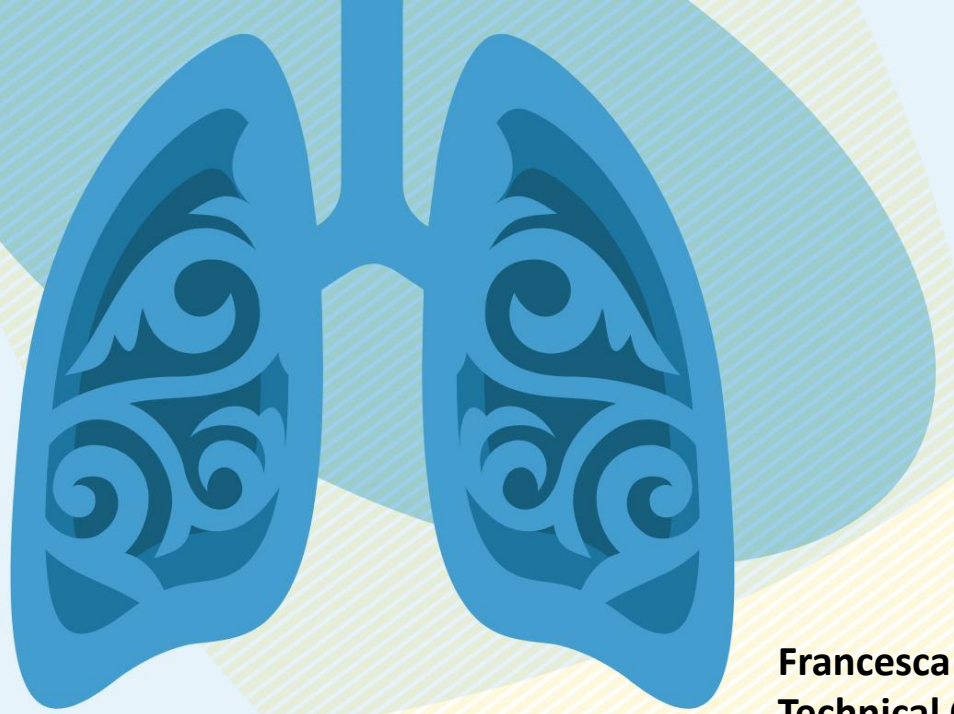
6-month bedaquiline, delamanid, linezolid, levofloxacin and clofazimine (BDLLfxC) regimen



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REGIONAL WORKSHOP ON ACCELERATED IMPLEMENTATION OF WHO GUIDELINES
ON TB PREVENTION, DIAGNOSIS, AND DRUG-RESISTANT TB (DR-TB) TREATMENT

Topics to be covered

- Source of evidence
- Composition and duration of the regimen
- Who is eligible for BDLLfxC?
- How is it the same as BPaL M?
- How does it differ from BPaL M

Source of evidence

BEAT Tuberculosis: conducted in South Africa at two sites

Population	**Intervention**	**Comparator**
Patients with microbiologically confirmed pulmonary MDR/RR-TB and with or without FQ resistance	6 Bdq-Dlm-Lzd-Lfx/Cfz (and/or)	9 Bdq(6)-Lzd(2)-Lfx-Cfz-Hh-Z-E (for Fq-susceptible) WHO currently recommended longer regimens (18-20 months) (for Fq-resistant)

Recommendation 1.2:
The 6-month BDLLfxC regimen

WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfxC) in MDR/RR-TB patients with or without fluoroquinolone resistance.

(Conditional recommendation, very low certainty of evidence).

Composition and duration of the regimen

Bedaquiline	• Two dosing strategies
	  • 400mg daily for two weeks followed by 200mg three times a week
	  • 200mg daily for two months, followed by 100mg daily for 4 months

Delaminid	• 100mg twice a day for 2 months then 200mg daily for 4 months • 200mg daily
Linezolid	• 600mg daily, with no planned reductions • Can be interrupted temporarily or stopped for adverse events
Levofloxacin	• 750 to 1000mg daily
Clofazimine	• 100mg daily

Duration of regimen

- 6 months of all medications (**24 weeks**)
- No change in doses for bedaquiline, delaminid, levofloxacin
- Linezolid can be interrupted or permanently stopped for adverse events but no scheduled reduction in doses
- Missed doses of less between 7 and 28 days should be made up
- Adherence support is very important

When and what to start

When RR-TB is diagnosed

- Do safety bloods, at least a hemoglobin, ECG
- **Start BDLLfxC without delay**
- Drug susceptibility testing (DST) for fluoroquinolones is **strongly encouraged** in people with MDR/RR-TB.

DST for fluoroquinolones DST

- Resistant: BDLC
- Susceptible: BDLLfx
- Unknown or not done: BDLLfxC

Who is eligible for BDLLfxC?

People with MDR/RR-TB or pre-XDR-TB	• Diagnosed with **pulmonary** RR-TB • Including **children, adolescents, PLHIV, pregnant and breastfeeding women**;
People with MDR/RR-TB and less than 1 month of previous exposure to bedaquiline, linezolid, delamanid or clofazimine	• When exposure is greater than 1 month, these patients may still receive the regimen if resistance to the specific medicines with such exposure has been ruled out;

Who is eligible for BDLLfxC?

People with most forms of extrapulmonary disease

People with **non-severe forms of extrapulmonary TB**, such as uncomplicated pleural effusions or peripheral lymph node disease

Except extrapulmonary involving the CNS, or osteoarticular or disseminated forms of TB with multiorgan involvement;

Any extent or severity of pulmonary TB

Minimal to moderate pulmonary TB disease

Extensive (advanced) pulmonary TB disease

- Bilateral cavitary disease
- Extensive parenchymal damage
- Advanced disease is usually defined in children and young adolescents aged below 15 by the presence of cavities or bilateral disease on CXR.

Children and adolescents who do not have bacteriological confirmation of TB do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with MDR/RR-TB).

Monitoring for efficacy

- Clinical monitoring
- Sputum smear and culture monthly followed by post-treatment at 6 and 12 months
- Chest X-ray at the beginning and end of treatment

Monitoring for safety

- HIV (and CD4+)
- HBA1C
- HBC and HCV
- Pregnancy test

At the start of treatment

- ECG
- Visual Acuity
- Full blood count or Hb
  - (repeat at 2 weeks)
- AST or ALT

At the start of treatment and **monthly**

What are the similarities between BPaL M and BDLLfxC?

You can start either without knowing the results of fluoroquinolone DST and change when you know the results	• It is still considered the same regimen
You can use both irrespective of the severity of the pulmonary disease	
You can use both in people living with HIV	• Irrespective of the degree of immunosuppression

What are the similarities between BPaL M and BDLLfxC?

- You can use both in uncomplicated extrapulmonary disease
- You can extend both(BPaL and BDLLC) slow for response to treatment
- Adverse events are similar and are driven by Linezolid

How does BDLLfxC differ from BPaL M?

BDLLfxC can be used in children of all ages, pregnant and breastfeeding women

BPaL M cannot be used for children under the age of 14 years or pregnant and breastfeeding women

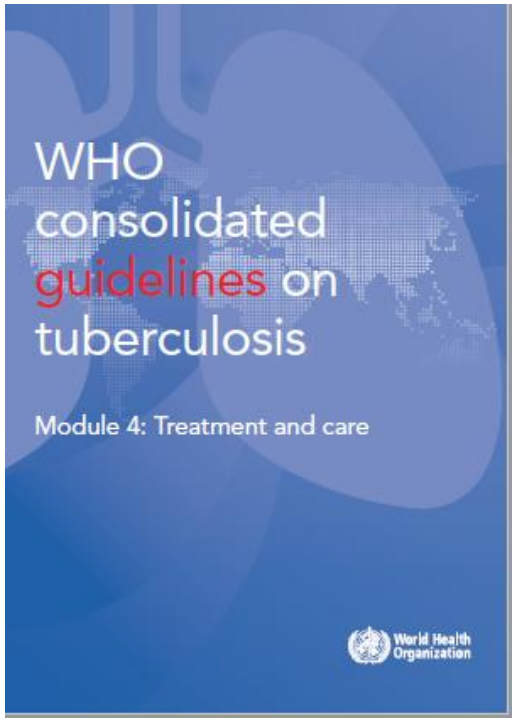
How does BDLLfxC differ from BPaL M?

Cost of delaminid is high between US$ 800- 1,190

	Regimen	Estimated regimen price (US$)
BEAT-TB trial regimens	6BDLLfx (FQ-S)	1374
	6BDLC (FQ-R)	1460
	6BDLLfxC (FQ – unknown)	1479
BPaL M	BPaL M	364

Treatment outcome definitions

Outcome	Definition
Treatment failed	A patient whose treatment regimen needed to be terminated or permanently changed[a] to a new regimen or treatment strategy.
Cured	A patient with pulmonary TB with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy, with evidence of bacteriological response[b] and no evidence of failure.
Treatment completed	A patient who completed treatment as recommended by the national policy but whose outcome does not meet the definition for cure or treatment failure.
Died	A patient who died[c] before starting treatment or during the course of treatment.
Lost to follow-up	A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome was assigned.[d]
Treatment success	The sum of all patients cured and treatment completed.
An optional definition was also proposed for use in operational research only	
Sustained treatment success	An individual assessed at 6 months (for DS-TB and DR-TB) and at 12 months (for DR-TB only) after successful TB treatment, who is alive and free of TB.



- Treatment outcome definitions are the same for DS &DR TB

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END TB

Main messages

- While 6-month regimens are the preferred choices for patients with MDR/RR-TB
- There are some limitations to the use of each
  - Age and pregnancy
  - Cost

THANK YOU!

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