Choosing an all-oral shorter regimen

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Agenda & Participant List

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Choosing an all-oral shorter regimen

Outline of this talk:

- Why use all-oral shorter treatment regimen (STRs)?
- Examples of all-oral shorter regimens being implemented under operational research conditions.
- Optimum duration of treatment.
- Some examples when changes to the primary regimen are needed.

The principles discussed today are all in ”*The Clinical Guide for All-oral ” Shorter Treatment Regimens*”.

Version 1.2 of the guide is provided in the workshop dropbox and sent to participants of the workshop in an email

The Clinical Guide for all-oral STRs Version 1.4 (a draft to be used during the workshop)

- Identifying patients that are candidates for use of an all-oral STR.
- Designing all-oral STRs to be used in a programmatic setting.
- Adjusting all-oral STRs based on individual patient characteristics, including co-morbidities and tolerance to the medications.
- Implementing close monitoring of patients for response to treatment and for potential adverse events (AEs).
- Assuring treatment is implemented under operational research conditions.

A POST-WORKSHOP VERSION WILL BE SENT TO YOU

The guide is a living document and will be periodically updated and published at www.endTB.org

WHO Options for treating FQ-susceptible MDR-TB

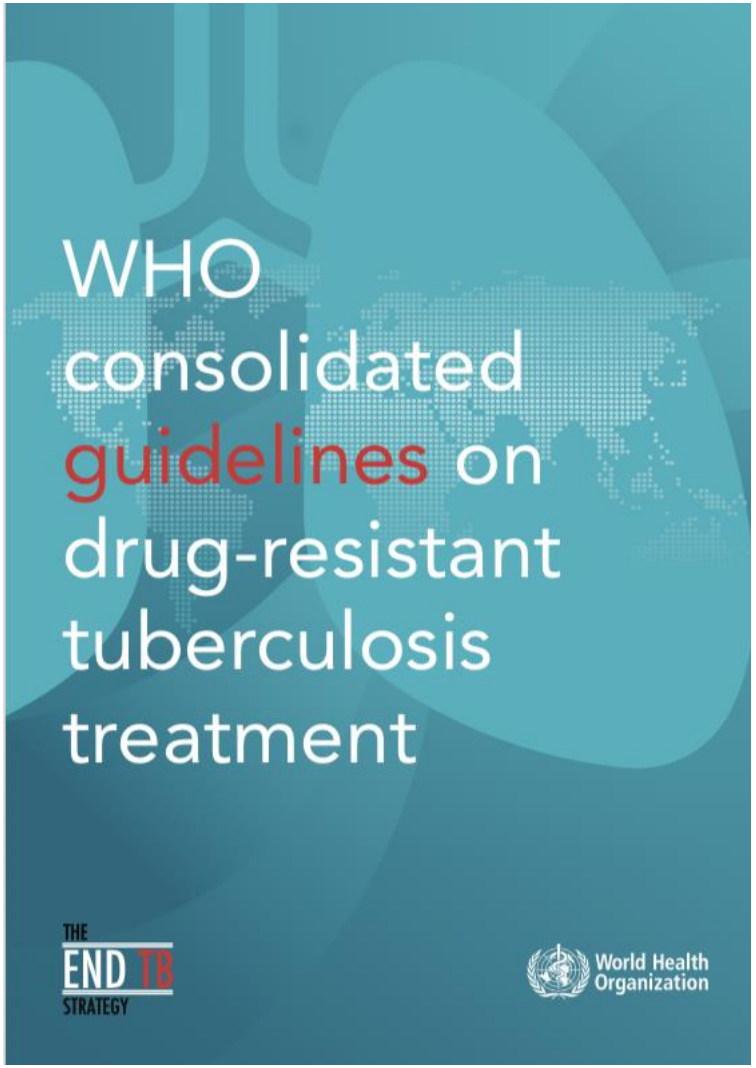
Regimen	Success	Failure or relapse	Death	Grade 3 or 4 SAEs	Comment
Old longer regimen*	99/124 (79.8%)	7/124 (5.6%)	All patients: 9/141 (6.4%) **HIV: 4/50 (8.0%)**	64/141 (45.4%)	**NO LONGER RECOMMENDED**
Shorter regimen with injectable*	193/245 (78.8%)	26/245 (10.6%)	All patients: 24/282 (8.5%) **HIV: 18/103 (17.5%)**	136/282 (48.2%)	• Recommended by WHO • 6% had severe hearing loss • Only 1 drug from Group A is used in this regimen
All-oral longer regimen (based on the new hierarchy of drug groups)	Never compared to the older longer regimen Never compared to the shorter regimen with the injectable **Never compared to any regimen**				Recommended by WHO
All-oral shorter regimen under operational research conditions	Never compared to any regimen				Recognized as acceptable for NTPs to choose if done under operational research conditons

* STREAM Stage 1 trial data (mITT population used for Success and Failure/relapse assessment, ITT population for death and SAEs).

Why offer patients an all-oral STR?

- Can use all of the Group A drugs FQs, Bdq, and Lzd (these are the drugs determined by the WHO to be associated with more success, less death and less failure relapse).
- Can use the same duration as the standard STR but NO INJECTABLE:
  - No painful injections
  - No hearing loss; no tinnitus; no vertigo
  - No drug-induced renal failure that can result in death
  - No drug-induced electrolyte disturbances that can result in
  - No need for DOT to be done by person trained to give injections
- The WHO recognizes that modifications to the present STR with the injectable are promising. Advises NTPs to only use all-oral STRs under operational research conditions.

2019 WHO Guidelines for MDR-TB



The WHO 2018 Guidelines are the biggest change in decades in the management of MDR-TB.

The big highlights:

- **There is a new hierarchy of drugs used to treat MDR-TB.**
- **Fully oral treatment regimens are possible for almost all patients with MDR-TB.**
- **Bedaquiline is now recommended for all MDR-TB patients (except if there is an intolerance or resistance to Bdq).**

Other highlights:

- The re-purposed antibiotic linezolid may also play an important role in many patients with MDR-TB.
- Difficult to take oral drugs like PAS, ethionamide and prothionamide are prioritized less.
- Kanamycin and capreomycin are removed.

Drug	Group	Efficacy	Safety (common or significant side effects)	Likelihood of susceptibility (DST assessment)	Overall ranking
Lfx	A	Excellent	Excellent	Excellent (rapid DST exists and low background resistance)	Excellent
Mfx	A	Excellent	Excellent (mild QT prolongation)	Excellent (rapid DST exists and low background resistance)	Excellent
Bdq	A	Excellent	V. Good (QT prolongation and hepatotoxicity)	Excellent (low background resistance)	Excellent
Lzd	A	Excellent	Poor (peripheral neuropathy, myelosuppression)	Excellent (low background resistance)	V. Good
Cfz	B	Good	Good (skin pigmentation, GI distress)	V. Good (low background resistance except in previously treated MDR-TB patients with shorter regimen or contacts)	Good
Cs	B	Good (bacteriostatic)	Poor (psychosis, seizures, depression, peripheral neuropathy)	Fair (background resistance not known, may be high in previously treated MDR-TB patients or contacts of an MDR-TB failure patient).	Fair
E	C	Good (bacteriostatic)	Very Good	Poor (very high background resistance in MDR TB strains and no reliable DST)	Poor
Dlm	C	Good (Bactericidal)	Excellent	Excellent (low background resistance)	V. Good
Z	C	Excellent	Fair (hepatotoxicity)	Fair (moderate to high background resistance in MDR-TB strains and DST difficult to perform)	Fair

Design of the regimen: This is for both for all-oral STRs and LTRs.

Step 1: Use as many Group A drugs as possible (considering FQ susceptibility, previous exposure, contraindications and concomitant treatment)

FQ-Bdq-Lzd-

(Most all-oral STRs contain this backbone but other options do exist)

Step 2: Add one to two drugs from Group B or Group C to complete the regimen.

How do I choose the Group B and C drugs?

Answer: Consider efficacy, safety and likelihood of resistance.

Our expert opinion is that all-oral STRs include 4 to 5 drugs from the following list:

- Group A drugs:
  - Levofloxacin (or Moxifloxacin)
  - Bedaquiline
  - Linezolid
- Group B drugs:
  - Clofazimine
- Group C drugs:
  - Delamanid
  - Pyrazinamide

Examples of all-oral regimens being used in Randomized controlled trials (RCTs) that use drugs that are available through the GDF

(using regimens that are also used in RCTs will help add evidence to those regimens)

Regimen being used in the MDR END clinical trial:

- **MDR END:** Lfx-Lzd-Dlm-Z (36-52 weeks)

Regimens being used in the endTB clinical trial:

- **endTB regimen 1:** Mfx-Bdq-Lzd-Z (39 weeks)
- **endTB regimen 2:** Lfx-Bdq-Lzd-Cfz-Z (39 weeks)
- **endTB regimen 3:** Lfx-Bdq-Lzd-Dlm-Z (39 weeks)
- **endTB regimen 4:** Lfx-Lzd-Cfz-Dlm-Z (39 weeks)
- **endTB regimen 5:** Mfx-Dlm-Cfz--Z (39 weeks)

Stream 2 Trial:

- **Regimen C:** 40 weeks of Lfx, Bdq, Cfz, E, Z,, supplemented by H and Pto for the first 16 weeks

Note: All-oral STRs that use pretomanid are not included as this drug is not yet commercially available.

Examples of regimens that are not used in RCTs but are good candidates:

- **Lfx-Bdq-Lzd-Cfz** (a common all-oral LTR, which can be used as an all-oral STR under operational research conditions)

- **Lfx-Bdq-Lzd-Cfz-Dlm** (adds a fifth bactericidal drug, delamanid, to a potent and common backbone of drugs. A disadvantage of this regimen is it has three QT prolonging drugs)

- **Lfx-Bdq-Lzd-Dlm** (similar to endTB regimen 3 but no pyrazinamide).

Examples of all-oral STRs

- ATTENTION: THE FOLLOWING EXAMPLES ARE NOT MEANT TO SUGGEST THAT ALL COUNTRIES IN A SPECIFIC AREA USE THE SAME ALL-ORAL STR. THE EXAMPLES GIVE ONE POSSIBLE PRIMARY REGIMEN DESIGN ALONG WITH THE ADVANTAGES AND DISADVANTAGES OF CHOOSING THAT REGIMEN. FOR ANY GEOGRAPHICAL AREAS THERE ARE MANY ACCEPTABLE ALL-ORAL SHORTER REGIMENS THAT ARE LIKELY TO PRODUCE GOOD RESULTS.

EXAMPLE 1: COUNTRY IN WEST AFRICA

Epidemiological situation	In strains of MDR-TB there is approximately < 2% resistance to FQs, and approximately 30% resistance to Z.
Access to DST	In-country rapid second-line DST is under development for FQs and no DST is planned for Z. Phenotypic DST is sent to a supra-national reference laboratory with a two-month turn-around time for FQs, injectables, E, Eto, and Z.
Primary all-oral STR regimen	**Lfx-Bdq-Lzd-Cfz-Z**
Advantages	• Uses all three Group A drugs and at least one Group B drug. • Moderate costs for the drugs in the regimen. • Z is effective in 70% of patients and can be dropped at the 2-month mark if resistance is documented. • It is a regimen being used in an RCT (endTB Clinical Trial).
Disadvantages	• Has two moderate QT prolonging drugs (Bdq and Cfz); however, both drugs are endorsed to be used together as an option for LTR by the WHO. • May have drug-drug interactions with some ARTs.

How the country in West Africa intends to modify the regimen based on DST

Start all patients with RR-TB (who consent to OR):

Lfx, Bdq, Lzd, Cfz, Z

DST

FQ- Unknown
Z –Unknown

→ Continue regimen

FQ- Suscep.
Z – Suscep.

→ Continue regimen

FQ- Suscep.
Z – Resist.

→ Continue regimen without Z

FQ- Resist.
Z – Suscep.

→ Design individualized LTR.

Continue Lfx if low level resistance; Stop Lfx if high level resistance.

Consider adding Dlm

Example:
18 Bdq-Lzd-Cfz-Dlm-Z +/-Lfx

FQ- Resist.
Z – Resist. or unknown

→ Design individualized LTR.

Continue Lfx if low level resistance; Stop Lfx if high level resistance.

Consider adding Dlm and Cs

Example:
18 Bdq-Lzd-Cfz-Dlm-Cs +/-Lfx

Cost of 9 months of Lfx, Bdq, Lzd, Cfz, Z ($USD)

Drugs	Cost per pill		9-month cost	12 months	18 months
Bdq			**$ 600.00**	**$ 800.00**	**$ 1,200.00**
Lzd (600)	0.97		**$ 261.90**	**$ 349.20**	**$ 523.80**
Cfz (100)	0.98		**$ 264.60**	**$ 352.80**	**$ 529.20**
Lfx (1000 mg)	0.12		**$ 32.40**	**$ 43.20**	**$ 64.80**
Z (500 mg) x 3 tabs	0.10		**$ 27.00**	**$ 36.00**	**$ 54.00**
Lfx-Bdq-Lzd-Cfz-Z TOTAL COST			**$ 1,126.50**	**$ 1,501.99**	**$ 2,253.00**

NOTE: The STR drug cost is 500 to 700 USD - without the injectable works (needles, syringes, sterile water, alcohol)

EXAMPLE 2: COUNTRY IN SOUTHERN AFRICA

Epidemiological situation	In strains of MDR-TB there is approximately < 5% resistance to FQs, and approximately 60% resistance to Z. 80% HIV prevalence in TB patients.
Access to DST	In-country rapid second-line DST for FQs in available and no DST is planned for Z. Second-line phenotypic DST is available for FQs.
Primary all-oral STR regimen	**Lfx-Bdq-Lzd-Cfz-Dlm**
Advantages	• Uses all three Group A drugs and at least one Group B drug • Z is avoided as it is more than 50% resistant. • Since the regimen has five likely effective drugs, if intolerability develops in one drug, the drug can usually be stopped with no need for substitution in most circumstances.
Disadvantages	• The regimen is not being used in a registered RCT. • Has two moderate QT prolonging drugs (Bdq and Cfz) and one mild QT prolonging drug (Dlm). • May have drug-drug interactions with some ARTs.

EXAMPLE 3: COUNTRY IN EASTERN EUROPE OR CENTRAL ASIA

Epidemiological situation	In strains of MDR-TB in the country there is approximately 10% resistance to FQs, and approximately 60% resistance to Z.
Access to DST	In-country rapid DST is available for FQs and in liquid culture for FQs and Z.
Primary all-oral STR regimen	**Lfx-Bdq-Lzd-Dlm-Z** (Z will be continued whether susceptible or resistant).
Advantages	• Uses all three Group A drugs. • Has only one moderate QT prolonging drug. • It is a regimen being used in an RCT (endTB Clinical Trial).
Disadvantages	• Does not use any of the Group B drugs (this is due to the personal preference of some TB experts to use Dlm over Cfz or Cs). • Uses Z that is likely ineffective in most MDR-TB strains circulating in the area. • May have drug-drug interactions with some ARTs.

EXAMPLE 4: COUNTRY IN EASTERN EUROPE OR CENTRAL ASIA

Epidemiological situation	In strains of MDR-TB in the country there is approximately 20% resistance to FQs, and approximately 80% resistance to Z.
Access to DST	In-country rapid DST is available for FQs and in liquid culture for FQs and Z.
Primary all-oral STR regimen	**Lfx-Bdq-Lzd-Cfz-Cs**
Advantages	• Uses all three Group A drugs and both Group B drugs • Does not use Z, which is resistant in most MDR-TB strains circulating in the area
Disadvantages	• Not used in any registered RCT • Uses Cs which has a poor side-effect profile and may have overlapping toxicities with Lzd • May have drug-drug interactions with some ARTs

EXAMPLE 5: COUNTRY IN SOUTH ASIA	
Epidemiological situation	In strains of RR/MDR-TB, there is approximately 30-49% resistance to Z. Resistance to FQs in MDR-TB strains is 30 to 50% (most of the FQ resistance in the area is low-level FQ resistance).
Access to DST	In-country rapid DST is available for FQs and in liquid culture for FQs, injectables, Eto, E, and Z.
Primary all-oral STR regimen	**Option 1: Lfx-Bdq-Lzd-Cfz** **Option 2: Lfx (or high-dose Mfx)-Bdq-Lzd-Dlm-Z**
Advantages	• Both Options include all three Group A drugs. • Option 1 allows a four-drug regimen in FQ-susceptible MDR-TB and avoids the use of Z as many areas have a high-prevalence of Z resistance. • Option 2 allows to employ high-dose Mfx in patients with strains that have low-level FQ resistance. This regimen uses Dlm (less QT prolongation) instead of Cfz. Note, Z is effective in only 50-70% of patients and can be dropped at the 2-month mark if resistance is documented. (Option 2 employs Lfx, instead of high-dose Mfx, in cases susceptible to the FQ, serves as a second option).
Disadvantages	• Option 1 has two moderate QT prolonging drugs (Bdq and Cfz), however this combination is acceptable by the WHO. • Option 2 has two moderate QT prolonging drugs (Bdq and high-dose Mfx), there is limited experience using this combination. • Both options may have drug-drug interactions with some ARTs

What to do if the patient has significant toxicity to a drug in the regimen?

- If toxicity develops early, BEFORE one can determine if the patient has converted, it is generally recommended to replace the drug.
- If significant toxicity develops after the patient's sputum has culture converted AND the patient is doing well, the drug can be stopped and not replaced. (For patients with severe disease one may consider replacing the drug).
- If significant toxicity develops and the treatment regimen is failing or suspected of failing, then restart a new regimen (and never add a single drug to a failing regimen).

In most cases the regimen is continued for 9 months

What can be done if the patient has a contraindication to a drug in the primary all-oral STR that is being used in the country?

- In most cases where a patient cannot take a drug due to contraindication the drug can be substituted with another effective drug.
- For example, in a patient with severe peripheral neuropathy where 9 months of Lfx-Bdq-Lzd-Cfz-Z is the primary all-oral STR being used, programs can still offer the patient an all-oral STR by replacing the linezolid with delamanid (**9 months of Lfx-Bdq-Dlm-Cfz-Z**).
- Because this regimen now uses three drugs that can potentially prolong the QT interval more frequent QT monitoring may be needed for the first 2 months (for example every 2 weeks) until it is documented that the regimen is well tolerated.

Duration of the regimen in all-oral STR

- In general, all-oral STRs are standardized four- or five-drug regimens that are given for 9 to 12 months.
- The Month 4 clinical assessment and bacteriological response is routinely used to determine if the patient is responding to treatment. If there is no response to treatment at 4 months (on clinical assessment or month 4 culture is positive) then consideration for stopping the all-oral STR and designing a new individualized LTR can be done. Treatment can also be stopped before 4 months if there is evidence of a poor clinical response and the treatment regimen is determined to be failing.
- Some programs may choose to extend total treatment to 11 or 12 months if the smear or culture is still positive at month 4 or 5, and the patient is clinically doing well.
- If the culture is still positive at month 6 or beyond, then the treatment outcome should be declared failed and a new LTR should be individually designed. Salvage regimens for patients in whom an all-oral STR has failed are discussed in Appendix 2 of the clinical guide.

Use of an all-oral STR in FQ-resistant TB

- STRs for FQ-resistant MDR-TB have limited evidence; however, the the Nix-TB which used 6 to 9 months of pretomanid, bedaquiline, and linezolid is under evaluation and initial results are very promising.
- Until more evidence on STRs and FQ-resistant MDR-TB is available, programs may want to treat all FQ-resistant MDR-TB with LTRs.
- If the FQ-resistance is discovered a few months after the start of the all-oral STR, the patient should be assessed, and regimen reviewed.
  - In many cases, the patient will be doing well, and the regimen has enough drugs that are “likely effective” against the FQ-resistant strain, that either the regimen can be continued or reinforced with one or two drugs. (Be sure to never add a single drug to a regimen that may be failing).
  - The regimen is usually extended in time, often to 18 months total. Using shorter durations, like 12 months, is possible under operational research conditions.

Duration of the post-end-of-treatment follow-up after an all-oral STR is 12 Months

Activity	3 months post-end-of-treatment	6 months post-end-of-treatment	9 months post-end-of-treatment	12 months post-end-of-treatment
In-person clinic visit* or telephone contact**	√	√	√	√
Monitoring smear and culture (done regardless of signs of recurrence being present.	If indicated	√	If indicated	√
Chest X-ray	If indicated	If indicated	If indicated	If indicated
Any positive culture in the post-treatment period	Send baseline and post-end-of treatment culture for LPA to second-line drugs and DST to FQs, Bdq, Lzd, Dlm, Cfz, Z, and injectables			
Genetic fingerprinting	Perform genotyping on baseline strain to compare with any positive post-treatment period culture (if possible)			