico	31 000	10.7%	24.0
Haiti	19 000	6.5%	166.6
Colombia	19 000	6.5%	37.3
Argentina	14 000	4.8%	31.0
Venezuela (Bolivarian Republic of)	13 000	4.5%	45.7
Bolivia (Plurinational State of)	12 000	4.1%	102.8
Ecuador	8500	2.9%	48.2
El Salvador	3600	1.2%	55.5
Paraguay	3400	1.2%	47.7
Guyana	620	0.2%	78.8
Dominica	34	0.0%	47.2
Total in high-burden countries	**258 154**	**88.7%**	**46.6**
Total in the Region	**291 000**	**100%**	**28.5**



Note: High-burden countries are those with an estimated absolute number of TB cases greater than 10 000 per year and those with an incidence rate of more than 45 per 100 000 population.
Source: World Health Organization. Global Tuberculosis Report 2021. Geneva: WHO; 2021. Available at: https://www.who.int/publications/i/item/9789240037021.

Table 4. Countries with the highest burden of multidrug-resistant or rifampicin-resistant tuberculosis, 2020

Country	Reported MDR/RR-TB cases		
	Number	Percentage	Rate
Peru	1424	38%	4.3
Brazil	881	23%	0.4
Mexico	270	7%	0.2
Ecuador	253	7%	1.4
Dominican Republic	149	4%	1.4
Colombia	134	4%	0.3
Argentina	110	3%	0.2
Bolivia (Plurinational State of)	98	3%	0.8
Haiti	93	2%	0.8
Guatemala	77	2%	0.4
Total	3489	92%	

Note: Rates per 100 000 population.
MDR/RR-TB: multidrug-resistant or rifampicin-resistant tuberculosis.
Source: World Health Organization. Global Tuberculosis Report 2021. Geneva: WHO; 2021. Available at: https://www.who.int/publications/i/item/9789240037021.

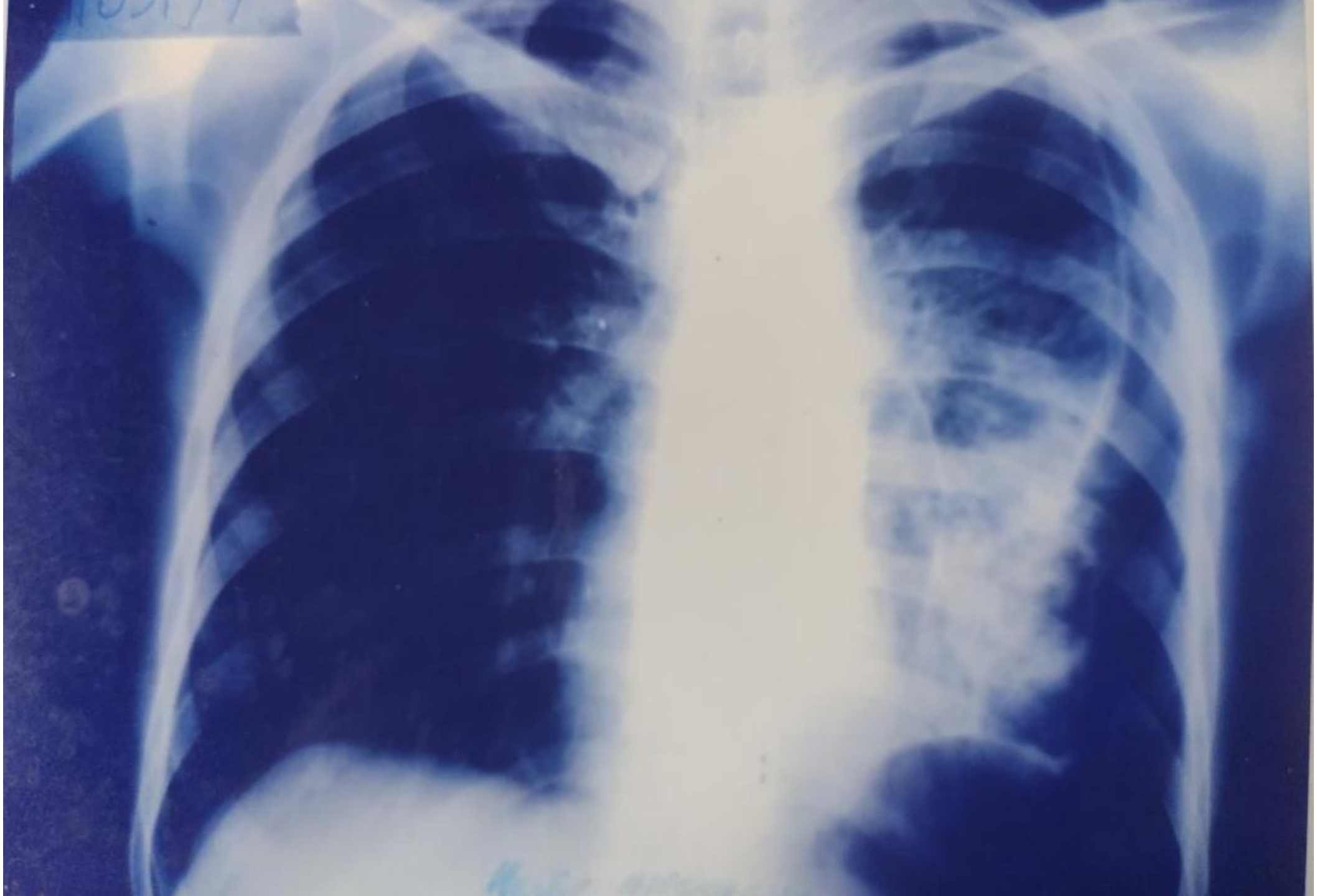
FACTORES DE RIESGO PARA TUBERCULOSIS ACTIVA ENTRE PERSONAS QUE HAN SIDO INFECTADAS CON TUBERCULOSIS

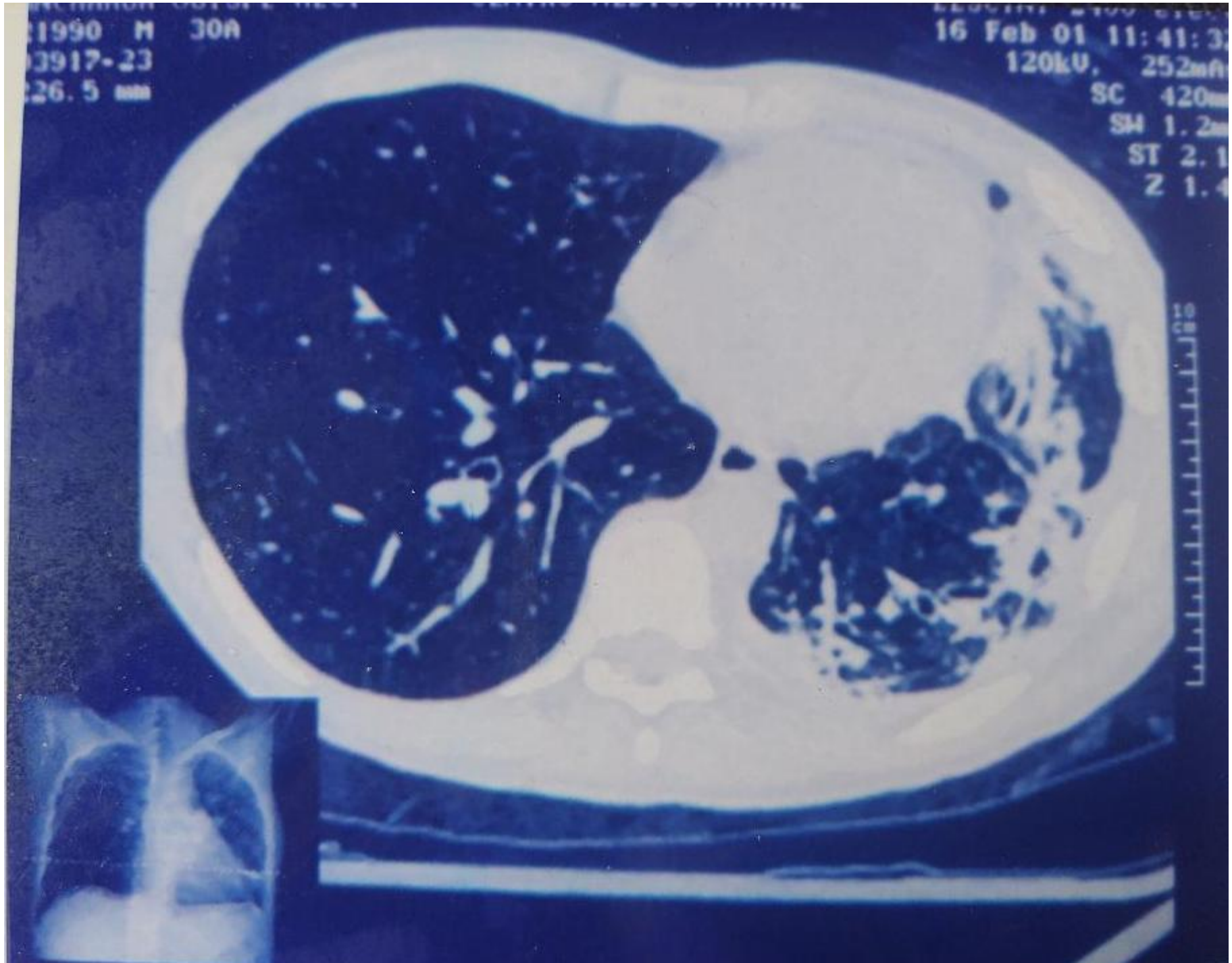
FACTOR	RIESGO RELATIVO/ODDS
INFECCION RECIENTE (MENOS DE 1 AÑO)	12.9
LESIONES FIBROTICAS (ESPONTANEAMENTE CICATRIZADAS)	2-20
COMORBILIDAD	
INFECCION VIH/SIDA	100
SILICOSIS	30
INSUFICIENCIA RENAL CRONICA/HEMODIALISIS	10-25
DIABETES MELLITUS	2-4
USO DE DROGAS INTRAVENOSAS	10-30
TRATAMIENTO INMUNOSUPRESOR	10
GASTRECTOMIA	2-5
BYPASS YEYUNOILEAL	30-60
PERIODO POST-TRANSPLANTE (RENAL, CARDIACO)	20-70
MALNUTRICION Y BAJO PESO SEVERO	2

MCKEAN SC ET AL. PRINCIPLES AND PRACTICE OF HOSPITAL MEDICINE. SECOND EDITION, 2017

Tabla 4: Principales factores de riesgo para TB resistente

1. Fracaso a esquema con medicamentos de primera línea. **(PARA TB-DS)**
2. Contacto de caso confirmado de TB resistente.
3. Recaída dentro de los siguientes 6 meses de haber sido dado de alta de un esquema con medicamentos de primera línea.
4. Recaída luego de haber sido dado de alta con medicamentos de segunda línea.
5. Personas privadas de su libertad (PPL) y residentes de albergues, comunidades terapéuticas, entre otros.
6. Antecedente de tratamientos múltiples (más de dos episodios previos de TB).
7. Antecedente de irregularidad al tratamiento, abandono o terapia no supervisada.
8. Contacto con persona que falleció por TB.
9. Comorbilidades o condición previa: VIH, diabetes mellitus, insuficiencia renal crónica, tratamiento inmunosupresor y otros.
10. Trabajadores y estudiantes de la salud.

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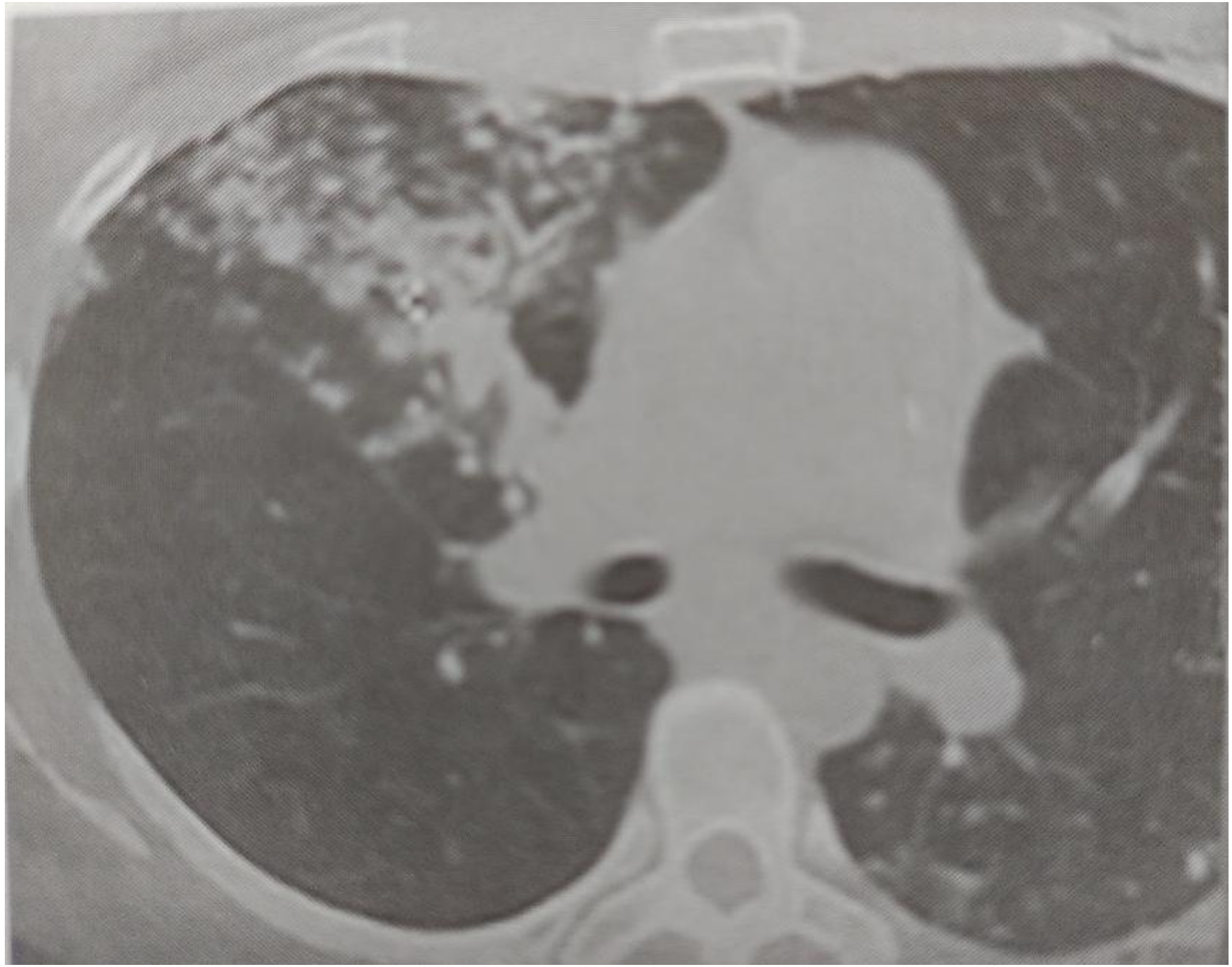
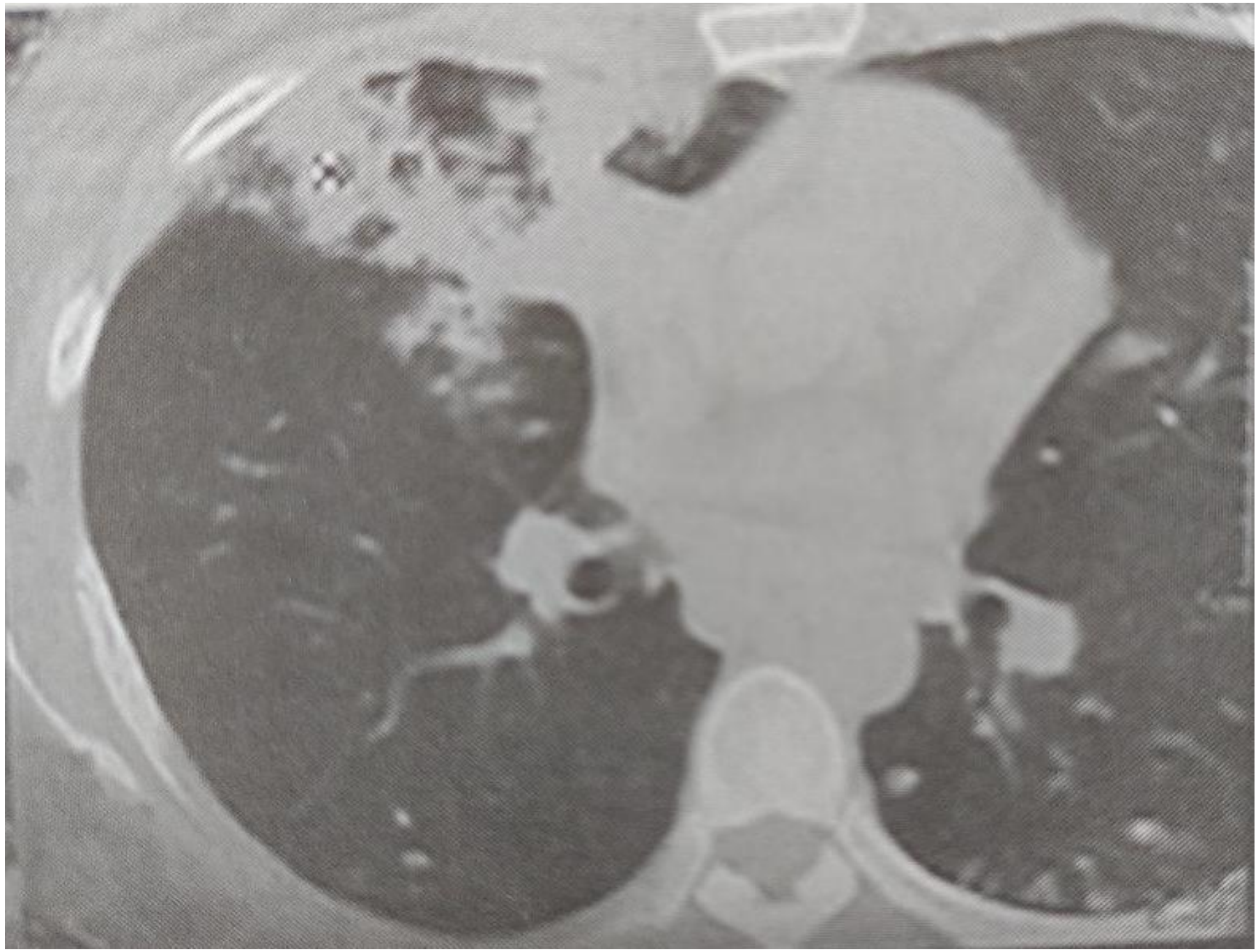
NATIONAL ACTIVE CASE-FINDING PROGRAM FOR TUBERCULOSIS IN PRISONS, PERU 2024

EMERGING INFECTIOUS DISEASES. MARCH 2025

PRISON NAME	No. SCREENED	No. (%) TB CASES	No. (%) RR-TB CASES
HUACHO	2,053	115 (5.6)	4 (3.5)
IQUITOS VARONES	1,179	56 (4.7)	1 (1.8)
ICA	4,273	194 (4.5)	33 (17.0)
HUARAL	1,885	63 (3.7)	3 (4.8)
LURIGANCHO	7,591	229 (3.0)	36 (15.7)
MIGUEL CASTRO	4,413	130 (2.9)	19 (14.6)
TRUJILLO VARONES	4,733	129 (2.7)	18 (14.0)
ANCON 1	1,716	45 (2.6)	3 (6.7)
PUCALLPA	2,358	41 (1.7)	1 (2.4)
TACNA VARONES	980	16 (1.6)	1 (6.3)
CALLAO	2,795	37 (1.3)	3 (8.1)
TRUJILLO MUJERES	87	1 (1.1)	0
PIURA	3,644	28 (0.8)	2 (7.1)
CHORRILLOS MUJERES	780	5 (0.6)	0
OTHERS	447	0	0
OVERALL	38,734	1,089 (2.8)	124 (11.4)





TUBERCULOSIS FARMACORRESISTENTE (TB-DR)

ES LA ENFERMEDAD TUBERCULOSA CON RESISTENCIA DETECTADA A CUALQUIER FARMACO ANTITUBERCULOSO. SEGÚN EL PERFIL DE RESISTENCIA SE CLASIFICA EN:

- **1) TB RESISTENTE A ISONIACIDA (TB-Hr): TUBERCULOSIS CON RESISTENCIA DETECTADA A LA ISONIACIDA (INH) Y SENSIBLE A LA RIFAMPICINA (RMP)**
- **2) TB RESISTENTE A RIFAMPICINA (TB-RR): TUBERCULOSIS CON RESISTENCIA DETECTADA A LA RMP**
- **3) TB MULTIDROGORRESISTENTE (TB-MDR): TUBERCULOSIS CON RESISTENCIA DETECTADA AL MENOS A INH Y RMP**
- **4) TB PRE-EXTREMADAMENTE RESISTENTE: (TB pre-XDR): TUBERCULOSIS QUE ES MDR CON RESISTENCIA ADICIONAL A FLUORQUINOLONA (LEVOFLOXACINA, MOXIFLOXACINA) O A RMP Y FLUORQUINOLONA**
- **5) TB EXTREMADAMENTE RESISTENTE (TB-XDR): TUBERCULOSIS MDR CON RESISTENCIA DETECTADA A FLUORQUINOLONA (LEVOFLOXACINA, MOXIFLOXACINA) Y AL MENOS A 1 FARMACO DEL GRUPO A (BEDAQUILINA O LINEZOLID)**

Tabla 7: Clasificación de medicamentos antituberculosis

Grupo	Medicamentos
Grupo 1: Agentes de primera línea	Isoniacida (H), rifampicina (R), etambutol (E), pirazinamida (Z), rifabutina (Rfb), estreptomicina (S).
Grupo 2: Agentes inyectables de segunda línea	Kanamicina (Km), amikacina (Am), capreomicina (Cm).
Grupo 3: Fluoroquinolonas	levofloxacina (Lfx), moxifloxacina (Mfx)
Grupo 4: Agentes de segunda línea bacteriostáticos orales	etionamida (Eto), cicloserina (Cs), ácido para-amino salicílico (PAS)
Grupo 5: Agentes con evidencia limitada	clofazimina (Cfz), linezolid (Lzd), amoxicilina/ clavulánico(Amx/Clv), meropenem (Mpm),imipenem/ cilastatina (Ipm/Cln), dosis altas de isoniacida, claritromicina (Clr), tioridazina (Tio)

GRUPOS DE FARMACOS RECOMENDADOS PARA USAR EN REGIMENES DE TB-MDR SEGÚN LA OMS

- **GRUPO A: INCLUIR LOS TRES FARMACOS (A MENOS QUE NO PUEDAN SER INDICADOS POR TOXICIDAD O RESISTENCIA):**
  - **LEVOFLOXACINA O MOXIFLOXACINA** — **Lfx / Mfx**
  - **BEDAQUILINA** — **Bdq**
  - **LINEZOLID** — **Lzd**
- **GRUPO B: AÑADIR UNO O AMBOS FARMACOS (A MENOS QUE NO PUEDAN SER INDICADOS POR TOXICIDAD O RESISTENCIA):**
  - **CLOFAZIMINA** — **Cfz**
  - **CICLOSERINA O TERIZIDONA** — **Cs / Trd**
- **GRUPO C: AÑADIR LOS FARMACOS HASTA COMPLETAR EL ESQUEMA Y CUANDO LOS FARMACOS DE LOS GRUPOS A Y B NO PUEDAN USARSE:**
  - **ETAMBUTOL** — **E**
  - **DELAMANID** — **Dlm**
  - **PIRAZINAMIDA** — **Z**
  - **IMIPENEM-CILASTATINA** — **Ipm-Cln**
  - **MEROPENEM** — **Mpm**
  - **AMIKACINA** — **Am**
  - **(O ESTREPTOMICINA)** — **(S)**
  - **ETIONAMIDA O PROTIONAMIDA** — **Eto / Pto**
  - **ACIDO P-AMINOSALICILICO** — **PAS**

TREATMENT CORRELATES OF SUCCESSFUL OUTCOMES IN PULMONARY MULTIDRUG-RESISTANT TUBERCULOSIS: AN INDIVIDUAL PATIENT DATA META-ANALYSIS

THE LANCET 2018; 392:821-834

FINDINGS: Of 12 030 patients from 25 countries in 50 studies, 7346 (61%) had treatment success, 1017 (8%) had failure or relapse, and 1729 (14%) died. Compared with failure or relapse, treatment success was positively associated with the use of linezolid (adjusted risk difference 0·15, 95% CI 0·11 to 0·18), levofloxacin (0·15, 0·13 to 0·18), carbapenems (0·14, 0·06 to 0·21), moxifloxacin (0·11, 0·08 to 0·14), bedaquiline (0·10, 0·05 to 0·14), and clofazimine (0·06, 0·01 to 0·10). There was a significant association between reduced mortality and use of linezolid (-0·20, -0·23 to -0·16), levofloxacin (-0·06, -0·09 to -0·04), moxifloxacin (-0·07, -0·10 to -0·04), or bedaquiline (-0·14, -0·19 to -0·10). Compared with regimens without any injectable drug, amikacin provided modest benefits, but kanamycin and capreomycin were associated with worse outcomes. The remaining drugs were associated with slight or no improvements in outcomes. Treatment outcomes were significantly worse for most drugs if they were used despite in-vitro resistance. The optimal number of effective drugs seemed to be five in the initial phase, and four in the continuation phase. In these adjusted analyses, heterogeneity, based on a simulated I2 method, was high for approximately half the estimates for specific drugs, although relatively low for number of drugs and durations analyses.

INTERPRETATION: Although inferences are limited by the observational nature of these data, treatment outcomes were significantly better with use of linezolid, later generation fluoroquinolones, bedaquiline, clofazimine, and carbapenems for treatment of multidrug-resistant tuberculosis. These findings emphasise the need for trials to ascertain the optimal combination and duration of these drugs for treatment of this condition.

TABLE 3. ASSOCIATION OF EACH DRUG WITH TREATMENT SUCCESS AND DEATH DURING TREATMENT

				PROPENSITY SCORE MATCHED MULTIVARIATE REGRESSION	PROPENSITY SCORE MATCHED MULTIVARIATE REGRESSION	PROPENSITY SCORE MATCHED MULTIVARIATE REGRESSION	PROPENSITY SCORE MATCHED MULTIVARIATE REGRESSION
	DRUG GIVEN (EVENTS/TOTAL)	DRUG NOT GIVEN (EVENTS/TOTAL)	CRUDE OR (95% CI)	PAIRS (n)	ADJUSTED OR (95% CI)	I^2	ADJUSTED RD (95% CI)
LEVOFLOXACIN SUSCEPTIBLE STRAINS SUCCESS DEATH	1361/1450 182/1632	258/355 292/647	5.7 (4.2-7.9) 0.2 (0.1-0.2)	1450 1632	4.2 (3.8-5.4) 0.6 80.5-0.7)	25.8% NC	0.15 (0.13 to 0.18) -0.06 (-0.09 to -0.04)
MOXIFLOXACIN SUSCEPTIBLE STRAINS SUCCESS DEATH	974/1031 114/1145	258/355 292/647	6.4 (4.5-9.2) 0.1 (0.1-0.2)	1031 1145	3.8 (2.8-5.2) 0.5 (0.4-0.6)	21.3% 33.4%	0.11 (0.08 to 0.14) -0.07 (0.10 to -0.04)
LINEZOLID SUSCEPTIBLE STRAINS SUCCESS DEATH	722/799 84/883	5066/5864 1456/7320	1.5 (1.2-1.9) 0.4 (0.3-0.5)	799 883	3.4 (2.6-4.5) 0.3 (0.2-0.3)	55.6% 77.0%	0.15 (0.11 to 0.18) -0.20 (-0.23 to -0.16)
CLOFAZIMINE SUSCEPTIBLE STRAINS SUCCESS DEATH	485/564 115/679	5321/6106 1292/7398	0.9 (0.7-1.2) 1.0 (0.8-1.2)	564 679	1.5 (1.1-2.1) 0.8 (0.6-1.0)	28-7% NC	0.06 (0.01 to 0.10) -0.04 (-0.08 to 0.00)

Lancet 2018; 392: 821-34

TABLE 3. ASSOCIATION OF EACH DRUG WITH TREATMENT SUCCESS AND DEATH DURING TREATMENT (CONT.)

				PROPENSITY SCORE MATCHED MULTIVARIATE REGRESSION	PROPENSITY SCORE MATCHED MULTIVARIATE REGRESSION	PROPENSITY SCORE MATCHED MULTIVARIATE REGRESSION	PROPENSITY SCORE MATCHED MULTIVARIATE REGRESSION
	DRUG GIVEN (EVENTS/TOTAL)	DRUG NOT GIVEN (EVENTS/TOTAL)	CRUDE OR (95% CI)	PAIRS (n)	ADJUSTED OR (95% CI)	I^2	ADJUSTED RD (95% CI)
BEDAQUILINE NO DRUG SUSCEPTIBILITY TESTING							
SUCCESS	431/491	6312/7220	1.0 (0.8-1.4)	490	2.0 (1.4-2.9)	NC	0.10 (0.05 to 0.14)
DEATH	59/550	1569/8789	0.6 (0.4-0.7)	548	0.4 (0.3-0.5)	33.5%	-0.14 (-0.19 to -0.30)
IMIPENEM AND MEROPENEM NO DRUG SUSCEPTIBILITY TESTING							
SUCCESS	130/139	6871/7861	2.1 (1.2-4.1)	138	4.0 (1.7-9.1)	57.8%	0.14(0.06 to 0.21)
DEATH	30/169	1674/9535	1.0 (0.7-1.5)	168	1.0 (0.5-1.7)	NC	-0.00 (-0.09 to 0.08)

Lancet 2018; 392: 821-34

TABLE 4. ASSOCIATION OF SELECTED DRUGS USED IN EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS WITH SUCCESS AND DEATH

	DRUG GIVEN EVENTS/TOTAL	DRUG NOT GIVEN EVENTS/TOTAL	PROPENSITY SCORE MATCHED MULTIVARIATE REGRESSION			
			PAIRS (n)	ADJUSTED OR (95% CI)	I^2	ADJUSTED RD (95% CI)
Levofloxacin or moxifloxacin‡						
Success	279/360	119/182	359	1·2 (0·8–1·6)	7·7%	0·01 (−0·05 to 0·06)
Death	122/482	253/435	482	0·6 (0·4–0·8)	NC	−0·07 (−0·12 to −0·02)
Linezolid						
Success	255/281	221/392	280	6·6 (4·1–10·6)	7·3%	0·31 (0·24 to 0·38)
Death	33/314	418/810	314	0·2 (0·1–0·3)	7·5%	−0·29 (−0·36 to −0·23)
Clofazimine						
Success	141/173	335/500	173	1·5 (0·9–2·6)	NC	0·04 (−0·04 to 0·13)
Death	43/216	408/908	216	0·4 (0·2–0·6)	19·7%	−0·18 (−0·27 to −0·10)
Bedaquiline						
Success	126/145	350/528	139	2·5 (1·3–4·8)	NC	0·12 (0·03 to 0·21)
Death	18/163	433/961	155	0·5 (0·2–0·9)	NC	−0·09 (−0·17 to −0·02)

TABLE A. LIST OF RECOMMENDATIONS IN THE 2022 UPDATE, WHERE (a) IS A NEW RECOMMENDATION BASED ON REVIEW OF THE NEW EVIDENCE AND (b) IS A REPRINTED RECOMMENDATION WHERE NO NEW EVIDENCE WAS AVAILABLE OR SEARCHED FOR THE REVIEW.

1. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB and pre-XDR-TB (a)	
1.1	WHO suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional recommendation, very low certainty of evidence)*
2. The 9-month all-oral regimen for MDR/RR-TB (a)	
2.1	WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty of evidence)*

TABLE A. LIST OF RECOMMENDATIONS IN THE 2022 UPDATE, WHERE (a) IS A NEW RECOMMENDATION BASED ON REVIEW OF THE NEW EVIDENCE AND (b) IS A REPRINTED RECOMMENDATION WHERE NO NEW EVIDENCE WAS AVAILABLE OR SEARCHED FOR THE REVIEW (CONT).

3. Longer regimens for MDR/RR-TB (b)	
3.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. *(Conditional recommendation, very low certainty of evidence)*
3.2	**Kanamycin and capreomycin** are not to be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.3	**Levofloxacin or moxifloxacin** should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*
3.4	**Bedaquiline** should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. *(Strong recommendation, moderate certainty of evidence)* **Bedaquiline** may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty of evidence)* In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing **bedaquiline** may be used. *(Conditional recommendation, very low certainty of evidence)*
3.5	**Linezolid** should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*

WHO CONSOLIDATED GUIDELINES ON TUBERCULOSIS. DRUG-RESISTANT TUBERCULOSIS TREATMENT. 2022 UPDATE

TABLE A. LIST OF RECOMMENDATIONS IN THE 2022 UPDATE, WHERE (a) IS A NEW RECOMMENDATION BASED ON REVIEW OF THE NEW EVIDENCE AND (b) IS A REPRINTED RECOMMENDATION WHERE NO NEW EVIDENCE WAS AVAILABLE OR SEARCHED FOR THE REVIEW (CONT).

4. Regimen for rifampicin-susceptible and isoniazid-resistant TB (b)	
4.1	In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis , treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months. *(Conditional recommendation, very low certainty in the estimates of effect)*
4.2	In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen. *(Conditional recommendation, very low certainty of evidence)*
5. Monitoring patient response to MDR/RR-TB treatment using culture (b)	
5.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. It is desirable for sputum culture to be repeated at monthly intervals. *(Strong recommendation, moderate certainty in the estimates of test accuracy)*
6. Starting antiretroviral therapy in patients on MDR/RR-TB regimens (b)	
6.1	Antiretroviral therapy is recommended for all patients with HIV and drug-resistant tuberculosis requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment. *(Strong recommendation, very low certainty of evidence)*
7. Surgery for patients on MDR/RR-TB treatment (b)	
7.1	In patients with rifampicin-resistant tuberculosis (RR-TB) or multidrug-resistant TB (MDR-TB), elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen. *(Conditional recommendation, very low certainty of evidence)*

BPaLM: bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin; HIV: human immunodeficiency virus; MDR/RR-TB: multidrug-resistant or rifampicin-resistant TB; TB: tuberculosis; WHO: World Health Organization; XDR-TB: extensively drug-resistant TB.

WHO CONSOLIDATED GUIDELINES ON TUBERCULOSIS. DRUG-RESISTANT TUBERCULOSIS TREATMENT. 2022 UPDATE

TABLA 1. ESQUEMAS DE TRATAMIENTO PARA LA TUBERCULOSIS

NOMBRE DEL ESQUEMA		INDICACION	COMPOSICION	NUMERO DE DOSIS
Sensible		TB-DS	2 (H-R-Z-E) / 4 (H-R)	150 dosis*
TB-Hr		TB-Hr	6 (R-E-Z-Lfx)	180 dosis
Orales TB-MDR	BPaLM	TB-RR/MDR	6 (Bdq-Pa-Lzd-Mfx)	180 dosis
	BLC	TB-RR/MDR	9 (Bdq-Lzd-Cfz-Lfx-Z)	270 dosis***
Orales TB pre-XDR.	BPaL	TB Pre-XDR	6 (Bdq-Pa-Lzd)	180 dosis**
	BLCC	TB Pre-XDR	6 (Bdq-Lzd-Cfz-Cs-Z) / 12 (Lzd-Cfz-Cs-Z)	540 dosis****
Parenteral TB-XDR.		TB-XDR	18-24 (Imp-Cln/Mpm-Dlm-Cs) y otros medicamentos según perfil de resistencia.	Dosis según medicamentos que componen el esquema (540-720 dosis).

NTS No. 221_MINSA/DGIESP-2024

1) ESQUEMA PARA TUBERCULOSIS RESISTENTE A ISONIACIDA: TB-Hr

Está indicado en la PAT con resultado de PS resistente a H.
La indicación la realiza el médico consultor con la elaboración y emisión de la receta única estandarizada (RUE). Se administra de lunes a domingo, incluyendo feriados.

Esquema TB-Hr: 6 meses (Lfx-R-E-Z) diario (180 dosis).

NTS No. 221_MINSA/DGIESP-2024

2) ESQUEMA ORAL PARA TUBERCULOSIS MULTIDROGORRESISTENTE/TUBERCULOSIS RESISTENTE A RIFAMPICINA: TB-MDR/TB-RR

Esquema BPaLM

Está indicado en:

- TB pulmonar y extrapulmonar, excepto TB SNC, osteoarticular o miliar.
- Con resultado de PS que indique TB-RR/MDR.
- PAT con 14 años o más y sin exposición por más de un mes a Bdq, Lzd, Pa o Dlm.

El tratamiento se administra de lunes a domingo, incluido feriados.

Esquema BPaLM: 6 meses (Bdq-Pa-Lzd-Mfx) diario (180 dosis).

NTS No. 221_MINSA/DGIESP-2024

TREATMENT OF RIFAMPIN-RESISTANT, FLUOROQUINOLONE-SUSCEPTIBLE TB

Recommended BPaLM Regimen[1]	
Bedaquiline	400 mg daily for 2 wk, then 200 mg three times/wk for subsequent 24 wk
Pretomanid	200 mg daily for 26 wk
Linezolid	600 mg daily for 26 wk
Moxifloxacin	400 mg daily for 26 wk

IDSA CLINICAL PRACTICE GUIDELINE, 12/30/2024

3) ESQUEMA ORAL PARA TUBERCULOSIS PRE-EXTENSAMENTE RESISTENTE: TB-preXDR

a) **Esquema BPaL**

Está indicado en:

- TB pulmonar y extrapulmonar, excepto TB SNC, osteoarticular o miliar.
- PAT con resultado de PS que indique TB pre-XDR.
- PAT de 14 años a más, y sin exposición por más de un mes a Bdq, Lzd, Pa o Dlm.

El tratamiento se administra de lunes a domingo, incluido feriados.

Esquema BPaL*: 6 meses (Bdq-Pa-Lzd) diario (180 dosis).

NTS No. 221_MINSA/DGIESP-2024

TREATMENT OF PRE-XDR TB (RIFAMPIN-RESISTANT, FLUOROQUINOLONE RESISTANT TB)

Recommended BPaL Regimen	
Bedaquiline	400 mg daily for 2 wk, then 200 mg three times/wk for subsequent 24 wk
Pretomanid	200 mg daily for 26 wk
Linezolid	600 mg daily for 26 wk

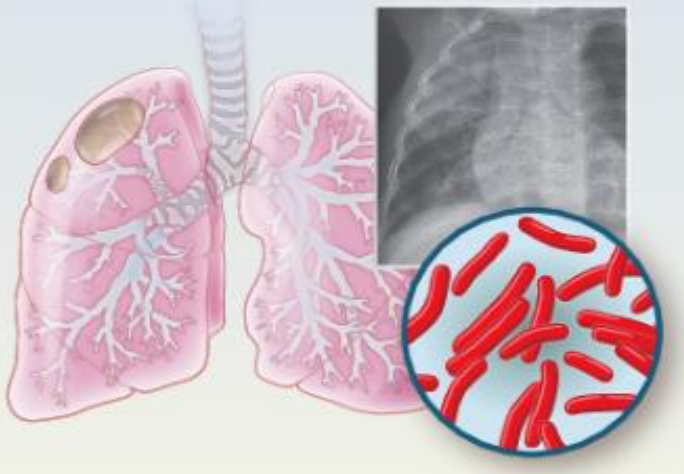
IDSA CLINICAL PRACTICE, 12/30/2024

The NEW ENGLAND JOURNAL of MEDICINE

Treatment of Highly Drug-Resistant Pulmonary TB

NIX-TB, AN OPEN-LABEL, SINGLE-GROUP STUDY

109 Patients
with confirmed tuberculosis



Three-drug regimen (26 wk)

Bedaquiline

Pretomanid
(recently approved)

Linezolid

XDR tuberculosis
N=71
(65%)

Nonresponsive or treatment-intolerant MDR tuberculosis
N=38
(34%)

Clinical resolution at 6 mo after therapy

90% of all patients had favorable outcomes
95% CI, 83–95

89%
95% CI, 79–95

92%
95% CI, 79–98

Linezolid associated with peripheral neuropathy (81%) and myelosuppression (48%)

F. Conradie et al. 10.1056/NEJMoa1901814

TREATMENT OF HIGHLY DRUG-RESISTANT PULMONARY TUBERCULOSIS

Outcome	XDR	MDR	Overall
Intention-to-treat population†			
No. of patients	71	38	109
Favorable outcome			
No. of patients	63	35	98
Percent of patients (95% CI)	89 (79–95)	92 (79–98)	90 (83–95)
Unfavorable outcome — no. (%)	8 (11)	3 (8)	11 (10)
Deaths — no.	6	1	7
Withdrawal during treatment — no.	1	0	1
Lost to follow-up after end of treatment — no.	0	1	1
Relapse — no.	1	1	2‡
Modified intention-to-treat population†			
No. of patients	70	37	107
Favorable outcome			
No. of patients	63	35	98
Percent of patients (95% CI)	90 (80–96)	95 (82–99)	92 (85–96)
Unfavorable outcome — no. (%)	7 (10)	2 (5)	9 (8)
Deaths — no.	5	1	6
Withdrawal during treatment — no.	1	0	1
Relapse — no.	1	1	2‡

NEJM 2020, MARCH 5

RESEARCH SUMMARY

Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

Conradie F et al. DOI: 10.1056/NEJMoa2119430

CLINICAL PROBLEM

Bedaquiline–pretomanid–linezolid has had efficacy against highly drug-resistant tuberculosis, but the incidence of adverse events with the 1200-mg daily dose of linezolid has been high. Whether a different dose and duration of linezolid treatment might reduce adverse events while maintaining efficacy is unclear.

CLINICAL TRIAL

Design: A dose-blind, randomized trial assessed the efficacy and safety of four regimens of linezolid as part of bedaquiline–pretomanid–linezolid treatment for highly drug-resistant tuberculosis.

Intervention: 181 participants (≥14 years of age in South Africa and the country of Georgia and ≥18 years of age in Russia and Moldova) with extensively drug-resistant (XDR) tuberculosis, pre-XDR tuberculosis, or rifampin-resistant tuberculosis that was not responsive to treatment or for which a second-line regimen had been discontinued owing to side effects were assigned to receive bedaquiline and pretomanid for 26 weeks, along with linezolid at one of two doses for either 26 weeks or 9 weeks. The primary end point was treatment failure or disease relapse (clinical or bacteriologic) at 26 weeks after completion of treatment. A favorable outcome was maintenance of negative culture status throughout follow-up in participants who had not had an unfavorable outcome previously.

RESULTS

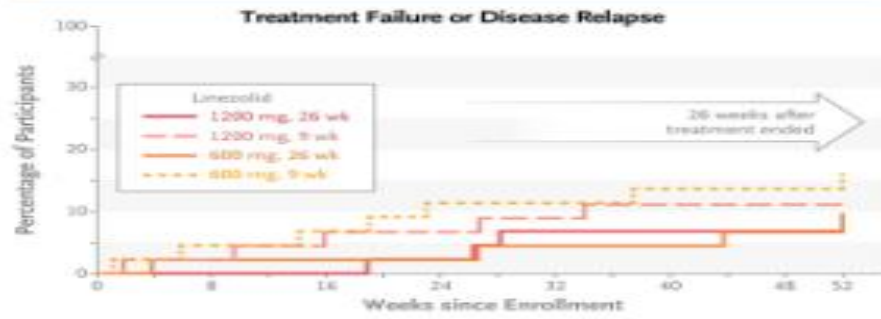
Efficacy: In the four treatment groups, the incidence of treatment failure or disease relapse (the primary end point) ranged from 7 to 16%; the incidence of a favorable outcome ranged from 84 to 93%.

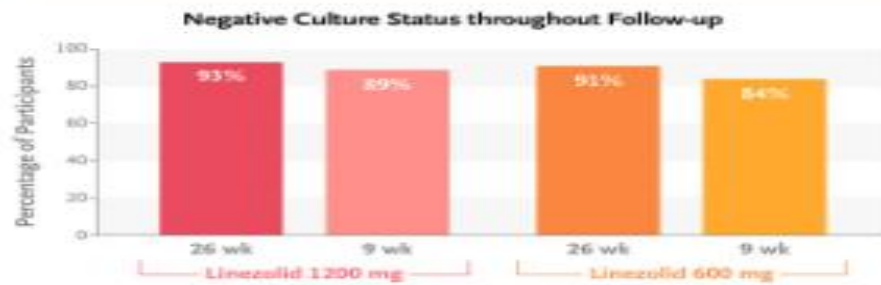
Safety: Fewer linezolid dose modifications, peripheral neuropathy episodes, and myelosuppression events occurred with the lower dose of linezolid than with the higher dose. The higher dose had a poorer safety profile in the 26-week group than in the 9-week group; there was less difference between the two lower-dose groups.

LIMITATIONS AND REMAINING QUESTIONS

- The small sample size limits the precision of estimates of efficacy.
- The trial was not powered for formal comparisons of efficacy among the treatment groups.

Links: Full Article | NEJM Quick Take | Editorial





CONCLUSIONS

In patients with highly drug-resistant tuberculosis, 600 mg of linezolid for 26 weeks resulted in a more favorable risk–benefit profile than other dose–duration regimens tested.

TABLE 1. BASELINE CHARACTERISTICS OF THE PARTICIPANTS WHO UNDERWENT RANDOMIZATION

Characteristic	Bedaquiline–Pretomanid–Linezolid Regimen				Total (N=181)
	Linezolid, 1200 mg, 26 wk (N=45)	Linezolid, 1200 mg, 9 wk (N=46)	Linezolid, 600 mg, 26 wk (N=45)	Linezolid, 600 mg, 9 wk (N=45)	
Median age (IQR) — yr	38 (30–44)	33.5 (26–42)	38 (30–46)	36 (32–41)	36 (30–44)
Male sex — no. (%)	30 (67)	30 (65)	31 (69)	31 (69)	122 (67)
Race — no. (%)†					
White	34 (76)	28 (61)	24 (53)	29 (64)	115 (64)
Black	11 (24)	18 (39)	21 (47)	16 (36)	66 (36)
Median weight (IQR) — kg	61.0 (55.0–67.3)	58.9 (52.9–69.0)	61.5 (52.4–66.5)	64.4 (58.0–70.7)	61.2 (54.0–67.8)
Median BMI (IQR)‡	20.3 (18.8–22.3)	21.0 (18.6–23.4)	20.9 (18.6–23.6)	20.8 (19.6–24.0)	20.8 (18.8–23.2)
HIV status — no. (%)					
Positive	9 (20)	9 (20)	9 (20)	9 (20)	36 (20)
Negative	36 (80)	37 (80)	36 (80)	36 (80)	145 (80)
Smoking status — no. (%)					
Never	20 (44)	15 (33)	16 (36)	17 (38)	68 (38)
Current	15 (33)	22 (48)	17 (38)	12 (27)	66 (36)
Former	10 (22)	9 (20)	12 (27)	16 (36)	47 (26)

N ENGL J MED 2022; 387: 810-823

TABLE 2. PRIMARY END-POINT EFFICACY ANALYSIS

Population and Outcome	Bedaquiline–Pretomanid–Linezolid Regimen				Total (N = 181)
	Linezolid, 1200 mg, 26 wk (N = 45)	Linezolid, 1200 mg, 9 wk (N = 46)	Linezolid, 600 mg, 26 wk (N = 45)	Linezolid, 600 mg, 9 wk (N = 45)	
Modified intention-to-treat population					
Assessable — no. (%)	44 (98)	45 (98)	45 (100)	44 (98)	178 (98)
Favorable outcome — no./total no. (%)	41/44 (93)	40/45 (89)	41/45 (91)	37/44 (84)	159/178 (89)
95% CI for favorable outcome — %	81–99	76–96	79–98	70–93	84–93
97.5% CI for favorable outcome — %	—	74–97	77–98	—	—
Unfavorable outcome — no./total no. (%)	3/44 (7)	5/45 (11)	4/45 (9)	7/44 (16)	19/178 (11)
Confirmed relapse during follow-up period — no.†	0	2	1	1	4
Lost to follow-up during treatment period — no.	0	0	0	1	1
Retreatment during follow-up period — no.‡	2	0	1	1	4
Withdrawn during treatment period — no.					
Because of adverse event	1	1	0	2	4
Because of investigator or sponsor decision	0	0	1	0	1
Because of participant decision	0	2	1	1	4
Treatment failure during treatment period†	0	0	0	1	1

N ENGL J MED 2022; 387: 810-823

The Effectiveness and Safety of Bedaquiline, Pretomanid, and Linezolid (BPaL)–Based Regimens for Rifampicin-Resistant Tuberculosis in Non-Trial Settings—A Prospective Cohort Study in Belarus and Uzbekistan

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Background. Only 63% of patients initiating multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) treatment in 2020 were treated successfully. 24-Week all-oral bedaquiline, pretomanid, and linezolid (BPaL)–based regimens have demonstrated higher rates of treatment success and have been recommended by the World Health Organization. Operational research is urgently required to evaluate these regimens in non-trial settings.

Methods. This was a prospective cohort study of patients with microbiologically confirmed MDR/RR-TB and pre–extensively drug-resistant TB (pre-XDR-TB) initiated on BPaL-based regimens in Belarus and Uzbekistan (February 2022–June 2023). All clinical care and research procedures were delivered by treating physicians. After treatment completion, patients were followed up at 6 and 12 months, including collecting sputum to ascertain recurrence. The primary objective was to estimate the effectiveness (cured or treatment completed) and safety (the occurrence of serious adverse events) of BPaL-based regimens.

Results. A total of 677 patients initiated treatment with BPaL-based regimens during the study. We documented successful treatment outcomes in 95.3% (427/448) of patients with MDR/RR-TB treated with BPaL plus moxifloxacin and 90.4% (207/229) of patients with pre–XDR-TB treated with BPaL plus clofazimine. 10.2% (69/677) experienced serious adverse events including 24 deaths (3.5%), 11 of which occurred during treatment. 83.3% (20/24) of deaths were not related to TB or TB treatment. Of patients who were successfully treated and completed 12-month follow-up, 0.5% (2/383) had recurrence.

Conclusions. BPaL-based regimens for MDR/RR-TB and pre–XDR-TB are safe and highly effective in non-trial settings. These regimens should be considered for widespread implementation globally, and further research is needed to evaluate their performance in other key populations.

CLINICAL INFECTIOUS DISEASES; FEBRUARY 18, 2025

TABLE 2. TREATMENT OUTCOMES AMONG PATIENTS RECEIVING BPaL-BASED REGIMENS

	Overall (n = 677; % of total)	MDR/RR (n = 448; % of total)	Pre-XDR (n = 229; % of total)	*P*
Overall treatment success	634 (93.6%)	427 (95.3%)	207 (90.4%)	.061[a]
Cured	573 (84.6%)	383 (85.5%)	190 (83.0%)	
Treatment completed	61 (9.0%)	44 (9.8%)	17 (7.4%)	
Death from any cause during treatment	11 (1.6%)	7 (1.6%)	4 (1.7%)	
Lost to follow-up	20 (3.0%)	9 (2.0%)	11 (4.8%)	
Treatment failed	5 (0.7%)	1 (0.2%)	4 (1.7%)	
Due to lack of culture conversion after 16 wk of treatment	2 (0.3%)	0 (0%)	2 (0.9%)	
Due to evidence of additional acquired resistance to drugs in the regimen	1 (0.1%)	0 (0%)	1 (0.4%)	
Due to permanent change of ≥2 anti-TB drugs in the regimen because of adverse drug reactions	2 (0.3%)	1 (0.2%)	1 (0.4%)	
Not evaluated	5 (0.7%)	2 (0.4%)	3 (1.3%)	
Withdrew consent	2 (0.3%)	2 (0.4%)	0 (0%)	

N = 677.

Abbreviations: BPaL, bedaquiline, pretomanid, and linezolid; MDR/RR, multidrug- or rifampicin-resistant; Pre-XDR, pre–extensively drug-resistant; TB, tuberculosis.

[a]Fisher's exact test comparing distribution of outcomes between MDR/RR-TB and pre–XDR-TB.

TABLA No. 20. RAM ANTITUBERCULOSIS COMUNES

MEDICAMENTOS DE PRIMERA LINEA	REACCIONES ADVERSAS COMUNES
Isoniacida	Incremento de transaminasas, hepatitis, neuropatía periférica, reacciones cutáneas.
Rifampicina	Incremento de transaminasas, elevación transitoria de bilirrubinas, hepatitis colestásica, anorexia, síntomas gastrointestinales (náuseas vómitos), reacciones cutáneas.
Rifapentina	Síntomas pseudogripales. Toxicidad hepática baja. Puede aparecer hipotensión y trombocitopenia.
Pirazinamida	Hepatitis, síntomas gastrointestinales, poliartralgias, mialgias hiperuricemia, reacciones cutáneas.
Etambutol	Neuritis retrobulbar, neuritis periférica, reacciones cutáneas.
Cicloserina	Cefalea, insomnio, cambio de conducta, irritabilidad, ansiedad, depresión, psicosis, convulsiones, vértigo.
Etionamida	Síntomas gastrointestinales (náuseas, vómitos, dolor abdominal), hepatitis, hipotiroidismo.
Fluoroquinolonas	Generalmente bien tolerados, artralgias, mialgias, síntomas gastrointestinales, prolongación del intervalo QT (levofloxacino - posible riesgo, moxifloxacino - alto riesgo).
Bedaquilina	Náuseas, vómitos, dolor abdominal, artralgias, cefalea, prolongación de intervalo QT, hiperuricemia, elevación de transaminasas.
Pretomanid	Cefalea, náuseas, dermatitis de contacto, anemia, diarrea y mareos. Menos frecuentes: Convulsiones, prolongación del intervalo QT, hepatotoxicidad (aumento de GGT); y mielosupresión.

NTS No. 221_MINSA/DGIESP-2024

TABLA No. 20. RAM ANTITUBERCULOSIS COMUNES (CONT.)

MEDICAMENTOS DE PRIMERA LINEA	REACCIONES ADVERSAS COMUNES
Clofazimina	Coloración oscura de piel, mucosas, y fluidos corporales; sequedad de piel, ictiosis, prurito, xerosis, fotosensibilidad, obstrucción y sangrado intestinal, prolongación de intervalo QT.
Linezolid	Mielosupresión, anemia, leucopenia, plaquetopenia, diarrea, vómitos, neuritis óptica, neuropatía periférica, acidosis láctica.
Delamanid	Náuseas, vómitos, prolongación del intervalo QT.
Carbapenem (imipenem-cilastatina/ meropenem)	Diarrea, náusea, vómitos, convulsiones (con infección de SNC), palpitaciones, colitis pseudomembranosa.

NTS No. 221_MINSA/DGIESP-2024

CONCLUSIONES

- **EL PERU ES UNO DE LOS PRINCIPALES PAISES EN AMERICA CON MULTIDROGORRESISTENCIA O RESISTENCIA A LA RIFAMPICINA**
- **LOS FARMACOS ACTUALES PARA TUBERCULOSIS FARMACORRESISTENTE SE DIVIDEN EN 3 GRUPOS (A, B Y C)**
- **EL ESQUEMA PARA TUBERCULOSIS RESISTENTE A ISONIACIDA ES CON 4 FARMACOS DURANTE 6 MESES: Lfx-R-E-Z**
- **EL ESQUEMA PARA TUBERCULOSIS RESISTENTE A RIFAMPICINA O MULTIDROGORRESISTENTE ES CON 4 FARMACOS (BPaLM) DURANTE 6 MESES**
- **EL ESQUEMA PARA TUBERCULOSIS PRE-EXTREMADAMENTE RESISTENTE ES CON 3 FARMACOS (BPaL) DURANTE 6 MESES**

Mecanismo de acción
Bedaquilina

Bedaquilina es una diarilquinolina. Bedaquilina inhibe específicamente a la ATP (adenosina 5'-trifosfato) sintasa micobacteriana, una enzima esencial para la generación de energía en Mycobacterium tuberculosis. La inhibición de la ATP sintasa produce efectos bactericidas para los bacilos tuberculosos tanto replicantes como no replicantes.

Guía Provisional del CDC BPAL | TB Resistente (CDCP)

Delamanid

Artículo Discusión

Delamanid, comercializado bajo el nombre **Deltyba**, es un medicamento que se usa para tratar la tuberculosis. Específicamente se usa, junto con otros medicamentos antituberculosos, para la tuberculosis activa resistente a múltiples fármacos. Se administra por vía oral.[1]

Los efectos secundarios comunes incluyen dolor de cabeza, mareos y náuseas.[2] Otros efectos secundarios incluyen la prolongación del intervalo QT. Para el año 2016 todavía no cuenta con estudios en el embarazo.[3] Delamanid actúa bloqueando la fabricación de ácidos micólicos y desestabiliza la pared celular bacteriana.[4] Se encuentra en la clase de medicamentos del nitroimidazol.[5]

Delamanid fue aprobado para uso médico en 2014 en Europa, Japón y Corea del Sur.[6] Está en la Lista de medicamentos esenciales de la Organización Mundial de la Salud, los medicamentos más efectivos y seguros que se necesitan en un sistema de salud.[7] En el año 2016, Stop TB Partnership tenía un acuerdo para obtener el medicamento por US$1.700 para un tratamiento de seis meses, para su uso en más de 100 países.[8]

Pretomanida

Artículo Discusión

Pretomanida, comercializado bajo la marca Dovprela, es un antibiótico utilizado para tratar la tuberculosis multirresistente que afecta a los pulmones.[1] Generalmente se utiliza junto con bedaquilina y linezolida. Este medicamento se toma por vía oral.[2]

Entre los efectos secundarios más frecuentes se incluyen lesiones nerviosas, acné, vómitos, dolor de cabeza, hipoglucemia, diarrea e inflamación hepática[1] ; otros efectos secundarios pueden ser supresión de la médula ósea, neuropatía óptica y prolongación del intervalo QT.[3] No está claro la seguridad de este medicamento durante el embarazo.[4] [5]

Este medicamento fue aprobado para uso médico en los Estados Unidos en 2019 y en Europa en 2020.[2] [1] Está en la Lista de Medicamentos Esenciales de la Organización Mundial de la Salud.[6] En el mundo en desarrollo costaba 364 dólares estadounidenses por 6 meses en 2019.[7] En los Estados Unidos esta cantidad cuesta alrededor de 3800 dólares estadounidenses a partir de 2021.[8] Fue desarrollado por la TB Alliance.[5] [1]

INDICADORES PRIORITARIOS FIN DE LA TUBERCULOSIS. LAS AMERICAS, 2021

Indicador		2021	META 2025
Cobertura de tratamiento anti-TB*		70%	≥ 90%
Tasa de éxito de tratamiento	Nuevos y recaídas	72%	≥ 90%
	RR-MDR	59%	
% de familias afectadas por TB que enfrentan gastos catastróficos por la TB		ND**	0%
% de pacientes nuevos de TB que fueron diagnosticados mediante pruebas rápidas recomendadas por la OMS		30%	≥ 90%
Cobertura de tratamiento de infección latente por TB:	< 5 años	35%	≥ 90%
	VIH	51%	≥ 90%
Cobertura de investigación de contactos		67%	≥ 90%
Cobertura de pacientes de TB con resultados de pruebas de sensibilidad a drogas***		56%	100%
Cobertura de tratamiento con nuevos medicamentos antiTB		28%	≥ 90%
% de pacientes con TB que conocen su estado de VIH		80%	100%
Tasa de letalidad por TB		9%	≤ 5%

* (incidencia notificada/incidencia estimada) ** No disponible ***en TB pulmonar bacteriológicamente confirmada

Tabla 4: Principales factores de riesgo para TB resistente

1.	Fracaso a esquema con medicamentos de primera línea.
2.	Contacto de caso confirmado de TB resistente.
3.	Recaída dentro de los siguientes 6 meses de haber sido dado de alta de un esquema con medicamentos de primera línea.
4.	Recaída luego de haber sido dado de alta con medicamentos de segunda línea.
5.	Personas privadas de su libertad (PPL) y residentes de albergues, comunidades terapéuticas, entre otros.
6.	Antecedente de tratamientos múltiples (más de dos episodios previos de TB).
7.	Antecedente de irregularidad al tratamiento, abandono o terapia no supervisada.
8.	Contacto con persona que falleció por TB.
9.	Comorbilidades: diabetes mellitus, insuficiencia renal crónica, tratamiento inmunosupresor, otros y coinfección con VIH.
10.	Trabajadores y estudiantes de la salud.

TB resistente a los medicamentos (TB-DR): Es la enfermedad por TB con resistencia detectada a cualquier medicamento antituberculosis. Según el perfil de resistencia, se clasifica en:

a. **TB resistente a isoniacida (TB-Hr):** Tuberculosis con resistencia detectada a la isoniacida y sensible a R.
b. **TB resistente a rifampicina (TB-RR):** Tuberculosis con resistencia detectada a la R.
c. **TB multidrogorresistente (TB-MDR):** Tuberculosis con resistencia detectada al menos a H y R.
d. **TB pre extensamente resistente (TB pre-XDR):** Tuberculosis que RR/MDR con resistencia adicional a cualquier fluoroquinolona.
e. **TB extensamente resistente (TB-XDR):** Tuberculosis RR/MDR, con resistencia detectada a cualquier fluoroquinolona y, al menos, a un medicamento del Grupo A (Bdq o Lzd).

Tabla N°14: Clasificación de medicamentos antituberculosis para TB-DR según OMS – 2022

GRUPO A	
Moxifloxacino / levofloxacina Bedaquilina Linezolid	Incluir los 3 medicamentos (a menos que no puedan ser indicadas por toxicidad o resistencia).
GRUPO B	
Clofazimina Cicloserina	Agregue ambos medicamentos (a menos que no puedan ser indicadas por toxicidad o resistencia).
GRUPO C	
Imipenem – Cilastatina / Meropenem Delamanid Pirazinamida Etambutol Amikacina Etionamida	Agregar medicamentos hasta completar el esquema, cuando no se pueden utilizar medicamentos de los grupos A y B.

TREATMENT CORRELATES OF SUCCESSFUL OUTCOMES IN PULMONARY MULTIDRUG-RESISTANT TUBERCULOSIS: AN INDIVIDUAL PATIENT DATA META-ANALYSIS

The Lancet 2018; 392: 821-834

BACKGROUND: Treatment outcomes for multidrug-resistant tuberculosis remain poor. We aimed to estimate the association of treatment success and death with the use of individual drugs, and the optimal number and duration of treatment with those drugs in patients with multidrug-resistant tuberculosis.

METHODS: In this individual patient data meta-analysis, we searched MEDLINE, Embase, and the Cochrane Library to identify potentially eligible observational and experimental studies published between Jan 1, 2009, and April 30, 2016. We also searched reference lists from all systematic reviews of treatment of multidrug-resistant tuberculosis published since 2009. To be eligible, studies had to report original results, with end of treatment outcomes (treatment completion [success], failure, or relapse) in cohorts of at least 25 adults (aged >18 years). We used anonymised individual patient data from eligible studies, provided by study investigators, regarding clinical characteristics, treatment, and outcomes. Using propensity score-matched generalised mixed effects logistic, or linear regression, we calculated adjusted odds ratios and adjusted risk differences for success or death during treatment, for specific drugs currently used to treat multidrug-resistant tuberculosis, as well as the number of drugs used and treatment duration.

FINDINGS: Of 12 030 patients from 25 countries in 50 studies, 7346 (61%) had treatment success, 1017 (8%) had failure or relapse, and 1729 (14%) died. Compared with failure or relapse, treatment success was positively associated with the use of linezolid (adjusted risk difference 0·15, 95% CI 0·11 to 0·18), levofloxacin (0·15, 0·13 to 0·18), carbapenems (0·14, 0·06 to 0·21), moxifloxacin (0·11, 0·08 to 0·14), bedaquiline (0·10, 0·05 to 0·14), and clofazimine (0·06, 0·01 to 0·10). There was a significant association between reduced mortality and use of linezolid (-0·20, -0·23 to -0·16), levofloxacin (-0·06, -0·09 to -0·04), moxifloxacin (-0·07, -0·10 to -0·04), or bedaquiline (-0·14, -0·19 to -0·10). Compared with regimens without any injectable drug, amikacin provided modest benefits, but kanamycin and capreomycin were associated with worse outcomes. The remaining drugs were associated with slight or no improvements in outcomes. Treatment outcomes were significantly worse for most drugs if they were used despite in-vitro resistance. The optimal number of effective drugs seemed to be five in the initial phase, and four in the continuation phase. In these adjusted analyses, heterogeneity, based on a simulated I2 method, was high for approximately half the estimates for specific drugs, although relatively low for number of drugs and durations analyses.

INTERPRETATION: Although inferences are limited by the observational nature of these data, treatment outcomes were significantly better with use of linezolid, later generation fluoroquinolones, bedaquiline, clofazimine, and carbapenems for treatment of multidrug-resistant tuberculosis. These findings emphasise the need for trials to ascertain the optimal combination and duration of these drugs for treatment of this condition.

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LANCET 2018; 392: 821-34

Webinar:Actualización en diagnóstico y Tratamiento de Tuberculosis

Por Gonzalo Sosa / noviembre 21, 2024

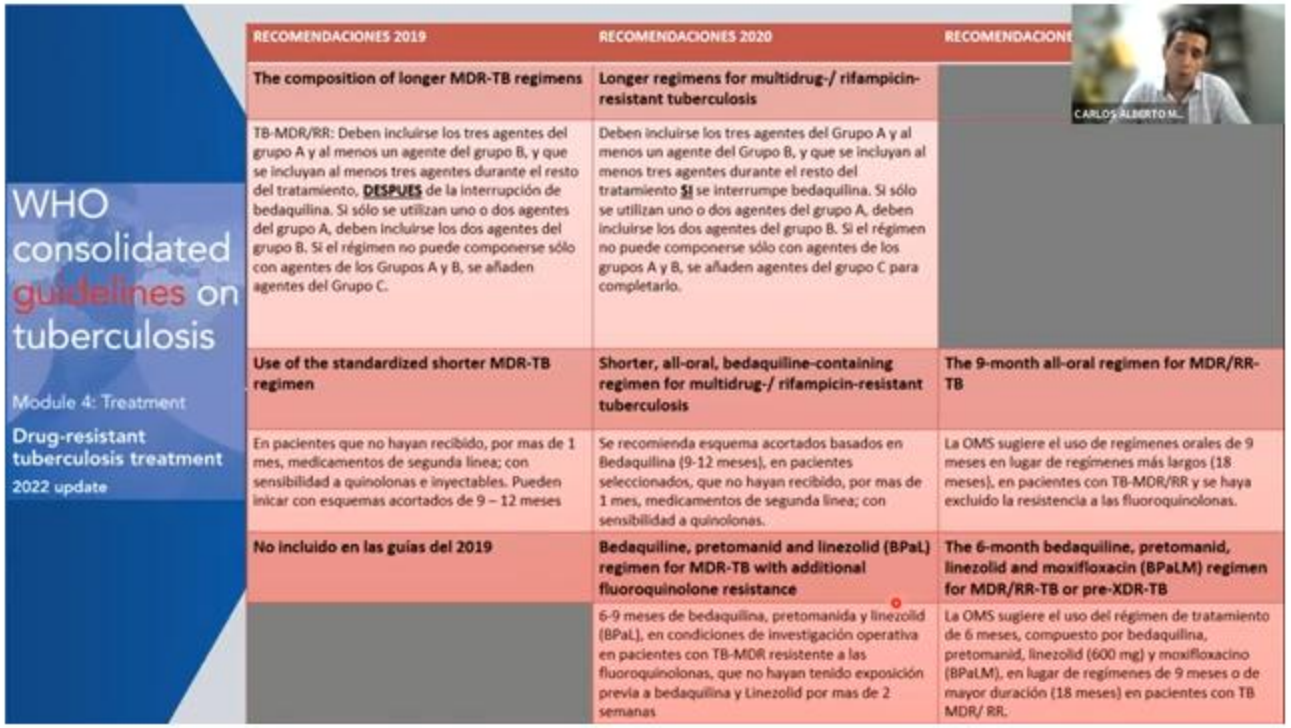

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TABLE A. LIST OF RECOMMENDATIONS IN THE 2022 UPDATE, WHERE (a) IS A NEW RECOMMENDATION BASED ON REVIEW OF THE NEW EVIDENCE AND (b) IS A REPRINTED RECOMMENDATION WHERE NO NEW EVIDENCE WAS AVAILABLE OR SEARCHED FOR THE REVIEW (CONT).

3.6	**Clofazimine and cycloserine or terizidone** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.7	**Ethambutol** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.8	**Delamanid** may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. *(Conditional recommendation, moderate certainty of evidence)* In children with MDR/RR-TB aged below 3 years **delamanid** may be used as part of longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.9	**Pyrazinamide** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.10	**Imipenem–cilastatin or meropenem** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*[9]
3.11	**Amikacin** may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions. *(Conditional recommendation, very low certainty in the estimates of effect)*

TABLE A. LIST OF RECOMMENDATIONS IN THE 2022 UPDATE, WHERE (a) IS A NEW RECOMMENDATION BASED ON REVIEW OF THE NEW EVIDENCE AND (b) IS A REPRINTED RECOMMENDATION WHERE NO NEW EVIDENCE WAS AVAILABLE OR SEARCHED FOR THE REVIEW (CONT).

3.12	**Ethionamide or prothionamide** may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation against use, very low certainty of evidence)*
3.13	***P*-aminosalicylic acid** may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation against use, very low certainty of evidence)*
3.14	**Clavulanic acid** should not be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation against use, low certainty of evidence)*[9]
3.15	In MDR/RR-TB patients on longer regimens, a **total treatment duration of 18–20 months** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*
3.16	In MDR/RR-TB patient on longer regimens, **a treatment duration of 15-17 months after culture conversión** is suggested for most patients; the duration may be modified according to the patient´s response to therapy. *(Conditional recommendation, very low certainty of evidence)*
3.17	In MDR/RR-TB patient on longer regimens containing amikacin or streptomycin, **an intensive phase of 6-7 months** is suggested for most patients; the duration may be modified according to the patient´s response to therapy. *(Conditional recommendation, very low certainty of evidence)*

WHO CONSOLIDATED GUIDELINES ON TUBERCULOSIS. DRUG-RESISTANT TUBERCULOSIS TREATMENT. 2022 UPDATE

TABLA 1. ESQUEMAS DE TRATAMIENTO PARA LA TUBERCULOSIS

Nombre del esquema		Indicación	Composición	Número de dosis	Indicado por:	Tiempo para inicio del tratamiento	Alta indicada por:
Sensible		TB-DS	2 (H-R-Z-E) / 4 (H-R)	150 dosis*	Personal médico del E.S.	Dentro de las 24 horas del diagnóstico de TB.	Personal médico del E.S.
TB-Hr		TB-Hr	6 (R-E-Z-Lfx)	180 dosis	Médico consultor.	Hasta 2 días desde el diagnóstico de TB-DR.	Médico consultor
Orales TB-MDR	BPaLM	TB-RR/MDR	6 (Bdq-Pa-Lzd-Mfx)	180 dosis	Médico consultor y validado por el CRER/CER.	Hasta 14 días desde el diagnóstico de TB-DR.	Médico consultor
	BLC	TB-RR/MDR	9 (Bdq-Lzd-Cfz-Lfx-Z)	270 dosis***			
Orales TB pre-XDR.	BPaL	TB Pre-XDR	6 (Bdq-Pa-Lzd)	180 dosis**			
	BLCC	TB Pre-XDR	6 (Bdq-Lzd-Cfz-Cs-Z) / 12 (Lzd-Cfz-Cs-Z)	540 dosis****	Médico consultor y validado por el CRER/CER.		Médico consultor de la UNET
Parenteral TB-XDR.		TB-XDR	18-24 (Imp-Cln/Mpm-Dlm-Cs) y otros medicamentos según perfil de resistencia.	Dosis según medicamentos que componen el esquema (540-720 dosis).	Médico consultor de la UNET y validado por el CNER.	Hasta 14 días desde el diagnóstico de TB-DR.	Médico consultor de la UNET
Modificados		PAT con condición médica especial o RAM.	Se incluyen diferentes medicamentos según perfil clínico.	Dosis según medicamentos que componen el esquema (270 a 540 dosis).	Médico consultor y validado por el CRER/CER/CNER.	Hasta 14 días de identificada la condición médica especial o RAM.	Médico consultor de la UNET

* Se modifica la segunda fase en caso TB no grave en niños, TB SNC, TB miliar y TB osteoarticular. El médico del E.S podrá indicar la segunda fase 3 veces por semana en EE.SS. donde se garantice el DOT durante todo el tratamiento.
** Se puede ampliar a 9 meses en caso de cultivo positivo entre el 4to. y 6to. mes sin que cumpla criterios de fracaso al tratamiento, previa evaluación del CNER.
*** En caso de TB del SNC, TB miliar y TB osteoarticular, se amplía a 18 meses: 9 (Bdq-Lzd- Cfz-Lfx-Z) / 9 (Lzd- Cfz-Lfx-Z) previa evaluación CNER.
**** En caso de que se requiera ampliación de Bdq, el caso debe ser evaluado por el CNER
- Para el esquema BLC en caso de RAM a Lfx se puede cambiar a Mfx y en caso de resistencia o RAM a Z se puede cambiar a Cs
- En casos excepcionales la DPCTB de la DGIESP puede realizar alguna variación en las indicaciones de los esquemas de tratamiento.
- En toda PAT que reciban H debe recibir suplemento de piridoxina (vitamina B6) a dosis de 50 mg/día para prevenir el desarrollo de neuropatías.

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b) Esquema BLC

Está indicado en:

- Aquellos que no cumplen criterios para recibir esquema BPaLM.
- TB pulmonar o extrapulmonar.
- Adultos y niños.
- Con resultado de PS que indique TB-RR/MDR.
- Sin exposición previa por más de un mes a fluoroquinolonas, Bdq, Lzd o Cfz.

El tratamiento se administra de lunes a domingo, incluido feriados.

Esquema BLC: 9 meses (Bdq-Lzd-Lfx-Cfz-Z) diario (270 dosis)*

* Esquema de elección.

b) Esquema BLCC

Está indicado en:

- PAT que no cumple criterios para recibir esquema BPaL.
- TB pulmonar o extrapulmonar.
- Adultos y niños.
- PAT con resultado de PS que indique TB pre-XDR.
- Sin exposición previa por más de un mes a Bdq, Lzd o Cfz.

El tratamiento se administra de lunes a domingo, incluido feriados.

Primera fase: 6 meses (Bdq-Lzd-Cfz-Cs-Z) diario (180 dosis).
Segunda fase: 12 meses (Lzd-Cfz-Cs-Z) diario (360 dosis).

4) ESQUEMA PARENTERAL PARA TUBERCULOSIS EXTENSAMENTE RESISTENTE

Está indicado en:

- TB pulmonar o extrapulmonar.
- Adultos y niños.
- Con resultado de PS que indique TB-XDR.

El tratamiento se administra de lunes a domingo, incluyendo feriados.

Medicamentos base: Imp-Cln/Mpm-Dlm-Cs y otros medicamentos según perfil de resistencia. Diario (540-720 dosis).

El esquema se elabora mediante un diseño individualizado, utilizando la clasificación de medicamentos para TB-DR de la OMS, que agrupa los medicamentos de manera prioritaria y secuencial en grupos A, B y C (Tabla N° 14), tomando en cuenta el perfil de resistencia y exposición previa a medicamentos. Se administra de lunes a domingo, incluyendo feriados.

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TABLE 1. BASELINE CHARACTERISTICS OF THE PARTICIPANTS WHO UNDERWENT RANDOMIZATION (CONT.)

Characteristic	Bedaquiline–Pretomanid–Linezolid Regimen				Total (N=181)
	Linezolid, 1200 mg, 26 wk (N=45)	Linezolid, 1200 mg, 9 wk (N=46)	Linezolid, 600 mg, 26 wk (N=45)	Linezolid, 600 mg, 9 wk (N=45)	
Diabetes — no. (%)					
Yes§	3 (7)	0	1 (2)	5 (11)	9 (5)
Not reported	42 (93)	46 (100)	44 (98)	40 (89)	172 (95)
Current tuberculosis type — no. (%)¶					
XDR tuberculosis	21 (47)	18 (39)	19 (42)	17 (38)	75 (41)
Pre-XDR tuberculosis	19 (42)	22 (48)	22 (49)	22 (49)	85 (47)
Rifampin-resistant tuberculosis					
Not responsive to treatment	2 (4)	5 (11)	2 (4)	3 (7)	12 (7)
Second-line regimen had been discontinued because of side effects	3 (7)	1 (2)	2 (4)	3 (7)	9 (5)
Cavitation on chest radiography — no. (%)	27 (60)	25 (54)	33 (73)	27 (60)	112 (62)
Median time to positive MGIT at baseline — days	11.1	9.2	9.9	9.3	10.1

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Tabla N° 18. Dosis de medicamentos antituberculosis para enfermedad renal crónica severa (*) o en hemodiálisis

Medicamento	Cambio en Frecuencia	Dosis recomendada y frecuencia
Isoniacida	**No requiere**	300 mg una vez al dia.
Rifampicina	**No requiere**	600 mg una vez al dia.
Etambutol	Si requiere	20 – 25 mg/kg. 3 veces por semana. No diario.
Pirazinamida	Si requiere	25 – 30 mg/kg. 3 veces por semana. No diario.
Levofloxacino	Si requiere	750 – 1000 mg por dosis, 3 veces por semana.
Moxifloxacino	**No requiere**	400 mg una vez al dia
Cicloserina	Si requiere	250 mg una vez al dia o 500 mg 3 veces por semana.
Etionamida	**No requiere**	500 – 750 mg una vez al dia
Delamanid	**No requiere**	50 mg al dia.
Pretomanid	**No requiere**	200 mg al dia.
Bedaquilina	**No requiere**	200 mg diario por 60 dosis, luego 100 mg diario por 120 dosis.
Linezolid	**No requiere**	600 mg al dia.
Clofazimina	**No requiere**	100 mg al dia.

(*) Enfermedad renal crónica severa (TFG < 30 ml por minuto)