



All-oral shorter regimens for MDR-TB

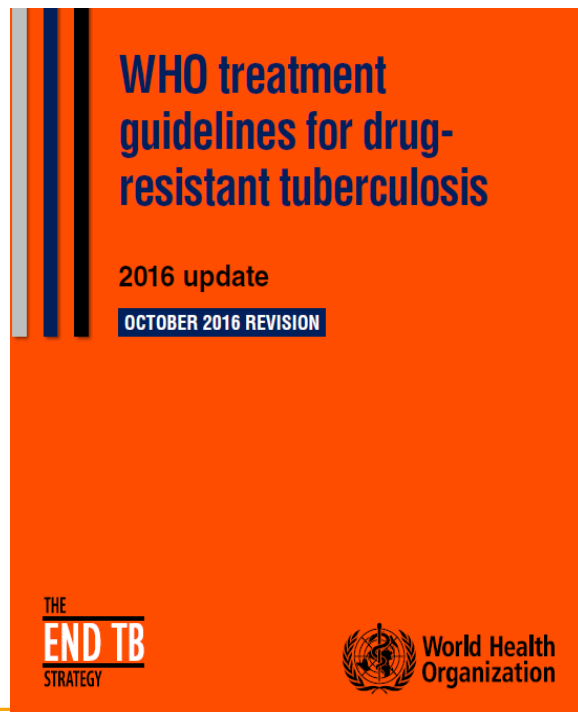
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2016 WHO shorter regimen



- Regimen composition
 - 4-6 months of:
 - Km-Mfx-Pto-Cfz-Z-H_h-E
 - followed by 5 months of:
 - Mfx-Cfz-Z-E



Concerns about the WHO short regimen

- STREAM control regimen was the old standard 20 month regimen that is no longer recommended.
- No clear benefit seen with respect to toxicity (e.g. hearing loss).
- Composition of the 2016 WHO shorter regimen is not consistent with recent WHO recommendations (e.g. includes an injectable, does not include bedaquiline or linezolid, etc.)



WHO Rapid Communication (August 2018)

- Programmes and their stakeholders considering the use of modified shorter regimens should note that evidence is currently lacking on the effect of replacing any of the agents with alternatives in the shorter regimen (e.g. replacing the injectable with bedaquiline or other oral agents; replacing moxifloxacin with levofloxacin).
- Programmes and their stakeholders are advised to consider any variations to the standardized shorter MDR-TB regimen only under operational research conditions, following these steps:
 - Preparation of a suitable protocol identifying the eligibility criteria, regimen composition, monitoring schedules and other key elements (see here for a generic template);
 - Approval by a national ethics review committee, ahead of any patient enrolment;
 - Treatment delivery under WHO-recommended standards, including informed consent, principles of good clinical practice; aDSM; and regular patient monitoring to assess regimen effectiveness.



"Modified shorter regimen"

		Km	H	Pto	Mfx	Cfz	E	Z	STREAM B
Lzd (2)	Bdq (6)		H	Pto	Mfx/ Lfx	Cfz	E	Z	South Africa
	Bdq		H	Pto	Lfx	Cfz	E	Z	STREAM C
	Bdq	Km	H		Lfx	Cfz		Z	STREAM D

N.B. STREAM regimens C and D are part of ongoing STREAM Phase 2 trial, expected to be completed in 2021.



Novel shorter MDR-TB regimens

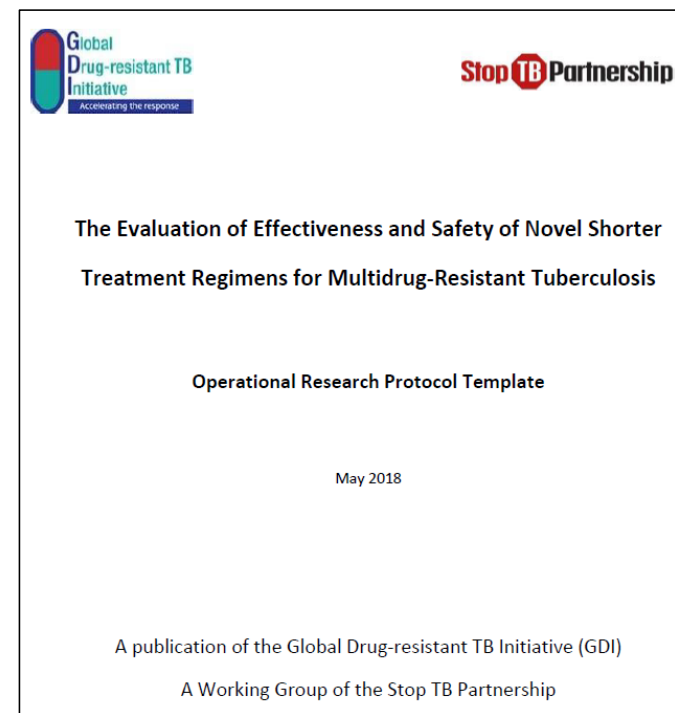
Clinical trial	Regimen	Ongoing / completed	All drugs are commercially available
STREAM 1 regimen B	Cfz, E, Z, Mfx, H, Km (16 weeks); followed by Cfz, E, Z, Mfx (24 weeks)	Enrollment complete	Yes
NiX-TB	Bdq, Pa, Lzd (24-36 weeks)	Enrollment complete	No
MDR END	Dlm, Lzd, Lfx, Z (36-52 weeks)	Enrolling	Yes
STREAM 2 regimen C	Bdq, Cfz, E, Z, Lfx, H, Pto (16 weeks); followed by Bdq, Cfz, E, Z, Lfx (24 weeks)	Enrolling	Yes
STREAM 2 regimen D	Bdq, Cfz, Z, Lfx, H, Km (8 weeks); followed by Bdq, Cfz, Z, Lfx (20 weeks)	Enrolling	Yes
PRACTECAL regimen 1	Bdq, Pa, Lzd (24-36 weeks)	Enrolling	No
PRACTECAL regimen 2	Bdq, Pa, Lzd, Cfz (24-36 weeks)	Enrolling	No
PRACTECAL regimen 3	Bdq, Pa, Lzd, Mfx (24-36 weeks)	Enrolling	No
endTB regimen 1	Bdq, Lzd, Mfx, Z (39 weeks)	Enrolling	Yes
endTB regimen 2	Bdq, Cfz, Lzd, Lfx, Z (39 weeks)	Enrolling	Yes
endTB regimen 3	Bdq, Dlm, Lzd, Lfx, Z (39 weeks)	Enrolling	Yes
endTB regimen 4	Dlm, Cfz, Lzd, Lfx, Z (39 weeks)	Enrolling	Yes
endTB regimen 5	Dlm, Cfz, Mfx, Z (39 weeks)	Enrolling	Yes

N.B. The dosing and timing of the above regimens are complicated and cannot be fully described in this table. Please look at the respective trial protocols for a fuller description of the above regimens.



Operational research protocol template

- Generic protocol:
<http://www.stoptb.org/wg/mdrtb/assets/documents/GDI%20OR%20generic%20protocol%20final.pdf>
- Adapted from STREAM 1 trial and other protocols (e.g. endTB observational study)
- Adapt to your setting—with a little help from your friends: WHO taskforce, endTB, other organizations and universities.





Study objectives

- Primary objective:
 - To determine the treatment outcomes of patients who are treated with novel shorter MDR-TB regimen.
- Secondary objectives:
 - To assess the safety of a novel shorter MDR-TB regimen through rates of adverse events.
 - To determine the proportion of patients with recurrence during 12 months after successful treatment with a novel shorter MDR-TB regimen.



Patient selection: exclusion criteria

Exclusion criteria:

- Strain resistant to any drug in the regimen.
- Previous second-line drug treatment > 1 month.

To be decided if other exclusion criteria apply:

- Severe forms of TB (e.g. Potts disease, meningitis)
- Pregnant women (? Just 1st trimester, but older drugs more toxic than some newer ones).
- Age limit of children? (children can be included: discuss with experts).
- Other exclusions: unable to consent, unable to follow treatment, already in a trial.
- Medical exclusions: QT > 500 msec, ALT/AST > 5 times, allergy to drug, severe renal insufficiency.



Patient selection: informed consent and sites

Informed consent

- Patient education materials.
- Discussion and respond to questions.

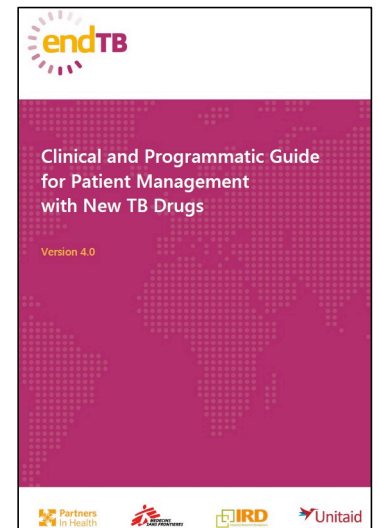
Treatment site and number of patients

- Which sites will participate?
 - All country, some geographical areas, some sites?
- Estimate number of patients.



Monitoring and management of adverse events

- Regular monitoring schedule (WHO schedule) adapted to regimen.
 - Certain patients will need more regular monitoring.
- Management of adverse events.
 - WHO companion handbook.
 - endTB Clinical Guide (www.endTB.org/resources).
 - Consult an expert committee for complicated cases.
- Reporting of adverse events.
 - Use a severity scale such as MSF, DAIDS, CTCAE.
 - More resources available here: (www.endTB.org/resources).





Data management and project monitoring

Use routine NTP documentation.

- Treatment cards.
- Registers.

Don't collect more data than you need!

- Patient safety and well being.
- Program monitoring.
- Answer study questions.

Review data quarterly.

- Convene an expert committee for assistance in patient management and to monitor study progress.



Outcomes

- Cured.
- Treatment completed.
- Treatment stopped due to baseline drug resistance: Patients who receive culture-based DST results several months after starting a shorter regimen may be switched to a longer regimen if resistance to drugs in the shorter regimen is discovered. For such patients, this outcome should be reported.
- Treatment failed.
- Died.
- Lost to follow-up.
- Not evaluated.



How to deal with difficult cases?

- Impossible to predict or know all scenarios – but international experts are ready to help
- endTB medical committee: on case by case basis **for endTB countries**
- WHO consillium: <http://www.euro.who.int/en/health-topics/communicable-diseases/tuberculosis/areas-of-work/technical-cooperation/ers-who-e-consilium>



Conclusions

- Good patient and programmatic monitoring and data collection is essential for all TB programs.
- Operational research standardises certain aspects of data collection under routine program conditions.
- Operational research does not need to be complex and data collection to be limited to what will be analysed.
 - Know the study questions before starting.
- Partners are available to assist and train.
- Can be a good solution for early introduction of all-oral shorter regimens.