Anti-mycobacterial agents

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Properties of anti-TB drugs

- Bactericidal
- Sterilizing
- Ability to prevent resistance

Properties of anti-TB drugs

- Isoniazid and Rifampicin are the most powerful **bactericidal** drugs, active against all populations of TB bacilli
- Pyrazinamide and streptomycin are also **bactericidal** against certain populations of TB bacilli.
  - Pyrazinamide is active in an acid environment against TB bacilli inside macrophages.
  - Streptomycin is active against rapidly multiplying extracellular bacilli
- Ethambutol is **bacteriostatic.**

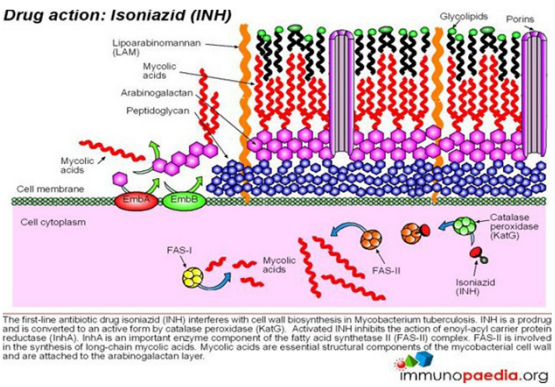
Treatment regimens

- **Intensive phase** & **continuation phase**
- **Intensive phase**: Bacilli are rapidly eradicated from sputum, clinical improvement
- **Continuation phase**: sterilizing effect of treatment eliminates the remaining viable bacilli

First line	Second line
• isoniazid	• kanamycine/amikacin
• rifampicin	• fluoro-quinolones
• pyrazinamide	• cycloserine
• ethambutol	• ethionamide
• ~~streptomycin~~	• capreomycin
	• p-amino-salicylic acid

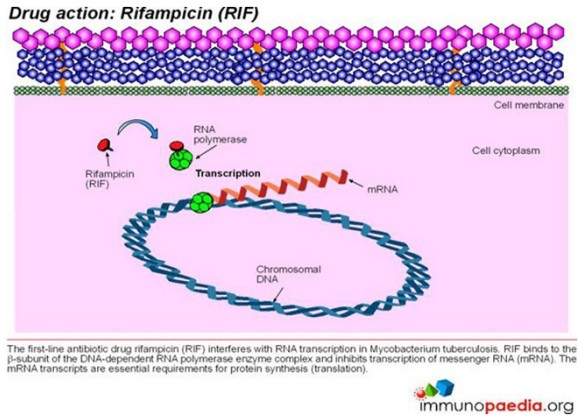
Isoniazid

- 1952
- **Bactericidal** against actively growing TB bacilli
- **Bacteriostatic** against *non-replicating* organisms
- Inhibits synthetic pathways of mycolic acid
- Inhibits catalase peroxidase enzyme
- Well absorbed orally
- Metabolised in the liver



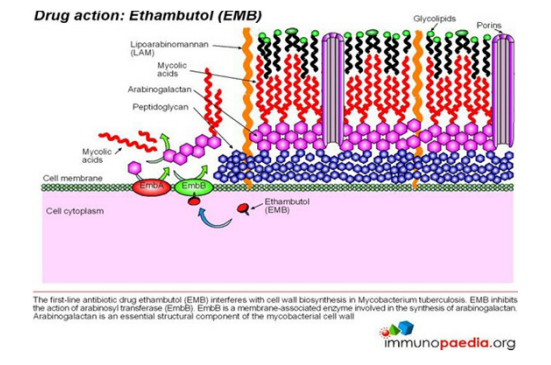
Rifampicin

- 1967
- Inhibits DNA-dependent RNA polymerase
- Bactericidal against actively replicating bacilli
- Also active against intracellular, slowly replicating bacilli
- *Some* activity against nearly dormant organisms in nectrotic foci
- Well absorbed orally; penetrates CSF



Ethambutol

- 1961
- Interferes with cell wall biosynthesis → inhibits the action of arabinosyl transferase (membrane associated enzyme) involved in the synthesis of arabinogalactan – essential structural component of the mycobacterial cell wall
- **Bacteriostatic** *in vitro* or within macrophages

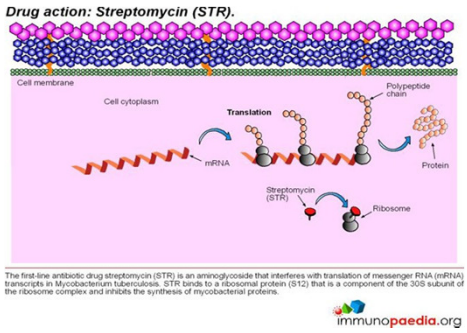


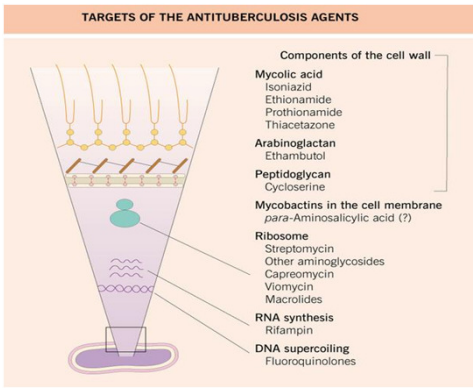
Pyrazinamide

- Nicotinamide derivative, exact mechanism of action unknown ? Inhibits cell wall synthesis
- **Bactericidal;** optimal activity is against semi-dormant organisms in acid pH environment (intra-cellular bacilli in phagolysosome)
- Well absorbed orally, metabolized in the liver

Streptomycin

- 1st drug to reduce TB mortality
- Inhibits protein synthesis (binds 30S unit of ribosome)
- Bactericidal against extra-cellular bacilli in alkaline medium of cavity walls.





1st line treatment

- **6/12 combi. Rx**
- **2 months**
  - **Rifampicin**
  - **Isoniazid**
  - **Pyrazinamide**
  - **Ethambutol**
- **4 months**
  - **Rifampicin & Isoniazid**
- **Combination:**
  - **To decrease resistance to a single agent**
  - **To kill both intracellular & extra cellular forms**

TREATMENT REGIMEN MONO- AND POLY DR-TB

Resistance	SA Regimen
H	Rifafour for full duration 6-9 months RHZ + EMB <8yrs RHZE >8YRS
R	Standardized MDR-TB regimen plus H for 18 months after culture conversion
R.E (S)	MDR-TB Regimen
H.E.S	

Slide courtesy of Dr C. Mojapelo

2nd and 3rd line agents

- MDR strains
- Toxicity to 1st line agents

- eg.
  - Kanamycin/amikacin
  - Ethionamide
  - Cycloserine/Terizidone
  - Fluoroquinolones (levo, moxi, oflox)

- XDR

- Capreomycin
- Ethionamide
- PAS
- Cycloserine/Terizidone
- Clofazamine

2nd line agents

- **Para-aminosalicylic acid**: inhibits growth by impairment of folate synthesis
- **Cycloserine/Terizidone**: inhibits cell wall synthesis
- **Ethionamide:** Bacteriostatic, inhibition of oxygen-dependent mycolic acid synthesis.
- **Capreomycin:** ? Protein synthesis
- **Clofazamine:** ???

Grouping of MDR TB Drugs

Group	Drugs
Group 1: First-line oral drugs	Ethambutol (E) Pyrazinamide (Z)
Group 2: Injectable drugs	Kanamycin (Km) Amikacin (Am) Capreomycin (Cm) Viomycin (Vm)
Group 3: Fluoroquinolones	Levofloxacin (Lvx) Moxifloxacin (Mfx) Gatifloxacin (Gfx)
Group 4: Oral bacteriostatic second-line drugs	Ethionamide (Eto) Prothionamide (Pto) Cycloserine (Cs) Terizidone (Trd) Para-Aminosalicylic Acid (PAS)
Group 5: Drugs of unclear efficacy (Not recommended for routine use in MDR-TB patients)	Clofazimine (Cfz) Amoxicillin/clavulanate (Amx/Clv) Clarithromycin (Clr) Azithromycin (Azr) Linezolid (Lzd) Thioacetazone (Th) Imipenem High-dose INH

WHO 2012 MDR TB Guidelines

COMMON SIDE EFFECTS

Side effects	Agent	Management
Hearing loss	Am, Km, Cm,	Audiometry; ↓dose; give 3x/week; discontinue
Nephrotoxicity	Am, Km, Cm,	U&E; ↓dose; give 3x/week; discontinue
Hepatitis	Z, H, R, FQ, Eto/Pto, PAS	Stop therapy; LFT; Introduce drug individually
Optic neuritis	E	Stop agent, refer eye clinic
Seizures	Trd, FQ, Cs	Anticonvulsant, ↑pryidoxine to 200mg/dy; ↓dose; discontinue
Peripheral neuropathy	Trd, Km, Am, Cm, Cs, Eto, Pto, FQ	↑pyridoxine to 200mg/dy; physio; tricyclic antidepressant; discontinue

Slide courtesy of Dr C Mojapelo

COMMON SIDE EFFECTS cont.

Side effects	Agent	Management
Psychosis	Cs, Trd, FQ, Eto/Pto	Antipsychotic drugs e.g. haloperidol; ↓dose; discontinue
Depression	Cs, Trd, FQ, Cm, Eto/Pto	↑pyridoxine to 200mg/dy; antidepressant;↓dose; discontinue
Nausea, vomiting	Eto/Pto, PAS, Cm , Z, E	Rehydration; antiemetic; ↓dose, discontinue
Gastritis	PAS, Eto/Pto, Z, E	Administer with food; antacid; ↓dose; discontinue
Tendon rupture, muscle weakness	Mfx	

Slide courtesy of Dr C Mojapelo

INH prophylaxis

- **Exclude active TB:** patients should be screened for signs and symptoms of active TB disease
- **IF THERE IS ANY SUSPICION THAT THE PATIENT HAS ACTIVE TB THE PATIENT SHOULD NOT BE STARTED ON IPT!**
- IPT can be given in:
  - pregnant pts
  - pts on ART
  - pts previously treated for TB

INH prophylaxis

- **Who is Not Eligible for TB Preventive Therapy?**
  - Patients with signs and/or symptoms of TB

  - Patients with active liver disease or who are actively abusing alcohol should not be offered TB preventive therapy because of the risk of hepatotoxicity .

INH prophylaxis

Recommended Regimen

The standard regimen for TB preventive therapy is:

- Adults: Isoniazid (**INH**) 5 mg/kg/day (maximum **300 mg per day**).
- Children: Isoniazid (**INH**) 10 mg/kg/day (maximum **300 mg per day**).

Vitamin B6 (pyridoxine) 25 mg per day should be given concomitantly with isoniazid to prevent the occurrence of peripheral neuropathy.

The recommended duration is: **6 months of continuous treatment (can be completed over 9 months).**

If a patient has an interruption in TB preventive therapy for no more than three months, he/she can be restarted if still asymptomatic.

TB preventive therapy should be given once only. The protective effect of TB preventive therapy is expected to last for approximately 18 months.

Guidelines For Tuberculosis Preventive Therapy Among HIV Infected Individuals In South Africa 2010