Update แนวทางการดูแลรักษาวัณโรคดื้อยา (RR/MDR/preXdR-TB)

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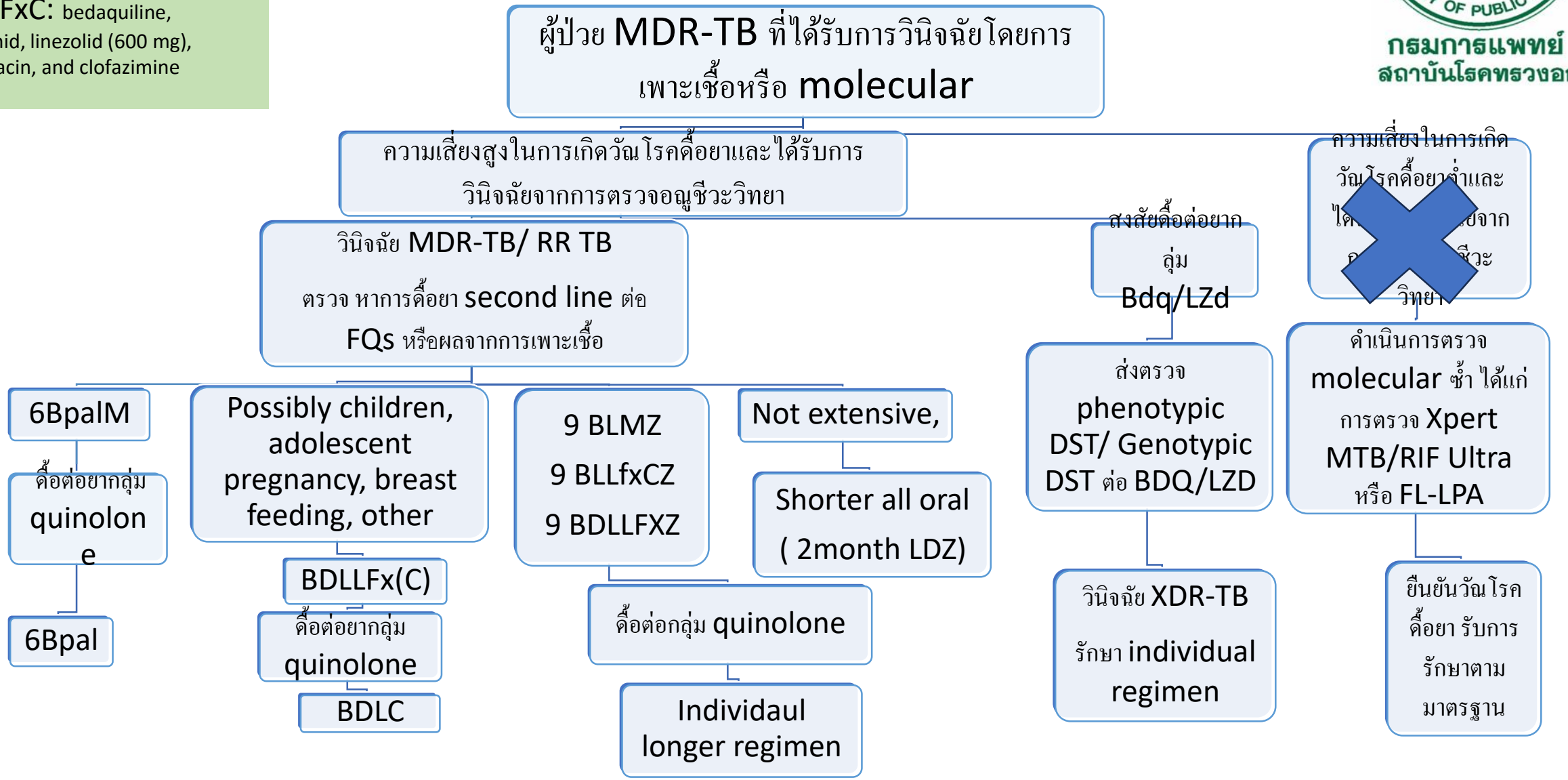
การรักษาวัณโรคดื้อยา (WHO consolidated guidelines expected in early 2025)

BDLLFxC: bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine



Limit of detection for *M. tuberculosis*

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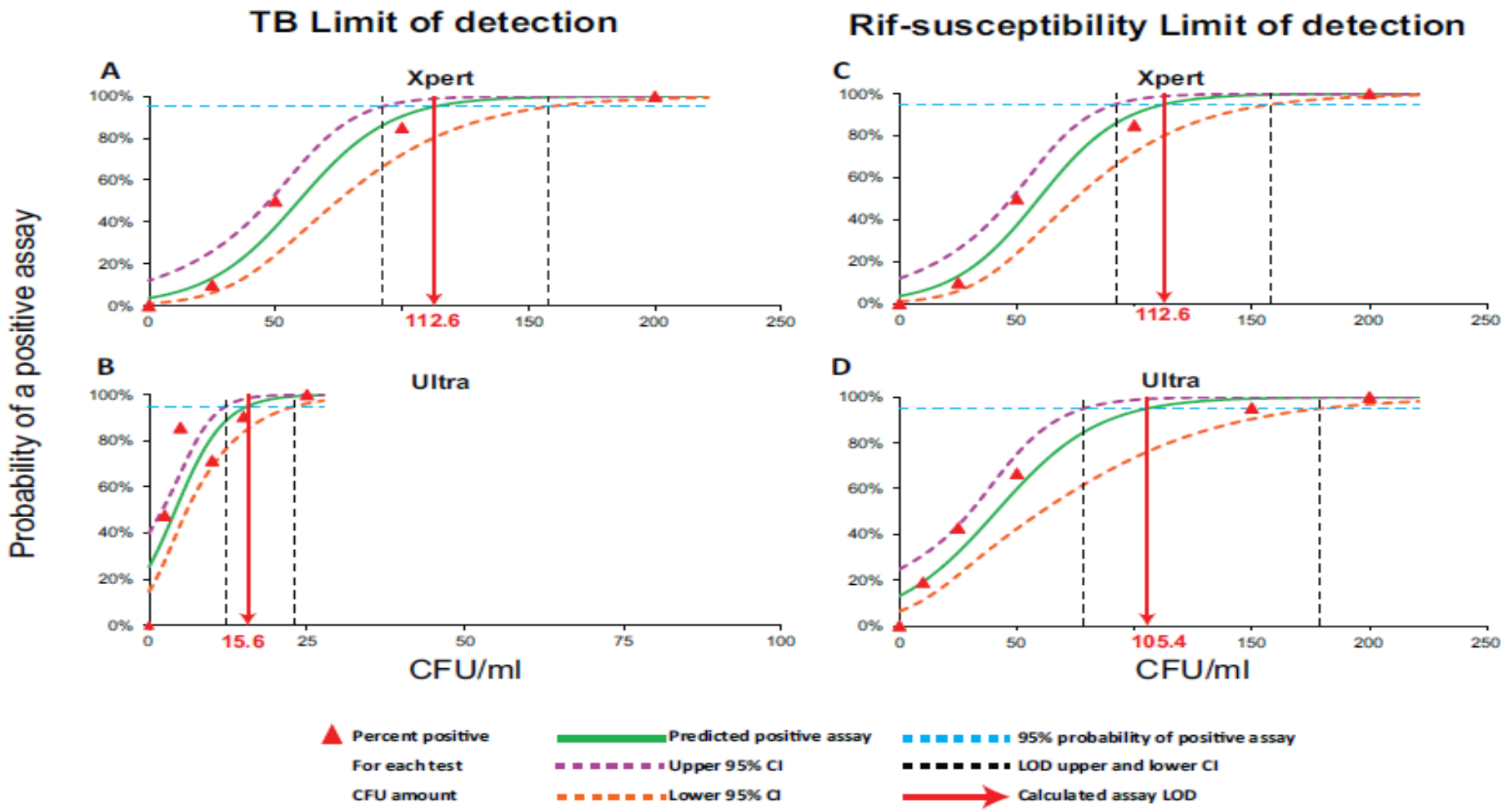
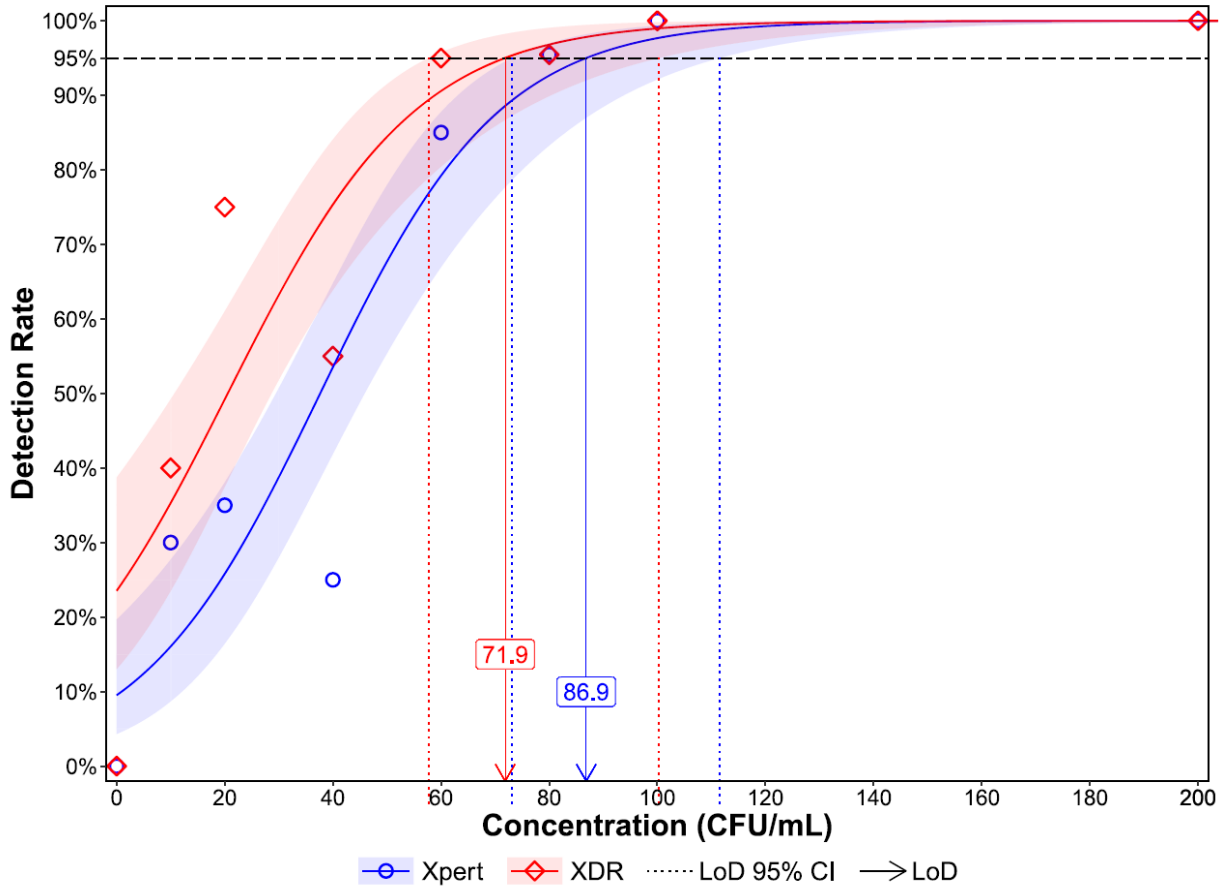


The limit of detection of tuberculosis detection is shown for Xpert (A) versus Ultra (B). The limit of detection for generating a rifampin susceptibility rather than an indeterminate result is shown for Xpert (C) versus Ultra (D)

Xpert MTB/XDR: a 10-Color Reflex Assay Suitable for Point-of-Care Settings To Detect Isoniazid, Fluoroquinolone, andSecond-Line-Injectable-Drug Resistance Directly from Mycobacterium tuberculosis-Positive Sputum



Thus, if the **inhA probe does not result in a detectable T_m (WT or mutant), the result will be "MTB not detected" and no resistance result output will be available** irrespective of whether T_m values are generated by the other targets in the assay

30 non-tuberculous Mycobacterium (NTM) species, 19 Gram-positive and Gram-negative bacteria, along with Candida albicans at 106 to 107 CFU/ml (see Tables S1 and S2 in the supplemental material). All of the samples generated "MTB not detected" results by the Xpert MTB/XDR assay,

Journal of Clinical Microbiology 2021; 59 (3): e02314-20

Rank	Assay	Technology	Approximate LOD
1	BD MAX MDR-TB	Multiplex real-time PCR	**0.5–6 CFU/mL**
2	Roche Cobas MTB	Real-time PCR	**7–9 CFU/mL**
3	STANDARD M10 MTB-INH-RIF	Real-time PCR + melt curve	**~10 CFU/mL**
4	Seegene Anyplex MTB/NTM	Multiplex real-time PCR	**~10–50 copies/reaction***
5	Abbott RealTime MTB	Real-time PCR	**~17 CFU/mL**
6	Xpert MTB/RIF Ultra	Nested real-time PCR	**~16 CFU/mL**
7	FluoroType MTBDR	PCR + melting curve	**~22 CFU/mL**
8	TB-LAMP	LAMP	**80–200 CFU/mL**
9	Xpert MTB/RIF (G4)	Real-time PCR	**131 CFU/mL**
10	GenoType MTBDRplus	PCR + line probe hybridization	**10^2–10^3 CFU/mL**
11	GenoType MTBDRsl	PCR + line probe hybridization	**10^2–10^3 CFU/mL**
12	AFB smear microscopy	Microscopy	**5×10^3–10^4 CFU/mL**

Xpert MTB/RIF ultra for detection of M.TB and Rifampicin resistance: a prospective multicenter diagnostic accuracy study

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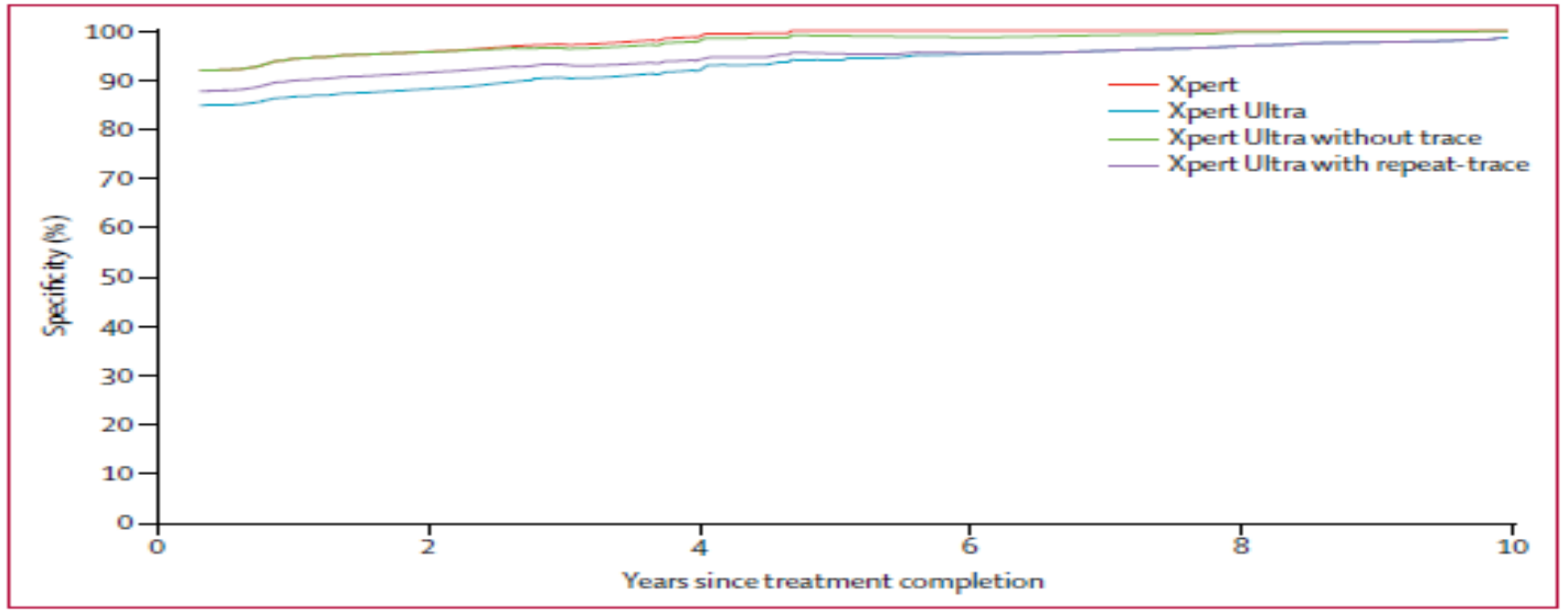

Lancet Infect Dis **2018;**18: 76–**84**

In adults with signs and symptoms of pulmonary TB without a prior history of TB or with a remote history of TB treatment (> 5 years since end of treatment), Xpert Ultra should be used as the initial diagnostic test for TB and for rifampicin-resistance detection rather than smear microscopy/culture and phenotypic DST (WHO 2020)

ความหมาย

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Extensive TB disease is defined in this document as the presence of **bilateral cavitary disease, or extensive parenchymal damage on chest radiography**. In children **aged under 15 years**, advanced disease is usually defined by **the presence of cavities or bilateral disease on chest radiography**

Severe extrapulmonary TB: presence of miliary TB, TB meningitis, osteoarticular or pericardial TB. In children aged below 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered severe (WHO 2025)

การรักษาวัณโรคดื้อยา (WHO consolidated guidelines expected in early 2025)

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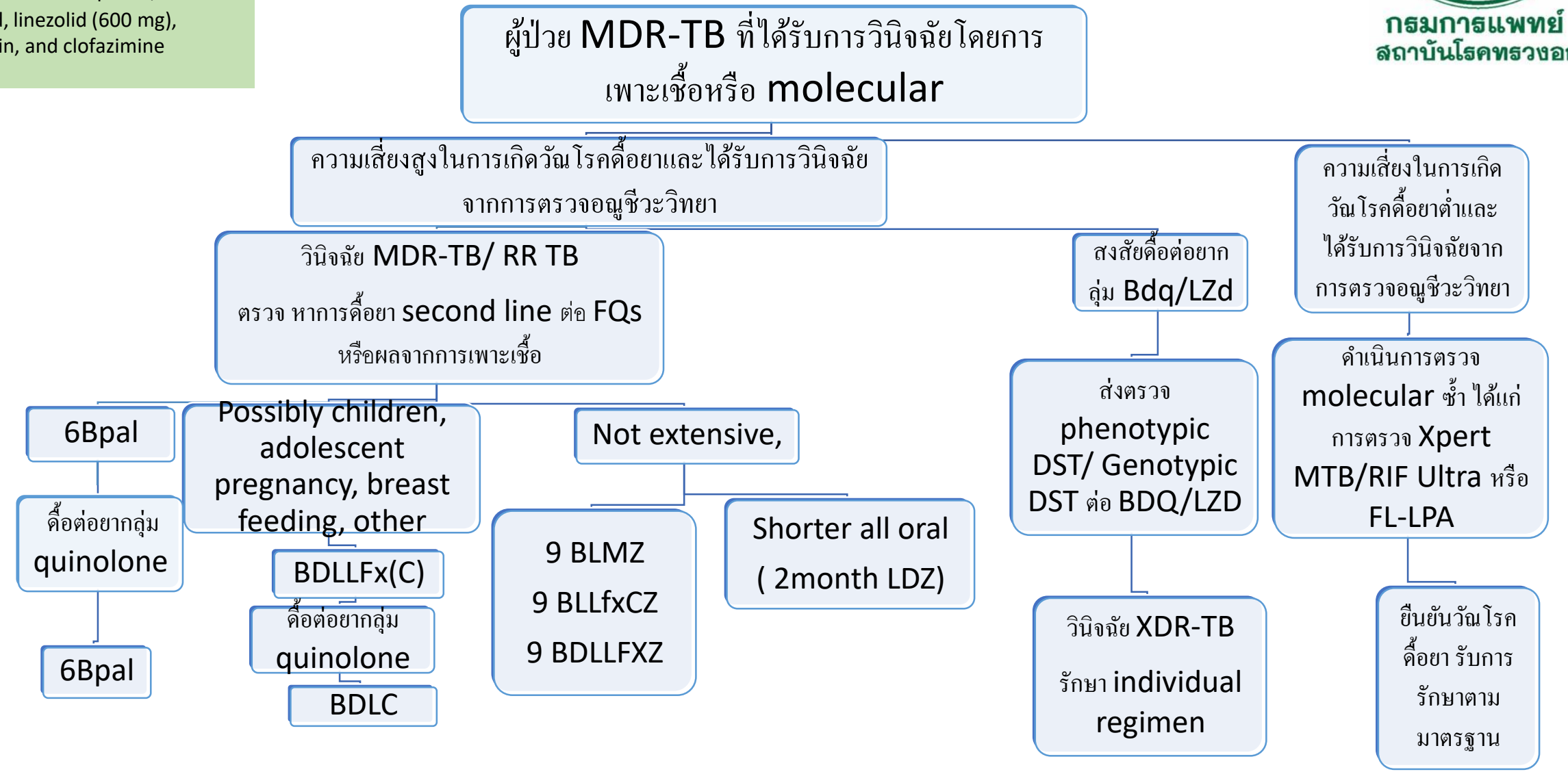
BDLLFxC: bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine



Guidelines for the treatment of Tuberculosis (DR) WHO 2025

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site	6 BpalM/ Bpal	6 BDLLFx(C)	Shorter all oral (2-month LDZ)	9 BLMZ 9 BLLfxCZ 9 BDLLFXZ	Longer all oral
Lymph node					recommended
Bone and joint	**Not recommended**	**Not recommended**	**Not recommended**	**Not recommended**	
Pleural disease					
pericarditis			**Not recommended**		
CNS tuberculosis including meningitis	**Not recommended In TB meningitis**	**Not recommended In TB meningitis**	**Not recommended In TB meningitis**	**Not recommended**	
Disseminated disease	May be not recommended	**Not recommended**	**Not recommended**	**Not recommended multiorgan involvement**	
Genitourinary/ peritoneal					
Extensive TB			**Not recommended**	**Not recommended**	

SHORTER all oral REGIMEN

(9 month)

สูตรยาวัณโรคดื้อยาด้วยสูตรระยะสั้น (shorter all oral)

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ระยะ	ยารักษาวัณโรค	ขนาดยา (มิลลิกรัม/ กิโลกรัม/ วัน)	ขนาดยาโดยทั่วไป (มิลลิกรัม/วัน)**	
			35-50 kg	>50 kg
ระยะเข้มข้น(อย่างน้อย 4 เดือน หรือจนกว่าการย้อมเชื้อไม่เจอเชื้อ และ ไม่เกิน 6 เดือน)	**-Bedaquiline (BDQ) 6 month**		**400 mg/d first 2wk**	**Then 200 mg 3/wk**
	-Moxifloxacin(MFX)	**7.5-10**	**400 OD**	**400 OD**
	or levofloxacin	**15**	**500 OD**	**750 OD**
	-high dose isoniazid (High-dose H)*	**10**	**400 OD**	**600 OD**
	-pyrazinamide (PZA)	**25-30**	**1000 OD**	**1500 OD**
	-Ethambutol (EMB)	**15-20**	**800 OD**	**1000-1200 OD**
	-clofazamine (CFM)	**2-5**	**100 OD**	**100 OD**
	-Protionamide/Ethionamide (PTO/ETO)	**15**	**500 (B.i.d)**	**750 (B.i.D)**
	Or 2 month Linezolid		**600 OD**	**600 OD**
ระยะต่อเนื่อง	**-Moxifloxacin (MFX) or levofloxacin**	**7.5-10**	**400 OD**	**400 OD**
	-Pyrazinamide (PZA)	**25**	**1000 OD**	**1500 OD**
	Ethambutol (EMB)	**15-20**	**800 OD**	**1000-1200 OD**
	-clofazamine (CFM)	**-**	**100 OD**	**100 OD**

ข้อแนะนำในการเลือกใช้ยาสูตรระยะสั้น (SHORTER COURSE REGIMEN)

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1. ได้รับการยืนยันวัณโรคดื้อยา (MDR-TB) โดยไม่มีภาวะดื้อต่อยา 2nd line กลุ่ม quinolone
2. patients with **less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid and clofazimine;** when **exposure is greater than 1 month, these patients may still receive this regimen if resistance to the specific medicines with such exposure has been ruled out**
3. ไม่เคยมีประวัติการแพ้ยาหรืออาการข้างเคียงจากยาที่อยู่ในสูตร shorter course
4. ไม่ตั้งครรภ์
5. No severe extrapulmonary TB และ no extensive disease
6. ต้องใช้ยาตามสูตรครบทุกตัวไม่สามารถลดหรือหยุดการใช้ยาบางชนิด
7. หลังจากเริ่มการรักษาผู้ป่วย มีอาการข้างเคียงจากการใช้ยา หรือหยุดยาเป็นระยะเวลามากกว่าเท่ากับ 2 เดือน หรือล้มเหลวในการรักษาแนะนำให้กลับมาใช้ยาวัณโรคดื้อยาสูตรมาตรฐาน

QTcF interval of ≥ 500 exclusion WHO

Longer regimen

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Relative risk for

(i) treatment failure or relapse and

(ii) death (versus treatment success)

Medicine		Treatment failure or relapse versus treatment success		Death versus treatment success	
		Number treated	Adjusted odds ratio (95% CL)	Number treated	Adjusted odds ratio (95% CL)
A	Levofloxacin *or* moxifloxacin	3143	0.3 (0.1–0.5)	3551	0.2 (0.1–0.3)
	Bedaquiline	1391	0.3 (0.2–0.4)	1480	0.2 (0.2–0.3)
	Linezolid	1216	0.3 (0.2–0.5)	1286	0.3 (0.2–0.3)
B	Clofazimine	991	0.3 (0.2–0.5)	1096	0.4 (0.3–0.6)
	Cycloserine *or* terizidone	5483	0.6 (0.4–0.9)	6160	0.6 (0.5–0.8)
C	Ethambutol	1163	0.4 (0.1–1.0)	1245	0.5 (0.1–1.7)
	Delamanid	289	1.1 (0.4–2.8)[b]	290	1.2 (0.5–3.0)[b]
	Pyrazinamide	1248	2.7 (0.7–10.9)	1272	1.2 (0.1–15.7)
	Imipenem–cilastatin *or* meropenem	206	0.4 (0.2–0.7)	204	0.2 (0.1–0.5)
	Amikacin	635	0.3 (0.1–0.8)	727	0.7 (0.4–1.2)
	Streptomycin	226	0.5 (0.1–2.1)	238	0.1 (0.0–0.4)
	Ethionamide *or* prothionamide	2582	1.6 (0.5–5.5)	2750	2.0 (0.8–5.3)
	P-aminosalicylic acid	1564	3.1 (1.1–8.9)	1609	1.0 (0.6–1.6)
Other medicines	Kanamycin	2946	1.9 (1.0–3.4)	3269	1.1 (0.5–2.1)
	Capreomycin	777	2.0 (1.1–3.5)	826	1.4 (0.7–2.8)
	Amoxicillin–clavulanic acid	492	1.7 (1.0–3.0)	534	2.2 (1.3–3.6)

Table 3.2. Relative risk for treatment failure or relapse, and death (versus treatment success), 2018 IPD meta-analysis for longer MDR-TB regimens and delamanid Trial 213 (intent-to-treat population)[a]

สูตรยาวัณโรคดื้อยาด้วยสูตรระยะยาว Longer regimen

Group A: **Include all three medicines (unless they cannot be used)**	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline[1,4]	Bdq
	Linezolid[2]	Lzd
Group B: **Add both medicines (unless they cannot be used)**	Clofazimine	Cfz
	Cycloserine OR Terizidone	Cs Trd
Group C: **Add to complete the regimen and when medicines from Groups A and B cannot be used**	Ethambutol	E
	Delamanid[3,4]	Dlm
	Pyrazinamide[5]	Z
	Imipenem-cilastatin OR Meropenem[6]	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)[7]	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

regimens last 18 months or more

WHO 2020

Regimen with five agents

- **two of the four agents are likely to be stopped** before the end of treatment (e.g. if bedaquiline is stopped at month 6 and linezolid is stopped early because of toxicity);
- reliable DST is not available for one or more of the agents in the regimen but **background resistance to the agent is known to be high**; and
- the regimen cannot be constructed from **at least four effective agents from Groups A and B.**

สูตรยาวัณโรคดื้อยาด้วยสูตรระยะยาว Longer regimen

Group A: Include all three medicines (unless they cannot be used)	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline[1,4]	Bdq
	Linezolid[2]	Lzd
	Clofazimine	Cfz
Group B: Add both medicines (unless they cannot be used)	Cycloserine OR Terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[3,4]	Dlm
	Pyrazinamide[5]	Z
	Imipenem-cilastatin OR Meropenem[6]	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)[7]	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

Total duration 18-20 months, 15-17 month after sputum conversion

Build Best regimen
Mfx/Lvx+ Bdq+Lzd+Cfz (4)
Mfx/Lvx+ Bdq+Lzd+Cs (4)

In MDR/RR-TB patients on longer regimens, **all three Group A agents and at least one Group B agent** should be included to ensure that treatment starts with at least **four** TB agents likely to be effective, and that **at least three agents are included for the rest of the treatment** if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it

WHO 2020

BPAL

Indication

- People with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB).
- People with confirmed pulmonary TB and all forms of extrapulmonary TB **except for TB involving the CNS, osteoarticular and disseminated (miliary) TB.**
- Adults and adolescents aged **14 years and older.**
- All people regardless of HIV status.
- Patients **with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid**. When exposure is greater than 1 month, **these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out**
- does not apply to pregnant and breastfeeding women

Proper dose of linezolid

- The data from the ZeNix study made it possible to identify the linezolid dose that offers the best balance in terms of efficacy and safety in patients aged above 14 years. The assessment of evidence from this study suggested that **the optimal dosing of linezolid is 600 mg daily and that programmes should strive to maintain this dose throughout the treatment regimen to ensure optimal efficacy**, with the possibility of dose reduction in the event of toxicity or poor tolerability.

Rapid communication May 2022

BpalM or Bpal 6-9 months: 26 wk

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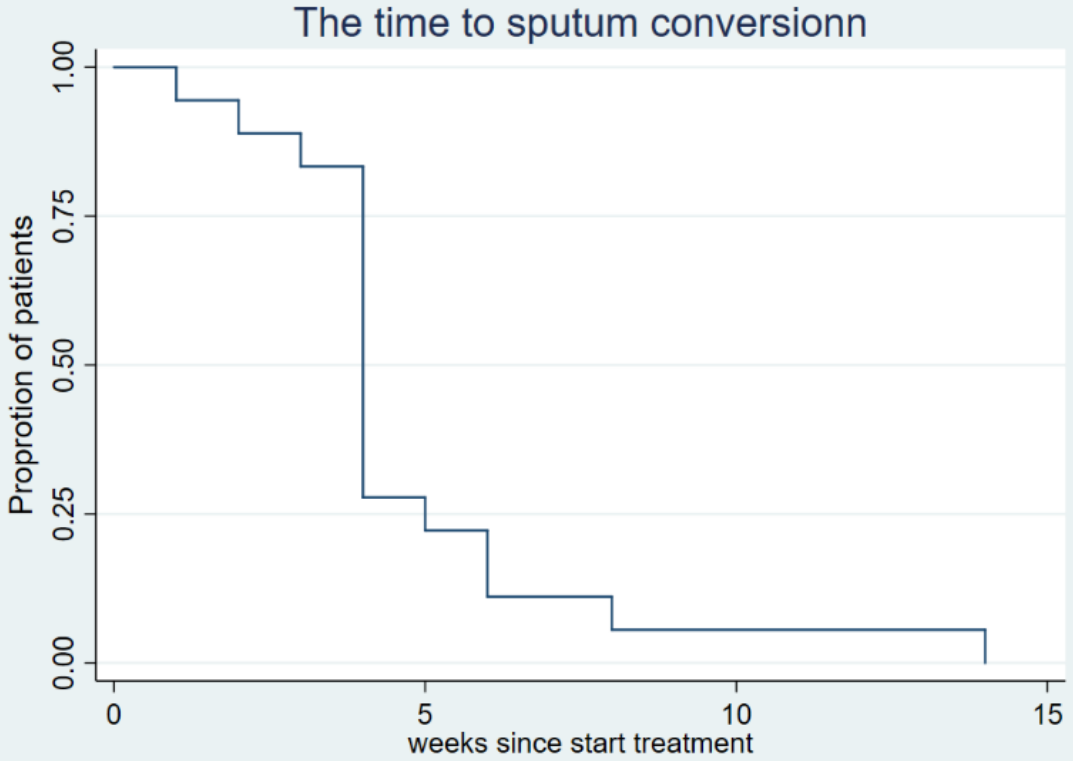
ชนิดยา	ขนาด
Bedaquiline (100 มก ชนิดเม็ด)	**400 มก วันละ 1 ครั้งจากนั้น 200 มก อาทิตย์ละ 3 ครั้ง 24 สัปดาห์ พร้อมอาหาร**
Pretomanid (200 มก ชนิดเม็ด)	**200 มก วันละ 1 ครั้ง พร้อมอาหาร**
Linezolid (600มก ชนิดเม็ด)	**600 มก วันละ 1 ครั้ง ห่างอาหาร**
moxifloxacin	**400 มก วันละ 1 ครั้ง ห่างอาหาร**

Sputum conversion

- Thailand experience
- the median value of sputum conversion was found to be at 4.4 weeks
- one pre-XDR-TB patients who extended lesion with large cavity (8.5 cm) delayed sputum conversion to 14 weeks.



	BPaL regimen, N = 10	BPaLM regimen N = 18
Sputum culture conversion at 4 week, n(%)	4 (40%)	18 (100)
Sputum culture conversion at 8 week, n(%)	8 (80%)	18 (100)

Extended to 9 month

KNCV Tuberculosis Foundation

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- If clinical and bacteriological responses to treatment are poor, a change in the treatment regimen should be considered. **DST should be repeated if culture is still positive at month 4**, **whether or not the regimen is changed**, in order to inform future management decisions.
- If the sputum **culture** taken after the patient has **taken 4 months** of treatment is still **positive**, the patient can receive an **additional 3 months of treatment (total 9 months)** as long as the patient is clinically well and /or improving

One patients with extensive lesion (80%) and cavitation 8.5 cm
Extend treatment to 9 months

Treatment failure of BPAL to longer course

- Lack of culture conversion at the **6th month of treatment**, or
- Culture **reversion at 5th month** or later in a patient with **previous culture conversion to negative**
- Decision to terminate treatment early because of:

  – **poor clinical or radiological response** as decided by the expert committee; or

  – **permanent discontinuation** of either **Bdq or Pa** at any time, or **Lzd** if having **less** than **four weeks** of full dosage, or **having a total of four weeks full dosage but without smear conversion and clinical improvement**.

Interrupt Rx

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TB-PRACTECAL	ZeNix (linezolid 600 mg/26-week arm)
Maximum allowed 2 consecutive weeks of treatment interruption	Maximum allowed total of treatment interruptions – 5 weeks (if 26 weeks duration) and 8 weeks (if 39 weeks duration). All treatment interruptions above 7 consecutive days should have been made up by extending treatment duration. Minimum taken total doses of linezolid – at least 9 weeks

WHO 2025

Side effect

Bedaquiline side effect

- >10%:

Cardiovascular: Chest pain (11%)

Central nervous system: Headache (28%)

Gastrointestinal: Nausea (38%)

Hepatic: Increased serum transaminases (9% to 11%)

Neuromuscular & skeletal: Arthralgia (33%)

Respiratory: Hemoptysis (18%)

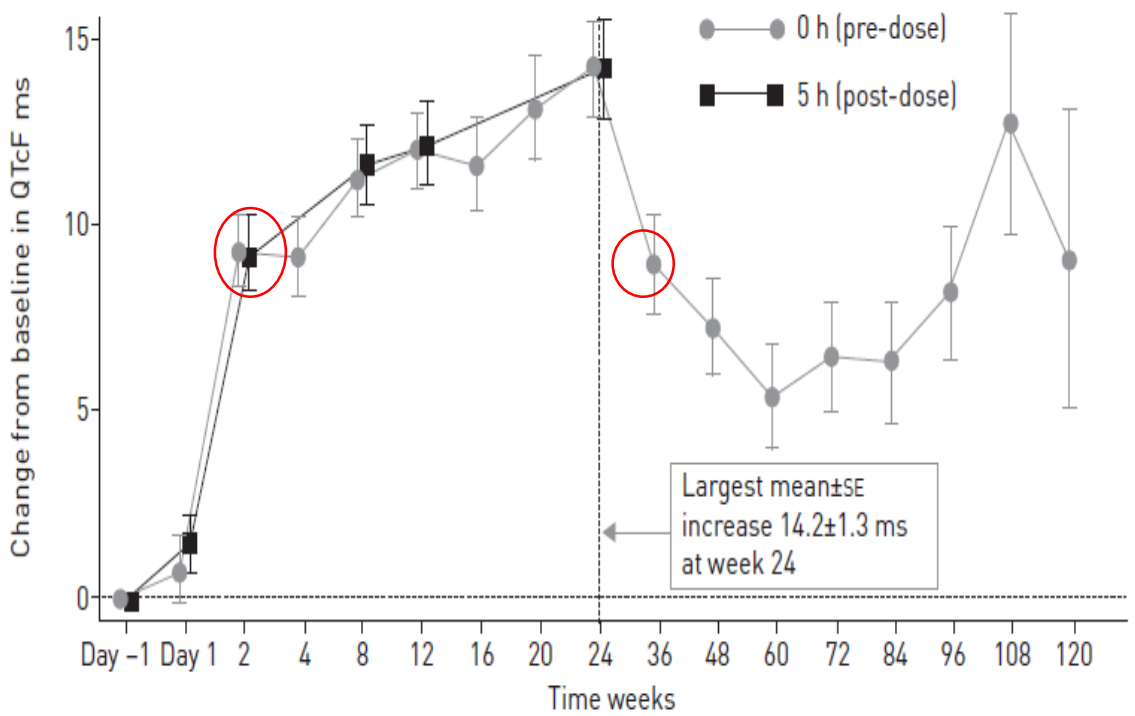
- 1% to 10%:

Dermatologic: Skin rash (8%)

Gastrointestinal: Anorexia (9%), increased serum amylase (3%)

<1%, post marketing, and/or case reports: Hepatotoxicity, prolonged Q-T interval on ECG

Bedaquiline in the treatment of multidrug and extensively drug resistant tuberculosis



Patients n

The two patients with an increase in QTcF interval >500 ms were both taking clofazimine and one had concurrent hypokalaemia. No episodes of clinically significant dysrthymia were reported. The mean maximum change in QTcF interval from baseline was 14.2 ms. This fell to <10 ms after bedaquiline was stopped.In the patients taking clofazimine at week 24 (n=17), **the mean maximum change in QTcF interval from baseline to week 24 was 31.9 ms compared with 12.3 ms for those not taking clofazimine (n=177).**

Eur Respir J 2016; 47: 394–402 [DOI: 10.1183/13993003.01891-2015].

Long-term outcome and safety of prolonged bedaquiline treatment for multidrug- resistant Tuberculosis

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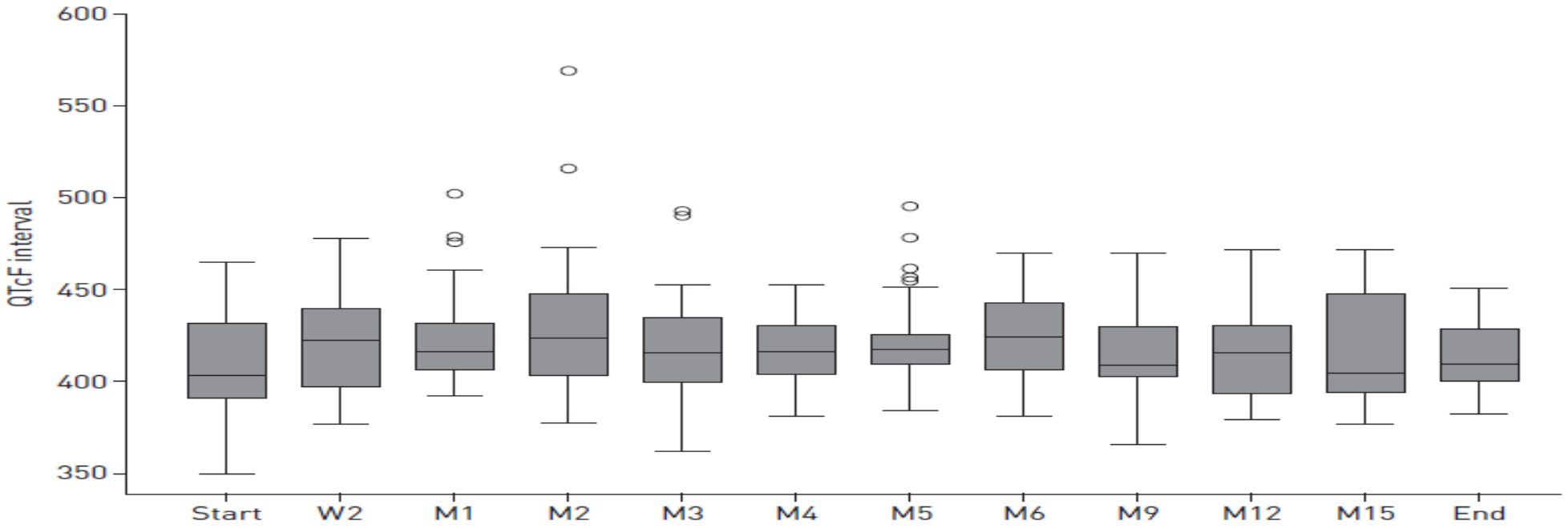

Box plot of the Fridericia-corrected QT (QTcF) values of the 45 patients at treatment start, at week 2 of treatment (W2), at month 1, 2, 3, 4, 5, 6, 9, 12 and 15 of treatment (M1, M2, M3, M4, M5, M6, M9, M12 and M15), and at the end of treatment. Data are presented as median and interquartile range; minimum and maximum values are shown by whiskers; outliers are indicated by circles.

Long-term outcome and safety of prolonged bedaquiline treatment for multidrug- resistant Tuberculosis

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Prerequisites and criteria used in this cohort for bedaquiline prolongation beyond 24 weeks

Treatment safety in the whole cohort and comparison between patients receiving standard (⩽190 days) or prolonged(>190 days) bedaquiline treatment

	Whole cohort	Standard bedaquiline treatment	Prolonged bedaquiline treatment	p-value[#]
Subjects	45	12	33	
Any adverse event	44 (97.8)	12 (100)	32 (97.0)	1.000
Any severe adverse event	28 (62.2)	5 (41.7)	23 (69.7)	0.163
Any serious adverse event	7 (15.6)	1 (8.3)	6 (18.2)	0.655
At least one drug stopped due to adverse events	37 (82.2)	8 (66.7)	29 (87.9)	0.181
Bedaquiline stopped due to adverse events	3 (6.7)	1 (8.3)	2 (6.1)	1.000
Liver enzyme elevation	17 (37.8)	6 (50.0)	11 (33.3)	0.325
Pancreatitis	1 (2.2)	1 (8.3)	0	0.267
QTcF >500 ms	5 (11.1)	0	5 (15.2)	0.303
QTcF >60 ms increase	13 (28.9)	4 (33.3)	9 (27.3)	0.721
Maximum QTcF increase during treatment	36.2 (17.9–68.5)	31.9 (16.0–73.3)	41.6 (19.7–63.7)	0.437

No association was found between clofazimine treatment and QTc prolongation

Pretomanid

- Food increases pretomanid absorption.
- Steady state concentration is achieved in 4-6 days after repeated oral administration of 200 mg pretomanid once daily. **The mean plasma half-life of pretomanid is 17.4 hours**
- . Approximately **20%** metabolism occurs via **Cytochrome P450 3A enzyme**. Metabolites of pretomanid are excreted predominantly via urine (53%) and faeces (38%). Data **regarding dose modification based on patient age, renal or hepatic impairment is not yet available**.

indian journal of tuberculosis 68 (2021) 287 e291

Pretomanid

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Side effect

- peripheral neuropathy
- Acne
- Anaemia
- nausea, vomiting
- musculoskeletal pain
- increased liver enzymes (transaminases and gamma-glutamyltransferase)
- tremor

with the use of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid.

should not be administered with other CYP 3A4 inducers like rifampicin, efavirenz:

indian journal of tuberculosis 68 (2021) 287 e291

Pretomanid

- Hepatic adverse reactions were reported with the use of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid. Monitor symptoms and signs and liver-related laboratory tests. Interrupt treatment with the entire regimen if evidence of liver injury occurs
- Pretomanid caused **testicular atrophy** and impaired fertility in **male rats**. Advise patients of reproductive toxicities seen in animal studies and that the potential effects on **human male fertility have not been adequately evaluated**

Full prescription information

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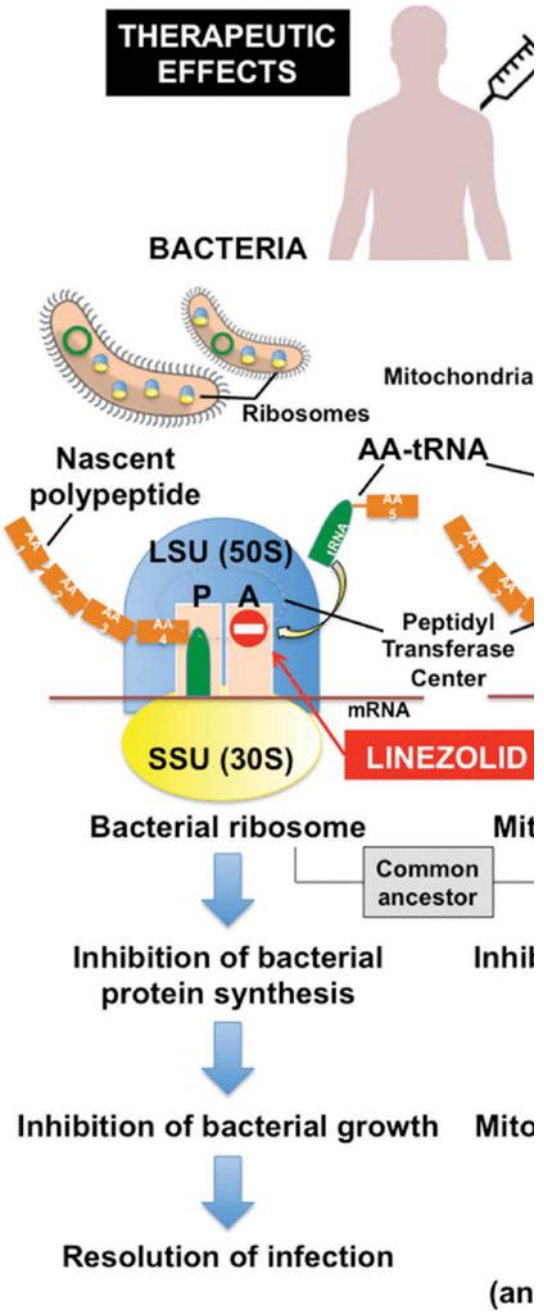
Linezolid

- Linezolid belongs to a family of **antibiotics (oxazolidinones)** that **inhibit bacterial protein synthesis** by binding to 23S rRNA in the large ribosomal subunit and preventing the fusion of 30S and 50S ribosomal subunits and the formation of the translation initiation complex
- linezolid has a **100% oral bioavailability**
- **Time-dependent antimicrobial action**, **but** an influence of linezolid concentration on **adverse effects** has previously been suggested by hematological alterations in patients with renal failure which is provably associated with **linezolid or metabolite accumulation**
- **No hepatic or renal impairment which could influence linezolid pharmacokinetics** was present among the studied patients.



Common linezolid side-effects

- Headache: relief pain with NSIAS
- Diarrhea
- Feeling sick (nausea) or being sick (vomiting): Stick to simple meals - avoid rich or spicy foods
- Metallic taste in the mouth: Try taking your doses with some food or a drink to take away the taste

linezolid

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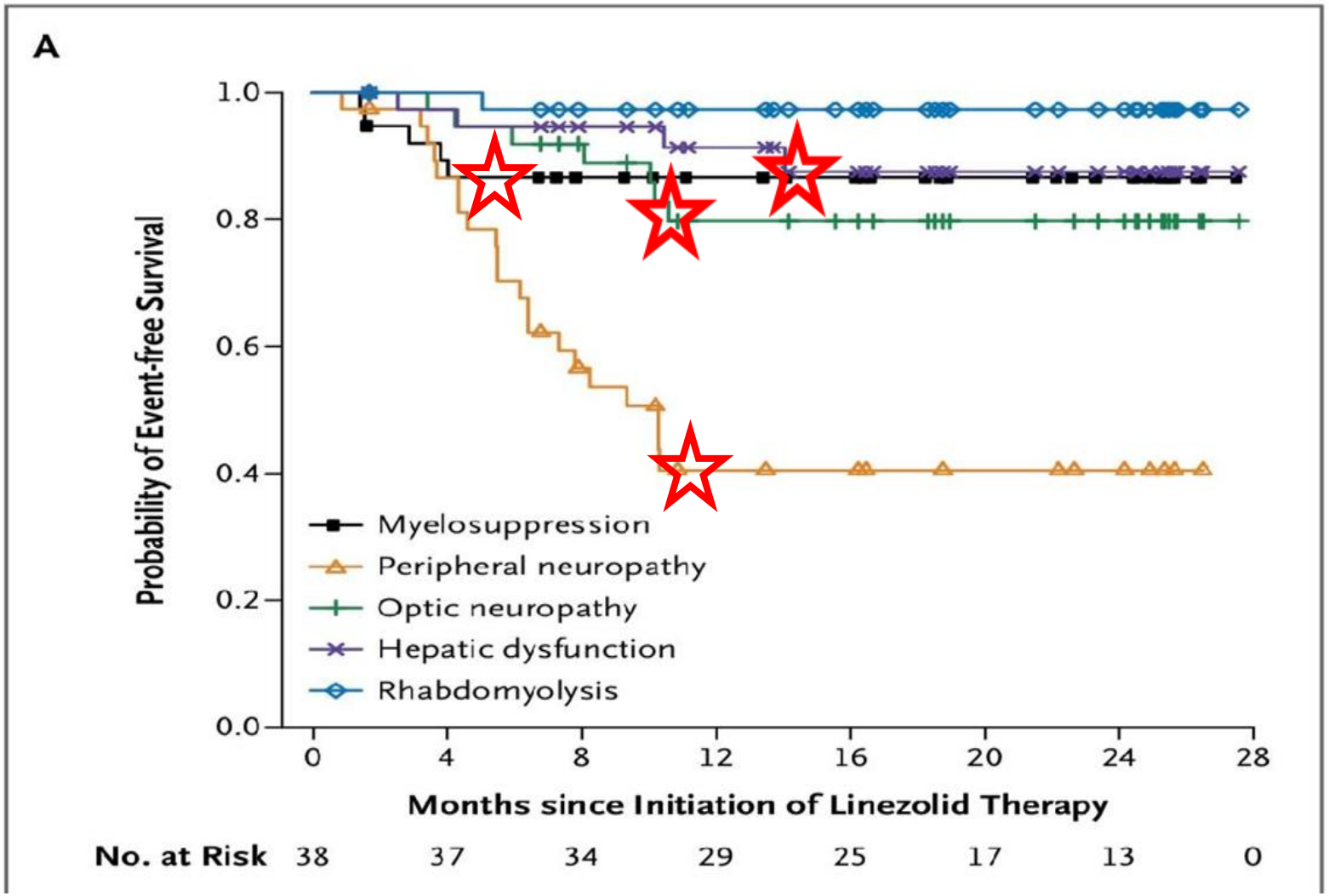
Should **not be administered concomitantly with selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), or a diet high in tyramine-containing foods (such as cheese, red wine, cured meats, soy sauce, and fermented foods)**, given the risk of serotonin syndrome. If linezolid therapy is planned and when possible, SSRIs and TCAs should be withdrawn at least two weeks in advance (given the long half-lives of these agents).

TABLE 2

Spectrum of symptoms of serotonergic toxicity

Severity	Neuromuscular excitation	Altered mental status	Autonomic dysfunction
Mild	Hyperreflexia Tremor Myoclonus	Anxiety Restlessness Insomnia	Diaphoresis Mydriasis Tachycardia
Moderate	Opsoclonus Spontaneous or inducible clonus	Agitation	Hypertension Hyperthermia (< 40°C, < 104°F) Hyperactive bowel sounds Diarrhea, nausea, vomiting
Severe	Rigidity Respiratory failure Tonic-clonic seizure	Coma Delirium Confusion	Severe hyperthermia (≥ 40°C, ≥ 104°F) Dynamic blood pressure

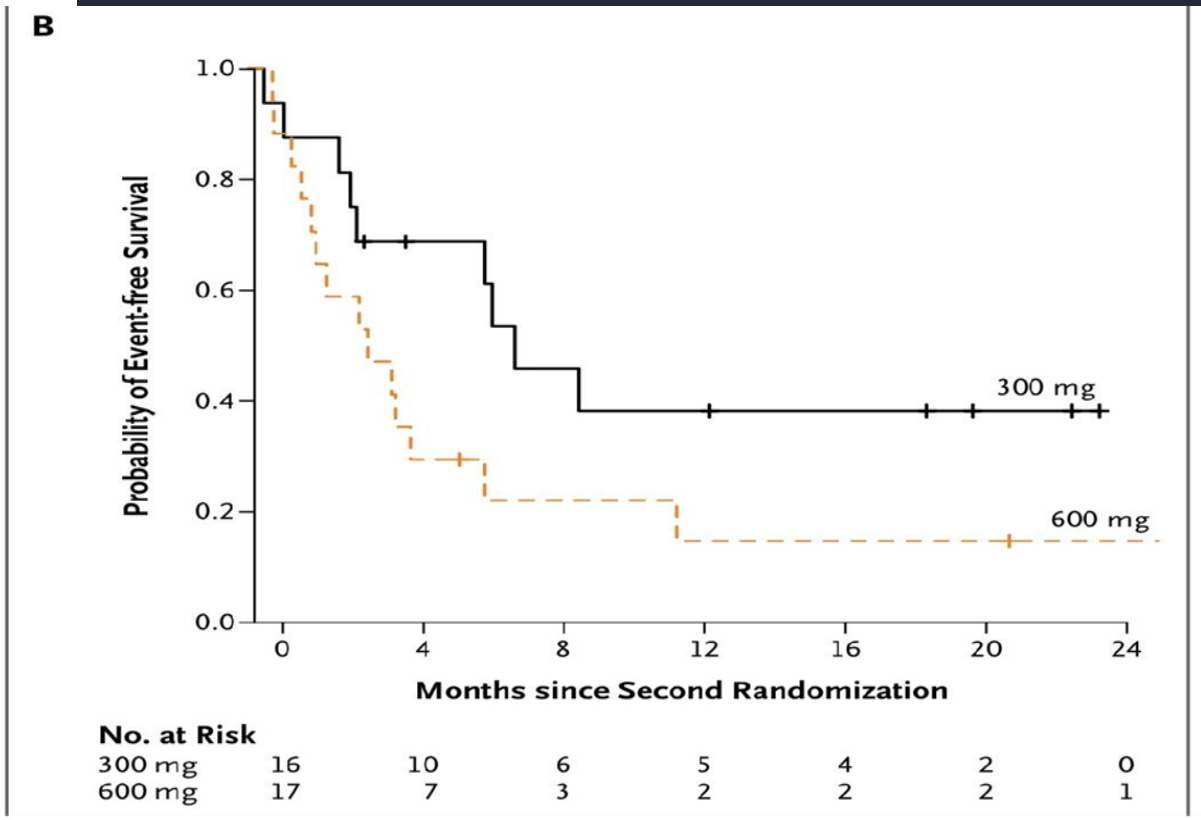
Linezolid side effect



show the time to the onset of clinically significant adverse events that resulted in a drug holiday or dose adjustment during the study. Symbols indicate data-censoring points for patients remaining in the study

n engl j med 367;16 nejm.org october 18, 2012

Linezolid side effect



A Cox proportional-hazards analysis showed that, after the second randomization, the group **receiving the 600-mg dose was 2.7 times** (95% confidence interval, 1.1 to 6.5) as likely to have an **adverse event** as the group receiving the 300-mg dose (P = 0.03)

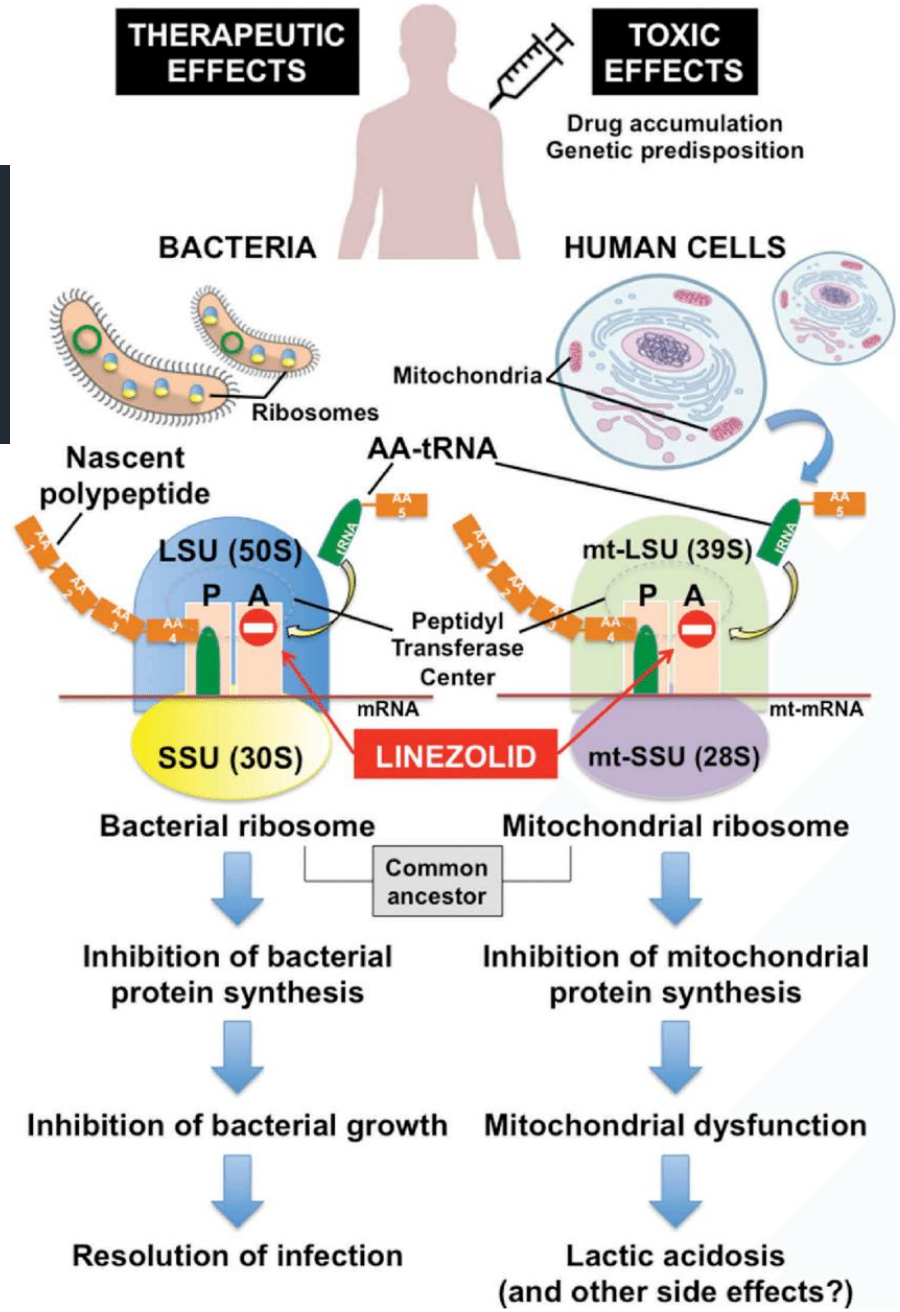
show the time to the first adverse event in patients after the second randomization to either a continuation of the 600-mg daily dose or a reduced dose of 300 mg per day. Tick marks indicate data-censoring points for individual patients who continued to receive the study drug.

n engl j med 367;16 nejm.org october 18, 2012

Linezolid-induced lactic acidosis: the thin line between bacterial and mitochondrial ribosomes

Interfere with mitochondrial function due to similarities between bacterial and mitochondrial ribosomes

linezolid-induced lactic acidosis **should be suspected only after exclusion of other,**



Expert Opinion on Drug Safety · May 2017

Linezolid (Lzd)

DRUG CLASS: OXAZOLIDINONES

Activity against TB, mechanism of action, and metabolism	Has in vitro bactericidal activity – increasing clinical experience; inhibits protein synthesis.
Dose	**Adults:** 600 mg, once daily. (Reduce to 400–300 mg/day if serious adverse effects develop). **Children:** 10 mg/kg three times daily in children up to 11 years of age and 10 mg/kg (maximum dose 600 mg) twice daily in older children.[5] 10 mg/kg/dose every 12 hours. **Vitamin B6:** All patients should receive vitamin B6 while receiving linezolid.
Preparation	Coated tablets: 400 and 600 mg; intravenous solution: 2 mg/ml: 100, 200 or 300 mg bags. Intravenous doses are administered over 30–120 minutes. Oral powder for suspension: 100 mg/5 ml, 240 ml bottle.
Storage	Store tablet at room temperature (15–25 °C). Reconstituted oral suspension may be stored at room temperature for 21 days. Parenteral preparation should be stored at room temperature (protect from light and do not freeze).
Oral absorption	Nearly complete oral absorption.
CSF penetration	CSF concentrations are about 1/3 of those in serum in animal models, and linezolid has been used to treat meningitis in humans.
Special circumstances	**Use in pregnancy/breastfeeding:** Not recommended during pregnancy or breastfeeding due to limited data. **Use in renal disease:** No dose adjustment is recommended, but metabolites may accumulate. **Use in hepatic disease:** Rarely associated with increased transaminases.
Adverse reactions	Myelosuppression (decreased level of platelets, decreased level of white blood cells, and/or anaemia). Diarrhoea and nausea. Optic and peripheral neuropathy may be irreversible and linezolid should stopped if these develop; weigh against the risk of permanent blindness or disabling permanent neuropathy. Lactic acidosis – patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving linezolid should receive immediate medical evaluation, including a lactic acid blood test.
Contraindications	**Hypersensitivity to oxazolidinones.** **Symptoms of neuropathy** (pain, numbness, tingling or weakness in the extremities).

[5] Zyvox: linezolid injection, linezolid tablets, linezolid for oral suspension package insert. Kalamazoo, MI: Pharmacia & Upjohn Company; 2002.

Drug Interactions	Avoid use with patients taking serotonergic agents, such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (e.g. fluoxetine, paroxetine), lithium, tricyclic antidepressants, etc. as it may cause serious CNS reactions such as serotonin syndrome.
Monitoring	Monitor for peripheral neuropathy and optic neuritis (visual eye tests every two months or if symptoms develop, clinical examination for peripheral neuropathy monthly or if symptoms develop). Monitor a complete blood count weekly during the initial period, then monthly, and then as needed based on symptoms; there is little clinical experience with prolonged use.
Patient instructions and alerting symptoms	This medicine may be taken with or without food. Take it with food if it irritates the stomach. Avoid food and drinks that contain tyramine: aged cheeses, dried meats, sauerkraut, soy sauce, tap beers and red wines. Make sure your doctor knows if you are taking medicines for colds, congestion or depression. **Instruct patients to inform their health care provider right away if any of the following occurs:** • Pain, numbness, tingling or weakness in the extremities • Black, tarry stools or severe diarrhoea • Unusual bleeding or bruising • Unusual tiredness or weakness • Headache, nausea or vomiting.

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Linezolid was withdrawn when a severe adverse event was observed (a platelet count of <100,000 cells/mm^3, a hemoglobin concentration of <9 g/liter, or severe gastrointestinal manifestations).

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Management of linezolid toxicity

No patients had severe anemia (Hb < 8 g/dl) or thrombocytopenia/neutropenia.

Retrospective comparison of levofloxacin and moxifloxacin on multidrug-resistance tuberculosis treatment outcomes

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	Total MDR-TB	Levofloxacin	Moxifloxacin	*p* value
No. of subjects	171 (100)	123 (71.9)	48 (28.1)	
Duration of treatment, days, median (IQR)	614 (494-776)	594 (481-772)	673 (530-778)	0.814
Surgical resection	20 (11.7)	14 (11.4)	6 (12.5)	0.838
No. of used drugs	5 (4-6)	5 (4-6)	5 (4-6)	0.244
No. of susceptible drugs used	5 (4-5)	5 (4-5)	4 (4-5)	0.048
No. of resistant drugs	4 (3-6)	4 (3-5)	5 (4-7)	< 0.001
Resistance to ofloxacin	35 (20.5)	18 (14.6)	17 (35.4)	0.005
Adverse drug reactions	81 (47.4)	56 (45.5)	25 (52.1)	0.440
Eye toxicity	2 (1.2)	2 (1.6)	-	1.000
Ototoxicity	17 (9.9)	10 (8.1)	7 (14.6)	0.255
Hepatotoxicity	13 (7.6)	10 (8.1)	3 (6.3)	1.000
Hematologic abnormalities	6 (3.5)	2 (1.6)	4 (8.3)	0.053
Gastrointestinal trouble	50 (29.2)	33 (26.8)	17 (35.4)	0.267
Dermatological abnormalities	6 (3.5)	4 (3.3)	2 (4.2)	0.674
Endocrinological abnormalities	4 (2.3)	4 (3.3)	-	0.578
Neurological abnormalities	20 (11.7)	13 (10.6)	7 (14.6)	0.463
Allergic reaction	7 (4.1)	7 (5.7)	-	0.193
Musculoskeletal abnormalities	13 (7.6)	12 (9.8)	1 (2.1)	0.114

Central nervous system: Headache , dizziness , insomnia

The Korean Journal of Internal Medicine Vol. 26, No. 2, June 2011

Comparison of Levofloxacin versus Moxifloxacin for Multidrug-Resistant Tuberculosis

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	Levofloxacin Group ($n = 78$)	Moxifloxacin Group ($n = 77$)	*P* Value
Gastrointestinal trouble	30 (38.5%)	29 (37.7%)	0.92*
Musculoskeletal abnormalities	28 (35.9%)	11 (14.3%)	0.002*
Neurologic abnormalities	8 (10.3%)	11 (14.3%)	0.44*
Dermatologic abnormalities	9 (11.5%)	7 (9.1%)	0.62*
Others[†]	7 (8.9%)	9 (11.7%)	0.58*
Hepatotoxicity	8 (10.3%)	7 (9.1%)	0.81*
Ototoxicity	5 (6.4%)	4 (5.2%)	1.00[‡]
Allergic reaction	1 (1.3%)	6 (7.8%)	0.06[‡]
Cardiovascular abnormalities[§]	3 (3.8%)	2 (2.6%)	1.00[‡]
Eye toxicity	1 (1.3%)	2 (2.6%)	0.62[‡]
Endocrinologic abnormalities	0	1 (1.3%)	0.50[‡]
Hematologic abnormalities	0	0	—
Any adverse drug reactions	54 (69.2%)	46 (59.7%)	0.22[‡]

Am J Respir Crit Care Med 2013

Hypoglycemia in quinolone

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- Hypoglycemia typically occurs **within the 1st 3 days of fluoro-quinolone therapy** and has also been reported after the first dose of either intravenous or oral administration
- more common in **elderly patients with a history of type 2 diabetes** who are receiving treatment with an oral sulfonylurea
- Exact **mechanism** of fluoro-quinolones causing alterations in blood glucose levels is **unknown**. It has been postulated that glucose alterations may be due to blockage of the adenosine 5'-triphosphate (ATP)-sensitive potassium channels in pancreatic β-cells that help regulate calcium influx and thus augment insulin release. Older fluoro-quinolones (lomefloxacin, enoxacin, sparfloxacin, tosufloxacin) close the ATP-sensitive potassium channel. This leads to depolarization of the β-cell membrane and opening of voltage-dependent calcium channels allowing calcium movement into the cells with subsequent insulin release. Quinolones may also augment effect of oral sulfonylureas in patients with diabetes mellitus.

Indian J Pharmacol. 2013 May-Jun; 45(3): 301–302

Which FQs have been associated with tendinopathy/tendon rupture?

EATURE	OBSERVATIONS/FINDINGS
Causative quinolones reported	Ciprofloxacin (most commonly reported), norfloxacin, pefloxacin, ofloxacin, levofloxacin
Associated risk factors	**Age >60 years, corticosteroid therapy, renal failure, diabetes mellitus, history of tendon rupture**
Relative risk of tendon disorders	1.7-fold increase for all tendinopathies 1.3-fold increase for tendon rupture 4.1-fold increase of Achilles tendon rupture 46-fold increase of tendon rupture with concurrent corticosteroid exposure 1.5-fold increase in tendon disorders if age >60 years 2.7-fold increase in tendon rupture if age >60 years
Affected tendons	Achilles tendon most commonly affected (89.8% of cases) Multiple other tendons reported **Up to 50% of cases with bilateral involvement**
Latency period of tendinopathy	**Symptoms of tendinitis often precede tendon rupture by up to 2 weeks** **Median onset of 6 days (85% of cases within first month)** **Up to 50% of cases after fluoroquinolone discontinued**

J Clin Aesthet Dermatol. 2010 Apr; 3(4): 49–54

Selection of fluoroquinolone

- the evidence from South Africa available for the review – 83% of patients analysed using this dataset received levofloxacin, and the rest received moxifloxacin at standard dose.
- Both levofloxacin and moxifloxacin have shown **similar efficacy** for treating drug-resistant TB.
- The choice between levofloxacin and moxifloxacin was guided by the potential risk of cumulative **cardiotoxicity,** using moxifloxacin in a shorter regimen with injectables and levofloxacin in an all-oral shorter regimen. Levofloxacin is often preferred because of **moxifloxacin's slightly higher potential for cardiotoxicity;** however, levofloxacin has been associated with musculoskeletal disorders in paediatric populations. Therefore, irrespective of the choice of fluoroquinolone

WHO 2020

levofloxacin with and without meal ?

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- Can use both **with and without meal**
- Oral levofloxacin tablets can be administered without regard to food. Take oral **levofloxacin solution one hour before or two hours after food.**
- Take levofloxacin at least two hours before or two hours after antacids or preparations containing iron or zinc.

Cycloserine for treatment of multidrug-resistance Tuberculosis: a retrospective cohort study in China

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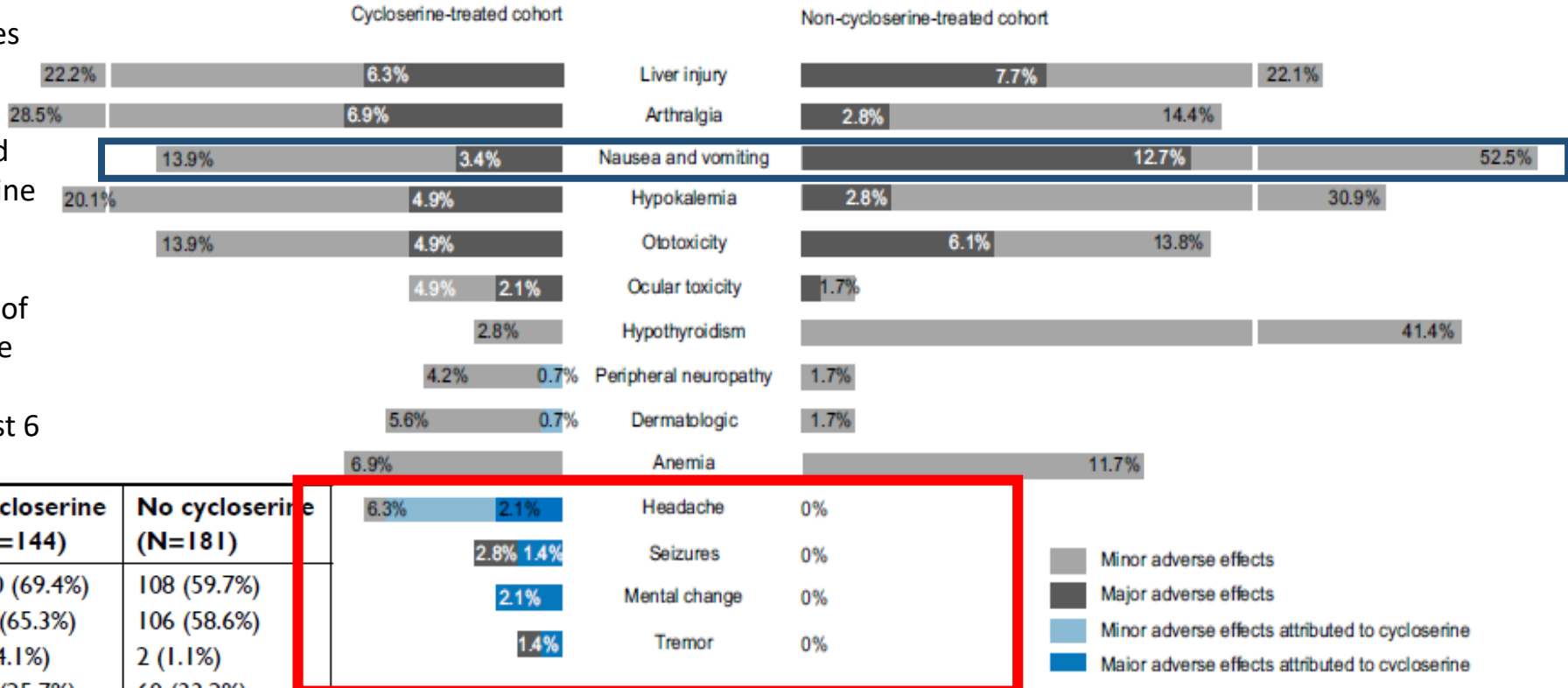
A total of 16 patients reported 17 episodes related to cycloserine, including nine patients who discontinued cycloserine temporarily or permanently. We observed eight episodes of headache, and cycloserine was permanently withdrawn from the treatment regimen in two patients. Moreover, two cases of seizure, one case of depression, and two cases of anxiety were observed, with these events resulting in cycloserine discontinuation within the first 6 months of treatment

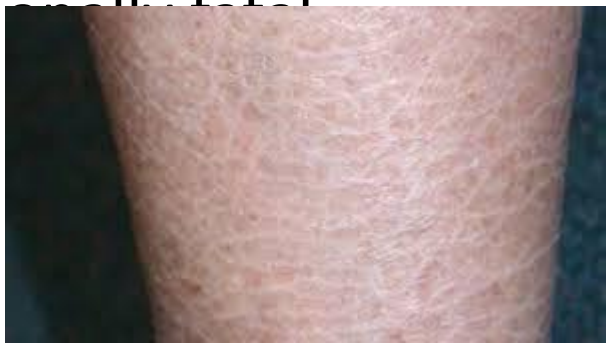


Treatment outcomes	Cycloserine (N=144)	No cycloserine (N=181)
Treatment success	100 (69.4%)	108 (59.7%)
Cure	94 (65.3%)	106 (58.6%)
Treatment completion	6 (4.1%)	2 (1.1%)
Treatment failure	37 (25.7%)	60 (33.2%)
Fail to conversion at 6 months	13 (9.0%)	26 (14.4%)
Reversion	8 (5.6%)	9 (5.0%)
Adverse drug reactions	16 (11.1%)	25 (13.8%)
Death	0 (0.0%)	1 (0.5%)
Default	7 (4.9%)	12 (6.6%)

Infection and Drug Resistance 2019:12 721–731

Clofazamine

- Skin discoloration: reddish-brown discoloration seen in skin and conjunctiva were gradually reversible on cessation of therapy, as reported
- gastrointestinal intolerance: may **be mild to moderate** (abdominal/epigastric pain, nausea, diarrhea, vomiting, gastrointestinal intolerance) or, less frequently, severe (splenic infarction, bowel obstruction, bleeding), and occasi[illegible]



Adverse Events	Cfz Group (n = 53), No. (%)	Control Group (n = 52), No. (%)	*P* Value
Anemia	1 (1.9)	1 (1.9)	1
Thrombocytopenia	2 (3.8)	2 (3.8)	1
Leukopenia	4 (7.5)	5 (9.6)	1
Nausea/vomiting	6 (11.3)	5 (9.6)	1
Peripheral neuropathy	2 (3.8)	1 (1.9)	1
Optic neuropathy	1 (1.9)	1 (1.9)	1
Liver injury	6 (11.3)	5 (9.6)	1
Tinnitus or hearing loss	2 (3.8)	3 (5.8)	.68
Rash or pruritus	2 (3.8)	2 (3.8)	1
Arrhythmia	3 (5.7)	3 (5.8)	1
Hypokalemia	3 (5.7)	4 (7.7)	.72
Pink to brownish-black discoloration of skin	50 (94.3)	0 (0)	0
Ichthyosis	25 (47.2)	0 (0)	0

Pregnancy

- Pregnancy is not a contraindication for treatment of TB and MDR-TB
- Birth control is strongly recommended for all non-pregnant women receiving therapy for specially MDR-TB.

	Pregnancy
INH	safe
RF	safe
EMB	safe
PZA	Safe (CDC: caution or avoid)
moxifloxacin	Category C
levofloxacin	Category C
aminoglycoside	**Avoided, category D**
linezolid	Category C, some studies suggest it can be safe, particularly in the late third trimester
Ethionamide	**Not recommended**
cycloserine	careful consideration, no data teteratogenicity in human, safe in animal
Clofazamine	May be safe
Bedaquilline	careful consideration particularly in the first trimester.
delamanid	careful consideration particularly in the first trimester.
Pretomanid	**safety not established**

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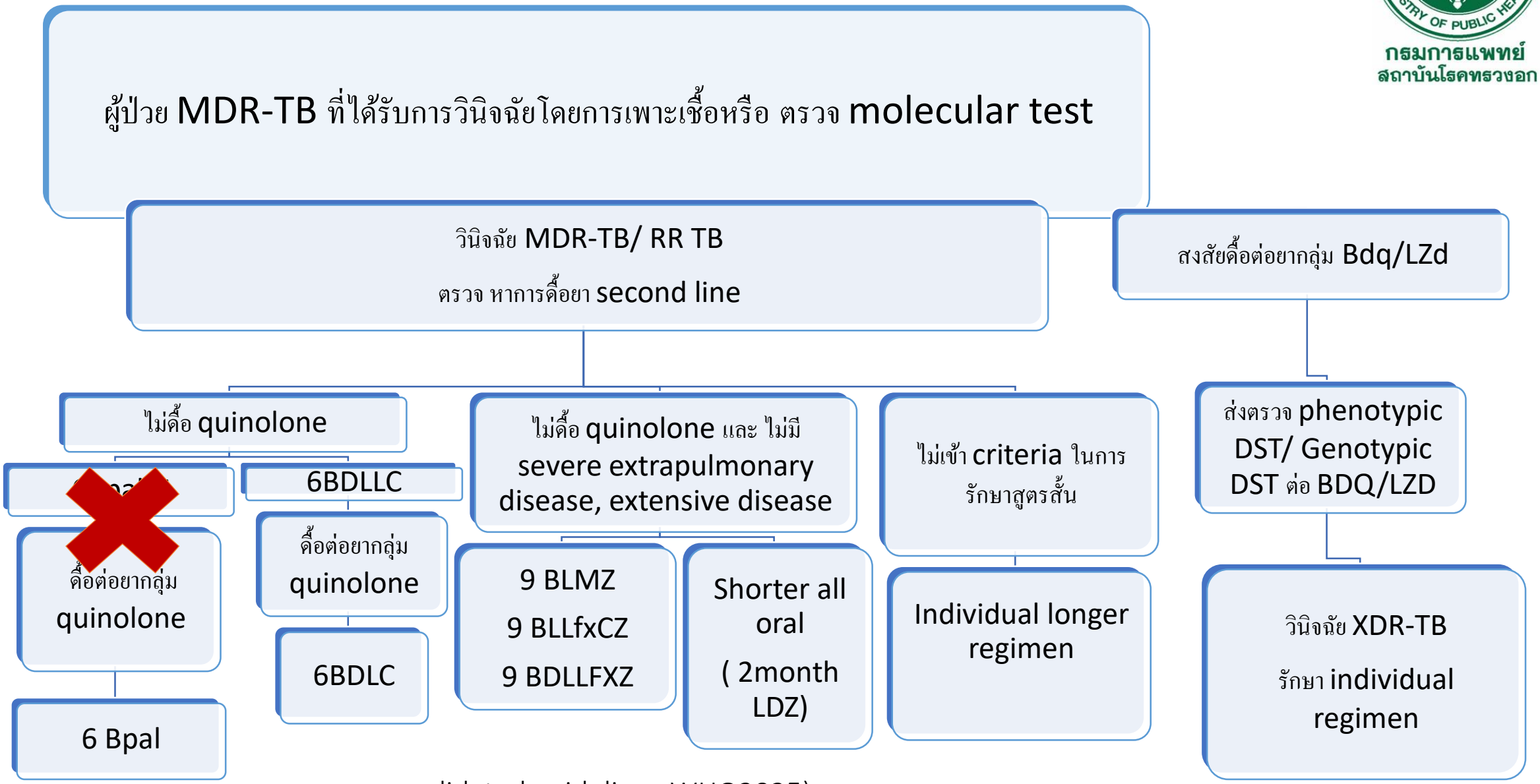
Category C: Studies in animals have revealed adverse effects on the fetus and there are **no controlled studies in women, or studies in women and animals are not available.**
Category D indicates that there is positive evidence of human fetal risk, but the potential benefits of using the drug in pregnant women may be acceptable despite the risk.

การรักษาวัณโรคดื้อยา **pregnancy, breast feeding**



consolidated guidelines WHO2025)

	Renal insufficiency	Hepatic Impairment	Recommended
aminoglycoside	Not recommended	No adjust	OD IM vs IV
Bedaquiline	caution in patients with severe renal impairment requiring dialysis. (case report in ESRD) No Dose adjust in mild to moderate	avoided in severe (Child-PughC). administered in mild to moderate impairment (Child-Pugh A or B)	With meal
linezolid	No dose adjust	No dose adjusted	Without meal, bedtime?

	Renal insufficiency	Hepatic Impairment	Recommended
clofazamine	No adjust dose. Use with caution in severe	Avoid in patients with hepatic impairment (Child-Pugh classes A, B, and C)	With meal. capsules must be swallowed whole and should not be opened
quinolone	No adjust (moxifloxacin) Reduced dose in levofloxacin	No adjust (Moxifloxacin linked to rare but occasionally severe and even fatal cases of acute liver injury)	Without meal Administer at least 4 hours before or 8 hours after products containing magnesium, aluminum, iron, or zinc, including antacids, sucralfate, multivitamins, and didanosine

	Renal insufficiency	Hepatic Impairment	Recommended
Delamanid	No adjust in mild-moderate no data on the use of delamanid in patients with severe renal impairment	not recommended in patients with moderate to severe hepatic impairment	With meal
Pretomanid	have not been established.	have not been established	With meal

	Renal change	Recommended dose and frequency for patients with creatinine clearance (< 30 ml/min or for patients receiving hemodialysis
moxifloxacin	Not change	
levofloxacin	**yes**	750-1000 mg per dose ×3 times per wk
aminoglycoside	**yes**	12-15 mg per dose ×2-3 times per wk
linezolid	Not change	
Ethionamide	No change	
cycloserine	**yes**	250 mg once daily or 500 mg, 3 times per week
Clofazamine	No change	
Bedaquilline	No change	**Not use in severe renal impairment**
delamanid	No change	**Not use in severe renal impairment**
pretomanid	**Not data**	

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	Renal insufficiency	Hepatic Impairment	Recommended
Delamanid	No adjust in mild-moderate no data on the use of delamanid in patients with severe renal impairment	not recommended in patients with moderate to severe hepatic impairment	With meal
Pretomanid	have not been established.	have not been established	With meal

การรักษาวัณโรคดื้อยา ใน **hepatic failure**

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ผู้ป่วย MDR-TB ที่ได้รับการวินิจฉัยโดยการเพาะเชื้อหรือ ตรวจ molecular test

วินิจฉัย MDR-TB/ RR TB

ตรวจ หาการดื้อยา second line

สงสัยดื้อต่อยากลุ่ม Bdq/LZd

ส่งตรวจ phenotypic DST/ Genotypic DST ต่อ BDQ/LZD

วินิจฉัย XDR-TB

รักษา individual regimen

ไม่ดื้อ quinolone

6BpalM

6BDLLC

ดื้อต่อยากลุ่ม q[illegible]e

6 Bpal

ดื้อต่อยากลุ่ม [illegible]e

6BDLC

ไม่ดื้อ quinolone และ ไม่มี severe extrapulmonary disease, extensive disease

9 BLMZ

9 B[illegible]Z

9 BDLLFXZ

Shorter all [illegible]th LDZ)

ไม่เข้า criteria ในการรักษาสูตรสั้น

Individual longer regimen eg, Ldz, cs, Amk,EMB, (PZA)

Not recommend, no data prove

Moderate to severe impairment

Severe hepatic impairment

Thank you