LIFTB
Leveraging Innovation for Faster Treatment of Tuberculosis

International Tuberculosis Research Center

KNCV TUBERCULOSIS FOUNDATION

TB Alliance

aDSM in the BPaL OR: component drugs in the BPaL regimen

Training of Trainers for the BPaL Operational Research
Philippines, 19-21 May 2021

Mamel Quelapio, MD
Consultant, KNCV

New grouping of second-line TB medicines

GROUPS & STEPS	MEDICINE	
Group A: Include all three medicines	Levofloxacin OR	Lfx
	Moxifloxacin	Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cycloserine OR	Cs
	Terizidone	Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin OR	Ipm-Cln
	Meropenem	Mpm
	Amikacin	Am
	(OR Streptomycin)	(S)
	Ethionamide OR	Eto
	Prothionamide	Pto
	p-aminosalicylic acid	PAS

Longer MDR-TB regimens (Drugs, 2011 to 2020 WHO Guidelines)

WHO 2011 TB drugs classification		WHO 2016 TB drugs classification		
GROUP 1. First-line oral anti-TB drugs	Isoniazid Rifampicin Ethambutol Pyrazinamide	GROUP A Fluoroquinolones		Levofloxacin Moxifloxacin Gatifloxacin
GROUP 2. Injectable anti-TB drugs (injectable or parenteral agents)	Streptomycin Kanamycin Amikacin Capreomycin	GROUP B Second-line injectable agents		Amikacin Capreomycin Kanamycin (Streptomycin)
GROUP 3. Fluoroquinolones	Levofloxacin Moxifloxacin Gatifloxacin Ofloxacin	GROUP C Other Core Second-line Agents		Ethionamide/ Prothionamide Cycloserine/Terizidone Linezolid Clofazimine
GROUP 4. Oral bacteriostatic second-line anti-TB drugs	Ethionamide/Prothionamide Cycloserine/Terizidone p-aminosalicylic acid	GROUP D Add-on agents (not core MDR-TB regimen components)	D1	Pyrazinamide Ethambutol High-dose isoniazid
GROUP 5. Anti-TB drugs with limited data on efficacy and/or long-term safety in the treatment of drug-resistant TB	(Bedaquiline) (Delamanid) Linezolid Clofazimine Amoxicillin/Clavulanate Imipenem/Cilastatin Meropenem High-dose isoniazid Thioacetazone Clarithromycin		D2	Bedaquiline Delamanid
			D3	p-aminosalicylic acid Imipenem-Cilastatin Meropenem Amoxicillin-Clavulanate (Thioacetazone)

Anti-TB drugs with future potentialities for upgrade: linezolid, delamanid, bedaquiline, carbapenemics

GROUP	MEDICINE	Abbreviation
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

Slide courtesy of Ron Wehrens, GDF Consultant

Novel treatment regimen - BPaL

BPaL regimen: 6(–9) Bdq- Pa-Lzd

Medicine	Preparation	Dose
Bedaquiline (Bdq)	100 mg /tab	400 mg daily for 2 weeks, then 200 mg thrice weekly for 24 weeks
Pretomanid (Pa)	200 mg /tab	200 mg daily
Linezolid (Lzd)	600 mg/tab	1200 mg daily

TB survivors … but with permanent disabilities

"I am free of TB but I suffer from permanent hearing loss."

Mildred Fernando-Pancho, Philippines, XDR-TB survivor and Champion
https://www.pri.org/stories/2011-11-14/face-tb-mildred-fernando

"Tuberculosis Made Me Blind, but we can make sure no one else needs to suffer like I did"

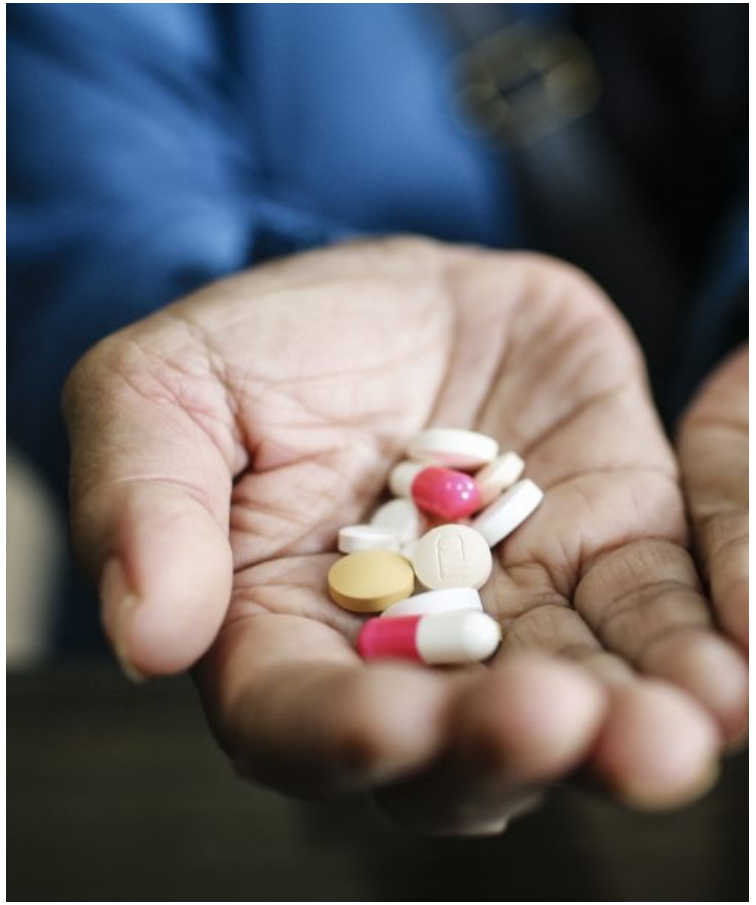
Louie Z, Philippines, MDR-TB survivor and Champion
https://www.huffingtonpost.com/louie-zepedateng/tuberculosis-made-me-blind_b_9543108.html

Fortunately, saved from permanent hearing loss!

New options: new drugs and regimens

"I was put on an injectable and after 2 months I experienced ringing in my ears which was very uncomfortable. Fortunately, they changed the injectable to an oral one."

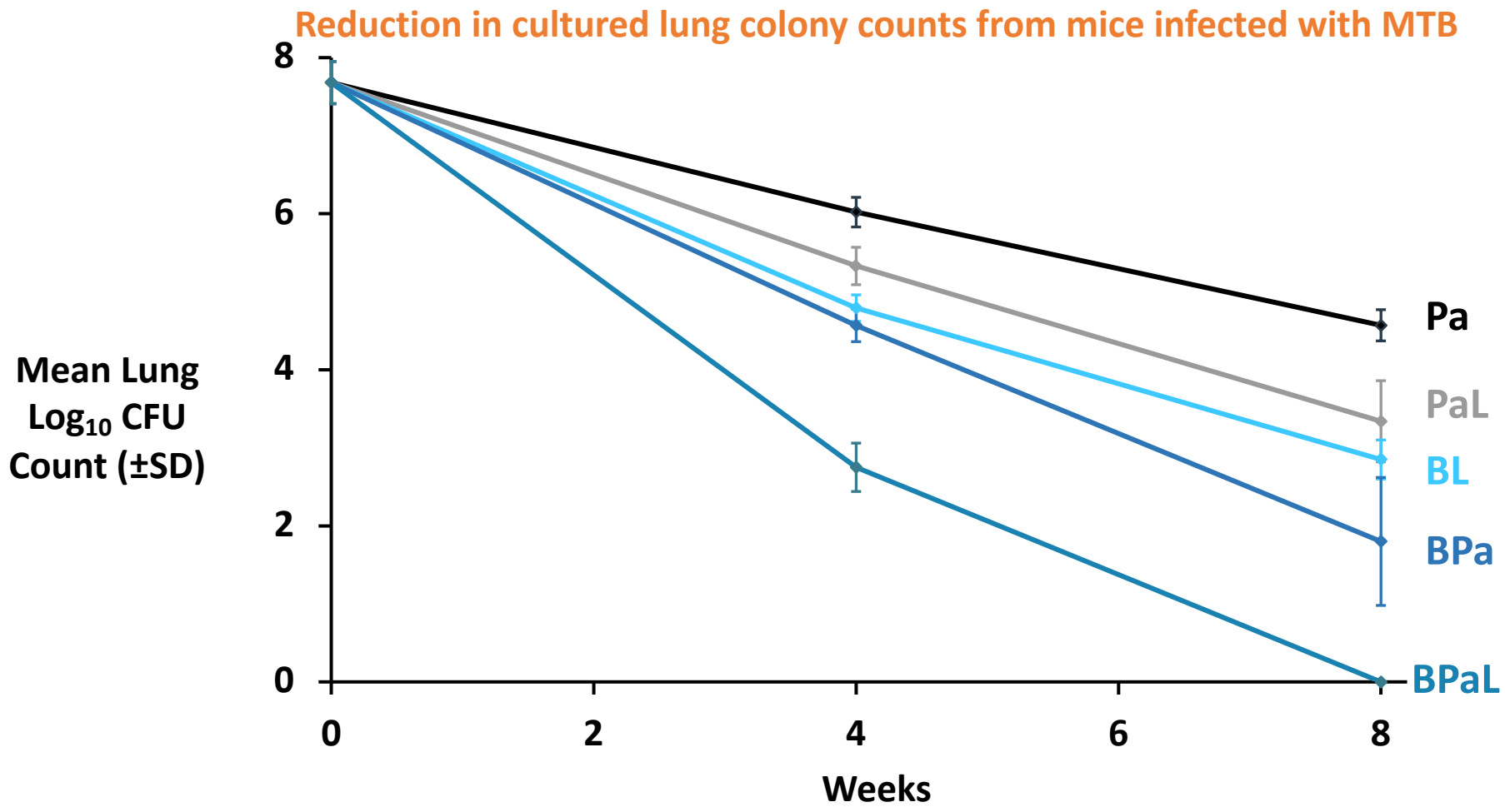
J. T. Philippines, Patient Support Group Leader



Nix-TB Pivotal Study Presented Opportunity to Evaluate Novel Regimen with Transformative Potential

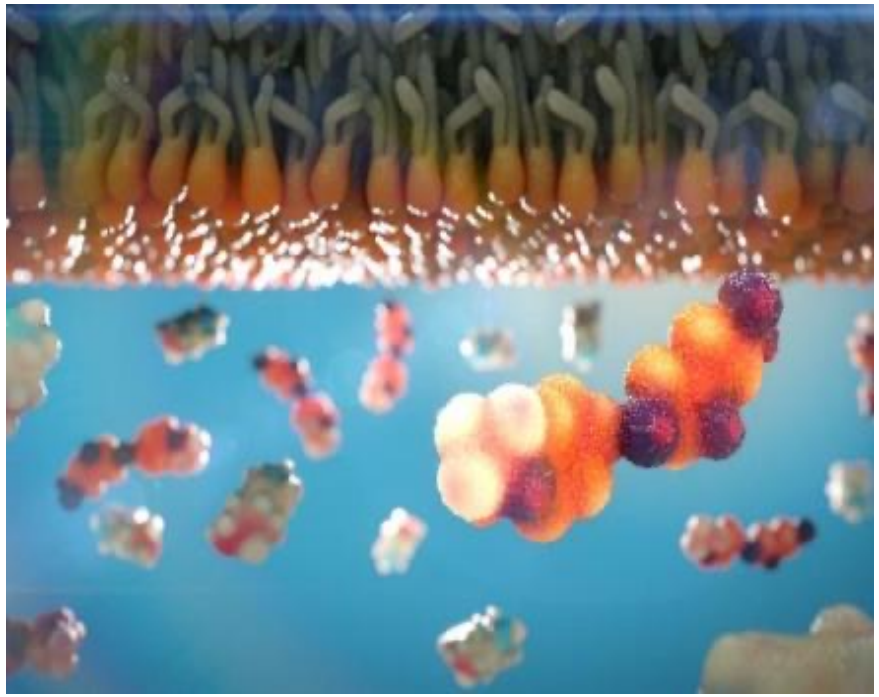
- BPaL = bedaquiline (**B**) + pretomanid (**Pa**) + linezolid (**L**)
  - First regimen introduced since HRZE
  - Each drug has potent preclinical and clinical anti-TB activity
  - Minimal pre-existing resistance
  - All 3 drugs contribute to bactericidal and curative activity

Potent bactericidal activity with pretomanid alone, greatest with full BPaL Regimen



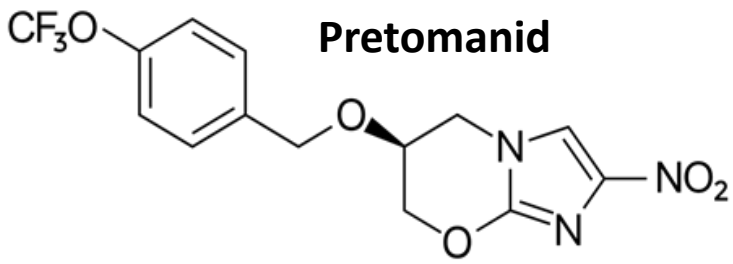
Pretomanid (1)

- The third new anti-TB drug approved for use by U.S. FDA (Aug 2019), after rifapentine, bedaquiline, and delamanid
- The first anti-TB drug to be developed and registered by a not-for-profit organization (TB Alliance)
- Approved as part of a defined regimen

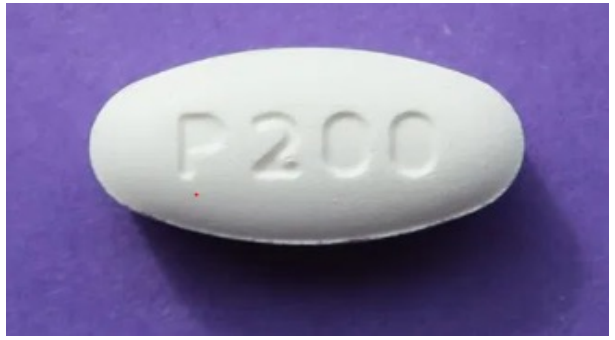


Pretomanid (2):
New chemical entity developed specifically to treat TB

- Class of nitroimidazooxazine (nitroimidazole, same chemical class as Delamanid)
  - Nonclinical and clinical studies showed anti-TB activity against drug-susceptible and drug-resistant *M. tuberculosis*
  - Possesses bactericidal and curative abilities
  - Half-life of 18 hours
  - Eliminated 53% in the urine, and 38% in feces



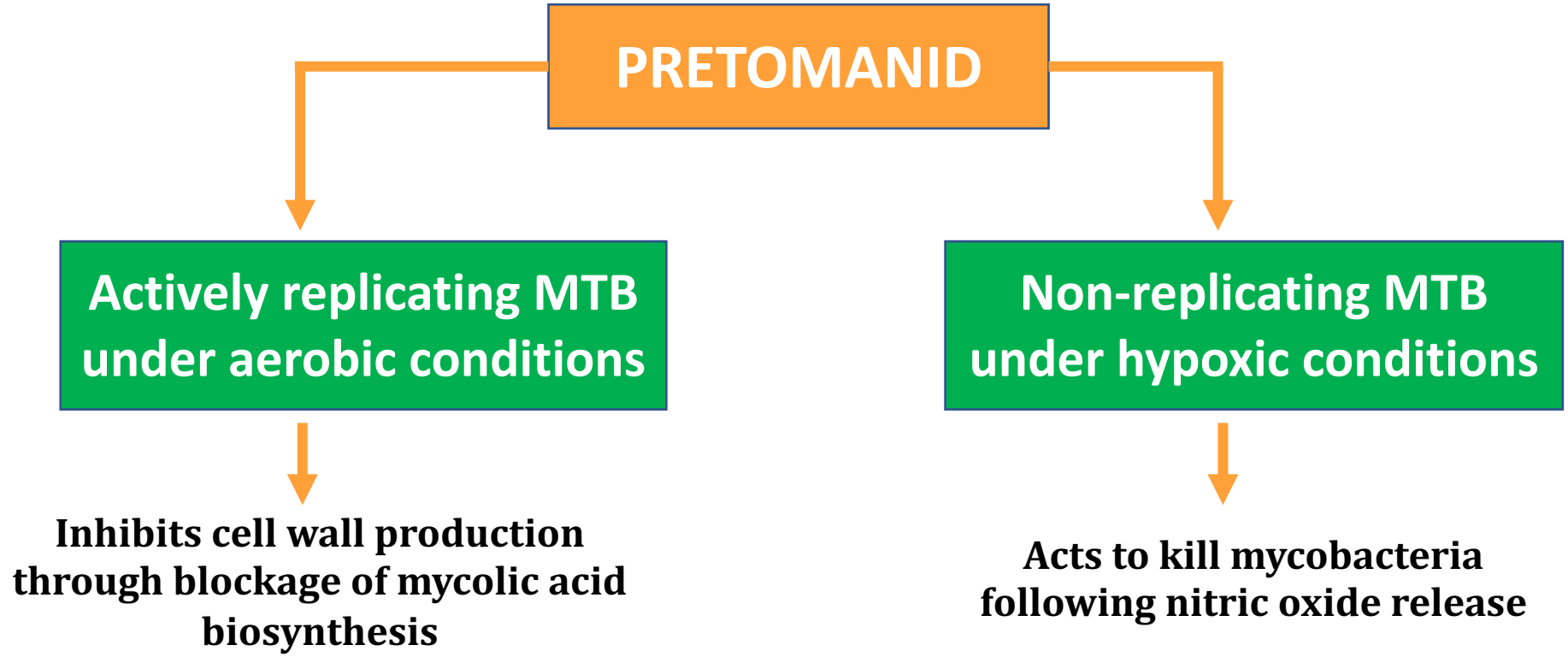
Pretomanid



Pretomanid (3)

Mode of action: complex, requires metabolism of drug to active form

- *Pretomanid kills replicating and non-replicating M. tuberculosis bacteria*

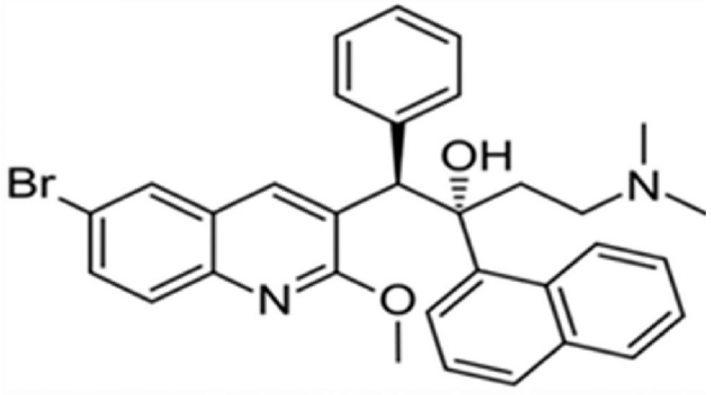


Adverse drug reactions attributable to Pretomanid

- The safety profile of Pretomanid alone is often **confounded** by other drugs in the regimen.
- The safety of Pa has been evaluated across **19** trials and over **1100** patients and healthy volunteers
- Per the **Investigators Brochure**, the following may be attributable to pretomanid:
  - Mild to moderate nausea and vomiting
  - Mild to moderate rash
  - Transaminases increased
  - Headache
- In male rats, Pretomanid caused testicular atrophy and impaired fertility.
- **Drug interaction**: Efavirenz also reduces pretomanid exposures significantly.

Bedaquiline (1)

- Drug class diarylquinoline
- Approved as part of a combination therapy
- First new drug to be developed specifically to treat TB in over 40 years
- **Novel mechanism of action**:
  - inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, an enzyme that is essential for the generation of energy in *M. tuberculosis*.
- Granted accelerated approval by the US Federal FDA in December 2012



Bedaquiline (2)

- Pharmacology/Pharmacokinetics

Parameter	Bedaquiline
Metabolism	Primarily hepatic by cytochrome P450 (CYP3A4) system enzymes in the liver.
Elimination	Primarily excreted in the feces; renal elimination (<0.001%)
Half-life	5.5 months
Protein Binding	>99%
Tmax	~5 hours
Bioavailability	When taken with a standard meal (~22 grams of fat, 558 Kcal total), relative bioavailability increased by about 2-fold compared to administration under fasting conditions

Bedaquiline (3)

- Limited experience in <6 years but growing experience in adolescents, elderly, EPTB disease and PLHIV
- Early trial: increased risk of deaths 11.4% vs. placebo 2.5%, but risk not definitively attributed to Bdq or any known toxicities, e.g., QT interval prolongation. Additional analyses rather highlighted **improved survival** with and **favourable safety profile** when used with other TB medicines.
- Bdq is metabolized by the cytochrome P450 system enzymes in the liver: drug–drug interactions affecting Bdq blood levels.
  - **CP450 inducers** decrease blood levels of Bdq, resulting in the possibility of **inadequate levels of Bdq** in the body for elimination of TB infection.
  - Conversely, **CP450 inhibitors increase blood levels of Bdq**, resulting in the possibility of an **increased risk of toxicity**.

Possible drug-drug interactions of Bdq and other medicines

Drug-drug interactions	Medicines	Notes and instructions
Strong/moderate inducers of cytochrome P450[2] may decrease blood levels of bedaquiline	Efavirenz (EFV)[a] Rifamycins: Rifampicin, Rifapentine, Rifabutin Phenytoin, Carbamazepine, Phenobarbital, St. John's Wort	[a] Results in low levels of Bdq in the blood; advised to substitute with nevirapine (NVP) or an integrase inhibitor [b] For a more comprehensive list of drugs affecting/affected by the cytochrome P450 system, see Department of Medicine of Indiana University http://medicine.iupui.edu/clinpharm/ddis/
Strong/moderate inhibitors of cytochrome P450 may increase blood levels of bedaquiline	Ritonavir-boosted protease inhibitors[c] Oral azole antifungals (can be used up to 2 weeks): Itraconazole, fluconazole[d] Macrolide antibiotics other than azithromycin[e] : Clarithromycin, Erythromycin	[c] Results in high levels of Bdq; advised substitute with an integrase inhibitor, e.g., dolutegravir or raltegravir. If ritonavir-boosted PI is needed, do an ECG every 2 weeks for the 1st 8 weeks. [d] All four oral azoles inhibit CYP3A4; itraconazole and posaconazole are more potent inhibitors than fluconazole or voriconazole. [e] Does not inhibit CYP isoenzymes but does prolong the QT interval so this drug may be avoided for this reason.
Possible interactions: medicines metabolized by CYP3A4 may increase bedaquiline exposure	Elvitegravir[f] Cobicistat[f] Emtricitabine[f] Tenofovir Alafenamide[f]	[f] Concomitant use for >14 consecutive days should be avoided. Because Bdq is also metabolized by CYP3A4, these drugs may increase Bdq exposure, potentially increasing the risk of adverse reactions.

WHO Operational Handbook, June 2020

Bedaquiline (6)

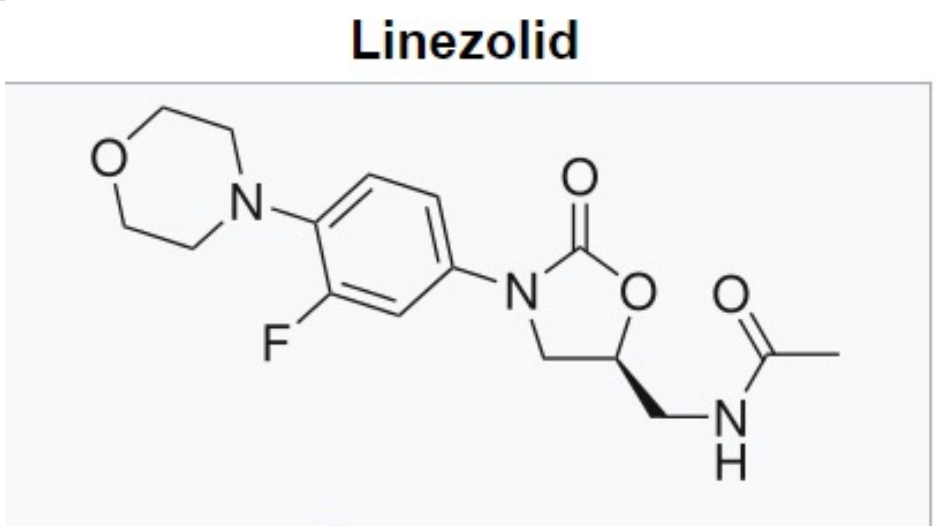
- No additional safety concerns for the use of a) Bdq >6 months, b) concurrently with Dlm or c) in pregnancy
  - New evidence from observational study in South Africa:
  - 58 mothers on Bdq during pregnancy: associated with low birth weight (<2500 g), with no other significant differences in infant outcomes, pregnancy outcomes or maternal treatment outcomes, including weight gain in the infants until 1 year of age.

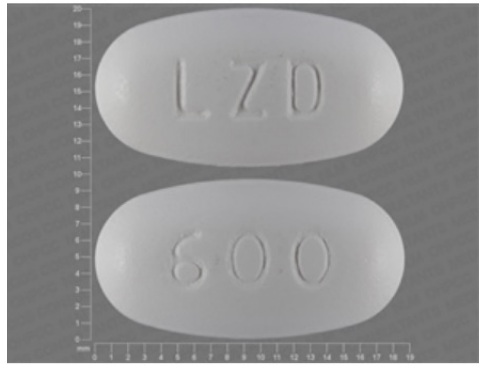
- **Breastfeeding:** knowledge still sparse.
- The emergence of **Bdq resistance** should be monitored in settings where it is used.

2020 WHO Operational Handbook

Linezolid (1)

- Drug class: Oxazolidinones
- Discovered in the 1990s: first approved for use in 2000,
- Mechanism of action: inhibits protein synthesis; stops the growth of bacteria by disrupting their production of proteins
- Has *in vitro* bactericidal activity
- Half-life of 5-7 hours
- Elimination: 30% in urine





Linezolid (2)

- Lzd is to be used as long as it is tolerated. Full duration may improve outcomes.
  - Greatest added effect (including protection against acquired DR in other SLDs) during the first months of treatment when the bacillary load is highest.
  - AEs significantly more frequent when the Lzd daily dosage exceeds 600 mg. The longer the use, the higher the risk of experiencing SAE.

Adverse events associated with Linezolid (3)

- **Major adverse events (AEs) are well-documented to be dose-related**
  - Myelosuppression: anemia, thrombocytopenia, neutropenia
  - Peripheral neuropathy
  - Optic neuritis
  - Lactic acidosis (rare): serum lactic acid and metabolic acidosis in arterial blood gas (ABG)

    Signs and symptoms:
    - nausea, vomiting, hyperventilation, tachypnea, weight loss
    - Severe: decreased contractility of myocardium, impairment of brain metabolism and confusion leading to death (decreased response to catecholamines)

Possible drug-drug interactions of Lzd with other medicines (4)

Drugs that increase **serotonin** levels

- Serotonin plays a role in digestion, blood flow and breathing regulation

Serotonergic signs and symptoms:

- Mild: shivering, diarrhea
- Moderate: restlessness, agitation, confusion, tachycardia, hypertension twitching, seating
- Severe: muscle rigidity, high fever, seizures
- Death, if untreated

WHO Operational Handbook, June 2020

Possible drug-drug interactions of Lzd with other medicines

1. Medicines that increase serotonin levels

- **Serotonin re-uptake inhibitors (SSRIs):**
  - anti-depressants: fluoxetine (Prozac) and paroxetine
- **Tricyclic antidepressants/anxiolytics:**
  - amitriptyline and nortriptyline
  - Serotonin 5-HT1 receptor agonists (opioid analgesic) and bupropion or buspirone and quetiapine

2. Zidovudine and Lzd may cause peripheral nerve toxicity and are known to have myelosuppression cross-toxicity.

WHO Operational Handbook, June 2020

Thank you!

Funding for LIFT-TB

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