Treatment

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SUMMARY OF KEY UPDATES (2022)

- Recognition of current evolving state of clinical evidence-base and guidelines informing treatment of drug-resistant *M. tuberculosis* (DR-TB), reinforcing the need for expert consultation and shared decision-making with persons undergoing care for DR-TB

- New recommendations for use of shorter (6 month) regimens, BPaL and BPaLM, consisting of bedaquiline (BDQ), pretomanid (Pa), linezolid (LZD) with or without moxifloxacin (MFX) for treatment of DR-TB, including discussions on 2022 recommendations from the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO)

- Updated recommendations for individualized, longer duration (15-24 month) regimens for multidrug-resistant *M. tuberculosis* (MDR-TB) and extensively drug-resistant *M. tuberculosis* (XDR-TB) aligned with the *Treatment of Drug-Resistant Tuberculosis Guidelines* for the United States (U.S.) released in 2019
  - Includes an updated list of prioritized drug ranking and stepwise guide for building an individualized regimen for DR-TB based on 2019 guidelines

- Updated regimen options for mono-resistant and poly-resistant TB based on pragmatic expert opinion and experience

- Expanded section on specific drugs used for treatment of DR-TB

After decades of stagnation, the field of DR-TB treatment has been reinvigorated by a growing evidence base supporting successful use of new or repurposed drugs and new regimens.

Consultation with experts

Treatment of tuberculosis (TB) caused by drug-resistant organisms should be done by, or in close consultation with, an expert in the management of these difficult conditions. Second-line regimens often present the best hope for cure for persons with DR-TB, and inappropriate management of drug resistance can have life-threatening consequences.

Expert consultation can assist with:

- Diagnostic decisions and support for access to and interpretation of rapid molecular and phenotypic drug susceptibility testing (DST)
- Initial regimen choices and adapting treatment regimen based on early DST results and exposure history
- Management of medication dosing, toxicities, and adjustments
- Case management recommendations and tools
- Guidance in managing contacts to people with DR-TB

See **Appendix 1, *Expert Resources for Drug-Resistant TB.***

Classification of anti-tuberculosis drugs

Anti-tuberculosis drugs have classically been categorized into first-, second-, and third-line drugs. First-line drugs are traditionally those drugs that are used as the core drugs in the treatment of drug-susceptible TB. Second-line drugs include the fluoroquinolones and other drugs that are used to treat MDR-TB. Third-line drugs were categorized as drugs used for DR-TB, but typically considered as having less activity and more adverse reactions. The distinction between second- and third-line drugs may no longer be relevant as views on the utility of specific drugs continue to shift amidst newer evidence and growing experience. The distinction between second- and first-line drugs may blur further as new regimens for drug-susceptible TB evolve.

U.S.-based guidance issued in 2019 by the American Thoracic Society/Centers for Disease Control and Prevention/ European Respiratory Society/Infectious Diseases Society of America (ATS/CDC/ERS/IDSA) did not specify classifications. WHO dropped the use of "third-line" and defines all agents used to treat DR-TB as "second-line".

WHO divides second-line drug choices for resistant disease into three categories of prioritization (A, B, C). WHO also specifically shifted streptomycin (SM) to be listed as a second-line, rather than a first-line, drug.

Proper treatment with a second-line regimen often represents the patient's best hope for cure. Seek expert consultation when considering treatment initiation for DR-TB.

A stepwise prioritization of drugs is also promoted in the 2019 ATS/CDC/ERS/IDSA DR-TB guidelines and may be a more relevant, practice-oriented way to categorize the drugs used to treat DR-TB. This approach is covered in detail in the section: ***Individualized, longer duration (15-24 month) regimens for MDR-TB*** with a listing of prioritized drugs (**Figure 1**).

Evolving options for DR-TB treatment

After decades of stagnation, the field of DR-TB treatment is now reinvigorated by a growing evidence base supporting successful use of new or repurposed drugs and new regimens. Successful options address person-centered priorities to reduce the long and difficult duration of treatment, and new guideline strategies re-prioritize drugs based on both safety concerns and efficacy.

Key message: ***DR-TB treatment is evolving.***

- Providers and programs need to remain alert and watch for ongoing changes and updates that can improve the care offered to reach successful and safe cures. Consult an expert.
- As more options arise, shared decision-making with persons undergoing treatment remains essential.

Choosing among regimens for MDR-TB

New standardized, shorter (6- to 9-month) regimens and updated advice on how to build a longer, individualized regimen are now available.

"Standardized regimens" refer to regimens in which the composition of drugs and duration are fixed by protocol. These regimens are often applied in lower-resource settings where access to DST may be limited only to identification of rifampin (RIF)-resistance (+/- isoniazid [INH]). The standardized regimens are not advised for use if any of the regimen drugs have reliable DST results available that document resistance, thus limiting application in countries where extensive DST panels may document additional resistance that excludes their use. "Individualized" regimens

are familiar to U.S. clinicians as the classic practice of building regimens in response to individual DST resistance patterns and patient-specific limitations (e.g., co-morbidities and side effects).

The decision to choose a longer, individualized regimen or shorter (6- to 9-month) standardized regimen is based on: isolate drug-resistance pattern; previous treatment history; availability of the regimen drugs and safety monitoring; co-morbidities; severity and site of disease; experience of the treating clinician; and preference of the person undergoing treatment. In the U.S., guidelines support the use of both shorter, standardized and longer, individualized regimens for specific populations of TB patients with drug-resistant disease, and additional updates are underway.

- BPaL, a 6-month regimen composed of BDQ, Pa and LZD, is a shorter, standardized regimen approved by the Food and Drug Administration (FDA) and currently recommended by CDC for some MDR-TB patients in the U.S.
- WHO currently recommends 3 different all-oral, standardized, shorter-course regimens (using LZD 600 mg daily initial dose): 6 months BPaL with MFX (BPaLM), 6 months BPaL, and a 9- to 12-month all-oral BDQ-containing regimen. WHO recommends a longer duration, individualized regimen when persons with DR-TB have failed or have resistance or intolerance to drugs in the shorter, standardized treatment regimens.

Shorter-course (6-month) regimens: BPaL and BPaLM

In 2019, the FDA approved the drug **Pa** for use as part of the new 6-month (26 weeks) BPaL regimen, consisting of BDQ, Pa, and LZD, for treatment of XDR-TB (defined at the time as resistance to INH, RIF, at least one fluoroquinolone, and an injectable agent) or drug-intolerant/nonresponsive MDR-TB.

In early 2022, CDC published provisional guidance for the use of BPaL (https://www.cdc.gov/tb/topic/drtb/bpal/default.htm), noting:

- BPaL is approved for pulmonary TB disease.
- Indications for use may include pre-XDR (resistance to INH, RIF, and at least one fluoroquinolone or an injectable agent) in addition to XDR-TB or drug-intolerant/nonresponsive MDR-TB.
- Treatment can be extended to 9 months (39 weeks) based on delayed treatment response within the first 8 weeks (earlier than the Nix-TB trial protocol, see below) as assessed by time to culture conversion, persistent culture positivity, clinical response to treatment, and other underlying clinical factors, or modified based on adverse events.

Of note, Pa is not yet FDA approved to be used outside of the BPaL regimen (recognizing that most second-line anti-TB drugs in use are not specifically FDA approved for treatment of DR-TB).

WHO first endorsed the use of BPaL under operational research conditions in 2019 and updated official guidance in May 2022 to recommend BPaL be used in persons with MDR-TB whose isolate is resistant to fluoroquinolones, who have no previous

exposure to BDQ and LZD or have been exposed to the drugs for less than one month. CDC does not apply restrictions based on prior use of BDQ or LZD if susceptibility for these drugs in these situations is confirmed.

Nix-TB: BPaL was studied in a single-arm, open-label, Phase 3 trial (TB Alliance, Nix-TB) in individuals with XDR-TB or treatment intolerant or nonresponsive MDR-TB. Enrollment required age > 14 years. *[N=109, age 17-60 (median 35) years]*

- The regimen was administered for 6 months (26 weeks, 7 days/week with food) with an option to extend to 9 months for slow bacteriologic responders (culture positive at 16 weeks). The starting total daily dose of LZD was 1200 mg, which was required for at least 1 month of use, after which time the dose could be reduced, held or LZD permanently discontinued based on adverse events. The regimen could be interrupted up to 35 days and missed doses added at the end. Among the 109 study participants, favorable outcomes were reported in 98 (90%) of the participants, with unfavorable outcomes in 11 (10%). One (1%) of 2 confirmed relapses was associated with acquired resistance (*Rv0678* mutation associated with an increase in BDQ MIC from 0.5 to 4.0 mcg/mL).
    - Given a study population that had significant risks for poor results (65% XDR-TB; 84% cavitary disease; 51% HIV-positive; and median BMI 19.7), the favorable outcomes were notable.
- Adverse events were common, with 81% of the cohort developing peripheral neuropathy and 48% cytopenias. All participants in the Nix-TB trial received LZD 1200 mg (daily or 600 mg twice per day) for the first month. Only 16 (15%) of participants completed a full 6-months of LZD 1200 mg, 50 (46%) interrupted LZD and resumed at the same or lower dose (600 mg or 300 mg daily), and 33 (30%) permanently stopped LZD at some point after the first month with all surviving patients (27) completing treatment.
- Of those who developed new peripheral neuropathy while on the study regimen, results at the final 24-month post-treatment evaluation showed that neuropathy symptoms resolved in 82%, remained mild to moderate in 12%, and severe in 1%. Myelosuppression generally occurred within the first 3 months and was managed with dose interruptions and/or reductions. Two cases of optic neuritis resolved after LZD was discontinued.
- No participant had QTc increases to > 480 msec and 8 had regimen interruption due to hepatic adverse events, but all restarted and completed the full 26 weeks.
- Pa pre-clinical rodent models raised concerns for male testicular toxicity. A 2022 meta-analysis reported no adverse effects to human male reproductive hormone levels to date and further investigations are ongoing. For more details, see section: ***Specific drugs – Pretomanid.***

ZeNix: To evaluate alternative LZD dosing strategies, the TB Alliance conducted the ZeNix trial, a Phase 3, multi-center, partially-blinded randomized study. Enrollment required age > 14 years (≥ 18) years in 2 of 4 trial sites). Participants were randomized to one of four regimens: BDQ[1] and Pa plus: 1) LZD 1200 mg daily for 26 weeks; 2) LZD 600 mg daily for 26 weeks; 3) LZD 1200 mg daily for 9 weeks; or

1 BDQ dosing in ZeNIX was 200 mg daily x 8 week load, then 100 mg daily x 18 weeks to simplify dosing based on PK modeling that showed equivalency to Nix-TB with a lower/longer load followed by daily dosing.

4) LZD 600 mg for 9 weeks. All participants were treated for 6 months (26 weeks) and the primary endpoint of the study was the incidence of bacteriologic failure, relapse or clinical failure through follow up until 6 months after the end of treatment. *(N = 181, interquartile range 30-44 [median 36] years).*

- Favorable outcomes were reported in 93% of those taking LZD 1200 mg for 26 weeks, 89% of those on LZD 1200 mg for 9 weeks, 91% for those on LZD 600 mg for 26 weeks, and 84% for those on LZD 600 mg for 9 weeks.
- Adverse events were less common with lower LZD doses and shorter durations of therapy. Based on these results, it appears that a LZD dose of 600 mg a day given for 26 weeks is highly effective with less adverse events than with 1200 mg daily.

TB PRACTECAL: When isolates are susceptible to fluoroquinolones, WHO recommends the BPaLM regimen. The data supporting this regimen comes from TB PRACTECAL, a multi-arm, multi-stage, randomized, controlled trial that evaluated the safety and efficacy of regimens containing BDQ, Pa, and LZD (600 mg x 16 weeks, reduced to 300 mg daily or 600 mg 3x/week for 8 weeks or earlier if moderately tolerated [not defined further]) with or without additional agents (MFX or CFZ) for treatment of MDR/rifampin-resistant (RR)-TB. Enrollment required age ≥ 15 years. In Stage 1, participants were randomized to receive one of three experimental arms (BPaLM, BPaL+ clofazimine (CFZ), BPaL) compared with WHO standard of care (longer) regimens. The best performing regimen was BPaLM, a regimen of BDQ, Pa, LZD, and MFX administered for 6 months (24 weeks). BPaLM then moved on to Stage 2 for comparison with standard longer WHO regimens. *(N=151 BPaLM arm and N=152 standard of care arm, age 18-71 [median 33] years).*

- The trial was stopped early due to an interim analysis demonstrating superiority of the experimental shorter regimen compared to the longer WHO standard of care regimen: 89% of the participants in the BPaLM arm were cured versus 52% in the standard of care group.
- Difference in the proportion of unfavorable outcomes was driven by a higher rate of treatment discontinuation in the control arm

Currently, results of TB PRACTECAL are not yet published in the peer-reviewed literature and are therefore only briefly mentioned in current U.S. guidelines. Note: TB PRACTECAL Stage 1 was not designed to directly compare the performance of the three experimental arms, but to efficiently identify the best comparator arm(s) for study continuation. All three experimental arms met criteria to move to Stage 2, but only one arm (BPaLM) was enabled to move forward (i.e., BPaL arm dropped not due to poor performance; instead, the study design allowed investigators to choose the best performing arm at an early analysis time point to optimize enrollment into Stage 2). CDC has shared an extensive provisional guidance document, updated February 2022, to serve as a helpful resource for use of BPaL. Experts in the U.S. have been expanding the use of BPaL and BPaLM in specific clinical situations, and updates to U.S. TB treatment guidelines are underway to review and incorporate new clinical trial results.

The supportive clinical trials had limited enrollment (modified intention to treat populations ranging from 178 [ZeNIX, 45-46 per treatment arm], 107 [Nix-TB], to 252 [TB PRACTECAL; 62 BPaLM and 60 BPaL arms at 72 weeks]), and data for use in special populations are not yet available. Therefore, these regimens should be implemented with expert consultation, appropriate monitoring, and with full disclosure and informed agreement. The compelling success and shorter duration have driven expanded off-label use within the U.S. for DR-TB beyond the FDA-approved indication for pulmonary XDR-TB and drug-intolerant/nonresponsive MDR-TB. This off-label use also includes when a rifamycin cannot be used; e.g., RIF mono-resistance or intolerance situations in which a longer 12- to 18-month regimen is being considered.

On a case-by-case basis, when clinical indications suggest use of BPaL or BPaLM is feasible, many experts consider off-label use with the following caveats:

- An **informed preference** remains central to care. Discuss with the person starting treatment the limited but growing data to date and the pros/cons of all treatment options. Newer human data on fertility issues in males are reassuring in the context of early animal data regarding fertility. Also discuss use in special populations where no data or limited information exists.
- The person with TB and the program/provider should commit to **close monitoring** during treatment for adverse events and post-treatment to watch for chance of relapse, allowing for early intervention if the shorter duration regimen fails. A suggested post-treatment monitoring strategy includes:
  - Symptom evaluation and sputum smear/culture (with or without CXR) every 3 months x 2, then every 6 months up to 2 years post-treatment.
  - Consider more frequent post-treatment checks, particularly within the first year, in the setting of extensive disease, slow culture conversion (> 8 weeks) or other co-morbidities that increase risk for relapse.

Additional practical considerations:

- CDC 2022 recommendations advise **extension of duration to 9 months (39 weeks)** based on delayed treatment response within the first 8 weeks as assessed by time to culture conversion, persistent culture positivity, clinical response to treatment, and other underlying clinical factors or modifications based on adverse events.
- Most U.S. experts initiate LZD at 600 mg daily dosing (similar to ZeNIX and TB PRACTECAL dosing and consistent with current WHO recommendations) rather than the initial FDA-approved LZD 1200 mg initial dose recommendations.
- Current expert practice includes therapeutic drug monitoring (TDM) for LZD, particularly for dose adjustment if trough > 2 mcg/mL to reduce potential for adverse effects (see section: ***Therapeutic Drug Monitoring***). Modeling analysis of Nix-TB data (LZD 1200 mg dosing) suggests that monitoring trends in CBC and simple neuropathy symptom review may also advise dose adjustments and support avoidance of LZD adverse effects. A hemoglobin (Hb) drop from baseline of > 10% after 1 month predicted risk for severe anemia (better than patient characteristics or trough). In this Nix-TB analysis, trough levels predicted toxicity to platelets, but not Hb or neuropathy.

- BPaL and BPaLM regimens require **7 day/week dosing with food.** Many programs have implemented asynchronous video directly observed therapy (vDOT) solutions to support weekend dosing.
- Consider drug-drug interactions (e.g., rifamycins, azole antifungals, protease inhibitor, others) as BDQ and Pa are metabolized by CYP3A4.
- Nix-TB exclusion criteria of interest: Persons with severe liver dysfunction (Grade 3: AST > 3x upper limit of normal (ULN), total bilirubin ≥ 2x ULN or ≥ 1.5-2.0 ULN with increase in other liver function tests), renal dysfunction (serum creatinine > 2x ULN), extrapulmonary TB requiring extended treatment, or if pregnant or breast-feeding. ZeNix and TB PRACTECAL exclusions were similar to Nix-TB for most criteria. Considering the multiple exclusion criteria for studies that form the evidence base for these new regimens, it is highly recommended to seek expert consultation when considering use.
- Monitoring for adverse effects (for individual drugs, see **Chapter 5, *Medication Fact Sheets***) includes key LZD concerns for peripheral/optic neuropathy and myelosuppression. BDQ use requires routine ECG and electrolyte monitoring (QTc-prolongation risk, including baseline testing for hypothyroidism) and hepatic function monitoring. Other notable but infrequent adverse effects in BPaL trials included lactic acidosis and acute pancreatitis.
- Access to BDQ and Pa may include 1- to 2-week delays for some programs. While awaiting new drugs, consider a temporary "bridging" regimen based on guidance for building a longer individualized DR-TB regimen (**Figure 1**) for persons who would benefit from immediate treatment initiation; e.g., persons who are severely ill or unstable, or persons in high-risk transmission settings. For stable patients who can be adequately isolated, holding off treatment may be preferable because bridging regimens can also introduce early side effects that can complicate treatment.
- Variations in drug procurement need attention. Wholesale (340B) pricing for BDQ requires a bulk 24-week supply purchase; providers using 340B pricing may need a plan for obtaining the final 2-week supply (for the 26-week regimen). NTCA supports a useful resource for BDQ procurement: https://www.tbcontrollers.org/resources/bdq-access/. Pa is typically supplied in 26-pill count bottles (less than a 30-day supply). Refills may need to be ordered sooner than expected especially because many pharmacies will need several days to fulfill the order. The CDC-sponsored TB Centers of Excellence (TB COEs) also serve as resources for procurement questions.

For more advice on drug access and case management tools for BPaL and BPaLM, see **Chapter 8, *Monitoring and Case Management.***

BPaL and BPaLM 6-month regimens

Expert consensus dosing recommendations (combining WHO and CDC):

For ages ≥ 15 years:

BPaL*

- **Bedaquiline** 400 mg once daily x 2 weeks (load), then 200 mg 3x/week x 24 weeks
- **Pretomanid** 200 mg once daily x 26 weeks
- **Linezolid** 600 mg once daily x 26 weeks

BPaLM* — same as above and add:

- **Moxifloxacin** 400 mg once daily x 26 weeks

Extend either regimen to 9 months (39 weeks) if evidence for delayed response to treatment (> 8 weeks per CDC criteria below).

***WHO May 2022 dosing guidance** reflects current practice by most experts in the U.S. (many include LZD TDM with dose adjustment as needed). Evidence base for WHO recommendations included early access to unpublished ZeNIX and PRACTECAL data.

CDC February 2022: *Provisional CDC Guidance for the Use of Pretomanid as Part of a Regimen (BPaL) to Treat Drug-Resistant Tuberculosis.* Notable differences with WHO recommendations include:

- Updated CDC guidance in progress (to include ZeNIX and TB PRACTECAL results)
- February 2022 recommendations limited to BPaL with LZD 1200 mg daily with reduction to 600 mg (or 300 mg) daily or interruption of dosing as necessary for adverse effects. Initiating BPaL with a reduced dose of LZD of 600 mg daily, as above, is the current practice by most U.S. expert clinicians and consistent with WHO.
- Treatment extension if delayed response (> 8 weeks): As assessed by time to culture conversion, persistent culture positivity, clinical response to treatment, and other underlying clinical factors or modifications based on adverse events.

NExT: An additional clinical trial of a 6-month regimen for MDR/RR-TB[2] was published in 2022. The NExT trial was a randomized, controlled, open-label, clinical trial in adults with MDR/RR-TB without fluoroquinolone or aminoglycoside resistance. Patients were randomized to receive an approximately 6-month, 5-drug, all-oral regimen that included LFX, BDQ, LZD (600 mg daily) plus two WHO Group B or C drugs (PZA and either ETO, high-dose INH or terizidone) or a ≥ 9-month WHO-approved injectable-based regimen. The study was stopped prematurely when BDQ became the standard of care in South Africa: 93/111 participants were included in the intention-to-treat analysis.

2 The term RR-TB is used to designate that RIF resistance has been identified, often using a rapid-molecular test such as Xpert MTB/RIF, but without confirmation of INH resistance or susceptibility. Because RIF resistance is highly associated with the presence of INH resistance (and additional DST testing may not be accessible), disease identified as RR-TB is treated the same as MDR-TB in WHO recommendations.

Participants in the intervention arm were more than twice as likely as those in the standard arm to experience a WHO-defined favorable 24-month outcome (51% vs. 22.7%) and less likely to require a toxicity-related substitution (34.7% vs. 65.9%). In the WHO outcome definitions used in the study, a change in drug due to toxicity was considered an unfavorable outcome and this was largely driven by LZD-related drug toxicity in the intervention arm and kanamycin (KM) in the control arm. Grade 3 adverse events were more common in the intervention arm.

When toxicity-related drug substitutions were not included as unfavorable outcomes, treatment success was 75% in the intervention arm and 70% in the standard of care arm in the per protocol population. No recommendations for implementation of this regimen have been made based on the partial study completion, particularly noting high toxicity in both treatment arms and notably lower efficacy of the intervention arm as compared with other 6-month MDR-TB regimens. This study does suggest that shorter durations of treatment may be possible if at least three WHO Group A drugs are used, and further clinical trials are warranted.

Individualized, longer duration (15-24 month) regimens for multidrug-resistant *M. tuberculosis* (MDR-TB)

Longer duration (formerly 18- to 24-month) regimens for treatment of MDR-TB have been the cornerstone of treatment recommendations in past versions of this *Survival Guide.* It is important to note:

- Evidence supporting a primary role for the shorter 6-month BPaL and BPaLM regimens is compelling and expert practice is shifting, with longer duration regimens considered when a shorter regimen cannot be safely and appropriately used.
- U.S. and WHO guidance will continue to evolve on the basis of growing evidence from clinical trials and frontline experience with shorter DR-TB regimens. Published guidelines may not yet reflect advances in the evidence base; seek expert consultation.
- The need to construct individualized, longer duration regimens on a case-by-case basis continues, particularly when key drugs in a standardized shorter regimen cannot be used or for bridging circumstances while awaiting new drug procurement.

Based on expert opinion, earlier versions of this *Survival Guide* recommended 4-6 likely effective drugs, and optimally at least 5, for the treatment of MDR-TB (noting 4 drugs may be sufficient in select cases with limited disease and/or limited extent of resistance) for a duration of 18-24 months beyond culture conversion. These recommendations were based on publications that reported better outcomes in terms of lower rates of mortality, treatment failure, and recurrent TB, and faster rates of sputum conversion in those who received at least 5 compared with 4 likely effective drugs.

The recommendations in this section on longer, individualized regimen construction reflect the 2019 ATS/CDC/ERS/IDSA treatment of DR-TB guidelines with additional practical clinical advice for application. The 2019 guidelines were supported by scientific evidence, including data derived from a propensity score (PS)-matched, individual patient data meta-analyses (IPDMA) of 12,000 patient records from 25 countries published in 2018. Of note, the 2019 ATS/CDC/ERS/IDSA guidelines and IPDMA were completed before data on the 6-month regimens (BPaL and BPaLM) were available and prior to the 2019 FDA approval for Pa as part of a BPaL regimen and the 2022 CDC provisional BPaL guidelines. Updated ATS/CDC/ERS/IDSA guidelines are currently in progress.

Key aspects of the 2019 guidelines emphasize a shift in strategy that:

- Promotes the use of newer or repurposed oral agents with greater efficacy
- Deemphasizes the use of injectable agents

Number of drugs and stepwise approach for building an individualized, longer (15-24 months) regimen

Number of Drugs for Intensive and Continuation Phase

2019 ATS/CDC/ERS/IDSA Treatment of DR-TB guidelines recommend:

(Conditional recommendations, very low certainty of evidence)

- **At least 5 drugs should be used in the intensive phase and 4 drugs in the continuation phase of treatment of MDR-TB.**
- Drugs of poor or doubtful efficacy should not be added to a regimen purely to ensure that the recommended number of drugs is obtained.

Using the IPDMA results, treatment success (both cure and treatment completion) was associated with regimens containing 5 effective drugs in the intensive phase, with mortality significantly reduced for those taking 5-6 effective drugs. Success was greatest when using 4 drugs in the continuation phase, with the greatest reduction in mortality seen when 4 or more effective drugs were used. The intensive phase was defined by the use of an injectable agent in the IPDMA dataset.

Both the 2019 ATS/CDC/ERS/IDSA and 2020 WHO guidelines used the IPDMA data to construct similar prioritized drug rankings and stepwise strategies for building individualized regimens. As with any TB regimen, final drug choices will be contingent on isolate drug-susceptibility results, co-morbidities, side effect risk profile, program capacity to adequately monitor for adverse events, and the preferences and values of the person undergoing DR-TB treatment.

Figure 1 describes a stepwise approach to building an individualized MDR-TB regimen.

FIGURE 1. **Building an individualized treatment regimen for MDR-TB**

2019 ATS/CDC/ERS/IDSA DR-TB guideline stepwise guidance for building a regimen using a prioritized ranking of drugs (with comparison to WHO 2020)

During the intensive phase choose **5 drugs**, then drop to **4 drugs** during the continuation phase.

ATS / CDC / ERS / IDSA				WHO
1.	**Choose one FQ**	Levofloxcin **or** Moxifloxacin	**LFX** **MFX**	**WHO Group A:** Include all three
2.	**Use BDQ and LZD**	Bedaquiline	**BDQ**	
		Linezolid	**LZD**	
3.	**Use CFZ and CS**	Clofazimine	**CFZ**	**WHO Group B:** Add one or both
		Cycloserine	**CS**	
4.	**Add inj. as needed**	Amikacin (**or** Streptomycin[1])	**AK** **(SM)**	**WHO Group C:** Add to complete the regimen WHO rank order: **EMB** **DLM** **PZA** **IMP/MPM** with **CLV** **AK (SM)** **ETA** or **prothionamide** **PAS**
5.	**Add as needed**	Delamanid[2]	**DLM**	
		Ethambutol	**EMB**	
		Pyrazinamide	**PZA**	
6.	**Add as needed**	Ethionamide	**ETA**	
		Imipenem-cilastatin **or** Meropenem (**plus** clavulanate)	**IPM** **MPM** **(+CLV)**	
		p-aminosalicylic acid	**PAS**	
		High-dose Isoniazid	**INH^{HD}**	

Note: Pretomanid not yet included in published U.S. or WHO prioritized lists

Capreomycin, kanamycin, macrolides, and amoxicillin/clavulanate no longer recommended

1 AK or SM should be used only when susceptibility documented and less toxic choice not available
2 DLM available only through compassionate use program in the U.S.

Intensive and continuation phases with all-oral regimens

With evidence supporting the efficacy of newer or repurposed oral agents, the use of the term intensive phase was redefined in the 2019 U.S. guidelines to reflect an initial treatment duration using a higher number of drugs, without reliance on an injectable agent. Recommendations continue to promote reducing the number of drugs once an adequate response has been achieved based on culture conversion — the "continuation phase". This strategy promotes: 1) increased bactericidal activity early in treatment when bacillary burden is greatest; then 2) reducing risk of toxicity and intolerability by decreasing the number of drugs for the final duration required for sterilization and cure.

From a practical standpoint, BDQ was FDA approved in 2012 to be used in DR-TB regimens for a duration of 6 months based on clinical trials supporting its safety and effectiveness, essentially transitioning to a continuation phase when using an all-oral regimen. If the strength of the continuation phase drug combination is in question, CDC guidance allows for prolonged use beyond 6 months on a case-by-case basis. Use of BDQ for longer durations may expand as ongoing safety studies and experience with prolonged BDQ durations accumulate; expert consultation is recommended.

Duration of therapy

If the shorter BPaL or BPaLM regimens are not appropriate for use, the treatment durations recommended in the 2019 ATS/CDC/ERS/IDSA guidelines for individualized regimens (using the stepwise strategy outlined in **Figure 1**) state:

Duration for Intensive and Continuation Phase

When using an individualized, longer treatment strategy:

2019 ATS/CDC/ERS/IDSA Treatment of DR-TB guidelines recommend:

(Conditional recommendations, very low certainty of evidence)

- **Intensive phase duration:** 5-7 months beyond culture conversion in patients with MDR-TB
- **Total treatment duration:** at least 15-21 months after culture conversion in patients with MDR-TB
- In patients with **pre-XDR or XDR-TB**, a total treatment duration of between 15-24 months is suggested

Note that the lower end of the duration range based on the IPDMA results is lower than older guidance (15 months post culture-conversion as opposed to 18 months post culture-conversion). The clinical context, extent of disease, and response to treatment, among other factors, will play a role in choosing a final duration from within the recommended ranges. The intensive phase duration does not apply to standardized shorter 9- to 12-month regimens discussed elsewhere in this chapter.

Additional considerations when choosing an MDR-TB regimen

When considering the BPaL or BPaLM regimens or designing an individualized, longer (15- to 24-month) treatment regimen, assess the following factors:

- *In vitro* susceptibility results of the drugs
- Cross-resistance
- Whether the patient has taken the drug before
- Potential overlapping drug toxicity, tolerability issues, or drug-drug interactions
- Tissue penetration of drugs for extrapulmonary sites

Cross-resistance

Be aware of potential cross-resistance when using DST results, particularly to guide the building of an individualized regimen. Mutations associated with resistance to specific drugs and those that confer risk for cross-resistance are clearly described for some anti-TB drugs; however, for many drugs currently in use, neither the mutations nor mechanisms for resistance are known.

Be aware of potential cross-resistance that can occur between certain drug classes (Table 1).

TABLE 1. **Cross-resistance for anti-tuberculosis drugs**

Drug	Cross-Resistance	Comments
FIRST-LINE		
Isoniazid	Ethionamide	Cross-resistance to ethionamide is very common (up to 70%) when there is low-level resistance to isoniazid due to a mutation in *inhA* or the promoter region.
Rifampin	Rifamycins	Cross-resistance among the rifamycin class of drugs is typical. In <20% of strains that are resistant to rifampin, rifabutin may retain susceptibility *in vitro.* The clinical significance of this is unknown.
Ethambutol	None	
Pyrazinamide	None	
SECOND-LINE (ORAL)		
Fluoroquinolones	Other fluoroquinolones	In general, there is a complete class effect cross-resistance among fluoroquinolones *in vitro*. However, data suggest that moxifloxacin may continue to demonstrate some activity despite *in vitro* resistance to ofloxacin/levofloxacin. For details, **see Chapter 3, *Laboratory***, Table 3.
Bedaquiline	Clofazimine	Cross-resistance has been demonstrated in both directions through efflux-based resistance.
Linezolid	None	
Clofazimine	Bedaquiline	Cross-resistance has been demonstrated in both directions through efflux-based resistance.
Cycloserine	None	
Delamanid	Pretomanid	
Ethionamide	Isoniazid	Low-level cross-resistance to isoniazid may occur due to mutation in *inhA* or the promoter region.
PAS	None	
SECOND-LINE (INJECTABLES)		
Amikacin	Kanamycin*	High likelihood of cross-resistance because it is associated with the same mutations (*rrs*).
Streptomcyin	Kanamycin*	Rarely may be cross-resistant to kanamycin.
Kanamycin*	Amikacin	High likelihood of cross-resistance because it is associated with the same mutations (*rrs*). However, there are some kanamycin mutations (*eis*) that do not cause amikacin resistance.
Capreomycin*	Amikacin/ Kanamycin*	Variable frequency of cross-resistance has been reported.

* Note: Capreomycin and kanamycin are no longer recommended for treatment of DR-TB. Clinicians may encounter a prior history of treatment using these drugs in some persons evaluated for care.

Avoid drugs used previously to treat the patient's TB

Data from National Jewish Health suggest that patients who have taken a drug for over 1 month in the past have less effect from that drug, even if *in vitro* susceptibility tests demonstrate the isolate to be susceptible. Despite this, most experts recommend that first- or second-line drugs with documented susceptibility be included in the treatment regimen. Some experts may choose not to count previously used drugs among the target number of likely effective drugs.

Consider side effects when choosing drugs

For example, in someone with depression, it may be desirable to avoid **CS**. When possible, try to avoid using drugs that have similar toxicity profiles. For example, the combination of **PAS** and **ETA** increases the risk of hypothyroidism and gastrointestinal toxicity. **BDQ**-based regimens may be avoided if significant cardiac conduction system conditions exist.

On the other hand, in some patients there is no choice because these drugs may be the only ones to which the isolate is susceptible, and potential complications like hypothyroidism can be managed with the addition of thyroid replacement medications until treatment completion. Additionally, in persons with renal or hepatic disease, certain drugs may be safer. Ultimately, choose the safest and most effective drugs to complete the treatment regimen. It is important to recognize that some drugs may be stopped early during treatment due to side effects, intolerance, or safety concerns with prolonged use (e.g., injectable agents); as such, the choice to initiate with a higher number of drugs for the intensive phase is a practical safeguard to ensure greater likelihood of effective treatment over the total duration of care.

Ultimately, choose the safest and most effective drugs to complete the treatment regimen.

- Note: Intolerance to one agent does not necessarily mean the patient will be intolerant to another agent in the same classification group. For example, LFX and MFX can sometimes be exchanged successfully when side effects or intolerance are encountered.
- Given the limited number of drug options, make every effort to manage side effects rather than prematurely stopping a drug that has value in the regimen. See **Chapter 9, *Adverse Reactions***, for details on management of side effects.

WHO recommendations for shorter (6 or 9 months) and longer (>18 months) duration DR-TB regimens

With ongoing waves of global migration and immigration, it is useful for U.S. providers to have a general understanding of how guidelines may differ for patients receiving treatment for DR-TB in countries that follow WHO recommendations. In addition, WHO guidance often incorporates new data not yet reflected in U.S.-based guidelines, providing important information that may apply to low-incidence, high-resource settings.

In mid-2022, WHO released a rapid communication highlighting key changes to its overall 2020 DR-TB treatment recommendations that:

1. Support the use of the 6-month BPaLM (or BPaL if fluoroquinolone resistant) regimens in patients aged ≥ 15 years with MDR/RR-TB[2] who have not had previous exposure of > 1 month to BDQ, Pa, or LZD. Where there is slow response to therapy, an extension of 3 months (total 9-month duration) is suggested.
2. Prioritize the WHO standardized, all-oral 9-month regimen for eligible patients over longer (≥18 months) regimens for adults and children with MDR/RR-TB without previous exposure to second-line treatment (including BDQ) or known fluoroquinolone resistance, and without extensive pulmonary or severe extrapulmonary TB disease.
3. Recommend a longer, individualized DR-TB regimen for patients with extensive resistance (e.g., XDR-TB: MDR-TB resistant to fluoroquinolone and BDQ or LZD) or those not eligible for or who have failed shorter treatment regimens.

For more details, see section: ***Shorter-course (6 month) regimens: BPaL and BPaLM.***

The **WHO standardized, all-oral 9-month regimen** replaced prior recommendations for a similar injectable agent-based, 7-drug regimen with an 83% success rate, as documented in a randomized, Phase 3, non-inferiority trial (STREAM). Support for the all-oral 9-month regimen has come from programmatic data from South Africa, which had used a longer injectable-containing (KM) regimen until 2017.

- From March 2013 to March 2015, BDQ was added to the regimen in selected patients with XDR-TB (using prior WHO definition of XDR-TB that included fluroquinolone and injectable resistance) and achieved treatment success rates of 73%. From 2015, all patients with RIF-resistant TB and ototoxicity received BDQ.
- In 2017, the shorter, standardized, 7-drug injectable-containing regimen (STREAM) that included KM, MFX, CFZ, ethionamide (ETA), high-dose INH, ethambutol (EMB) and pyrazinamide (PZA), administered for 9-12 months, was introduced in South Africa. However, ototoxicity and nephrotoxicity continued because of the inclusion of KM.
- South Africa adopted an all-oral BDQ-containing regimen since mid-2018 given for 9 months (using $LZD_{(2\ months)}$ rather than $ETA_{(4\ months)}$), which WHO now recommends. Overall,1387 (14%) of 10,152 patients with RR-TB treated during 2017 were included in a study that reported a treatment success rate of 70% versus 57% in those receiving an injectable-containing regimen.

The 2022 WHO standardized, 9-month regimen consists of:

- **Intensive Phase:** $BDQ_{(6\ months)}$ + [(MXF or LFX) + CFZ + PZA + EMB + $INH^{HD}]_{(4\ months)}$ + LZD (600 mg)$_{(2\ months)}$ or $ETA_{(4\ months)}$; *may extend 4 month drugs to 6 months if smear positive at the end of 4 months.*
- **Continuation Phase:** [(MXF or LFX) + CFZ + PZA + EMB]$_{(5\ months)}$

The WHO standardized 9-month regimen has **limited application in higher-resource countries** due to the eligibility criteria that excludes use if documented resistance is found to any drug used in the regimen (exception for high-dose INH).

WHO 2020 consolidated guidelines recommend, for situations not appropriate for a shorter-course regimen, choosing drugs for a longer duration regimen based on a ranked priority list that is similar to the stepwise process described in the 2019 ATS/CDC/ERS/IDSA guidelines, with only slight differences in prioritization (see **Figure 1** for comparison).

WHO treatment recommendations for longer duration MDR/RR-TB regimens include: *(conditional recommendation, very low certainty in the evidence)*

- Initiation with at least 4 agents likely to be effective.[3]
- If BDQ is stopped, the continuation of treatment should maintain at least 3 agents likely to be effective.
- Total treatment duration of 18-20 months (or 15-17 months after culture conversion) is suggested for most patients. The duration may be modified according to the patient's response to therapy.

Concerns exist regarding the applicability of WHO guidelines (derived to support care across all settings but particularly addressing realistic limitations in high-incidence/lower-resourced settings) to U.S.-based care of DR-TB. The ATS/CDC/ERS/IDSA guidelines, using an earlier, somewhat smaller dataset from the same IPDMA, reflect PICO queries and conclusions framed by the different practices and available resources in lower-incidence/higher-resourced settings.

More evidence is needed for practice guidance on optimum treatment duration using an individualized approach (based on phenotypic and molecular DST). With the capacity for earlier diagnosis using rapid molecular methods, successful and safer application of LZD, and strong overall treatment success rates, U.S. expert consensus continues to support using culture conversion as the primary guide for minimum treatment duration within the practice conditions of a high-resource setting. On an individual basis, the extent of disease, resistance pattern, and clinical response to treatment will influence final regimen choices and treatment duration.

3 A drug is deemed likely effective based on one or more of the following: Confirmed susceptibility, no known resistance to another drug with cross-resistance, rare use of the drug in a geographical area or setting (possibly supported by low drug-resistance levels from surveillance activities), and no previous use of the medicine in a regimen that failed to cure the individual patient.

Mono-resistant *Mycobacterium (M.) tuberculosis*

Isolated resistance to INH

INH mono-resistance is one of the most common forms of drug resistance and is more common in persons with a prior history of TB (17%), compared to those with no prior history of TB (9%), and more prevalent in those who are non-U.S. born (CDC surveillance data 2016-2020). Prior to 2019, the standard recommendation for treatment for INH mono-resistance was RIF, EMB, and PZA (+/- fluoroquinolone) for 6 months. Current ATS/CDC/ERS/IDSA and WHO guidelines recommend the addition of a **later-generation fluoroquinolone (MFX, LFX) with RIF, EMB, and PZA for the full 6 months** as the preferred INH mono-resistance regimen. ATS/CDC/ERS/IDSA guidelines further suggest that in selected situations, the duration of PZA may be reduced to 2 months (lower disease burden or increased risk of PZA toxicity).

- The addition of a later-generation fluoroquinolone for 6 months was associated with a significantly greater treatment success (but no significant effect on mortality) when compared to daily RIF, EMB, PZA (with or without INH) in the individual patient data meta-analyses used for 2020 WHO and 2019 ATS/CDC/ERS/IDSA guideline development.
- Peak plasma concentration and exposure to MFX is decreased by approximately 30% when combined with RIF. U.S. guidelines note that the clinical impact of this decrease in drug exposure has not been established, but many experts use LFX as the fluoroquinolone of choice for INH mono-resistant TB (note: some experts will use MFX but dose adjust based on TDM). WHO guidance states clear preference for use of LFX because of the drug-drug interactions and safety profile.
- Studies in the U.S. have reported relapse rates of 2 to 5% using 3- to 4-drug regimens administered for 6 or more months. However, a large proportion (26-59%) of patients had treatment discontinued or the duration of treatment extended because of drug-related adverse reactions, usually associated with PZA.
- Treatment outcomes do not differ based on whether the isolate has low- or high-level INH resistance *in vitro*.
- In the RIFAQUIN trial, a 6-month regimen that included daily RIF, EMB, PZA and MFX (400 mg) for 2 months followed by once-weekly doses of both MFX and high-dose rifapentine (RPT) (1200 mg) for 4 months, was reported to be as effective as a standard 6-month regimen in drug-susceptible TB. Therefore, the 6-month regimen should be effective for INH mono-resistant TB as long as the isolate is susceptible to the fluoroquinolones.

Conclusion: Based on current evidence, there are at least 3 options for treatment of patients with INH mono-resistant disease.

OPTION 1:

Daily RIF, EMB, PZA plus a later-generation fluoroquinolone for 6 months
(Preferred - 2019 ATS/CDC/ERS/IDSA guidelines)

- If a patient was initiated on a standard 4-drug regimen, INH can be replaced by the fluoroquinolone once resistance is documented, and RIF, EMB, and PZA continued, beginning the 6-month duration with the start of the fluoroquinolone (associated with greater treatment success in IPDMA). Based on clinical considerations (e.g., lower disease burden or adverse effects), some experts will stop treatment at 6 months total (counting treatment doses prior to start of fluoroquinolone).
- LFX may be preferred over MFX (due to drug-drug interactions with RIF).
- Confirm fluoroquinolone susceptibility with growth-based DST (if available, use molecular DST to provide more rapid results).
- In select situations, the duration of PZA may be reduced to 2 months (lower disease burden or increased risk of PZA toxicity).

OPTION 2:

Daily RIF, EMB, PZA for 6 months

- WHO supports as an option if fluoroquinolone resistance or intolerance. This option is a prior standard recommendation but less efficacious than Option 1.

OPTION 3:

Daily RIF, EMB, PZA and MFX (400 mg) for 2 months followed by once-weekly doses of both MFX and high-dose RPT (1200 mg) for 4 months
(RIFAQUIN study)

- Confirm fluoroquinolone susceptibility with growth-based DST (if available, use molecular DST to provide more rapid results).
- In general, intermittent once-weekly continuation phase dosing should be avoided in persons with HIV or cavitary disease (2016 ATS/CDC/IDSA guidelines for drug-sensitive TB), but the RIFAQUIN study included both persons with HIV and cavitary disease. Always use a treatment verification strategy (e.g., DOT) or other medication monitoring system when using intermittent dosing.
- Option 3 not widely adopted in the U.S.

Isolated resistance to RIF

RIF mono-resistance is uncommon but increasing in some areas of the world. The loss of RIF from the treatment regimen has, to date, required a longer duration of therapy, but shifting expert practice includes consideration for the new shorter (6-month) BPaL and BPaLM regimens, recognizing the successful early results published to date and evolving guidelines for MDR-TB. Many experts with experience implementing these regimens for MDR-TB are also applying these regimens on a case-by-case basis for clinically appropriate RIF mono-resistant situations. See ***Shorter-course (6-month) regimens: BPaL and BPaLM*** for important considerations. In addition:

- Resistance to RIF is associated in most cases with **cross-resistance to rifabutin (RFB) and RPT.** In approximately 80% of strains where RIF resistance is documented, the strain is also resistant to RFB. Therefore, use RFB only when *in vitro* or molecular susceptibility is documented. Some experts may use RFB under these conditions, but not consider it a fully reliable drug in the regimen.
- Use molecular testing to identify the particular mutation associated with RIF resistance; it may help to rapidly identify isolates that retain susceptibility to RFB (see **Chapter 3, *Laboratory***). This is also important as various labs use different cut points to test RFB susceptibility, and the molecular test is likely a better indicator.
- Resistance to RPT is universal in RIF-resistant isolates.

In situations of resistance, intolerance, or co-morbidities that preclude use of BDQ, Pa, or LZD, or if the person with RIF mono-resistance states a preference for an alternative, other options exist. The evidence base for treatment options is very limited, with past recommendations in the *Survival Guide* driven by expert opinion and prior U.S. guidelines.

- Older (1977) Hong Kong Chest Service, British Medical Research Council (BMRC) study findings supported efficacy of both daily and 3x weekly regimens of INH, PZA, and SM for 9 months.
- Based on the BRMC findings and acknowledging that prolonged injectable agent use was not optimal, 2003 ATS/CDC/IDSA TB guidelines recommended: INH + PZA + EMB (+/- fluoroquinolone if extensive disease) for 12 months for RIF mono-resistant disease. An injectable agent was recommended for the initial 2 months in the presence of extensive disease and/or to shorten to a 9-month duration.
- Expert review (past surveys and peer review) for the three prior editions of the *Survival Guide* developed and supported the pragmatic optional regimen substituting a fluoroquinolone for the prolonged PZA and removing the use of an injectable agent (see **Option 2**).

OPTION 1:

BPaL or BPaLM for 6 months (extended to 9 months as needed)
(Preferred – expert opinion; case-by-case basis)

- See full discussion in section: ***Shorter-course (6-month) regimens: BPaL and BPaLM***
- Seek expert consultation, noting that use for RIF mono-resistance is currently not included within 2022 *Provisional CDC Guidance for the Use of Pretomanid as part of Regimen [BPaL] to Treat Drug-Resistant Tuberculosis.*

OPTION 2:

INH, EMB, and a fluoroquinolone daily for 12 to 18 months, supplemented with PZA for at least 2 months during the intensive phase

- In patients with extensive cavitary disease, or to shorten the duration of therapy (e.g., 12 months), consider addition of LZD.

Isolated resistance to EMB, PZA, or SM

Isolated resistance to EMB, PZA, or SM will have little impact on the efficacy of the treatment regimen.

- Loss of EMB or SM from the regimen will not decrease the efficacy or change the treatment duration.
- **Loss of PZA** from the regimen, however, requires prolonging the duration of therapy with INH and RIF by 3 months, for a **total of 9 months of therapy.**
- Most PZA mono-resistant isolates are due to *Mycobacterium (M.) bovis.*

Poly-resistant *M. tuberculosis*

TB due to organisms that demonstrate *in vitro* drug resistance to more than one anti-TB drug (but not both INH and RIF) is referred to as poly-resistant TB. Any number of combinations of resistance can occur, but the outcome of treatment is usually good.

- Treatment should include the use of as many first-line agents as possible, i.e., INH or RIF plus other remaining first-line drugs, in addition to a later-generation fluoroquinolone. The strategy for picking additional drugs would follow the same prioritized list as when building an MDR-TB regimen.
- Drug combinations and durations of treatment for poly-resistant options do not, for the most part, have supportive clinical trial data. Treatment options have been suggested by experts based on evidence that does exist and assumptions on drug substitutions or contributions to build a desired bactericidal and sterilizing combination (see **Table 2**).

Extensively drug-resistant *M. tuberculosis* (XDR-TB)

XDR-TB was previously defined as resistance to at least INH, RIF, a fluoroquinolone, and 1 of 3 second-line injectable agents (AK, KM, or CM). Because of the recommendations to use all-oral regimens, the WHO revised its definitions in 2021, added a new pre-XDR-TB definition that does not include reference to injectable agent resistance (MDR-TB plus resistance to a later generation fluoroquinolone) and defining XDR-TB as MDR-TB plus resistance to a later generation fluoroquinolone and additional resistance to one of the other Group A drugs (currently LZD, BDQ). CDC's updated definition of XDR-TB and the new inclusion of pre-XDR-TB for surveillance reporting were published in 2022 and represent a hybrid between old and new WHO definitions (keeping injectable agents in definitions, reasoning that a shift away from injectable use may not be immediate or all-encompassing).

New Pre-XDR and XDR definitions: WHO January 2021 and CDC January 2022

Pre-extensively drug-resistant (Pre-XDR): MDR plus resistance to

- Fluoroquinolones WHO January 2021
- Fluoroquinolones or second-line injectable CDC January 2022

Extensively drug-resistant (XDR): MDR plus resistance to

- Fluoroquinolones + [BDQ or LZD] WHO January 2021
- Fluoroquinolones + [BDQ or LZD or second-line injectable] CDC January 2022

Until recently, treatment of patients with extensive resistance (MDR + fluoroquinolone + injectable agent; using prior XDR-TB definition) has been challenging because of the lack of potent anti-TB drugs, frequency of adverse reactions, and poor treatment outcomes. Uptake of the new shorter, all-oral BPaL regimen should make treatment of more extensive resistance patterns less challenging. When a longer regimen is needed (particularly in circumstances precluding use of BDQ, Pa, and/or LZD), the approach to designing a treatment regimen is the same as with MDR-TB (**Figure 2**). Duration of treatment for resistance to MDR + fluoroquinolone + [BDQ or LZD] should be at least 15-24 months beyond culture conversion. Surgery may be a consideration in patients with XDR-TB.

- Seek expert consultation to assist management throughout the treatment duration.

TABLE 2. **Treatment regimens for mono-resistant and poly-resistant TB**

No evidence base exists for many resistance combinations; regimens are based instead on pragmatic expert opinion and experience. Consider safety, tolerability, site/extent of disease, patient preference, and response to treatment when choosing a regimen and final duration.

Pattern of resistance	Suggested regimen	Minimum duration of treatment	Comments
INH RESISTANT (RIF susceptible)			
INH	RIF, later-generation fluoroquinolone, EMB, and PZA (2-6 months) [More options, see section: ***Isolated resistance to INH***]	6 months	A shorter duration of PZA (2 months) should be considered in selected situations (e.g., non-cavitary and lower-burden disease or toxicity from PZA).
INH and **EMB***	RIF, later-generation fluoroquinolone and PZA (2-6 months)	6 - 9 months	The longer duration of treatment should be used for patients with extensive disease. With this resistance pattern there is a risk for acquired RIF-resistance when HRZE (RIPE) is used initially pending DST results.
INH and **PZA***	RIF, later-generation fluoroquinolone and EMB	9 - 12 months	The longer duration of treatment should be used for patients with extensive disease (and some experts consider substituting LZD for EMB).
INH, EMB, and **PZA***	RIF, later-generation fluoroquinolone, and LZD	9 - 12 months	An additional drug (choose from prioritized list, see **Figure 1**) may strengthen the regimen for patients with extensive disease and consider the longer duration of treatment.
INH and **FQ***	RIF, EMB, PZA	6 - 9 months	LZD may strengthen the regimen for patients with extensive disease and consider the longer duration of treatment.
RIF RESISTANT (INH susceptible; +/- additional resistance to EMB or PZA)			
RIF*	BPaL or BPaLM [More options: see section ***Isolated resistance to RIF***]	6 - 9 months	Standard regimen is 6 months (26 weeks); extend to 9 months (39 weeks) if evidence for delayed clinical, radiographic, or microbiologic response (lack of culture conversion) to treatment at 8 weeks.
PZA RESISTANT (RIF and INH susceptible)			
PZA	INH, RIF	9 months	Most commonly seen in *M. bovis* infections.

*Option based on expert opinion – seek expert advice when considering.

When to consider an expanded empiric treatment regimen

Molecular diagnostics have greatly decreased the time to obtain DST results, allowing earlier initiation of an appropriate treatment regimen while awaiting additional phenotypic results. **With broader access to rapid molecular DST, an empiric regimen is generally not needed in clinically stable cases.** For many drugs, however, accurate molecular tests are not available, and the risk of drug resistance must be anticipated.

The decision to start an expanded empiric regimen with the inclusion of second-line drugs prior to availability of susceptibility results (molecular or growth-based) will be determined by the level of suspicion for DR-TB and the severity of illness. When suspicion for DR-TB is high (e.g., concern for treatment failure or previous treatment, especially if self-administered), an expanded empiric treatment regimen may be warranted, especially in cases with life-threatening TB.

Expanded empiric treatment regimen

An expanded empiric regimen usually consists of the 4 first-line drugs (INH, RIF, EMB, PZA) and 2 or more additional new drugs considered likely to be effective. Additional drugs to consider include:

- A later-generation fluoroquinolone: MFX or LFX
- LZD
- If more options are needed, use the stepwise guide for choosing an MDR-TB regimen (**Figure 1**) to find the best empiric options

The use of the standard 4 first-line drugs with **the addition of a single drug (a fluoroquinolone or other second-line agent) is not a sufficient expanded empiric regimen** for MDR-TB due to concerns for potential resistance to multiple first-line agents. When extensive disease or resistance is suspected, do not limit the empiric regimen to just 6 drugs.

When choosing 2 or more empiric second-line drugs, consider:

- The previous treatment history of the patient
- The drug-resistance pattern of the source case
- The likely patterns of resistance in the patient's region of origin
- Potential drug-drug interactions (e.g., BDQ with a rifamycin)

Given the importance of drug-susceptibility results, make every effort to obtain high-quality specimens for culture and DST.

The treatment regimen should be changed once the DST results are available.

There are also situations in which it **may be more appropriate to defer treatment start or initiate a 4-drug (first-line) regimen.**

- This is particularly true if an inappropriate regimen may risk amplification of drug resistance. If few treatment options remain, definitive treatment may be the patient's last chance for cure.
- Deferring treatment until DST results are available is an appropriate option only if the patient is not severely ill and can be isolated to prevent transmission to contacts.
- Initiation with an empiric 4-drug (first-line) regimen may be appropriate if prior first-line treatment for pan-sensitive disease was completed under well-documented DOT conditions, and primary suspicion is relapse due to the original pan-sensitive strain.

Specific drugs

Priority drugs (WHO Groups A and B)

Later-generation fluoroquinolones: Levofloxacin and Moxifloxacin (LFX, MFX)

The fluoroquinolones have potent *in vitro* and *in vivo* activity against *M. tuberculosis* and the loss of a fluoroquinolone from an MDR treatment regimen is associated with poor treatment outcomes. Data from *in vitro*, murine, and human studies have demonstrated that later-generation fluoroquinolones (LFX, MFX) are more active than ciprofloxacin or ofloxacin (OFX). Resistance to the fluoroquinolones is conferred by mutations in gyrase A and B. Cross-resistance among the fluoroquinolones is common but not universal. Studies report that approximately 30% of OFX-resistant strains are still susceptible to MFX. Several recent studies have evaluated the significance of this retained susceptibility. In a 2014 retrospective study from the Republic of Korea by Jo et al., MDR-TB patients with OFX-resistant disease had significantly better treatment outcomes when the isolate was MFX-susceptible (treatment success in 73% vs. 42%).

- A 2018 IPDMA demonstrated that in patients with fluoroquinolone-susceptible isolates, LFX (aOR 4.2; 95%, 3.3-5.4) and MFX (aOR 3.8; 95%, 2.8-5.2) were associated with treatment success and fewer deaths. There were no significant differences between the two fluoroquinolones.
- In two retrospective studies, LFX (500-1000 mg/day) and MFX (400 mg/day) showed similar treatment success in MDR-TB patients.
- In a 2012 randomized open label trial LFX (750 mg/day) and MFX (400 mg/day) were shown to have similar culture conversion rates at 3 months.
- The later-generation fluoroquinolones tend to be tolerated well. The IPDMA demonstrated that LFX had to be discontinued due to adverse effects in 4.0% of recipients and MFX in 3.5% of patients.
- The most frequent adverse events are gastrointestinal in 3% to 17% and CNS in 0.9% to 2.8%. QTc interval prolongation occurs.

- FDA strengthened warnings regarding the use of fluroquinolones because of the rare but significant risk of hypoglycemia, certain mental health side effects and tendonitis, as well as risks of ruptures or tears of the aorta.
- The risk of tendonitis and tendon rupture is increased in older patients (usually over 60 years of age), in patients taking corticosteroids, and in patients with kidney, heart, or lung transplantation.
- LFX requires dose adjustment with renal impairment (if creatinine clearance < 50 mL/min) but is presumed to be safe to use with liver disease.
- MFX does not require dose adjustment in renal failure but is infrequently associated with hepatotoxicity and thus should be used with caution in cases of liver impairment.
- MFX metabolism is increased in combination with RIF (through glucuronide conjugation pathway) with peak plasma concentration decreased by approximately 30%; LFX may be preferred fluoroquinolone for combination with RIF.
- For more details see **Chapter 5, *Medication Fact Sheets.***

Conclusion: MFX or LFX (750-1000 mg) should be used in the treatment of all cases of MDR- and XDR-TB when using a longer individualized treatment regimen except in the setting of documented *in vitro* resistance to high concentrations of MFX. Recent studies suggest no clinical advantage between MFX or LFX for MDR-TB. When fluoroquinolone resistance is found by critical concentration or by molecular testing, an MIC—usually for MFX—can help inform whether an increase in dose may benefit the patient. Although there is minimal published evidence to support this approach, some MDR-TB experts use "high-dose" MFX at 600 mg or 800 mg daily for patients with MFX MIC of 1 or 2 mcg/mL. For further information on use of MICs or on mutations for fluoroquinolone resistance, see **Chapter 3, *Laboratory.***

Bedaquiline (BDQ)

BDQ is a diarylquinoline drug with significant *in vitro* and *in vivo* activity against *M. tuberculosis.* BDQ was approved by the FDA in 2012 for the treatment of MDR-TB when used as part of a multidrug regimen for pulmonary MDR-TB when an effective regimen cannot otherwise be provided. BDQ has bactericidal and sterilizing activity and acts through ATP synthase inhibition. Cross resistance has been reported with clofazimine. BDQ is also notable for a prolonged terminal half-life of approximately 5.5 months. Both WHO and CDC have issued guidelines for the use of BDQ in the treatment of MDR- and XDR-TB.

- Efficacy of BDQ was assessed in three Phase IIb studies, two of which were randomized placebo-controlled trials and the other a noncomparative single-arm open-label trial.
  - Sputum culture conversion at 8 weeks and 24 weeks was higher in the BDQ arm compared with placebo.
  - A higher mortality was noted in the BDQ (12.6%) compared with the control arm (4.9%) in the 2014 Phase IIb studies. Although the mortality was higher in the BDQ arm, the mortality rate in the control was unexpectedly low. Seven patients died during the trial at a median of 386 days after the last dose. No common cause for the excess mortality was identified and follow-up observational studies have not reported a high mortality rate.

- A propensity-score matched 2018 IPDMA that included 411 patients who received BDQ and 10,932 who did not receive BDQ reported that treatment success was slightly greater with BDQ (70% vs. 60%). Failure/relapse (6% vs. 9%), death (10% vs. 15%) and loss to follow-up (14% vs. 16%) were less with BDQ-containing regimens.
- In the IPDMA, the combination of BDQ and LZD or CFZ was associated with higher treatment success than when the combinations were not used.
- An all-oral BDQ-containing regimen was associated with a treatment success rate of 70% versus 57% in regimens containing an injectable agent in a programmatic assessment from South Africa.
- BDQ has been well tolerated in clinical trials and programmatic reports. In the IPDMA, only 3.5% of 1,266 patients discontinued BDQ due to adverse events. Only 8 (0.9%) of 875 discontinued because of QT interval prolongation and 2 restarted without incident.
- CDC recommends that BDQ be used for 24 weeks of treatment in adults with laboratory-confirmed pulmonary MDR-TB when an effective treatment regimen cannot be provided without it. BDQ may be used on a case-by-case basis in children, people with HIV, pregnant women, people with extrapulmonary MDR-TB, and patients with co-morbid conditions. It may be used on a case-by-case basis for longer than 24 weeks. In addition, CDC recommends BDQ be administered for 26 weeks as part of BPaL regimen. EKG monitoring at baseline and 2, 12, and 24 weeks of treatment is advised (additional monitoring if clinically indicated; see **Chapter 8, *Monitoring and Case Management***).

Conclusion: BDQ is a well-tolerated drug that is associated with treatment success and lower mortality than BDQ-free regimens. It is highly recommended for the treatment of MDR- and XDR-TB.

Linezolid (LZD)

LZD is an oxazolidinone antibiotic that inhibits protein synthesis by preventing the fusion of the 30S and 50S ribosomal subunits. LZD also binds to mitochondria and inhibits protein synthesis that can lead to drug-related toxicity. There is no cross resistance with other currently used antimycobacterial drugs.

- In a 2018 IPDMA, patients who received LZD-containing regimens were more likely to achieve treatment success (aOR 3.4;95% CI, 2.6-4.5) and have a lower rate of death (aOR 0.3; 95% CI 0.1-0.2) than those who did not receive LZD.
- In two randomized studies, XDR-TB (pre-2021 WHO definition: resistance to INH, RIF, fluoroquinolone, and injectable agent) patients treated with LZD had higher culture conversion and treatment success than those in control arms.
  - In both studies, 82% of patients had clinically significant adverse events; of these patients, 93% had events that were possibly or probably related to LZD. A 300-mg dose was associated with a lower rate of adverse reactions, but there was a trend towards acquired resistance at the lower dose.
- LZD has been associated with high frequencies of hematologic and neurologic adverse events including in the Nix-TB trial (LZD 1200 mg daily for at least the first month) of the BPaL regimen. In most patients, interruption of dosing or dose reduction was required to complete the regimen.

- Hematologic toxicity was reported most frequently from 2 to 8 weeks (25%) but can occur throughout the duration of treatment. Anemia was the most frequent (37%), followed by neutropenia (8%) and thrombocytopenia (5%).
- Median time to onset of severe anemia was 10 weeks, and a 10% decrease in hemoglobin at 1 month of treatment predicted risk for severe anemia.
- Post-treatment 24-month follow-up showed that neuropathy symptoms resolved in 82%, remained mild-moderate in 12%, and severe in 1% of participants.
- The subsequent ZeNix trial showed comparable efficacy with reduced adverse effects using LZD 600 mg for the full 6-month treatment duration.

- Hematologic toxicity can occur quickly after starting therapy. Neurotoxicity (peripheral neuropathy and optic neuritis) usually occurs after 12-20 weeks of therapy.
- Current expert practice includes TDM for LZD, particularly adjusting dosing if trough > 2 mcg/mL to reduce potential for adverse effects (see section: **TDM**).
  - Of note, a sub-analysis of Nix-TB data suggests that neuropathy symptom screening performed better than LZD trough for predicting risk for neuropathy; and symptom screening for neuropathy with hemoglobin may be a more pragmatic monitoring strategy for LZD, with trough measurements having potential value for studying toxicity on a population level.
- Administration of LZD concurrently with serotonergic agents (antidepressants such as selective serotonin reuptake inhibitors [SSRI]) can lead to serious (sometimes fatal) reactions such as serotonin syndrome or neuroleptic malignant syndrome-like reactions. Alternative medications or nonpharmaceutical modes of depression treatment should be used when possible.
- Prior expert recommendations suggested use of vitamin B6 while taking LZD. However, the mechanism of toxicity for LZD is unclear and may be associated with mitochondrial toxicity. B6 is not thought to play a role in most LZD-related adverse events and unlikely to have protective benefits.

Conclusion: LZD is an active drug and should be considered for all MDR- and XDR-TB regimens except when in vitro resistance to LZD is documented. To avoid toxicity, LZD should be initiated in patients with TB at 600 mg once daily (with dose adjustments as needed). Closely monitor patients for development of neurologic or hematologic toxicity. Many experts adjust dosing to achieve trough concentrations < 2 mcg/mL, using 3x week dosing or dose reduction if necessary.

Clofazimine (CFZ)

CFZ is a fat-soluble riminophenazine approved for treatment of multibacillary *M. leprae.* The drug has both *in vitro* and *in vivo* sterilizing activity against *M. tuberculosis*, but the exact mechanism of action is not fully understood. In 2004, the manufacturer, Novartis, discontinued drug distribution in the U.S., but CFZ is available through an expanded access program with Novartis. See **Chapter 5, *Medication Fact Sheets*** for procurement information.

- In a propensity-score matched 2018 IPDMA, treatment success was more likely with the use of CFZ than regimens that did not use CFZ with an adjusted OR of 1.5 (95% CI, 1.1-2.1). The combination of BDQ and CFZ was associated with an adjusted OR of 5.0 (95% CI, 2.4-10.6) for treatment success versus failure/relapse.

- CFZ-containing regimens have been associated with a higher percentage of culture conversion (40% vs 29%) and an independent predictor of conversion and survival in patients with XDR-TB (pre-2021 WHO definition, resistance to INH, RIF, fluoroquinolone, and injectable agent).
- In a small randomized controlled trial from China, sputum culture conversion and cavity closure occurred earlier in patients in the CFZ-containing regimen, and treatment success was higher (74% vs. 54%).
- Systematic reviews examining the use of CFZ for the treatment of MDR-TB have reported that CFZ is well tolerated (despite associated skin discoloration and photosensitivity). Pooled estimate for frequency of severe adverse drug reactions requiring withdrawal of CFZ was 0.1%.
- In an IPDMA, 2 of 81 (2.5%) of patients treated with CFZ had treatment discontinued for adverse events. Brownish skin discoloration has been described in 75 to 100% of recipients whereas ichthyosis has been reported in 8% to 20%, gastrointestinal intolerance in 40% to 50%, and neurological disturbances in up to 13% of patients. Adverse events can persist for months after discontinuation of CFZ because of the long half-life.
- QT prolongation can occur with CFZ but is most notable when combined with other QT-prolonging drugs like BDQ, DLM, and later-generation fluoroquinolones.
- Cross-resistance with BDQ can occur through an efflux-mediated process.
- Procurement through the Novartis expanded access program can be labor-intensive; potential delays in access should be anticipated.

Conclusion: CFZ appears to be a relatively well-tolerated drug and likely contributes activity to a multidrug regimen. CFZ should be used as part of longer individualized treatment regimens.

Cycloserine (CS)

CS is an oral bacteriostatic drug that inhibits cell wall synthesis by competitively blocking the enzymes that incorporate alanine into an alanyl-alanine dipeptide, which is an essential component in the mycobacterial cell wall. CS has no cross resistance with other antimycobacterial drugs. Few laboratories perform DST to CS because of specific technical challenges, poor accuracy of testing in liquid media, no accepted critical concentration or breakpoint, and poor reproducibility of results. Early studies using CS monotherapy produced rapid clinical response. When combined with INH, patients also improved, but INH resistance emerged.

- In the 2018 IPDMA, the inclusion of CS was associated with an adjusted OR for treatment success of 1.5 (95%, 1.4-1.7) and a decrease in mortality (aOR 0.6; 95% CI, 0.5-0.6).
- CS has good penetration into the CSF.
- Some experts recommend obtaining serum peak concentrations within the first 1 to 2 weeks of therapy, with appropriate drug dosage adjustment and repeat concentrations periodically or as clinically indicated by new side effects or change in creatinine clearance.
- The primary limitation to the use of CS is the high frequency of neurologic toxicity in comparison to other second-line drugs.

- Stepwise initiation of dosing may be used to support tolerability. See section: Escalation of dosages (drug ramping). Most patients will achieve target serum concentrations on 250 mg (for smaller patients) to 500 mg total daily dose.
- In a systematic review, the pooled estimate for the frequencies of any adverse reaction resulting in discontinuation from CS was 9.1%, 5.7% for psychiatric reactions, and 1.1% for CNS-related adverse drug reactions.
- Although there are little supporting data, many MDR-TB experts recommend that patients should receive vitamin B6 while taking CS to prevent neurologic adverse events.

Conclusion: CS appears to be an effective drug but can be associated with significant neurological and psychiatric toxicity, particularly with elevated serum concentrations. CS can be administered safely with monitoring of serum drug concentrations.

Add-on drugs as needed (WHO Group C)

Second-line: Injectable agents, Amikacin and Streptomycin (AK, SM)

The aminoglycosides (AK, KM, and SM) and polypeptide (CM) are active *in vitro* against *M. tuberculosis* and have traditionally represented a critical component in treatment regimens during the intensive phase of therapy. However, the adoption of all-oral regimens has decreased the need for aminoglycosides/polypeptides in the treatment of MDR-TB. These drugs block protein synthesis at the ribosomal level by binding to the 16S ribosomal subunit. Aminoglycosides use concentration-dependent killing, have a post-antibiotic effect, and show synergism with other antibacterial drugs. Resistance to the aminoglycosides and polypeptides is most commonly conferred through a mutation in the rrs gene. Studies have reported variable rates of cross-resistance among these drugs, but in general:

- AK-resistant isolates are resistant to KM and occasionally CM.
- KM-resistant isolates are usually resistant to AK and possibly CM.
- CM-resistant isolates are variably resistant to KM and AK.
- SM-resistant isolates are usually susceptible to other injectables unless the other drugs have been used previously.

AK and SM can be given either intramuscularly (IM) or intravenously (IV). SM is relatively well tolerated, but resistance to SM is common in some areas. When choosing an injectable agent, weigh toxicity profiles, cost, and likelihood of cross-resistance of the different drugs.

- AK has excellent *in vitro* activity against *M. tuberculosis* and is widely available in the U.S. It is easier to obtain AK serum concentrations than CM concentrations.
- In the 2018 IPDMA, SM and AK were associated with treatment success, including in subgroup analyses of those with underlying fluoroquinolone-resistant isolates. Among patients with XDR-TB, AK was associated with decreased death.

- Neither KM nor CM were associated with any benefits, but KM was associated with fewer treatment successes and CM with an increased risk of death. **KM (not available in U.S.) and CM are no longer recommended for use in ATS/CDC/ERS/IDSA or WHO guidelines.**
- AK was shown to be superior to SM, KM, and CM.
- All the injectable agents have potential for ototoxicity, vestibular toxicity, renal toxicity, and electrolyte disorders.
- SM should be considered in patients for whom the drug is likely to be effective (*in vitro* susceptible and no history of prior use). SM may be less painful than AK when given IM.

Conclusion: With the availability of all-oral regimens, use of injectable agents is discouraged. When needed in a longer regimen, AK is usually the first choice for an injectable because of its superiority in treatment success over other injectables, and ease of procurement, administration, and of obtaining serum levels. CM and KM are no longer recommended.

Delamanid (DLM)

DLM is a nitro-dihydro-imidazooxazole derivative that was approved for the treatment of MDR-TB by the European Medicines Agency (EMA) in 2013. Although data regarding the use of DLM in the treatment of MDR-TB are limited, in 2014 WHO issued recommendations for the use of DLM followed by updated recommendations in 2018. Although DLM is not FDA approved in the U.S., the drug can be accessed through a compassionate use program.

- Several reports, clinical trials, and cohort studies reported that DLM-containing regimens had treatment success rates of 77% to 84%.
- In a 2012 randomized controlled trial, 481 patients were randomized to receive DLM 100 mg twice daily, 200 mg twice daily, or placebo for 2 months in combination with a WHO-recommended regimen. Sputum culture conversion in liquid broth occurred in 45.4% of the patients taking DLM at 2 months compared with 29.6% on the placebo regimen. QT prolongation was more common, but there were no clinical events related to QT prolongation.
- DLM has been well tolerated. QT prolongation is possible and routine EKG monitoring is recommended. When combined with BDQ, the QTc interval has a mean change from baseline from 11.9 ms with BDQ alone, 8.6 ms with DLM alone, and 20.7 ms when BDQ and DLM are given in combination.
- DLM is in the same drug class as, and has cross-resistance with, Pa.

Conclusion: DLM appears to be a well-tolerated, active agent in a multidrug regimen and may be considered for treatment of MDR/XDR-TB through a compassionate use program.

Ethambutol (EMB, E)

EMB is an ethylenediamine that inhibits mycobacterial cell wall arabinosyl transferases, leading to depletion of arabinogalactan and lipoarabinomannan. EMB has bacteriostatic activity against *M. tuberculosis.*

- The primary role of EMB in the treatment of drug-susceptible TB is the prevention of the emergence of resistance to other drugs.
- In an IPDMA that was performed before BDQ and LZD were commonly used, administration of EMB among patients with EMB-susceptible isolates was associated with an adjusted OR of 1.7 (95% CI, 1.2-2.4) for cure/completion versus failure/relapse compared with those with resistant isolates.
- Resistance to EMB is conferred by mutations in *embB* but this only accounts for 60% of resistance.
- EMB resistance is common among MDR-TB patients, having been reported to occur in as many as 50-60% of MDR-TB cases, but this varies widely.
- Reproducibility of DST is relatively poor and not currently recommended by WHO although commonly performed in the U.S.

Conclusion: EMB provides some protection against the emergence of resistance to companion drugs and can be used as part of an individualized regimen when susceptibility has been demonstrated.

Pyrazinamide (PZA, Z)

PZA is a nicotinic analog and prodrug that is converted *in vivo* into pyrazinoic acid that interferes with mycobacterial fatty acid synthase. PZA is an essential first-line drug with substantial sterilizing capacity that allows shortening of an INH- and RIF-based regimen to 6 months. Resistance occurs due to mutations in the *pncA* gene. Its role in the treatment of MDR-TB has been uncertain because of limited availability, reliability, and reproducibility of phenotypic DST.

- In a 2012 retrospective analysis of the outcomes of MDR-TB in Hong Kong, 194 patients were stratified by PZA use and drug susceptibility. PZA use with documented PZA susceptibility was more likely to demonstrate early culture conversion and treatment success than non-PZA user and PZA user with PZA-resistant organisms.
- In a 2015 retrospective study of 668 patients with MDR-TB in Peru, the mortality rate for a regimen of 5 likely effective drugs, including likely effective PZA (usually based on DST results), was similar to the mortality rate for regimens of 5 likely effective drugs without PZA. There was no demonstrated benefit of PZA when the drug was considered unlikely to be effective.
- An IPDMA demonstrated that treatment success was significantly less likely with regimens containing PZA (aOR, 0.7; 95% CI, 0.5-0.9). This may have been due to the possibility that patients who did not take PZA were more likely to have received LZD.

- Common adverse events include gastrointestinal upset and arthralgias. A review reported that PZA was associated with adverse events in 56 (2.8%) of 2023 patients.
- Hepatic enzyme elevations are common and significant hepatoxicity can occur.
- Modest elevations in uric acid are common but usually asymptomatic.

Conclusion: PZA may be included if deemed likely to be effective (drug susceptible and/or never used) but is prioritized lower when building a DR-TB regimen. In situations in which PZA resistance is documented, the drug should be discontinued.

Carbapenems (Imipenem [IMP], Meropenem [MPM])

β-lactam antibiotics undergo rapid hydrolysis by β-lactamase enzymes in *M. tuberculosis* rendering them inactive. The carbapenem antibiotics (imipenem, meropenem, ertapenem) have variable *in vitro* and *in vivo* activity against *M. tuberculosis*. The combination of carbapenems with the β-lactamase inhibitor clavulanate has been shown to improve the MIC of MPM and is bactericidal in murine tuberculosis. Clinical experience with carbapenems for the treatment of MDR/XDR-TB is limited and the duration of treatment is generally restricted to the intensive phase.

- 8 of 10 patients treated with intravenous IMP, 1000 mg every 12 hours as part of a multidrug regimen, converted sputum cultures to negative, and 7 remained culture negative after treatment.
- 5 of 6 patients with severe XDR-TB converted cultures to negative with a regimen containing MPM plus amoxicillin/clavulanate (included as a source for clavulanate which is not available as a free-standing drug).
- A systematic review noted that carbapenems were safe and likely effective for treatment of MDR-TB and XDR-TB.
- The 2018 IPDMA demonstrated improved treatment success (aOR4.0; 95% CI1.7-9.1) in persons treated with a carbapenem but no had no effect on death or culture conversion.
- Carbapenems with clavulanate are generally well tolerated with discontinuation rates of 0% to 3% and minor adverse effects in 5% to 6%.

Conclusion: Carbapenems plus clavulanate are associated with improved treatment success and are well tolerated. They can be used as an active component of an MDR/XDR-TB regimen but require intravenous administration.

Ethionamide (ETA)

ETA is a derivative of isonicotinic acid which is similar in structure to INH. ETA is a prodrug and requires activation that enables it to inhibit mycobacterial fatty acid synthesis, thereby impairing cell wall synthesis and repair.

- ETA is generally bacteriostatic but may be weakly bactericidal at higher doses.
- Mutations in the *inhA* region of *M. tuberculosis* can confer resistance to ETA as well as to INH at low concentrations. In this situation, ETA may not be the best choice of a second-line drug unless the organism has been shown to be susceptible with *in vitro* testing and/or no *inhA* mutation is detected.

- Previous studies demonstrated an increase in the likelihood of treatment success when ETA was included in the treatment regimen. However, an updated IPDMA showed no benefit with the use of ETA in MDR-TB treatment regimens, even in the setting of phenotypic susceptibility.
- Gastrointestinal side effects are common with ETA. Hypothyroidism occurs in approximately 20% of patients receiving ETA and is particularly common with the co-administration of PAS.

Conclusion: When choosing a final tier, oral second-line drug, ETA may be considered except in the setting of low-level INH resistance and/or the presence of an *inhA* mutation. The combination of ETA and PAS is associated with high rates of gastrointestinal intolerance and hypothyroidism.

Para-aminosalicyclic acid (PAS)

PAS is a bacteriostatic drug that was one of the first antimycobacterial drugs used to treat TB. The mechanism of action is not known. There is no cross resistance with other mycobacterial drugs, but PAS protects against the emergence of resistance to companion drugs.

- In an IPDMA, PAS was not associated with success but was associated with an increased risk of death (aOR 1.2; 95% CI, 1.1-1.4).
- Gastrointestinal upset is the most common adverse event.
- Rare hepatotoxicity and thrombocytopenia have been reported.
- Hypothyroidism is particularly common with co-administration of ETA.

Conclusion: PAS is bacteriostatic and associated with significant gastrointestinal adverse events. Because no benefit was demonstrated in the IPDMA, PAS should be reserved for patients in whom more active drugs cannot be used to complete a regimen with ≥ 5 likely effective drugs.

High-dose INH (INH^{HD})

Resistance to INH is most commonly conferred through mutations in *katG* or *inhA*. Resistance to *katG* results in inhibition of catalase activity and the development of high-level resistance (resistance at 1.0 mg/mL on solid media) to INH whereas mutations in *inhA* or the promoter region result in lower levels of resistance (resistance at 0.2 mg/mL). Theoretically, it may be possible to overcome the resistance in the setting of low-level resistance by increasing the dose of INH.

- Use of INH (standard dose) was associated with better survival rates in patients with the "W-strain" variety of multidrug-resistant *M. tuberculosis* that was susceptible to higher concentrations of INH.
- In a double-blind randomized controlled trial of INH^{HD} (16-18 mg/kg; adult dosing) vs placebo in addition to second-line drugs, those who received high-dose INH were 2.4 times more likely to convert cultures to negative than those on placebo and they had a 2.4 times higher rate of being culture negative at 6 months. There was a higher frequency of peripheral neuropathy in the high-dose INH arm (but pyridoxine was not provided).

- INH^{HD} is used in 9-month treatment regimens such as the STREAM regimen and the all-oral BDQ-containing regimen recommended by WHO.

Conclusion: INH^{HD} may be considered in patients whose isolate has low-level resistance *in vitro* and evidence of an *inhA* mutation with no evidence of a *katG* mutation.

Other drugs

Pretomanid (Pa, PMD) – New drug

Pa (previously PA-824) is a novel oral bicyclic nitroimidazooxanine with bactericidal activity against *M. tuberculosis* with MICs ranging from 0.015 to 0.25 mcg/mL and sterilizing activity in a non-replicating model. Pa kills actively replicating *M. tuberculosis* by inhibiting mycolic acid synthesis and kills non-replicating organisms by nitric oxide release.

- Pa is in the same drug class and has cross resistance with DLM.
- The combination of BDQ, Pa, and LZD (BPaL regimen, Nix-TB trial) was associated with good treatment success in a single arm study of patients with XDR-TB or treatment-intolerant or nonresponsive MDR-TB. Based on this study, Pa was approved by the FDA in August 2019 and recommended by CDC for use with BDQ and LZD. Similar supportive results for BPaL and BPaLM regimens were seen in ZeNix and TB PRACTECAL studies respectively.
- Adverse reactions due to Pa require additional study because the drug was administered with other drugs during the clinical trials.
- Rodent studies demonstrated testicular toxicity although this was not replicated in monkeys and there was no evidence of this toxicity in human trials.
- New data on the safety of Pa based on hormone evaluations in four clinical trials and a paternity survey have largely alleviated previous concerns on reproductive toxicities observed in animal studies, suggesting that adverse effects on human male fertility are unlikely.
- A study assessing semen in men undergoing treatment that includes Pa is in progress and will address any remaining concerns.

Conclusion: Use of Pa in combination with BDQ and LZD (BPaL) is recommended by CDC for the treatment of pre-XDR and XDR-TB (pre-2022 CDC definition: resistance to INH, RIF, fluoroquinolone, and injectable agent), as well as MDR-TB (treatment intolerant/non-responsive). WHO recommends BPaLM if fluoroquinolone susceptible. Many experts consider BPaL or BPaLM attractive options for other situations in which rifamycins cannot be used.

Rifamycins

The rifamycins (RIF, RFB, RPT) are essential first-line drugs for the treatment of drug-susceptible TB. Loss of RIF from the treatment regimen results in the need to prolong the duration of therapy to 12-18 months. By definition, MDR- and XDR-TB are resistant to RIF *in vitro* or by molecular assays documenting mutations in the *rpoB* region of the genome.

- RIF-resistant strains may be susceptible to RFB in < 20% of strains tested by various DST methods. Susceptibility to RFB and resistance to RIF is strongly associated with a specific mutation, *rpoB* 435Val (516Val using prior *E.coli* codon numbering), that can be identified by line-probe assays or sequencing.
- RPT should not be used to treat MDR- or XDR-TB because cross-resistance with RIF is 100%.

Conclusion: Expert opinion differs, but RFB may be considered for addition to the MDR-TB treatment regimen when *in vitro* susceptibility has been documented in a reliable laboratory and especially if molecular assays document the *rpoB* mutation. However, rifamycins have drug interactions with BDQ and MFX so the use of rifamycins will generally be limited.

Administration of the treatment regimen

Adherence verification/directly observed therapy (DOT)

Case management and supportive adherence verification systems (e.g., DOT) are key activities that contribute to quality care and successful outcomes in the treatment of DR-TB.

For detailed information on monitoring and case management best practice, see **Chapter 8, *Monitoring and Case Management.***

Outcomes of treatment are worse with MDR-TB compared with susceptible disease, and drug-related toxicities are common. Although the cure rate remains high with TB caused by mono-resistant organisms, additional resistance can develop as a result of treatment errors, nonadherence to treatment, or amplification of mono-resistance. Therefore, supportive treatment adherence, e.g., DOT, is strongly recommended for all forms of DR-TB.

MDR-TB can be treated primarily in the outpatient setting.

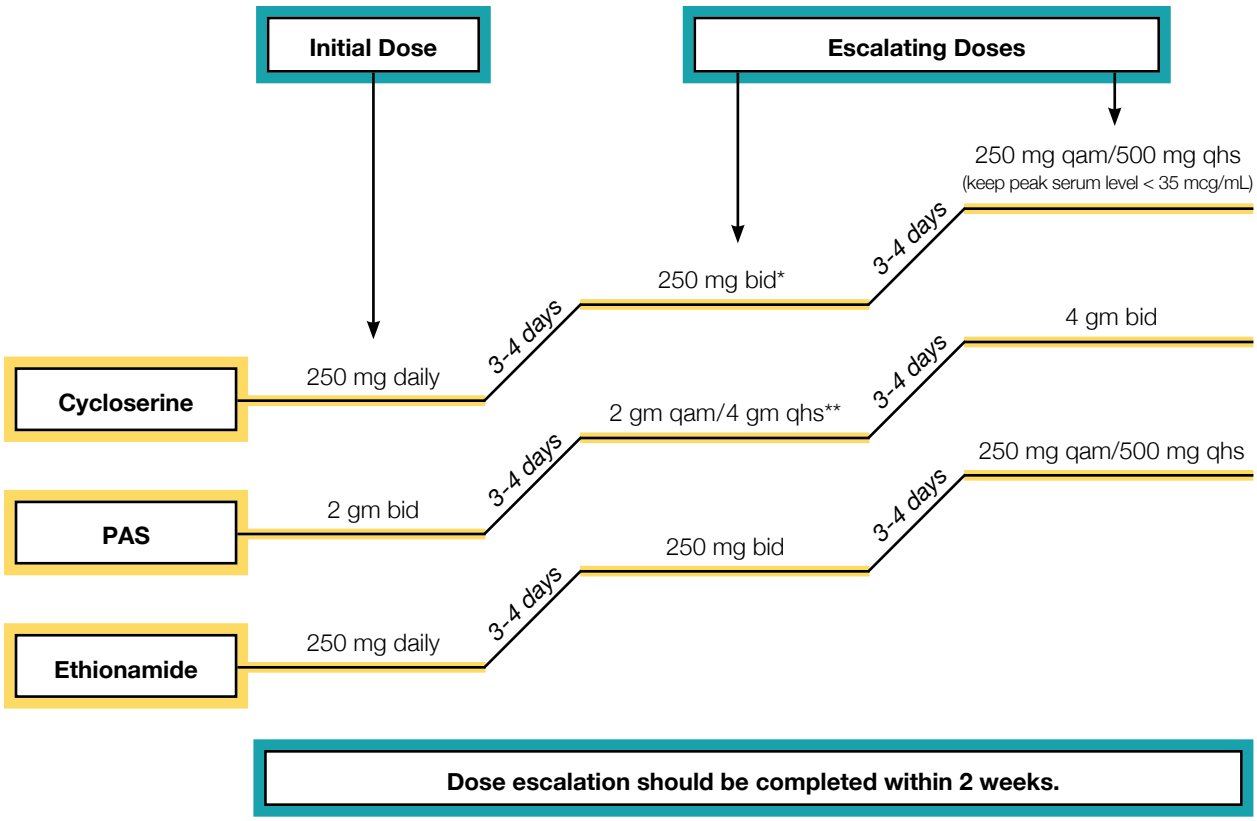
Treat all forms of DR-TB by using strong case management, DOT, and in consultation with experts in the treatment of resistant disease

- Treatment verification can be achieved in the community or clinic (e.g., in-person DOT, v-DOT)
- Person-centered, supportive case management should be implemented (psychological support, financial/material support, nursing assessments) and may occur in the community (during in-person DOT or using telehealth sessions) or in the clinic.
- All DR-TB regimens should be given 7-days per week. Although 7-days per week DOT is optimal, this may not be programmatically feasible. If 7-days-per-week is not possible, 5-days-per-week DOT can be used for patients who are not hospitalized or institutionalized or if no electronic or vDOT systems are in place, with medications self-administered on weekends (some programs will choose not to count unobserved weekend doses in total count).
- Dosing of oral medications for MDR/XDR-TB should always be daily, not intermittent (unless specified by standard dosing recommendations or adjusted due to measured drug levels or indicated in renal impairment).
- Injectable agents are typically given 5 days per week for at least 2-3 months (and until culture conversion is documented); after which, 3-days per week dosing may be considered (some experts will begin with 3-days per week). In severely ill patients, use injectable drugs 7-days per week until the patient is stabilized.

Escalation of dosages (drug ramping)

Most drugs should be started at full dose except **CS**, **ETA**, and **PAS**, in which case the dose of the drug can be increased over a 1- to 2-week period. Beginning with a low dose and gradually increasing the dose leads to greater tolerability and allows the clinician time to manage drug-related adverse effects. This approach of slowly escalating drug dosage is referred to as "drug ramping." Obtain serum drug levels (especially for CS) 1-2 weeks after the goal dose has been reached. See examples of drug ramping in **Figure 2**.

FIGURE 2. **Dose escalation (drug ramping)**



The patient is begun on a low starting dose and the dose is increased every few days until the targeted dose is reached. The dose escalation should be completed within 2 weeks. Some patients will tolerate consolidation of the drugs to once daily dosing which can enhance adherence.

* For many patients, daily dose of cycloserine 250 mg or 500 mg may achieve goal serum concentration. Check level before moving to 250/500 step.

Therapeutic drug monitoring (TDM)

When to order TDM

TDM is routinely used in several circumstances:

- **Aminoglycoside/CM** serum concentrations, especially in patients with **renal impairment**
- **CS** concentrations to minimize risk of **CNS toxicity** and to safely use optimal dose
- **LZD** concentrations to **minimize risk of hematologic and neurologic toxicity** (trough concentration) and ensure efficacy (peak concentration)
- **EMB** concentrations in patients with significant **renal impairment**

TDM is often considered for patients with:

- Known or suspected **malabsorption** (e.g., diabetes, HIV, gastrointestinal disorders)
- **Lack of expected clinical response** or **relapse** while on appropriate drugs and doses, administered by DOT
- **Few effective drugs** in their regimen, to optimize the effect of available drugs
- Potentially significant **drug-drug interactions** such as rifamycins and antiretrovirals
- **Obesity** or **very low body weight** to ensure appropriate dosing

Some experts measure serum drug concentrations in patients with immunosuppression, advanced age, or severe extrapulmonary TB to ensure optimal drug exposure in these potentially difficult to treat cases

Serum concentrations answer the question, "Does my patient have adequate drug exposure?"

- Published normal serum concentration ranges, under most circumstances, represent safe and effective drug exposures (for serum concentration ranges per drug, see **Chapter 5, *Medication Fact Sheets***).
- **If drug MICs are available, some experts will target peak concentrations to be 4-16x higher than the MIC,** using the obtained strain characteristics to guide dosing target as opposed to normative ranges.
- Like other tests, serum concentrations cannot by themselves predict failures or relapses. They can indicate if the patient has lower than expected drug exposure for a given dose of a given drug and demonstrate if it is correctable using concentration-guided dose escalation.
- If a reported drug concentration is not consistent with the clinical scenario, consider repeating the test prior to dose adjustment.

Many DR-TB experts routinely monitor specific TB drug concentrations in anticipation of toxicity (aiming for the lower end of drug a concentration range in patients at risk for specific toxicities or targeting trough values for specific drugs like LZD) and to escalate a drug dose when indicated.

Note: Expert opinion differs on the utility of routine TDM for all drugs in a regimen, based on limited evidence for impact on overall outcomes for populations treated. Experts concur that TDM can contribute to treatment success on an individual patient basis.

More user-friendly methods for measuring TDM are being investigated (e.g., finger-prick dried blood spot or saliva methods) which may improve TDM accessibility in the future.

Timing and interpretation of TDM

Interpret drug levels in the context of several factors:

- Timing of blood draw relative to administration (document and share with lab)
- Evidence for poor response to treatment or side effects
- Known factors likely to increase or decrease clearance of drug (e.g., renal or liver dysfunction, drug-drug interactions)
- Variability of pharmacokinetic (PK) and pharmacodynamic (PD) characteristics between drugs, and whether specific PK/PD targets are well defined for each drug.

Multiple blood draws done in relationship to time of drug dosing can offer more information, but application may differ based on drugs and programmatic limitations.

Timing for TDM may vary based on indication but should be measured once drug levels have reached a steady state after at least 4-5 half-lives have elapsed.

- In practice, **approximately 1-2 weeks after drug initiation** works well (dependent on half-lives of drugs being checked).
- Repeat levels after initial check are only indicated if needed after dose adjustments or if new clinical indications warrant evaluation.
- A shorter wait time can be used for checking drug levels after dose adjustments.

Levels drawn at 2- and 6-hours post-drug dosing are commonly suggested:

- The 2-hour time point approximates the anticipated peak for most desired drugs in a regimen, but it is important to review timing based on individual drugs and choose accordingly (see **Chapter 3, *Laboratory,* Table 9**).
- The 6-hour serum concentration (most commonly used; may vary by drug) can allow a pharmacist to calculate a **maximum concentration (C_{max}) and half-life ($t_{1/2}$)**. The calculated C_{max} should more accurately reflect peak concentrations.
- Calculation of C_{max} and $t_{1/2}$ is not appropriate when 6-hour values are higher than 2-hour values.
- Random samples generally are not informative, including for aminoglycosides.
- **Malabsorption** is suggested if both values are below the normal range.
- **Delayed absorption** is suggested if the 6-hour value approaches the normal range and is higher than the 2-hour value.

Trough levels can be clinically useful for some drugs:

- Elevated LZD troughs > 2 mcg/mL have been associated with impaired mitochondrial function and risk for mitochondrial toxicity-related adverse effects (peripheral neuropathy, optic neuropathy, and bone marrow suppression).

If multiple blood draws are not feasible for a program, providers may prioritize the timing that best addresses the clinical indication for TDM. If using LZD, many experts will prioritize obtaining a trough level.

Note: Proper processing of samples and timing and documentation of blood draws (date/time) relative to dose administration are critical. Any lapses during these steps can produce results that are inaccurate or difficult to interpret.

For more information on where to obtain TDM tests, instructions on timing of blood collected for specific anti-TB drugs, and processing of specimens, see **Chapter 3, *Laboratory.***

Clinical responses to TDM results:

- **If drug concentration is higher than target,** consider reducing dose of the drug especially if signs of toxicity are present (e.g., agitation or depression with a high CS level, or hearing loss with AK).
- **If drug concentration is lower than target,** consider increasing dose of the drug to achieve a concentration in the planned range. Typical "maximum" doses of drugs can be exceeded when serum concentrations are low, but this should be done with caution and monitoring (noting that measured serum levels represent only unbound drug and do not reflect tissue levels).
- **If LZD trough is > 2 mcg/mL,** many experts will change to 3x per week dosing (M/W/F), allowing time for concentration to drop further before the next dose and presumably allow periods of mitochondrial recovery. Note: In published studies, dose reduction to 300 mg (without TDM) has also been used successfully to reduce adverse events.

Role of surgery in the treatment of DR-TB

As treatment regimens have improved, the need for surgery to cure DR-TB has become infrequent. The decision to perform resectional surgery should be made in consultation with an expert in treating DR-TB and should be based on the degree of underlying drug resistance, the presence of focal cavitary disease, and the patient's ability to tolerate surgery.

Both WHO and ATS/CDC/ERS/IDSA guidelines recommend that elective partial lung resection (lobectomy or wedge resection) may be used with an appropriate treatment regimen in selected patients. Although there are no randomized studies assessing the added benefit of surgical resection over anti-tuberculosis chemotherapy alone, systematic reviews and data from an IPDMA have reported benefits in some patients. Treatment success varied between 45% and 77%; the median

postoperative culture conversion was 93.5% (47-100%). Outcome data from 26 cohort studies (18 surgical studies and 8 nonsurgical studies) participating in the IPDMA used for development of the WHO recommendations showed a pooled treatment success of 84% with failure in 6%, relapse in 3%, death in 5% and default in 3% of patients. In the analysis, statistically significant improvements in cure and treatment success were noted among patients who had surgery. However, these benefits were primarily seen in patients who had partial resection but not pneumonectomy.

Perioperative complications were reported in a median of 23% (0-39%) and perioperative mortality in 1.3% (0-5%). Risk factors that have been identified to increase the risk of postoperative bronchopleural fistula include positive cultures at the time of surgery, polymicrobial infections, right pneumonectomy, low FEV1, increased age, technique of bronchial closure, and endobronchial disease.

It appears that surgery for MDR/RR-TB can provide additional treatment benefit in selected patients, but the procedure should only be performed by experienced surgeons after the patient has been on appropriate therapy for several months with the goal of achieving smear and/or culture conversion preoperatively, if possible. Prognosis appears to be better in those who underwent partial resection after culture conversion.

Surgery should be considered:

- When cultures continue to be positive beyond 6 months of treatment for MDR/XDR-TB; and/or
- When extensive patterns of drug resistance exist that are unlikely to be cured with chemotherapy alone; and/or
- When patients develop complications such as massive hemoptysis or persistent bronchopleural fistula.

To maximize the potential success of surgery:

- The patient must represent an acceptable surgical risk and have adequate pulmonary function reserves to tolerate resectional surgery.
- Surgery should be performed by an experienced surgeon and only after several months of chemotherapy have been given.
- Whenever possible, the surgery should be performed after smear conversion has occurred, and ideally after culture conversion.
- Even after successful lung resection, the patient should complete a full course of treatment. If there are no positive cultures after surgery, the date of surgery can be considered the date of culture conversion.

Outcomes of treatment

Treatment outcomes for MDR-TB vary depending on several factors, including the drug-resistance pattern and the drugs used in the treatment regimen. Globally, treatment success is achieved in 60% of patients with MDR/RR-TB. Two systematic reviews including 36 observational studies reported pooled treatment success rates of 62% to 75%, although none of the studies included in the systematic reviews included new drugs such as BDQ, Pa, or DLM. Longer regimens that include newer agents have reported higher treatment success rates when BDQ, LZD, later-generation fluoroquinolones, CFZ or carbapenems have been included in the regimen. An all-oral standardized regimen that includes BDQ has been associated with success rates of 70% versus 57% in regimens that include an injectable instead. The shorter-course BPaL regimen was reported to have favorable outcomes in 90% of participants in a small nonrandomized study that included patients with XDR-TB or intolerant or unresponsive MDR-TB. When MFX was added to BPaL in TB PRACTECAL, 89% of the participants in the BPaLM arm were cured versus 52% in the standard of care group.

Treatment outcomes in the U.S. have also been reported:

Among 134 patients with MDR/XDR-TB who were alive at diagnosis and followed for treatment outcomes in the U.S. between 2005-2007, 78% completed therapy, 9% were transferred, 2% lost to follow-up, 1% stopped because of adverse reactions, and 9% died. Ninety-seven percent of the patients' sputum cultures converted to negative.

- Updated U.S. MDR-TB outcomes data were published within a recent provisional CDC guidance for use of Pa and BPaL regimen (2022). During the period of 2014–2018, 524 new cases of MDR-TB were reported in the U.S. and U.S.-affiliated areas (territories and freely associated states). Of these cases, the resistance patterns included resistance to INH/RIF (443), INH/RIF with the addition of a FQ or injectable agent (72), or the addition of both FQ and injectable agent (9). Of 518 MDR-TB patients alive at diagnosis, 63% were reported as completing treatment within 24 months, and 8% died before treatment completion.
- From 2002-2012, 140 of 339 DR-TB patients in California received expert consultation support provided by the state's MDR-TB service. The majority of these cases were resistant to INH/RIF (79%) but included pre-XDR (addition of FQ or injectable agent resistance) (17%) and XDR-TB (addition of both FQ and injectable agent resistance) (4%). Outcomes when utilizing this service exceeded the published national results: 123 (88%) completed therapy, 7 (5%) moved before completion, 4 (3%) stopped treatment due to adverse events, 5 (4%) died, and 1 (1%) outcome unknown. Mainstays of treatment included fluoroquinolones (94%) and injectable agents (96%) with growing use of LZD (56%) during this period of practice.
    - None of the California patients received newer agents like BDQ, DLM or Pa during this period, so even higher rates of treatment success may be expected going forward.

SUMMARY

- Consult with an expert in DR-TB for all cases of DR-TB.
- Base the choice and design of DR-TB regimens on DST results, prior history of TB treatment, potential for cross-resistance, potential for overlapping drug toxicities, and other key clinical and epidemiologic factors.
- BPaL may be administered for 26 weeks in patients with pre-XDR-TB, XDR-TB or treatment intolerant/nonresponsive MDR-TB per current CDC guidance. Expert practice and use of BPaL and BPaLM are evolving; seek expert consultation.
- Individualized, longer regimens for MDR-TB (15-21 months after culture conversion) and XDR-TB (15-24 months after culture conversion) should contain at least 5 likely effective drugs in the intensive phase and at least 4 in the continuation phase.
  - Choose drugs from the ATS/CDC/ERS/IDSA 2019 stepwise, prioritized list for building an individualized regimen
- Case management with close clinical and laboratory monitoring is critical to successful treatment of DR-TB.
- Treatment adherence should be verified (i.e., through DOT, vDOT, or other method) for all patients with DR-TB. Consider strategies for adherence support (e.g., material support, psychological support, education).
- New drugs may eventually lead to better outcomes and shorter durations of therapy.

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