World Health Organization

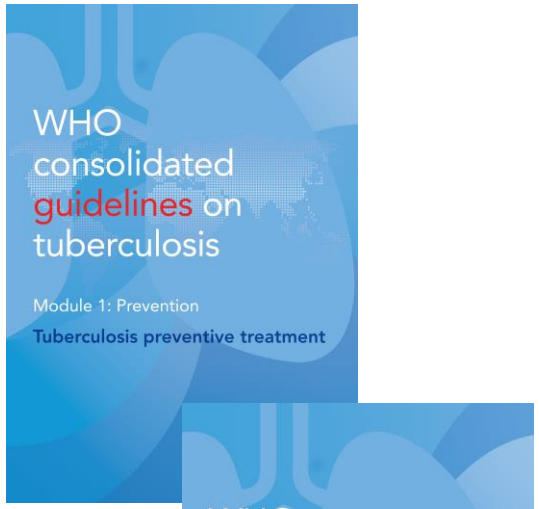
END TB

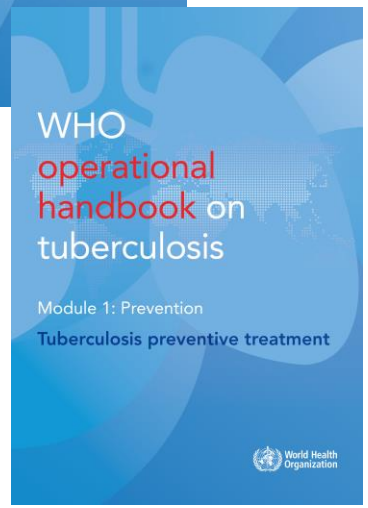
Update on new guidance on rapid diagnostics and drug-resistant TB treatment

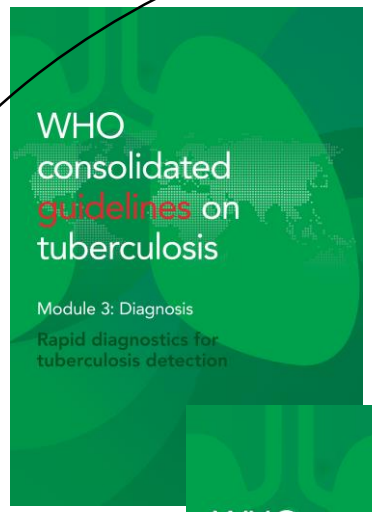
From Policy to Practice: Rolling out new WHO guidelines on rapid diagnostics and drug-resistant TB treatment

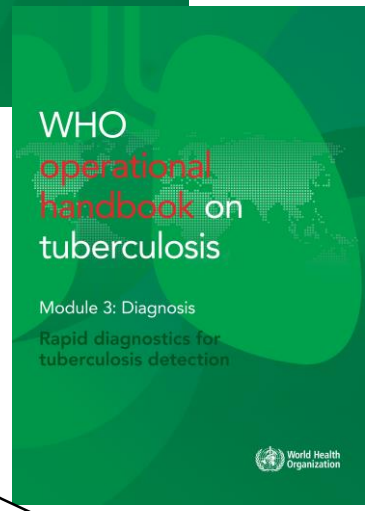
07 July 2020

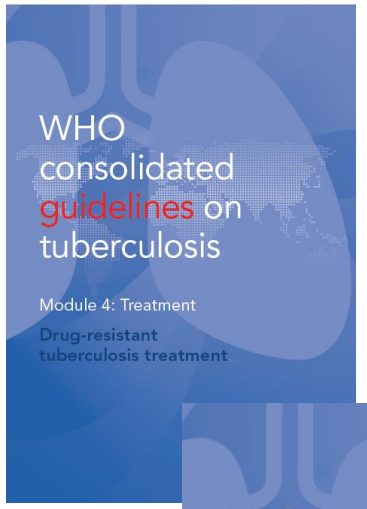
WHO consolidated guidelines on tuberculosis

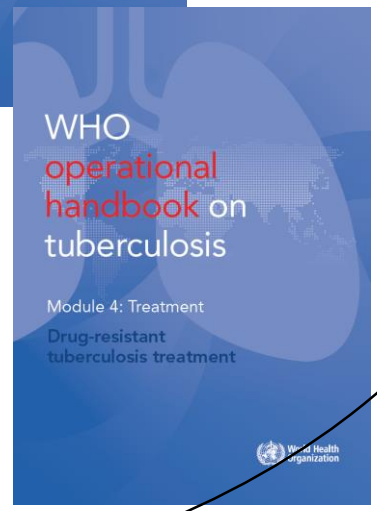












Module 3: Diagnosis – rapid diagnostics for TB detection

Structure of the document:

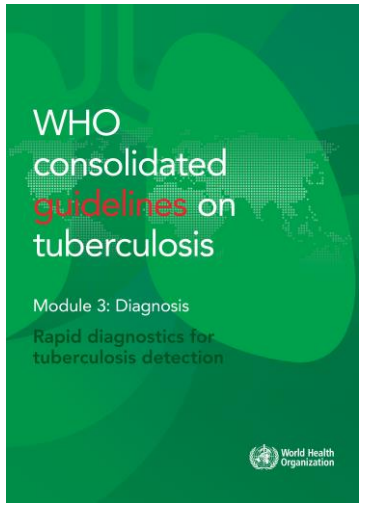
Section 1: Molecular assays intended as initial tests for TB (Xpert MTB/RIF, Xpert Ultra, Truenat)

Section 2. Loop mediated isothermal amplification (TB-LAMP)

Section 3: First-line line probe assay (FL-LPA)

Section 4: Second-line line probe assay (SL-LPA)

Section 5. Lateral flow urine lipoarabinomannan assay (LF-LAM)



- Consolidated guidance developed by WHO in 2015-2020 in line with GRADE approach
- Update on Molecular assays intended as initial tests for TB (Xpert MTB/RIF, Xpert Ultra, Truenat)

Xpert MTB/RIF, Xpert Ultra assays as the initial test to diagnose pulmonary TB and RR in adults

In adults with signs and symptoms of pulmonary TB:

- Xpert MTB/RIF should be used as an initial diagnostic test for TB and RR detection to replace smear microscopy /culture and phenotypic DST
- and without a prior history of TB (≤5 years) or with a remote history of TB Tx (>5 years since end of Tx), Xpert Ultra should be used as an initial diagnostic test for TB and for RR detection in sputum, to replace smear microscopy /culture and phenotypic DST
- and with a prior history of TB and an end of Tx within the last 5 years, Xpert Ultra may be used as an initial diagnostic test for TB and for RR detection in sputum, to replace smear microscopy /culture and phenotypic DST

Strength	**CoE***
Strong	High for test accuracy Moderate for patient-important outcomes**
Strong	High
Conditional	Low

* Certainty of Evidence ** Mortality, cure, pretreatment loss to follow-up, time to diagnosis, treatment, and mortality in PLHIV

Xpert MTB/RIF, Xpert Ultra assays as the initial test to diagnose pulmonary TB and RR in children

In children with signs and symptoms of pulmonary TB:

- Xpert MTB/RIF should be used as an initial diagnostic test for TB and RR detection in sputum, gastric aspirate, nasopharyngeal aspirate and stool to replace smear microscopy /culture and phenotypic DST
- Xpert Ultra should be used as the initial diagnostic test for TB and RR detection in sputum or nasopharyngeal aspirate, to replace smear microscopy /culture and phenotypic DST

Strength	**CoE***
Strong	Moderate for sputum Low for GA**, NPA*** and stool
Strong	Low for sputum Very Low for NPA***

* Certainty of Evidence ** Gastric aspirate *** Nasopharingeal aspirate

Truenat assay as the initial test to diagnose pulmonary TB and RR

In adults and children with signs and symptoms of pulmonary TB:

- Truenat MTB or MTB Plus may be used as an initial diagnostic test for TB to replace smear microscopy /culture
- Truenat MTB or MTB Plus positive result, Truenat MTB-RIF Dx may be used as an initial test for RR to replace phenotypic DST

Strength	**CoE***
Conditional	Moderate
Conditional	Very Low

* Certainty of Evidence

Xpert MTB/RIF, Xpert Ultra assays as the initial test to diagnose extrapulmonary TB and RR

In adults and children with signs and symptoms:

- of TB meningitis, Xpert MTB/RIF or Xpert Ultra should be used in cerebrospinal fluid (CSF) as an initial diagnostic test for TB meningitis to replace smear microscopy /culture
- of extrapulmonary TB, Xpert MTB/RIF may be used in LNA, LNB, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid or urine specimens as the initial diagnostic test to replace smear microscopy /culture
- of extrapulmonary TB, Xpert Ultra may be used in LNA and LNB as the initial diagnostic to replace smear microscopy /culture
- of extrapulmonary TB, Xpert MTB/RIF or Xpert Ultra should be used for RR detection to replace phenotypic DST
- of disseminated TB (HIV-positive), Xpert MTB/RIF may be used in blood, as an initial diagnostic test for disseminated TB

Strength	CoE*
Strong	Moderate for Xpert MTB/RIF Low for Xpert Ultra
Conditional	Moderate for pleural fluid; Low for LNA**, peritoneal fluid, synovial fluid, urine Very low for pericardial fluid,LNB***
Conditional	Low
Strong	High certainty for Xpert MTB/RIF Low certainty for Xpert Ultra
Conditional	Very Low

* Certainty of Evidence ** Lymph node aspirate *** Lymph node biopsy

Module 4: Treatment – drug-resistant TB treatment

Structure of the document:

Section 1. Regimen for rifampicin-susceptible and isoniazid-resistant tuberculosis

Section 2. Shorter, all-oral, bedaquiline-containing regimen for MDR/RR-TB

Section 3: Longer regimens for MDR/RR-TB

Section 4: The bedaquiline, pretomanid and linezolid (BPaL) regimen for MDR-TB with additional fluoroquinolone resistance

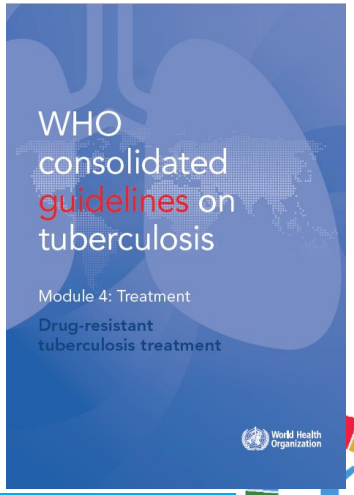
Section 5. Monitoring patient response to MDR-TB treatment using culture

Section 6. Start of antiretroviral therapy in patients on second-line antituberculosis regimens

Section 7. Surgery for patients on MDR-TB treatment

Section 8. Care and support for patients with MDR/RR-TB

- New shorter, all-oral regimen
- Updates in the longer regimen section related to the safety of bedaquiline use longer than 6 months and concurrent use of bedaquiline and delamanid
- New section on the BPaL regimen



Section 2: Shorter, all-oral, bedaquiline-containing regimen for MDR/RR-TB

Recommendation

2.1 A shorter, all-oral, bedaquiline-containing regimen of 9-12 months duration is recommended in eligible patients with confirmed MDR/RR-TB who have not been exposed to treatment with second-line TB medicines used in this regimen for more than one month and in whom resistance to fluoroquinolones has been excluded (conditional recommendation, very low certainty in the evidence).

Remarks

- The evidence review focused on the shorter regimen **4-6 Bdq (6 m) -Lfx-Cfz-Z-E-Hh-Eto / 5 Lfx-Cfz-Z-E**.
- After taking into account patient preference and clinical judgement for the following eligible group of patients this regimen can be a preferred option: patients with confirmed MDR/RR-TB (with at least confirmed resistance to rifampicin), with resistance to fluoroquinolones ruled out, without exposure to previous treatment with second-line medicines for > 1 month and those without extensive TB disease and no severe extrapulmonary TB.
- The evidence reviewed supports the use of this regimen in patient sub-groups such as people living with HIV infection.
- Implementation of this regimen requires access to perform rapid drug-susceptibility testing against fluoroquinolones.

Section 3: Longer regimens for MDR/RR-TB

New evidence

- Use of bedaquiline beyond 6 months (endTB observational study) was available but not possible to assess the impact on efficacy, due to the limited evidence and potential residual confounding in the data. However, the evidence supports the safe use of bedaquiline beyond six months.
- Use of bedaquiline and delamanid concurrently (end TB observational study and DELIBERATE trial). Evidence was insufficient to make an assessment of the efficacy or effectiveness of the concurrent use of bedaquiline and delamanid. There were no additional safety concerns with regards to the concurrent use of bedaquiline and delamanid.
- Observational study in South Africa on bedaquiline exposure during pregnancy showed that only low birth weight was associated with bedaquiline exposure in utero. It was not possible to conclusively ascribe this effect to bedaquiline, and more investigation is needed to explore this relationship. There were no significant differences in infant growth after birth (infants followed up until 1 year of age).

Section 4: The BPaL regimen for MDR-TB with additional fluoroquinolone resistance

Recommendation

4.1 **A treatment regimen lasting 6-9 months composed of bedaquiline, pretomanid and linezolid (BPaL) may be used under operational research conditions in MDR-TB patients with TB that is resistant to fluoroquinolones who have had no previous exposure to bedaquiline and linezolid for more than two weeks (conditional recommendation, very low certainty in the estimates of effect).**

Remarks

- The BPaL regimen may not be considered for routine programmatic use worldwide until additional evidence on efficacy and safety has been generated. However, in individual patients for whom the design of an effective regimen based on existing WHO recommendations is not possible, the BPaL regimen may be considered as a last resort under prevailing ethical standards.
- The evidence reviewed supports the use of this regimen in certain patient sub-groups such as people living with HIV infection.

Acknowledgments

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Thank you

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