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How to treat MDR/PDR Tuberculosis

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Athens, 21/Nov/2019

I declare that I do not have any competing interests

American Thoracic Society/Centers for Disease Control/European Respiratory Society/ Infectious Diseases Society of America Clinical Practice Guidelines

Sponsors

ATS We help the world breathe PULMONARY • CRITICAL CARE • SLEEP

CDC Centers for Disease Control and Prevention

ERS European Respiratory Society

IDSA

WHO consolidated guidelines on drug-resistant tuberculosis treatment

World Health Organization

Treatment of Drug-Resistant Tuberculosis

American Thoracic Society/Centers for Disease Control/European Respiratory Society/ Infectious Diseases Society of America Clinical Practice Guidelines

- ✓ Companion to the 2016 ATS/CDC/IDSA Treatment of Drug-Susceptible TB Practice Guidelines;
- ✓ 21 PICO questions relevant to the care;
- ✓ Strength of recommendations based on GRADE approach;
- ✓ Evidence profiles to address PICOs based on 2 IPDMA.

European Standards for Tuberculosis Care

ERS EUROPEAN RESPIRATORY SOCIETY

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

- ✓ Assessment of the evidence;

- ✓ Discussion and unilateral decision of the ECDC and ERS scientific boards.

Guidelines Leadership and GRADE Methodology Group

✓ **Chairs**

- B Seaworth (IDSA);
- GB Migliori and G Sotgiu (ERS);
- S Mase and T Chorba (CDC);
- P Nahid (ATS).

✓ **GRADE Methodology Group**

- R Menzies, F Fregonese, Z Lan, FA Khan, McGill University, Quebec, Canada;
- P Nahid, University of California, San Francisco, CA, USA;
- G Sotgiu, University of Sassari, Sassari, Italy;
- J Brozek, McMaster University, Ontario, Canada.

Formulate question

Select outcomes

Outcomes across studies

Create evidence profile

Rate certainty in evidence for each outcome

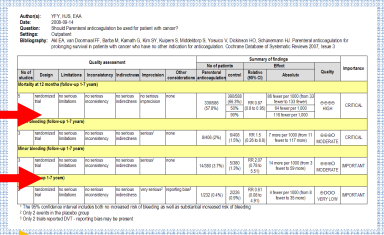
P
I
C
O

Outcome Critical

Outcome Critical

Outcome Important

Outcome Low importance



Summary of findings & estimate of effect for each outcome

High
Moderate
Low
Very low

Systematic review / individual patient data meta-analyses

Determine overall certainty in the evidence across outcomes based on lowest certainty for ***critical*** outcomes

Formulate recommendations:

- For or against (direction)
- Strong or weak (strength)

By considering:

- ❑ Certainty in evidence
- ❑ Balance benefits/harms
- ❑ Values and preferences

Revise if necessary by considering:

- ❑ Resource use (cost)

- "We recommend using…"
- "We suggest using…"
- "We recommend against using…"
- "We suggest against using…"

Treatment of Drug-Resistant Tuberculosis

- ✓ BEST PRACTICES FOR TREATING DR-TB
  - Diagnosing TB and identification of drug resistance;
  - Treatment and monitoring of DR-TB;
  - Infection control and DR-TB;
  - Case management for DR-TB;

- ✓ TREATMENT OF DR-TB
  - Number of drugs in the regimen;
  - Duration of intensive and continuation phases;
  - Drugs and drug classes.

Evidence-base supporting the guidelines

The Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB treatment

Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis

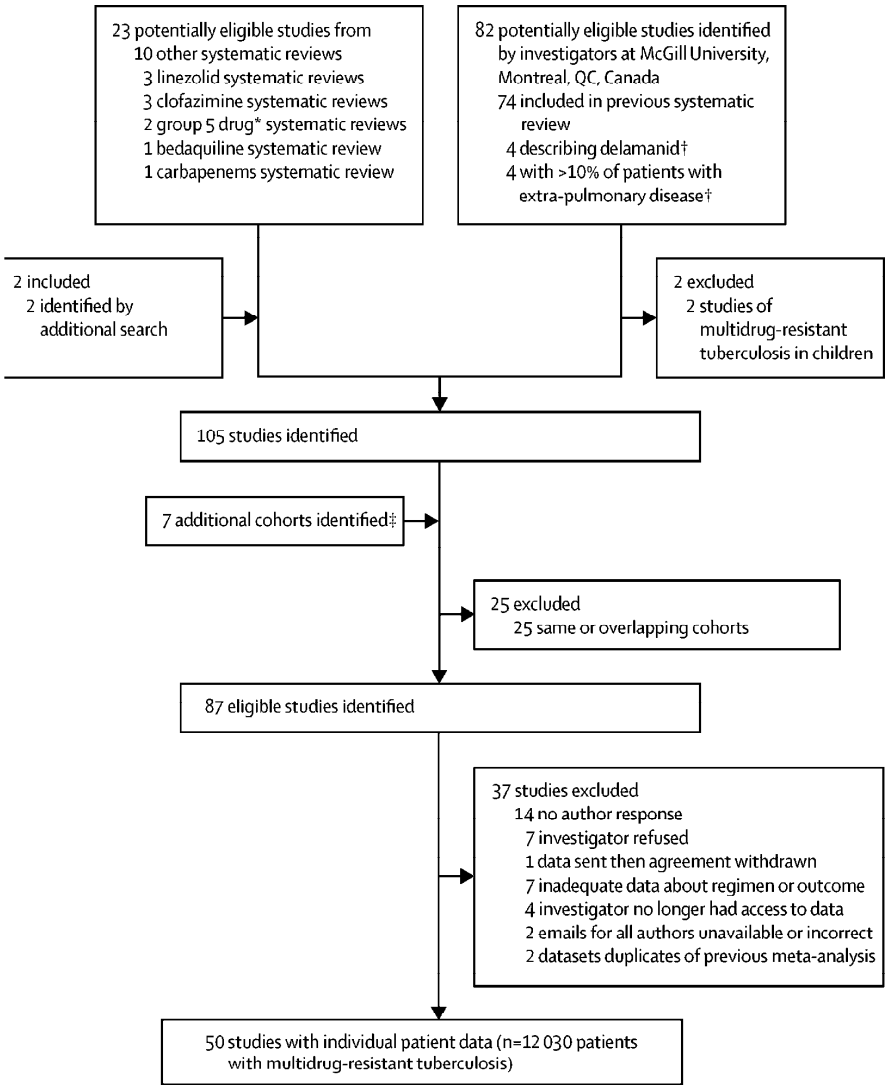
The Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017: Nafees Ahmad, Shama D Ahuja, Onno W Akkerman, Jan-Willem C Alffenaar, Laura F Anderson, Parvaneh Baghaei, Didi Bang, Pennan M Barry, Mayara L Bastos, Dzgeorgi Belilovski, Andrea Benedetti, Gregory P Bisson, Martin J Boeree, Marylène Bonnet, Sarah K Brode, James C M Brust, Yang Cai, Eric Caumes, J Peter Cegielski, Rosella Centis, Pei-Chun Chan, Edward D Chan, Kwok-Chiu Chang, Macarthur Charles, Andra Ciuole, Margareth Pretti Dalcolmo, Lia D'Ambrosio, Gerard de Vries, Kamran Dheda, Ahasgar Esmail, Jennifer Flood, Gregory J Fox, Mathilde Fréchet-Jachym, Geisa Fregona, Regine Gayoso, Medea Gegia, Maria Teresa Gler, Sue Gu, Lorenzo Guglielmetti, Timothy H Heldt, Jennifer Hughes, Petros Isaakidis, Leah Jarlsberg, Russell R Kempker, Salmaan Keshavjee, Faiz Ahmad Khan, Maia Kipiani, Serena P Koenig, Won-Jung Koh, Afranio Kritski, Lipa Kuksa, Charlotte L Kvasnovsky, Nakwon Kwak, Zhiyi Lan, Christoph Lange, Rafael Laniado-Laborín, Myungsun Lee, Vaira Leimane, Chi-Chiu Leung, Eric Chung-Ching Leung, Pei Zhi Li, Phil Lowenthal, Ethel L Maciel, Suzanne M Marks, Sundari Masoe, Lawrence Mbuagbaw, Giovanni B Migliori, Vladimir Milanov, Ann C Miller, Carole D Mitnick, Chawangwa Modongo, Erika Mohr, Ignacio Monedero, Payam Nahid, Norbert Ndjeka, Max R O'Donnell, Nesri Padayatchi, Domingo Palmero, Jean William Pape, Laura J Podewils, Ian Reynolds, Vija Riekstina, Jérôme Robert, Maria Rodriguez, Barbara Seaworth, Kwonjune J Seung, Kathryn Schnippel, Tae Sun Shim, Rupak Singla, Sarah E Smith, Giovanni Sotgiu, Gunnsteinn Sulfridsson, Payam Tabarsi, Simon Tiberi, Anete Trajman, Lisa Triest, Zarir F Udwadia, Tjip S van der Werf, Nicolas Veziris, Piret Viiklepp, Stalz Charles Vilbrun, Kathleen Walsh, Janice Westerhouse, Wing-Wai Yew, Jae-Joon Yim, Nicola M Zetola, Matteo Zignol, Dick Menzies

N. Ahmad, et al., Lancet, 2018

Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis

Federica Fregonese, Shama D Ahuja, Onno W Akkerman, Denise Arakaki-Sanchez, Irene Ayakaka, Parvaneh Baghaei, Didi Bang, Mayara Bastos, Andrea Benedetti, Marylène Bonnet, Adithya Cattamanchi, Peter Cegielski, Jung-Yien Chien, Helen Cox, Martin Dedicoat, Connie Erkens, Patricio Escalante, Dennis Falzon, Anthony J García-Prats, Medea Gegia, Stephen H Gillespie, Judith R Glynn, Stefan Goldberg, David Griffith, Karen R Jacobson, James C Johnston, Edward C Jones-López, Awal Khan, Won-Jung Koh, Afranio Kritski, Zhi Yi Lan, Jae-Ho Lee, Pei Zhi Li, Ethel L Maciel, Rafael Mello Galliez, Corinne S C Merle, Melinda Munang, Gopalan Narendran, Viet Nhung Nguyen, Andrew Nunn, Akihiro Ohkado, Jong Seo Park, Patrick P J Phillips, Chinnaiyan Ponnuraja, Randall Reves, Kamila Romanowski, Kwonjune Seung, H Simon Schaaf, Alena Skrahina, Dick van Soolingen, Payam Tabarsi, Anete Trajman, Lisa Triest, Velayutham V Bamuredkha, Piret Viiklepp, Jann-Yuan Wang, Takashi Yoshiyama, Dick Menzies

F. Fregonese, et al., Lancet Resp, 2018



Jan 2009-Apr 2016: cohorts ≥25 adults (>18 years).

Anonymized IPD on clinical characteristics, treatment, and outcomes.

Propensity score-matched generalized mixed effects logistic, or linear regression:
aORs and aRDs for success or death during treatment.

N. Ahmad, et al. Lancet, 2018

Drug / Drug Class	Recommendation		Certainty in the evidence	Death Relative (95% CI)	Success Relative (95% CI)
	For	Against			
Bedaquiline (BDQ)	Strong		Very Low	**aOR 0.4** (0.3 to 0.5) **RR 0.45** (0.34 to 0.55)	**aOR 2.0** (1.4 to 2.9) **RR 1.07** (1.04 to 1.09)
Fluoroquinolones: Levofloxacin (LFX)	Strong		Very Low	**aOR 0.6** (0.5 to 0.7) **RR 0.73** (0.65 to 0.81)	**aOR 4.2** (3.3 to 5.4) **RR 1.26** (1.24 to 1.29)
Fluoroquinolones: Moxifloxacin (MFX)	Strong		Very Low	**aOR 0.5** (0.4 to 0.6) **RR 0.65** (0.55 to 0.73)	**aOR 3.8** (2.8 to 5.2) **RR 1.25** (1.21 to 1.28)
Linezolid (LZD)	Conditional		Very Low	**aOR 0.3** (0.2 to 0.3) **RR 0.35** (0.24 to 0.53)	**aOR 3.4** (2.6 to 4.5) **RR 1.11** (1.09 to 1.12)
Clofazimine (CFZ)	Conditional		Very Low	**aOR 0.8** (0.6 to 1.0) **RR 0.83** (0.65 to 1.00)	**aOR 1.5** (1.1 to 2.1) **RR 1.04** (1.01 to 1.07)
Carbapenems with clavulanic acid	Conditional		Very Low	**aOR 1.0** (0.5 to 1.7) **RR 1.00** (0.55 to 1.51) [5]	**aOR 4.0** (1.7 to 9.1) **RR 1.10** (1.05 to 1.13)
Ethambutol (EMB)	Conditional		Very Low	**aOR 1.0** (0.9 to 1.2) **RR 1.00** (0.91 to 1.17)	**aOR 0.9** (0.7 to 1.1) **RR 0.99** (0.95 to 1.01)
Pyrazinamide (PZA)	Conditional		Very Low	**aOR 0.7** (0.6 to 0.8) **RR 0.73** (0.63 to 0.82	**aOR 0.7** (0.5 to 0.9) **RR 0.97** (0.93 to 0.99)
Injectables: Amikacin (Am)	Conditional		Very Low	**aOR 1.0** (0.8 to 1.2) **RR 1.00** (0.82 to 1.17)	**aOR 2.0** (1.5 to 2.6) **RR 1.06** (1.04 to 1.07)
Injectables: Streptomycin (S)	Conditional		Very Low	**aOR 0.8** (0.6 to 1.1) **RR 0.82** (0.64 to 1.08)	**aOR 1.5** (1.1 to 2.1) **RR 1.04** (1.01 to 1.06)
Cycloserine (Cs)	Conditional		Very Low	**aOR 0.6** (0.5 to 0.6) **RR 0.67** (0.58 to 0.67)	**aOR 1.5** (1.4 to 1.7) **RR 1.05** (1.05 to 1.07)
Delamanid (DLM)	Concur with WHO		Expert Opinion		

Drug / Drug Class	Recommendation		Certainty in the evidence	Death Relative (95% CI)	Success Relative (95% CI)
	For	Against			
Ethionamide (ETO) Prothionamide (PTO)		Conditional - Only use when limited options	Very Low	**aOR 0.9** (0.8 to 1.0) **RR 0.91** (0.82 to 1.00)	**aOR 0.8** (0.7 to 0.9) **RR 0.98** (0.96 to 0.99)
P-Aminosalicylic Acid (PAS)		Conditional - Only use when limited options	Very Low	**aOR 1.2** (1.1 to 1.4) **RR 1.16** (1.08 to 1.31)	**aOR 0.8** (0.7 to 1.0) **RR 0.97** (0.95 to 1.00)
Injectables: Kanamycin (Km)		Conditional	Very Low	**aOR 1.1** (0.9 to 1.2) **RR 1.08** (0.91 to 1.17)	**aOR 0.5** (0.4 to 0.6) **RR 0.90** (0.86 to 0.93)
Injectables: Capreomycin (Cm)		Conditional	Very Low	**aOR 1.4** (1.1 to 1.7) **RR 1.32** (1.08 to 1.54)	**aOR 0.8** (0.6 to 1.1) **RR 0.97** (0.93 to 1.01)
Amoxicillin-clavulanate (AMX/CLV)		Strong	Very Low	**aOR 1.7** (1.3 to 2.1) **RR 1.53** (1.24 to 1.80)	**aOR 0.6** (0.5 to 0.8) **RR 0.92** (0.89 to 0.97)
Macrolides: Azithromycin Clarithromycin		Strong	Very Low	**aOR 1.6** (1.2 to 2.0) **RR 1.46** (1.16 to 1.73)	**aOR 0.6** (0.5 to 0.8) **RR 0.92** (0.88 to 0.97)

Treatment success by duration of intensive phase after culture conversion (n= 4,122)

Intervals in months from sputum culture conversion to end of intensive-phase treatment	N patients		Propensity score matched analysis			
	Treatment Success	Total	N Pairs	aOR	(95% CI)	RD (95% CI)
0 – 1.0	239	251		1.0	(reference)	
1.01 – 3.0	668	695	694	1.5	(1.0, 2.3)	0.02 (0.00, 0.03)
3.01 – 5.0	878	917	906	1.4	(1.0, 2.0)	0.02 (0.00, 0.03)
5.01 – 7.0	1158	1179	1179	3.3	(2.1, 5.2)	0.04 (0.03, 0.05)
7.01 – 15.0	1025	1080	1079	1.1	(0.8, 1.5)	0.01 (-0.01, 0.02)

Treatment success by duration of treatment after culture conversion (n= 4,691)

Interval from sputum culture conversion to end of treatment, in months	N patients		Propensity score matched analysis			
	Treatment Success	Total	N Pairs	aOR	(95% CI)	RD (95% CI)
0.1 – 12.0	360	396	394	0.5	(0.4, 0.7)	-0.04 (-0.07, -0.01)
12.01 – 15.0	565	593		1.0	(reference)	
15.01 – 18.0	1206	1235	1223	2.1	(1.4, 3.1)	0.02 (0.01, 0.04)
18.01 – 21.0	1122	1158	1154	1.6	(1.1, 2.3)	0.02 (0.00, 0.03)
21.01 – 24.0	858	893	889	1.2	(0.9, 1.8)	0.01 (-0.01, 0.02)
24.01 – 69	386	416	413	0.7	(0.4, 1.0)	-0.02 (-0.05, 0.00)

N. of drugs in the intensive phase: aORs of treatment success versus failure or relapse.

Number of drugs	Number of patients	Propensity score matched analysis	
For the analysis of success vs. fail*/relapse**	N Success / N total (%)	aOR (95% CI)	RD % (95% CI)
0-2 drugs	1097/1236 (88.8)	1.0 (reference)	
3 drugs	1257/1407 (89.3)	1.7 (1.4, 2.0)	6 (4, 7)
4 drugs	1657/1847 (89.7)	1.2 (1.4, 2.0)	8 (6, 9)
5 drugs	926/986 (93.9)	3.0 (2.3, 3.9)	8 (7, 10)
6+ drugs	523/568 (92.1)	2.3 (1.6, 3.1)	4 (1, 7)
For the analysis of death vs success/fail*/relapse**	Death / total	Adjusted odds ratio (95% CI)	Risk difference % (95% CI)
0-2 drugs	205/1441 (14.2)	1.0 (reference)	
3 drugs	233/1640 (14.2)	0.9 (0.8, 1.1)	-1 (-3, 1)
4 drugs	345/2192 (15.7)	1.1 (0.9, 1.2)	-3 (-5, -1)
5 drugs	104/1090 (9.5)	0.6 (0.5, 0.7)	-2 (-3, 0)
6+ drugs	54/622 (8.6)	0.5 (0.4, 0.7)	2 (-0, 5)

N. of drugs in the continuation phase: aORs of treatment success VS. failure or relapse

Number of drugs	Number of patients	Propensity score matched analysis	
For the analysis of success vs. fail*/relapse**	Success / Total (%)	aOR (95% CI)	RD% (95% CI)
0-1 drug	1017/1144 (88.9)	1.0 (reference)	
2 drugs	1272/1425 (89.2)	1.1 (0.9, 1.3)	1 (-1, 3)
3 drugs	1623/1810 (89.7)	1.2 (1.0, 1.4)	3 (1, 5)
4 drugs	816/864 (94.4)	2.3 (1.7, 3.1)	3 (1, 5)
5+ drugs	346/383 (90.3)	1.2 (0.9, 1.8)	-4 (-8, -1)
For the analysis of death vs. success/fail*/relapse**	Death / Total (%)	aOR (95% CI)	RD% (95% CI)
0-1 drug	187/1331 (14.0)	1.0 (reference)	
2 drugs	193/1618 (11.9)	0.8 (0.6, 0.9)	-3 (-5, -1)
3 drugs	307/2117 (14.5)	1.0 (0.8, 1.1)	-4 (-5, -2)
4 drugs	78/942 (8.3)	0.5 (0.4, 0.7)	-1 (-4, 1)
5+ drugs	37/420 (8.8)	0.5 (0.4, 0.8)	5 (1, 8)

Best Practice Statements

We recommend…..

- ✓ **consultation with a TB expert in case of suspected or confirmed DR-TB**.

- ✓ **molecular testing for rapid detection of resistance-linked mutations**. Phenotypic DST for 1-line drugs is performed with molecular methods. When mutations are found, growth-based DST should be performed for 1-line drugs, fluoroquinolones, and aminoglycosides.

- ✓ **regimens include only drugs to which the patient's isolate has documented or high likelihood of susceptibility**. Ineffective drugs (*in vitro* resistance or clinical and epidemiological information) should NOT be used.

Best Practice Statements

We recommend…..

- ✓ **treatment response be monitored clinically, radiographically and bacteriologically (cultures at least monthly).** When cultures remain positive after 3 months, DST should be repeated. Clinical response and weight should be recorded monthly.

- ✓ **patients be asked about AEs at each visit.** All AEs should be thoroughly investigated.

- ✓ **patient-centered case management to help patients understand their diagnosis, to participate in the selection of the treatment, and to discuss barriers to treatment completion.**

2019 WHO Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment guidelines

Based on a modified set of data expanded on the IPD used for ATS/CDC/ERS/IDSA guidelines.

- ✓ Updated data from 625 patients were included from 8 datasets received in 2018 (Australia, Belarus, Brazil, France, Latvia, Rep of Korea, Russian Federation and the EndTB project), as well as a sample of 3,626 treated in South Africa (1,210 started on bedaquiline in 2015).

- ✓ They removed 3,367 records due to incomplete DST documentation.

- ✓ However, ATS/CDC/ERS/IDSA recommendations are largely concordant, being based on a similar approach (GRADE methodology and a multidisciplinary Guideline Development Group; IPDMA that overlapped substantially).

- ✓ WHO recommendations are focused on MDR and RR-TB;

- ✓ WHO duration of the injectable phase relates to its total length (6-7 months) rather than time after culture conversion. Total duration is similar in both guidelines.

2019 WHO Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment guidelines

- ✓WHO: LZD and BDQ were strong (moderate certainty); ATS/CDC/ERS/IDSA: lower certainty.

- ✓Composing a regimen: stepwise selection of agents different from WHO, which proposes three groupings. The ordering of drugs within groups is minimally different.

- ✓WHO n. medicines at the start is 4 (no pros for 5): increased prescription of BDQ and other effective drugs. ATS/CDC/ERS/IDSA chose 5 also to anticipate toxicities (≥1 agents would likely need to be permanently discontinued within the first 6 months).

2019 WHO Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment guidelines

- ✓WHO recommends the standardized shorter-course regimen, under specific conditions. ATS/CDC/ERS/IDSA: based on standardization with drugs for which there is documented or high likelihood of resistance (e.g., isoniazid, ethionamide, pyrazinamide), a recommendation for or against is not made (research for RCTs on newer susceptible oral agents).

- ✓WHO recommends evaluation of drug-resistance, but accepts empirical regimens. ATS/CDC/ERS/IDSA require microbiological data to create a regimen.

How to Build a Regimen

Clinical strategy to build an individualized treatment regimen

- ✓ Build a regimen using ≥5 drugs to which the isolate is susceptible (or low likelihood of resistance), preferably with drugs not used previously.
- ✓ Choice of drugs: capacity to monitor for AEs, comorbidities and preferences/values (subject to program and safety).
- ✓ In children contact of MDR-TB, the source case's isolate DST should be used if an isolate is not obtained from the child.
- ✓ TB expert medical consultation is recommended (ungraded good practice).

How to Build a Regimen

STEP 1 **Choose one later-generation fluoroquinolone**	**Levofloxacin** **Moxifloxacin**
STEP 2 **Choose both of these prioritized drugs**	Bedaquiline Linezolid
STEP 3 **Choose both of these prioritized drugs**	Clofazimine Cycloserine
STEP 4 **If a regimen cannot be assembled with 5 oral drugs, and isolate is susceptible, use one of the injectables**	Amikacin Streptomycin
STEP 5 **If needed or if oral agents preferred over injectable agents in STEP 4, use the following drugs[2]**	Delamanid Pyrazinamide Ethambutol
STEP 6 **If limited options and cannot assemble a regimen of five effective drugs, consider use of the following drugs**	Ethionamide or prothionamide Imipenem-cilastin/clavulanate or meropenam/clavulanate p-aminosalicylic acid High-dose isoniazid
The following drugs are no longer recommended for inclusion in MDR-TB regimens	Capreo and Kanamycin Amoxi/clavul (without carbapenem) Azithromycin and Clarithromycin

Standardized shorter-course 9-12 month regimen

Does standardized regimen for ≤12 months lead to better outcomes VS. 18–24 months?

It is standardized with kanamycin (recommendation against using), and includes drugs for which there is documented or high likelihood of resistance (e.g., isoniazid, ethionamide, pyrazinamide).

STREAM Stage 1 found it noninferior to longer injectable-containing regimens….but no recommendation if compared with all-oral regimens. RCTs needed on newer oral agents and drugs for which susceptibility is proved.

STREAM Stage 1 study

Standard Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB (STREAM Stage 1)

- ✓ RCT of non-inferiority: Ethiopia, South Africa, Vietnam, and Mongolia;
- ✓ Control: WHO recommended regimen in the countries;
- ✓ Study regimen is similar to the Bangladesh regimen (HD moxifloxacin replaces HD gatifloxacin).




Standardized shorter-course 9-12 month regimen

- Kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, HD isoniazid, ethambutol
  4-6 months

- Moxifloxacin, clofazimine, pyrazinamide, ethambutol
  5 months

Success rate: 83% (95 CI%: 71.0 – 90.3%)

383 included in the modified intention-to-treat population:
Favorable status in 79.8% in the long-regimen group and in 78.8% in the short-regimen

Standardized shorter-course 9-12 month regimen

- PS-matched IPDMA of 12,030 patients (n= 50 studies), 169 (n= 33 studies) were eligible for analysis of death and 1,369 (n= 33 studies) for treatment success.

- Data from 532 individuals (n= 3 studies) on the shorter regimen available for death and 498 (n= 3 studies) for treatment success.

- PS matching for age, sex, HIV, smear status, past TB treatment with first-line drugs, and number of effective drugs:

Treatment success (aOR 0.5, 95% CI 0.02 to 13); deaths (aOR 1.7, 95% CI 0.6 to 4.6).

Standardized shorter-course 9-12 month regimen

Benefits

Shorter duration=

- ✓ Less pill burden;
- ✓ Less medication cost ;
- ✓ Less associated provider administration costs ;
- ✓ Decreased lost productivity or lost wages;
- ✓ Decreased out-of-pocket costs.

Standardized shorter-course 9-12 month regimen

Harms

✓ STREAM Stage 1: short- VS. long-regimen

- AEs grade ≥3: 48.2% VS. 45.4%.
- Prolongation of QT-interval: 11.0% VS. 6.4% (P= 0.14).
- Death: 8.5% VS. 6.4%.
- Acquired resistance to fluoroquinolones or aminoglycosides: 3.3% VS. 2.3%.
- Death among HIV+: 17.5% VS. 8.0% (HR: 2.23; 95% CI, 0.76 to 6.60).

✓ IPDMA

- Deafness and ototoxicity: RR 1.5 (95%CI 0.6-4.0)
- Liver injury: RR 2.2 (95%CI 0.5-10.3); hepatitis: RR 2.5 (95%CI 0.3-21.2)
- Renal impairment: RR 4.5 (95%CI 0.6-35.2).

Hearing loss: 7.1% in a African study and 0-23% in a meta-analysis → <frequency in cohort studies because hearing loss was not monitored by audiometry in STREAM Stage 1

Standardized shorter-course 9-12 month regimen

- Minimal desirable effects:
  - ✓ treatment success,
  - ✓ mortality,
  - ✓ culture conversion.

- Small to moderate undesirable effects:
  - ✓ AEs,
  - ✓ limited applicability,
  - ✓ kanamycin and ineffective drugs (likelihood of resistance, e.g., isoniazid, ethionamide, pyrazinamide).