ANTI-MYCOBATERIAL DRUGS

Sources:

- Bertram G. katzung Basic & Clinical Pharmacology 15th Edition
- Goodman and Gilman's The Pharmacological Basis of Therapeutics13th edition. Laurence Brunton, Bjorn Knollmann, Randa Hilal-Dandan - (2017)

SECOND-LINE DRUGS FOR TUBERCULOSIS

The alternative drugs are usually considered only

- In case of resistance to first-line agents;
- In case of failure of clinical response to conventional therapy
- In case of serious treatment-limiting adverse drug reactions.

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Aminoglycosides

- Streptomycin
- Kanamycin
- Amikacin
- Viomycin

Active against *extra cellular* Mycobacteria.

Most mycobacteria are inhibited but non T. B. are resistant.

Streptomycin

- Belongs to Aminoglycosides antibiotics.
- Obtained from *streptomyces griseus*.
- First line Anti TB drug.
- It has last priority, may be used to kill resistant strains of organism.

Dose: 15 mg /kg/ day. Given I/m in dose of 1G daily.

Clinical Uses

1. Mycobacterium TB Infections

- Pulmonary Tuberculosis (MDR-TB)
- Miliary Tuberculosis
- Tuberculous Meningitis

2. Non Tuberculous Infections

a. With a tetracycline in
- Plague
- Tularemia
- Brucellosis

b. With Penicillin in
- Enterococcal Endocarditis
- Enterococcal Peritonitis

Adverse Effects

- Allergic reactions
- Dose related, more in elderly
- Ototoxicity
- Nephrotoxicity
- N.M.Blockade ***(Contraindicated in M. Gravis & With NMJ blocking drugs)***

Kanamycin and Amikacin

- Aminoglycosides
- Kanamycin Very toxic , so obsolete
- Amikacin is used for treatment of Streptomycin / multidrug resistant cases
- Dose: 15mg/mg/day I/Vor I/M

Capreomycin

- Peptide Antibiotic
- Source: *steptomyces capreolus*
- Given by I/m injection.
- Dose: 15 mg/kg Body wt./day
- Drug is nephrotoxic and ototoxic.
- Useful in treatment of
  - **multidrug resistant TB**

Ethionamide

It is chemically related to INH.

Blocks thy synthesis of mycolic acids.

It is given orally 1g/day.

Adverse effects.

1. Intense gastric irritation
2. Hepatotoxicity
3. Neurological symptoms

Low level cross resistant b/w INH and Ethionamide may occur.

Cycloserine

- Antibiotic---*Streptomyceus Orchidacious*
- Inhibitor of cell-wall synthesis.
- Given orally ½ -1g/day in 2-doses.

Adverse effects:

- Peripheral Neuropathy
- CNS dysfunction including depression and psychotic reactions.

Paraminosalicylic acid (PAS)

- Structure resembles PABA and sulfonamides.
- MOA: Folate antagonist
- Rapidly absorbed from GIT .
- widely distributed except CSF
- Dose is 8-12g/day.

A/Effect: 1. Severe GIT irritation ,peptic ulcer
2. Crystalluria
3. Hypersensitivity reactions

- Used infrequently b/c of

Poor tolerance & Primary resistance

Fluoroquinolones

- Ciprofloxacin, levofloxacin, gatifloxacin & moxifloxacin
- Active against atypical mycobacteria
- used in combination therapy for resistant cases.
- With Pyrazinamide as prophylactic in contacts of multi drug resistant TB.

LINEZOLID

- In combination with other ATT for drug resistant TB
- Use is associated with bone marrow suppression, irreversible peripheral and optic neuropathy
- Reduction of toxicity with pyridoxine

BEDAQUILINE

- Inhibits ATP synthase
- Active against replicating and non-replicating bacilli
- Good oral absorption
- Excretion in feces after CYP3A4 metabolism
- In combination with other ATT for MDR
- Associated with hepatotoxicity and cardiac toxicity

PRETOMANID

- Selective activation in bacilli under aerobic and anaerobic conditions
- Aerobic : inhibit mycolic acid synthesis
- Anaerobic : release of NO
- Oral absorption with urinary and biliary excretion after CYP3A4 metabolism
- Use in MDR and XDR-TB
- ADR include hepatotoxicity, convulsions and QT prolongation

Clofazimine

Anti-Leprosy drug but also has some activity against mycobacterium T B in vitro.

A drug of last resort for the treatment of multi drug resistant cases.

Dose: 200mg/day orally

But its efficacy not well established as a antituberculosis drug.

Thiacetazone

- Sulphonamide
- Active orally
- Low cost
- Side effects → G. intestinal

Corticosteroids

Indicated in: along with Anti TB treatment

- Massive T.B pleural effusion
- Massive T.B pericardial effusion
- T.B meningitis
- T.B choroiditis
- T.B ascites (massive)
- Hypersensitivity to ATT

AIMS OF TREATMENT

- To rapidly reduce the number of actively growing bacilli in the patient, thereby decreasing severity of the disease, halting transmission of M. Tuberculosis & preventing death
- To eradicate populations of persisting bacilli in order to achieve durable cure (prevent relapse) after completion of therapy
- To prevent acquisition of drug resistance during therapy

NTB Program Guidelines 2019

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Treatment failure

- High Resistance
- Poor compliance (Adherence)
  - » Long duration of treatment
  - » Side effects
  - » Fads

Core-Pharmacology
VERTICAL INTEGRATION WITH MEDICINE

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i 17.52 Treatment of new tuberculosis patients (World Health Organisation recommendations)

Intensive phase	Continuation phase	Comments
Standard regimen		
2 months of HRZE	4 months of HR	
2 months of HRZE	4 months of HRE	Applies only in countries with high levels of isoniazid resistance in new TB patients, and where isoniazid drug susceptibility testing in new patients is not done (or results are unavailable) before the continuation phase begins
Dosing frequency		
Daily*	Daily	Optimal
Daily*	3 times/week	Acceptable alternative for any new patient receiving directly observed therapy
3 times/week	3 times/week	Acceptable alternative, provided that the patient is receiving directly observed therapy and is NOT living with HIV or living in an HIV-prevalent setting

*Daily (rather than 3 times weekly) intensive-phase dosing may help to prevent acquired drug resistance in TB patients starting treatment with isoniazid resistance.
(H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol)
Adapted from World Health Organisation. Treatment of tuberculosis guidelines, 4th edn; 2010.

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Vertical integration with medicine

Table 2. Drug Regimens Used in the Treatment of Active Tuberculosis in Adults

Initial Phase				Continuation Phase			
Regimen	Drugs	Dosing Interval	Number of Doses	Sub-regimen	Drugs	Dosing Interval	Number of Doses
1	INH-RIF-PZA-EMB	7 day/wk (8 wk) or 5 day/wk (8 wk)	56 or 40	a	INH-RIF	7 day/wk (18 wk) or 5 day/wk (18 wk)	126 or 90
				b	INH-RIF	Twice weekly (18 wk)	36
				c	INH-RPT	Once weekly (18 wk)	18
2	INH-RIF-PZA-EMB	7 day/wk (2 wk), then twice weekly (6 wk); or 5 day/wk (2 wk), then twice weekly (6 wk)	26 or 22	a	INH-RIF	Twice weekly (18 wk)	36
				b	INH-RPT	Once weekly (18 wk)	18
3	INH-RIF-PZA-EMB	3 times/wk (8 wk)	24	—	INH-RIF	3 times/wk (18 wk)	54
4	INH-RIF-EMB	7 day/wk (8 wk) or 5 day/wk (8 wk)	56 or 40	a	INH-RIF	7 day/wk (31 wk) or 5 day/wk (31 wk)	217 or 155
				b	INH-RIF	Twice weekly (31 wk)	62

EMB: ethambutol; INH: isoniazid; PZA: pyrazinamide; RIF: rifampin; RPT: rifapentine.
Source: References 1, 9, 10.

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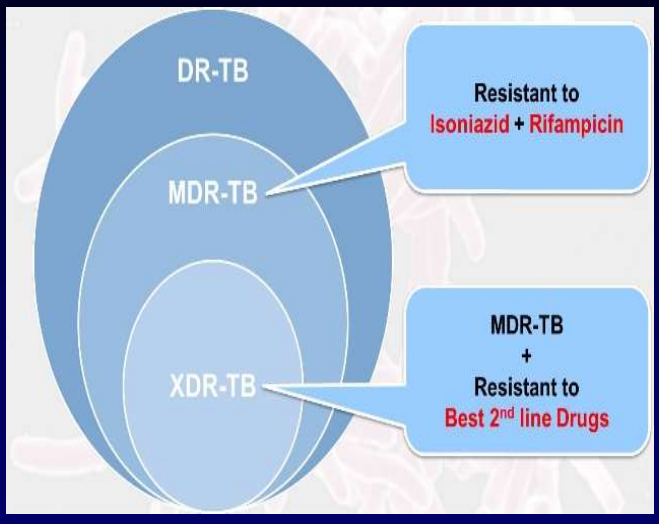
Multiple Drug Resistant Tuberculosis (MDR-T.B)

- If patient is resistant to INH and rifampicin after about 5 months treatment, still acute tuberculosis bacilli is present in sputum, the patient is labeled multiple drug resistant.
- Treatment is the use of second line drugs.
  Regimen--- 4 drugs, 18-24 months

DRUG RESISTANT TB



WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update

Table 3.1. Grouping of medicines recommended for use in longer MDR-TB regimens[a]

Groups and steps	Medicine	Abbreviation
Group A: Include all three medicines	Levofloxacin *or* moxifloxacin	Lfx Mfx
	Bedaquiline[b,c]	Bdq
	Linezolid[d]	Lzd
Group B: Add one or both medicines	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[e]	Dlm
	Pyrazinamide[f]	Z
	Imipenem–cilastatin *or* meropenem[g]	Ipm–Cln Mpm
	Amikacin (*or* streptomycin)[h]	Am (S)
	Ethionamide *or* prothionamide[i]	Eto Pto
	P-aminosalicylic acid[i]	PAS

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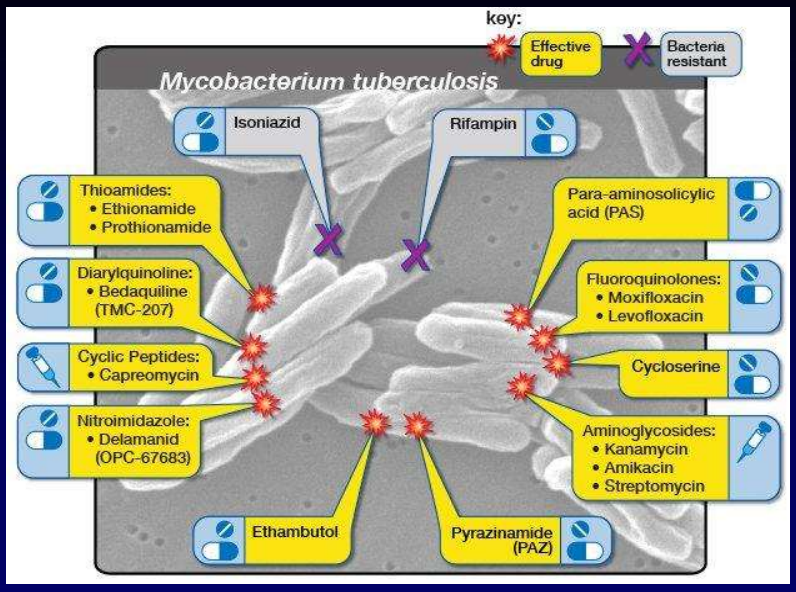

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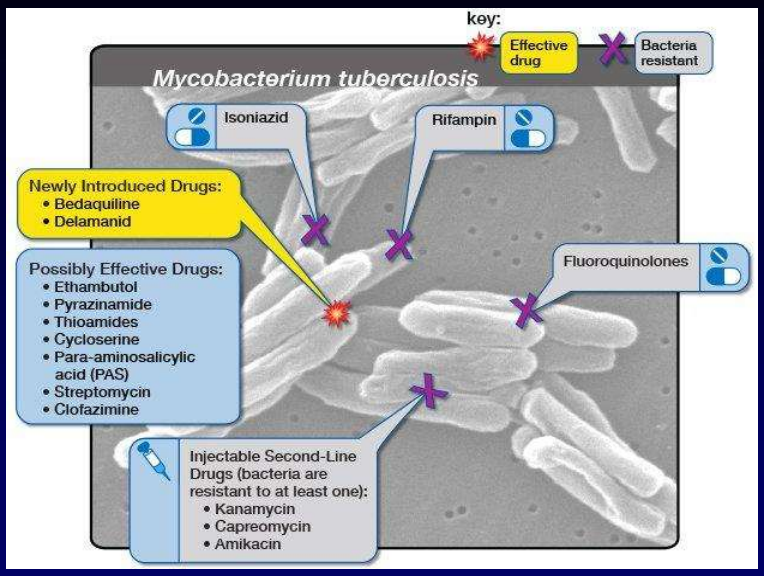
WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update

1. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB	
1.1	WHO suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional recommendation, very low certainty of evidence)*
2. The 9-month all-oral regimen for MDR/RR-TB (a)	
2.1	WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty of evidence)*
3. Longer regimens for MDR/RR-TB (b)	
3.1	In multidrug- or rifampicin-resistant tuberculosis (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. *(Conditional recommendation, very low certainty of evidence)*

Extensively Drug Resistant Tuberculosis (XDR-T.B)

- If patient is resistant to INH, rifampicin, fluoroquinolones and one of the injectables of 2nd line drugs (capreomycin / kanamycin / amikacin)



DIRECTLY OBSERVED TREATMENT (DOT)

- Treatment services should be provided as close to the patient's home as possible
- If any health facility is not near to his/her home, he will select a treatment supporter who will observe the daily intake of drugs at a mutually agreed place.
- The treatment supporter identified by the patient will be briefed by the DOTS facilitator at the TB Care facility of the protocols of observing the intake of drugs.
- The treatment supporter accompanied by patient will collect the drugs on monthly basis from TB Care Facility where patient is registered throughout full course of treatment
- Patients are referred to the TB Care Facility management of adverse reactions if any and for follow-up sputum examinations at the end of months 2, 5 and 6 and the sputum results recorded in TB-01 &TB03

D.O.T REGIMEN (Directly **Observed Treatment)**

It is the strategy to ensure cure by providing the most effective medicine and confirming that it is taken.

During the intensive phase **of treatment a health worker or other trained person watches as the patient swallows the drugs in his presence.**

During continuation phase, a blister pack is given to the patient and first dose is swallowed in the presence of a health worker. on his next visit, empty blister pack in inspected to confirm the compliance.

- ***In DOTS daily dosing regimens as well as intermittent dosing regimens may be applied***.

- During intensive phase usually four drugs are given for **02** months either on daily bases or intermittently.

- Then **two or three** drugs are continued for 4 to 6 months. (Continuation phase).

- INH 600 mg
- PYRAZINAMIDE 1500 mg
- ETHAMBUTOL 1200 mg
- STREPTOMYCIN 750 mg

} Intensive phase / intermittent

Drugs active against atypical Mycobacteria

- 10% cases occur
- Atypical mycobacteria have distinctive Lab characteristics.
- Disease is less severe
- Not communicable from person to person
- Atypical mycobacteria are present in environment
- less sensitive to usual anti-tuberular treatment

TABLE 47–3 Clinical features and treatment options for infections with atypical mycobacteria.

Species	Clinical Features	Treatment Options
M kansasii	Resembles tuberculosis	Amikacin, clarithromycin, ethambutol, isoniazid, moxifloxacin, rifampin, streptomycin, trimethoprim-sulfamethoxazole
M marinum	Granulomatous cutaneous disease	Amikacin, clarithromycin, ethambutol, doxycycline, levofloxacin, minocycline, rifampin, trimethoprim-sulfamethoxazole
M scrofulaceum	Cervical adenitis in children	Amikacin, erythromycin (or other macrolide), rifampin, streptomycin (Surgical excision is often curative and the treatment of choice.)
M avium complex (MAC)	Pulmonary disease in patients with chronic lung disease; disseminated infection in AIDS	Amikacin, azithromycin, clarithromycin, ethambutol, moxifloxacin, rifabutin
M chelonae	Abscess, sinus tract, ulcer; bone, joint, tendon infection	Amikacin, doxycycline, imipenem, linezolid, macrolides, tobramycin
M fortuitum	Abscess, sinus tract, ulcer; bone, joint, tendon infection	Amikacin, cefoxitin, ciprofloxacin, doxycycline, imipenem, minocycline, moxifloxacin, ofloxacin, trimethoprim-sulfamethoxazole
M ulcerans	Skin ulcers	Clarithromycin, isoniazid, streptomycin, rifampin, minocycline, moxifloxacin (Surgical excision may be effective.)

RESEARCH

Although tuberculosis (TB) is preventable and curable, the lengthy treatment (generally 6 months), poor patient adherence, high inter-individual variability in pharmacokinetics (PK), emergence of drug resistance, presence of comorbidities, and adverse drug reactions complicate TB therapy and drive the need for new drugs and/or regimens. Hence, new compounds are being developed, available drugs are repurposed, and the dosing of existing drugs is optimized, resulting in the largest drug development portfolio in TB history. This review highlights a selection of clinically available drug candidates that could be part of future TB regimens, including bedaquiline, delamanid, pretomanid, linezolid, clofazimine, optimized (high dose) rifampicin, rifapentine, and para-aminosalicylic acid. The review covers drug development history, preclinical data, PK, and current clinical development.

Jessica M Aguilar Diaz, Ahmed A Abulfathi, Lindsey HM te Brake, Jakko van Ingen, Saskia Kuipers, Cecile Magis-Escurra, Jelmer Raaijmakers, Elin M Svensson, Martin J Boeree; New and Repurposed Drugs for the Treatment of Active Tuberculosis: An Update for Clinicians. Respiration 3 February 2023; 102 (2): 83 100. https://doi.org/10.1159/000528274

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BIOETHICS

Provider Responsibility

Treatment of tuberculosis benefits both the community as a whole and the individual patient; thus, any public health program or private provider (or both in a defined arrangement by which management is shared) undertaking to treat a patient with tuberculosis is assuming a public health function that includes not only prescribing an appropriate regimen but also ensuring adherence to the regimen until treatment is completed.

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ARTIFICIAL INTELLIGENCE

Clemens DL, Lee B-Y, Silva A, Dillon BJ, Masleša-Galić S, Nava S, et al. (2019) Artificial intelligence enabled parabolic response surface platform identifies ultra-rapid near-universal TB drug treatment regimens comprising approved drugs. PLoS ONE 14(5): e0215607. https://doi.org/10.1371/journal.pone.0215607

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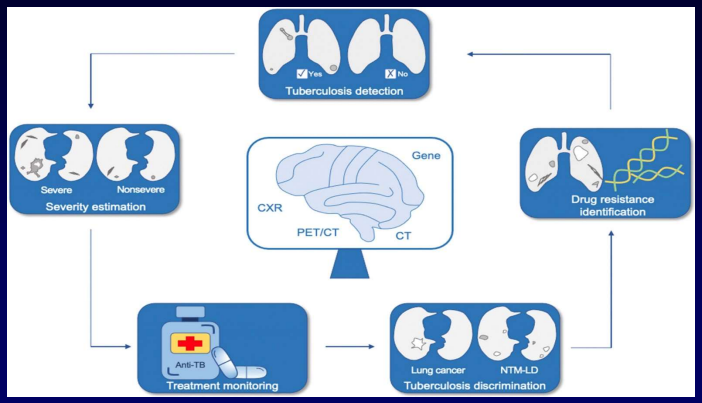
ARTIFICIAL INTELLIGENCE

The Application of Artificial Intelligence in the Diagnosis and Drug Resistance Prediction of Pulmonary Tuberculosis



Liang S, Ma J, Wang G, Shao J, Li J, Deng H, Wang C, Li W. The application of artificial intelligence in the diagnosis and drug resistance prediction of pulmonary tuberculosis. Frontiers in Medicine. 2022 Jul 28;9:935080.

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EOLA

A 60-year-old man presents to the emergency department with a 2-month history of fatigue, weight loss (10 kg), fevers, night sweats, and a productive cough. He is currently living with friends and has been intermittently homeless, spending time in shelters. He reports drinking about 6 beers per day. In the emergency department, a chest x-ray shows a right apical infiltrate. Given the high suspicion for pulmonary tuberculosis, the patient is placed in respiratory isolation. His first sputum smear shows many acid-fast bacilli, and an HIV test returns with a positive result. What drugs should be started for treatment of presumptive pulmonary tuberculosis? Does the patient have a heightened risk of developing medication toxicity? If so, which medication(s) would be likely to cause toxicity?

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