Drug Treatment of Tuberculosis

Drug Treatment of Tuberculosis

There are about 9 million new cases annually.
TB killed 1.7 million people worldwide in 2006.

Recommended Duration of Therapy

Regimen (in Approximate Order of Preference)	Duration in Months
Isoniazid, rifampin, pyrazinamide	6
Isoniazid, rifampin	9
Rifampin, ethambutol, pyrazinamide	6
Rifampin, ethambutol	12
Isoniazid, ethambutol	18
All others	≥24

Antituberculous Agents

Primary or First Line Drugs:

Isoniazid (INH)

Rifampin "Rifadin" or "Rimactane"

Ethambutal
Streptomycin
Pyrazinamide

Isoniazid(INH)

- Most active.
- Small molecule, water soluble,
- Structurally related to Pyridoxine.
- Prodrug, activated by KatG, the mycobacterial catalase-peroxidase,
- Blocks mycolic acid synthesis, and consequently mycobacterial cell wall synthesis, leading to a bactericidal effect in growing TB cells.

Isoniazid (INH)

- TB lesion contains more than 10^8 bacilli
- When used alone, resistance is 1 in 10^6.
- A lesion usually contains 10^8 cells.
- When used in combination, the probability of resistance will be 1 in

$$10^6 * 10^6 = 10^{12}.$$

- Readily absorbed
- Widely distributed, penetrates into macrophages.
- Metabolized by acetylation:
  - Slow and Fast Acetylators

Isoniazid(INH)

- **Adverse Reactions:**

Hepatitis: in about 1%

Anorexia, N,V, jaundice, pain, death.

Depends on age, alcohol, pregnancy

Neuropathy:10-20%

More in slow acetylators, malnutrition, alcoholism, DM, AIDS, uremia.

Due to pyridoxine defeciency.

Neurotoxicity: Memory loss, Psychosis, Seizures.

Hematologic, Tinnitus, GIT, Interactions

Rifampin

- ***Stretomyces miditerranei.***
- **Gram+ve and –ve**
- **Mycobacteria, enterococci and chlamydia.**
- **Binds to the beta subunit of bacterial RNA polymerase and therefore inhibits RNA synthesis.**

Rifampin

- Bactericidal
- Well absorbed, highly bound to proteins.
- Widely distributed.
- Hepatic metabolism and exhibits enterohepatic recirculation.

Uses of Rifampin

- **TB**
- **Leprosy**
- **Meningococcal Carrier State**
- **Prophylaxis in *H.influenzae.***
- **Serious Staph osteomyelitis and valve endocarditis.**

valve endocarditis It is an inflammation of the inner tissues of the heart, the endocardium, usually of the valves. It is caused by infectious agents, or pathogens, which are largely bacterial

Osteomyelitis (OM) is an infection of bone.[1] Symptoms may include pain in a specific bone with overlying redness, fever, and weakness.[1] The long bones of the arms and legs are most commonly involved in children while the feet, spine, and hips are most commonly involved in adults

Toxicity of Rifampin

- Imparts harmless orange color to secretions(tears, urine, sweat).
- Rashes
- Hepatitis
- Flu-like syndrome
- Liver Enzyme Inducer, so can lower serum levels of many drugs

Streptomycin

- **Primary---Second-line------ Primary anti-tuberculus agent.**
- **Plague, Tuleremia حمى الارانب, Brucellosis الحمى المالطيه.**
- **Endocarditis.**

Toxic:

Allergy: Fever, Rashes

Pain, after i.m injection.

Vestibular toxicity---- Irreversible.

Nephrotoxicity

Tularemia is an infectious disease caused by the bacterium Francisella tularensis. Symptoms may include fever, skin ulcer, and large lymph nodes

Antituberculous Agents

Secondary or Second Line Drugs:

- Ethionamide
- Capreomycin
- Cycloserine
- Para-Amino-Salicylic Acid (PAS)
- Amikacin
- Flouroquinolones
- Linezolid
- Rifabutin
- Rifapentine

Indications for Secondary or Second Line Drugs

- 1. Resistance to first –line drugs.
- 2. Failure of clinical response to conventional therapy.
- 3. Occurrence of serious treatment-limiting adverse drug reactions.
- 4. When expert guidance is available to deal with the toxic effects.

Secondary or Second Line Drugs

Ethionamide:

Related to Isoniazid

Blocks mycolic acid synthesis

Oral, Good distribution

Poorly tolerated:

- Severe GIT irritation
- Neurotoxic
- Hepatotoxic

Secondary or Second Line Drugs

Capreomycin:

Peptide protein synthesis inhibitor

Injectable

Nephrotoxic, ototoxic

Local pain and sterile abscesses may occur.

Secondary or Second Line Drugs

Cycloserine:

Inhibits cell wall synthesis.

Peripheral neuropathy and CNS toxicity including depression and psychotic reactions.

Secondary or Second Line Drugs

Para-Amino-Salicylic Acid (PAS):

Folate synthesis antagonist

Well absorbed

Dose 8-12 gm/day

Widely distributed, except CNS

Excreted in urine.

GI toxicity

Hypersensitivity reactions

Crystalluria

Secondary or Second Line Drugs

- **Amikacin:**

Multidrug-resistant strains

Atypical mycobacteria

Secondary or Second Line Drugs

- **Flouroquinolones:**

Are an important addition

Resistance develops rapidly if used alone.

Secondary or Second Line Drugs

Linezolid:

Multidrug-resistant strains.
Bone marrow suppression
Irreversible peripheral and optic neuropathy.

Drug of last resort الحل الاخير

Secondary or Second Line Drugs

Rifabutin
Rifapentine

Related to Rifampin.

Inhibit bacterial RNA polymerase.

Both, like Rifampin, are inducers for CYP P450 enzymes. But Rifabutin is less potent inducer.

Rifabutin is indicated in place of Rifampin in the treatment of TB in HIV-infected patients receiving protease inhibitor or nonnucleoside reverse transcriptase inhibitor (e.g. efavirenz)

Atypical Mycobacteria (Nontuberculus Mycobacteria)

- 10% of clinical isolates.
- Distinctive laboratory characteristics.
- Present in the environment.
- Not communicable from person to person.
- Less susceptible to drugs.

Atypical Mycobacteria (Nontuberculus Mycobacteria)

- ***M.tuberculosis* complex:**

Erythromycin

Sulphonamides

Tetracycline

- ***M.avium* complex:**

Important and common cause of disseminated TB in late stages of AIDS.

Azithromycin or Clarithromycin, plus

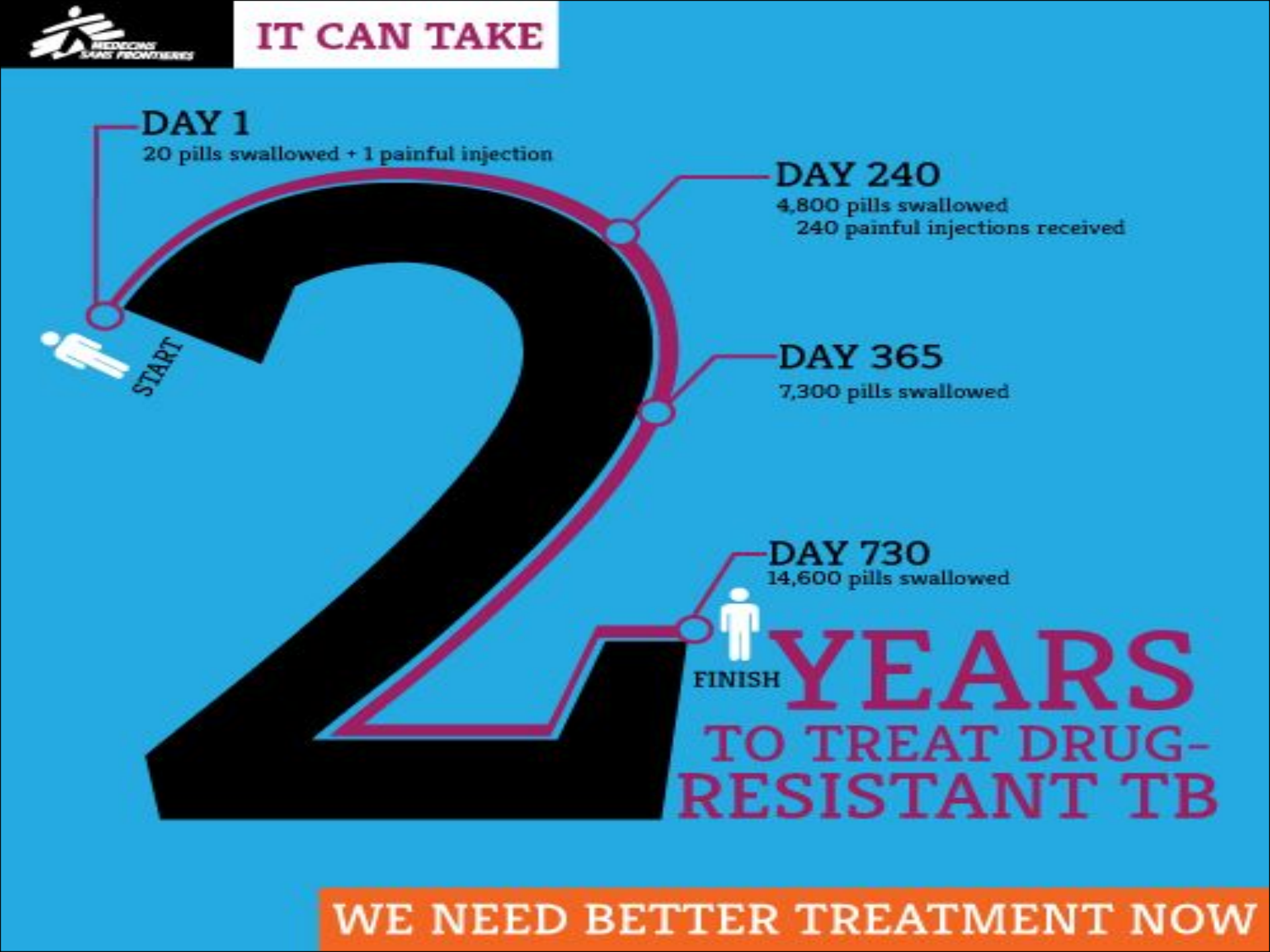
Ethambutal, plus

Ciprofloxacin

- Annually, 9 million cases are recorded.
- 5% of these are drug-resistant tuberculosis.
- Forty-nine percent of those with XDR-TB died compared to 19 percent of patients with ordinary MDR-TB,

Drug-Resistant TB (3)

Mono-resistant	Resistant to any one TB treatment drug
Poly-resistant	Resistant to at least any 2 TB drugs (but not both isoniazid and rifampin)
Multidrug resistant (MDR TB)	Resistant to at least isoniazid and rifampin, the 2 best first-line TB treatment drugs
Extensively drug resistant (XDR TB)	Resistant to isoniazid and rifampin, PLUS resistant to any fluoroquinolone AND at least 1 of the 3 injectable second-line drugs (e.g., amikacin, kanamycin, or capreomycin)


IT CAN TAKE
DAY 1
20 pills swallowed + 1 painful injection
START
DAY 240
4,800 pills swallowed
240 painful injections received
DAY 365
7,300 pills swallowed
DAY 730
14,600 pills swallowed
FINISH
2 YEARS
TO TREAT DRUG-RESISTANT TB
WE NEED BETTER TREATMENT NOW