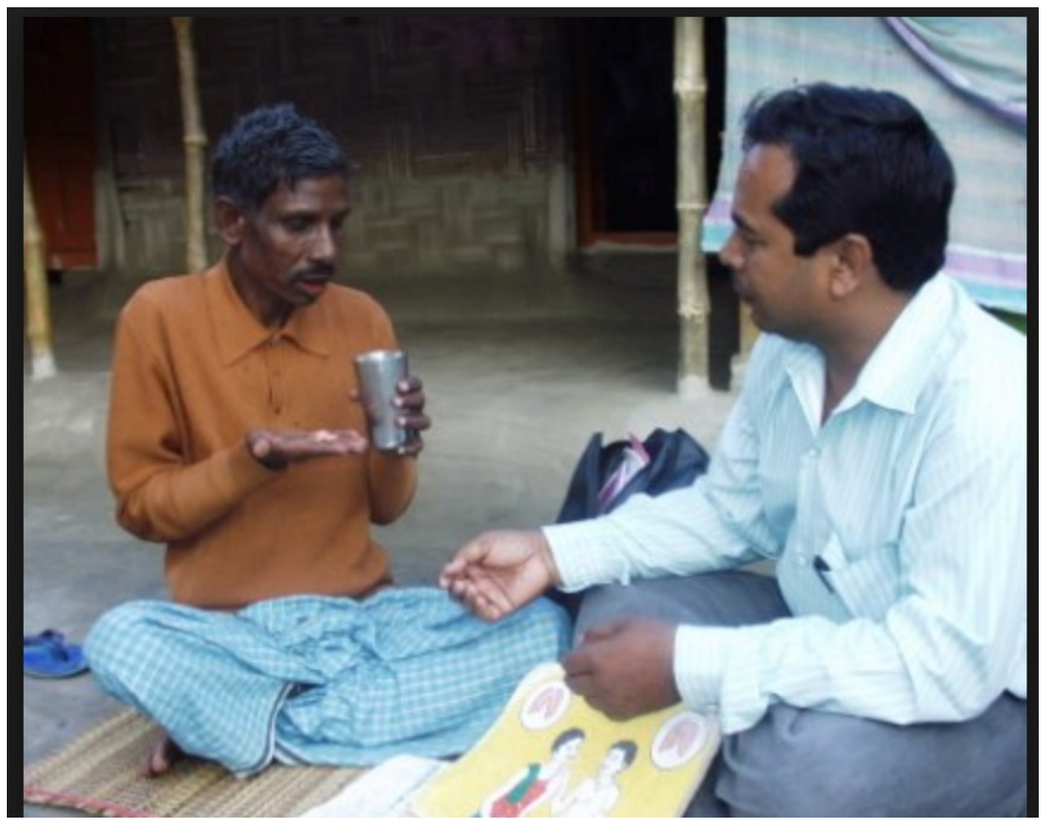
TB regimens

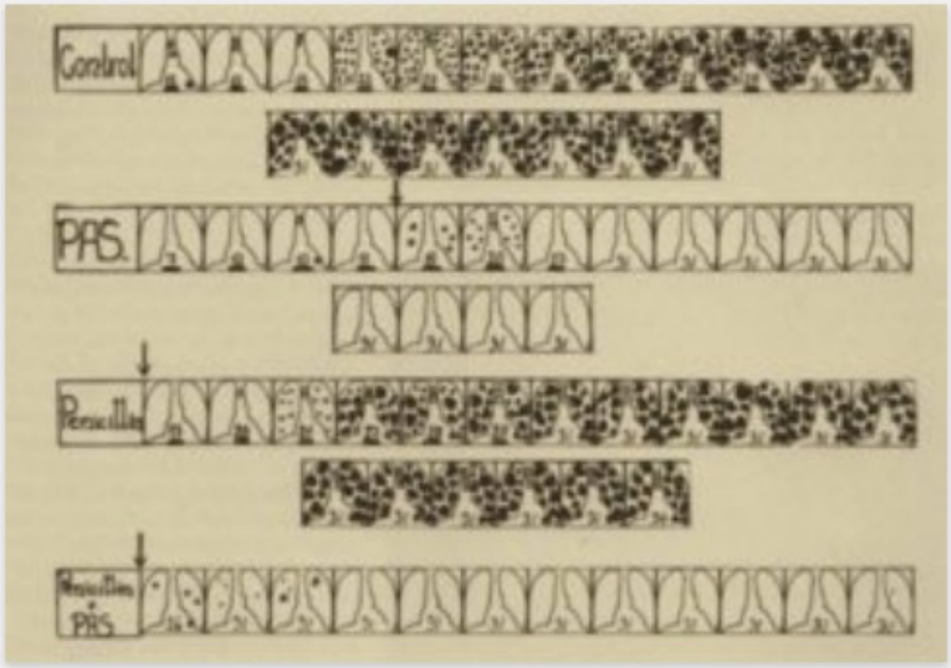
DOTS

- DOTS
  - Directly observed therapy short course
  - 5 major elements
    - Diagnosis by smear microscopy (so no DST)
    - SCC
    - Adherence support
    - Political will
    - Monitoring and evaluation



History of TB drugs: PAS

- 1940 paper reported aspirin increased MTB oxygen uptake
- Lehmann (US) proposed an aspirin analog that would block oxygen uptake.
- PAS tried in animals and small human trial in 1943.



The results of an early animal experiment with PAS

Streptomycin

- Selman Waksman and Albert Schatz studied soil microbes, noting that actinomycetes were inhibited by soil components.

- Eventually isolated streptomycin from streptomycin griseus.

- First human study at Mayo clinic and first clinical trial by MRC in England in 1946.

- Broad spectrum, injectable, substantial side effects including renal and ototoxicity.

Mechanism

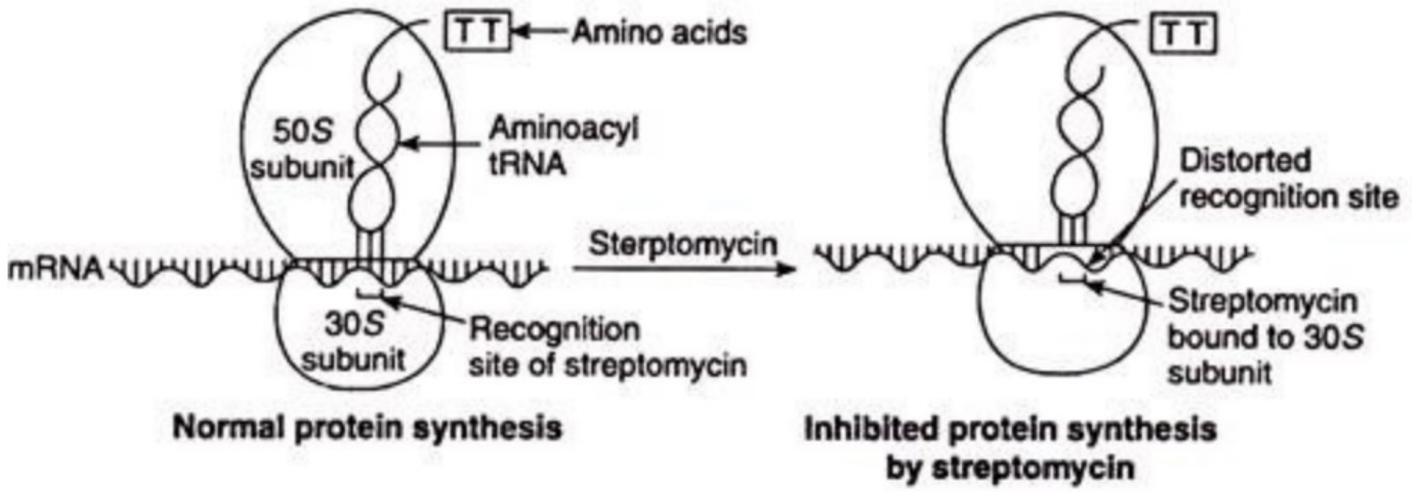
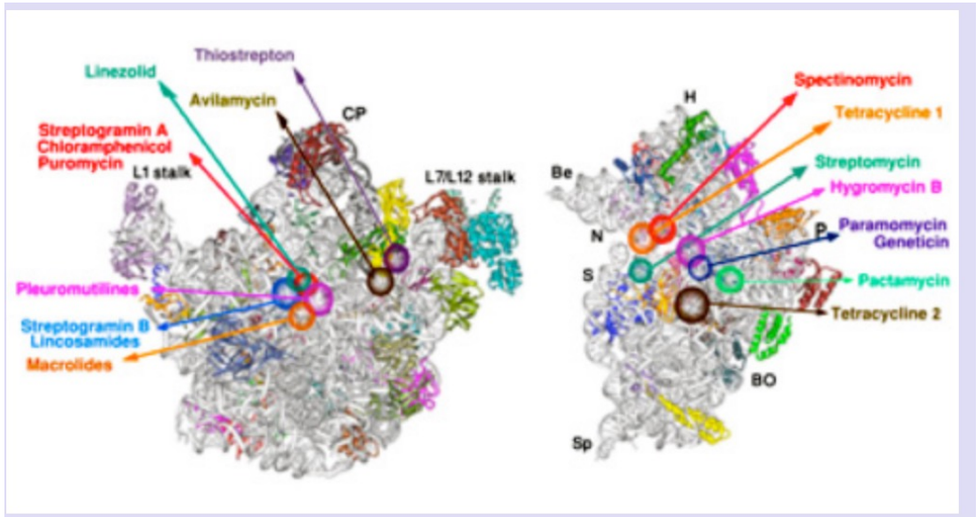


FIG. 45.10. Schematic representation of protein synthesis inhibition by streptomycin.

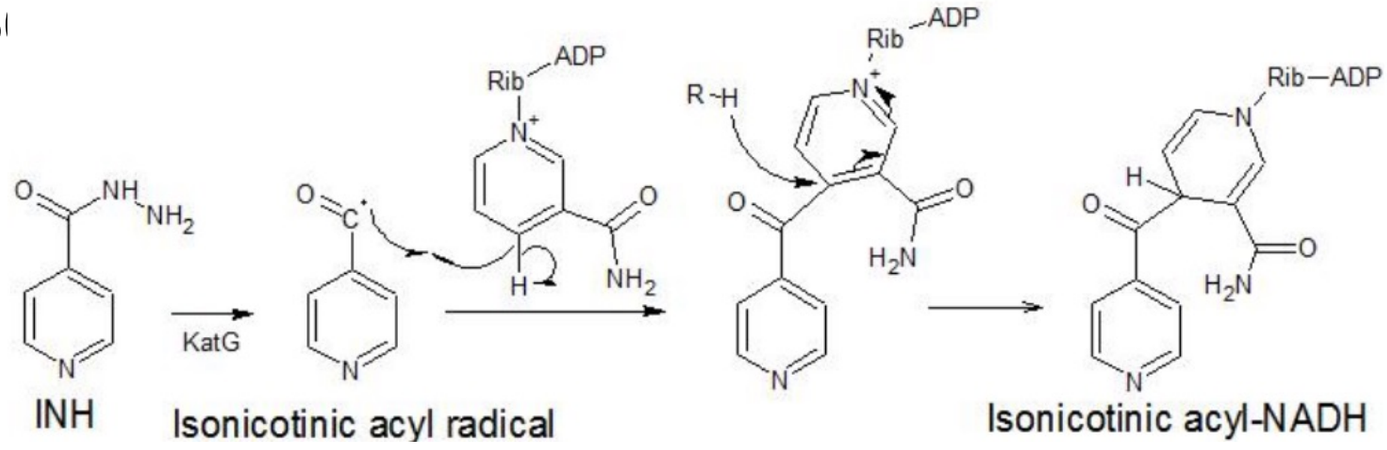
- Inhibits protein synthesis by binding to 30S subunit or ribosome.



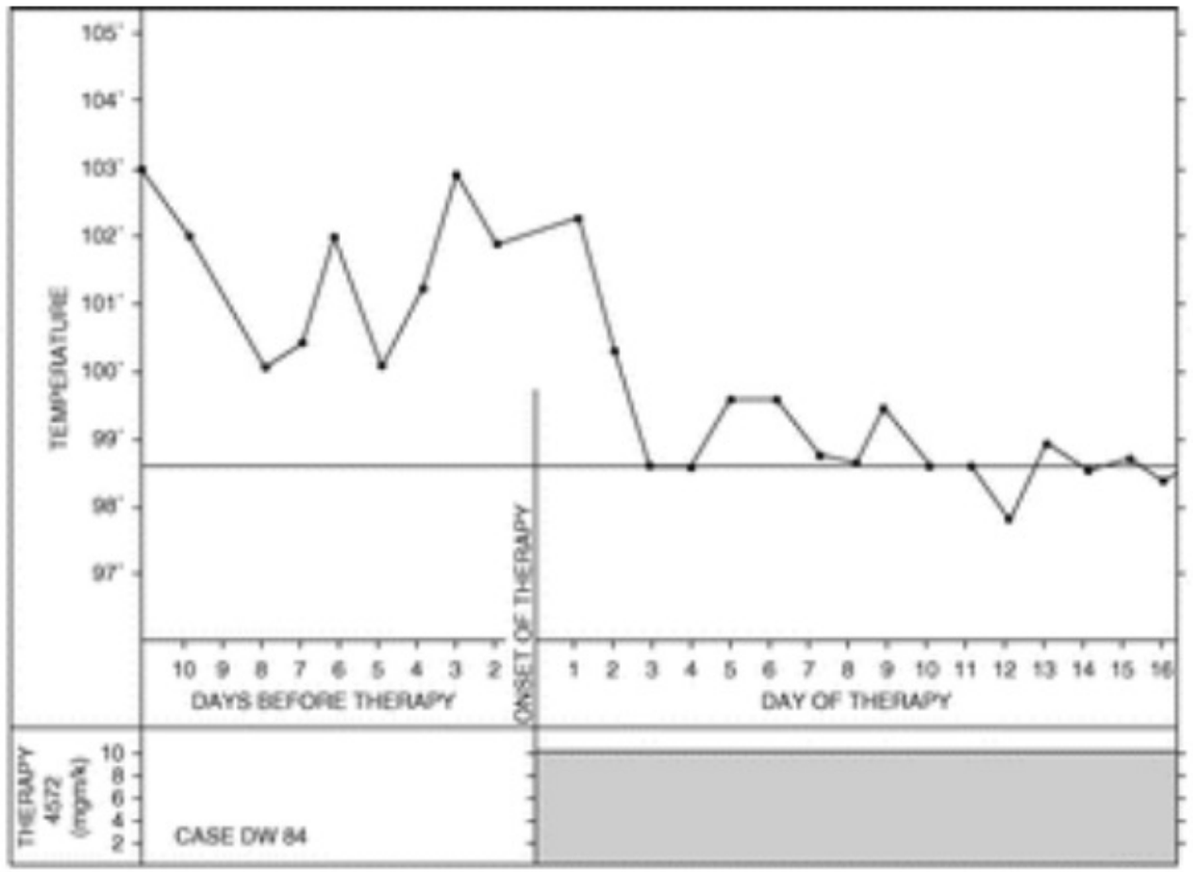
The ribosome as a target for antibacterial agents. Ribosomes are universal in organisms, and many current antibiotics target ribosomes in disease-causing organisms. Prof. Yonath's research has revealed how 20 different antibiotics functions.

INH

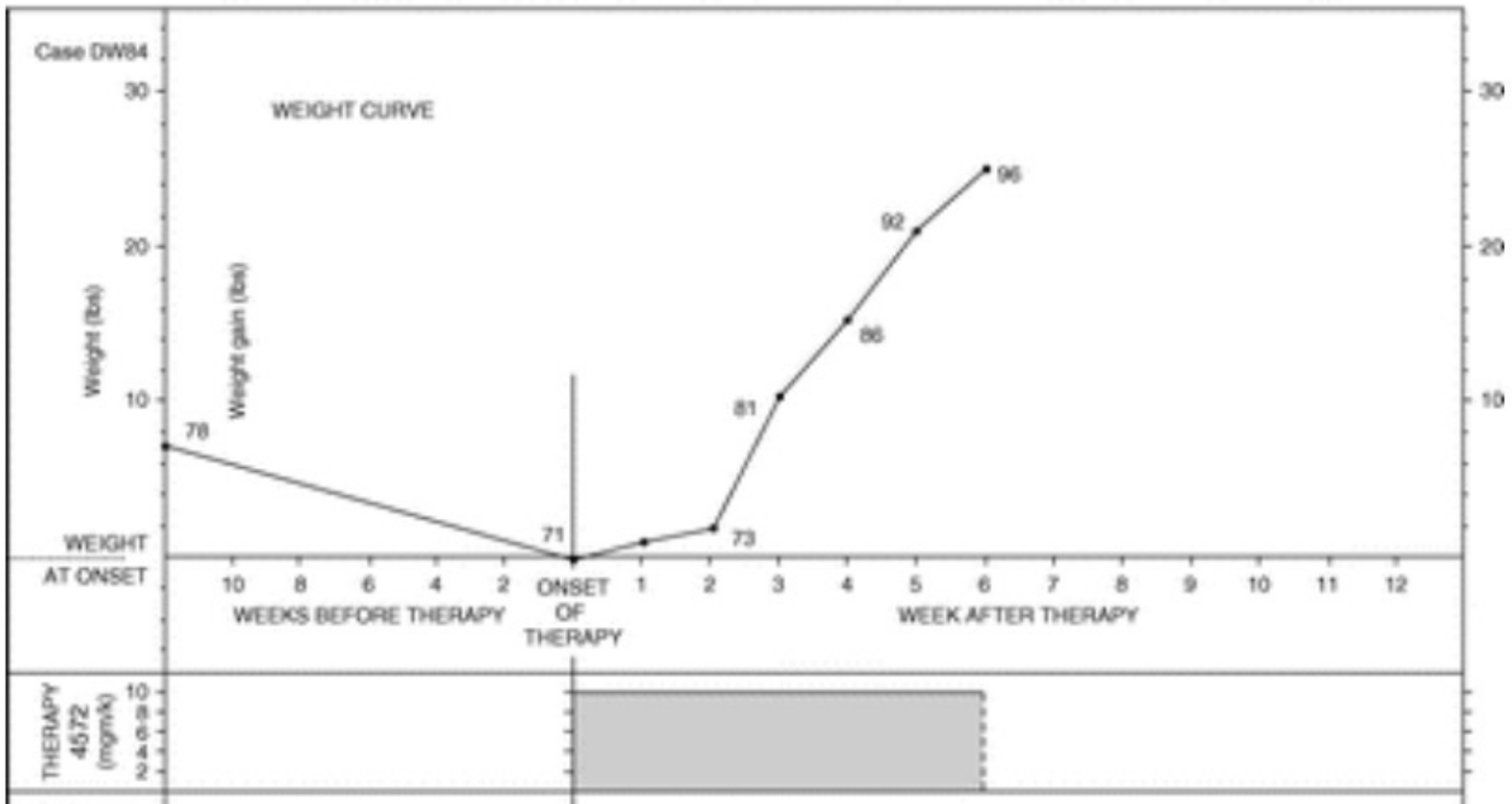
- Oral agent co-discovered by multiple groups in early 195



- Prodrug activated by KatG, a bacterial catalase-peroxidase enzyme in Mycobacterium tuberculosis. NAD-adduct binds to the enoyl-acyl carrier protein reductase InhA, ultimately inhibiting the synthesis of mycolic acids, which are remycobacterial cell wall components.
- A range of radicals are produced by KatG activation of isoniazid, including nitric oxide which has also been shown to be important in the action of another antimycobacterial prodrug pretomanid.
- Mild monoamine oxidase inhibitor (ie. antidepressant!).



Temperature curve indicating persistently elevated temperature returning to normal on the third day after institution of therapy.



INH side effects

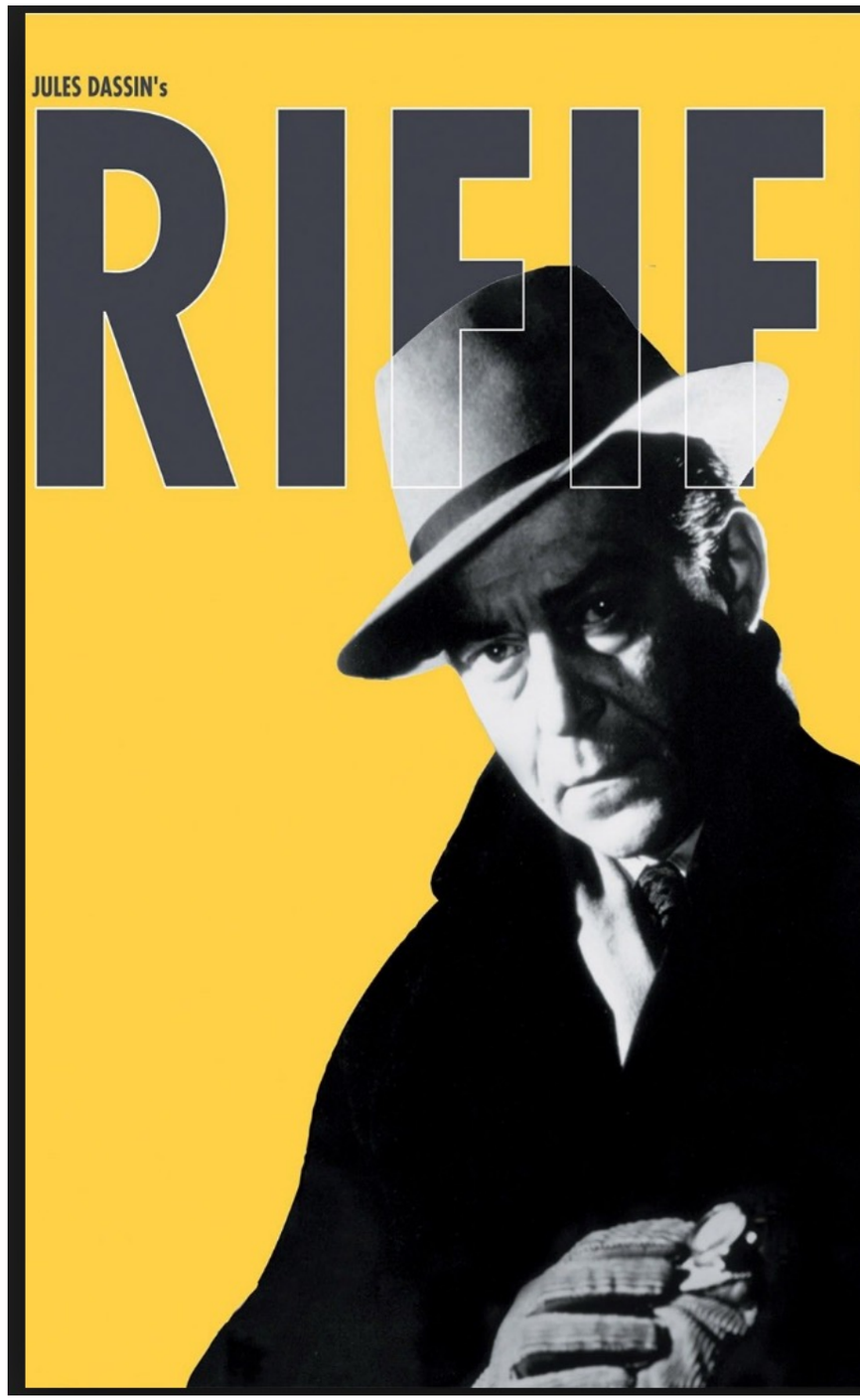
- 10-20% people develop peripheral neuropathy.
- 10-20% have increased liver function tests
- .3% develop serious hepatitis
    - More common in African american women
    - Very low rate of side effects in younger people
    - Possible role for Hep C

Triple therapy

- PAS, Streptomycin, INH X 18-24 months.
- Ethambutol added in 1960s substituting for PAS

Rifampicin

In 1957, a soil sample from a pine forest on the French Riviera was analyzed by Piero Sensi and Maria Teresa Timbal who discovered a new bacterium that produced a new class of molecules with antibiotic activity. Because Sensi and Timbal were particularly fond of the French crime story Rififi (about a jewel heist and rival gangs), they called these compounds "rifamycins". After two years of work, a new molecule with high efficacy and good tolerability was produced in 1965 and was named "rifampicin".



Mechanism

Side effects

- Rare hepatotoxicity, fever, GI symptoms, rash.
- Turns urine/sweat red.
- Induces P450 cytochrome system which increases metabolism of multiple drugs including oral contraceptives and some antiretrovirals.
- Standard dosing probably is too low.

Pyrazinamide

- Developed in the 30s as an analog of nicotinamide but not used until 1950s.

- Pro-drug converted to pyrazinoic acid by pncA.

- Only effective in acid environment. Synergistic with Rif.

- Is more effective against metabolically inactive MTB than replicating bacilli.

- Highly effective in first 2 months, used to reduce treatment duration.

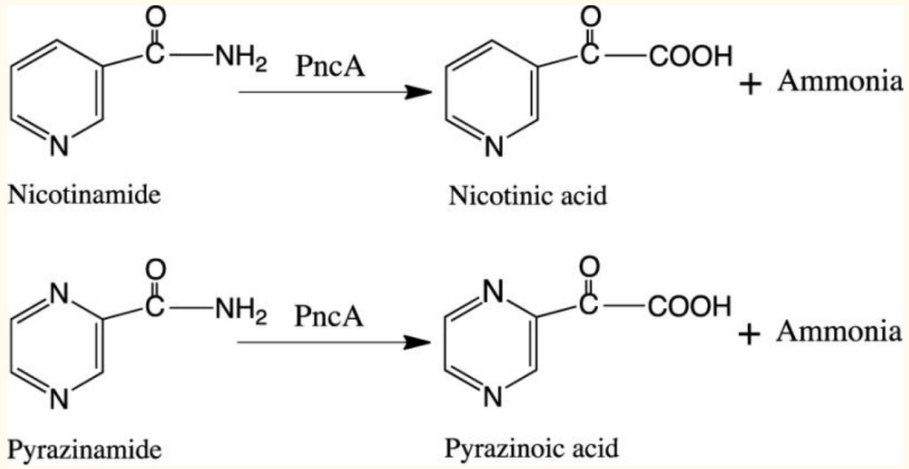
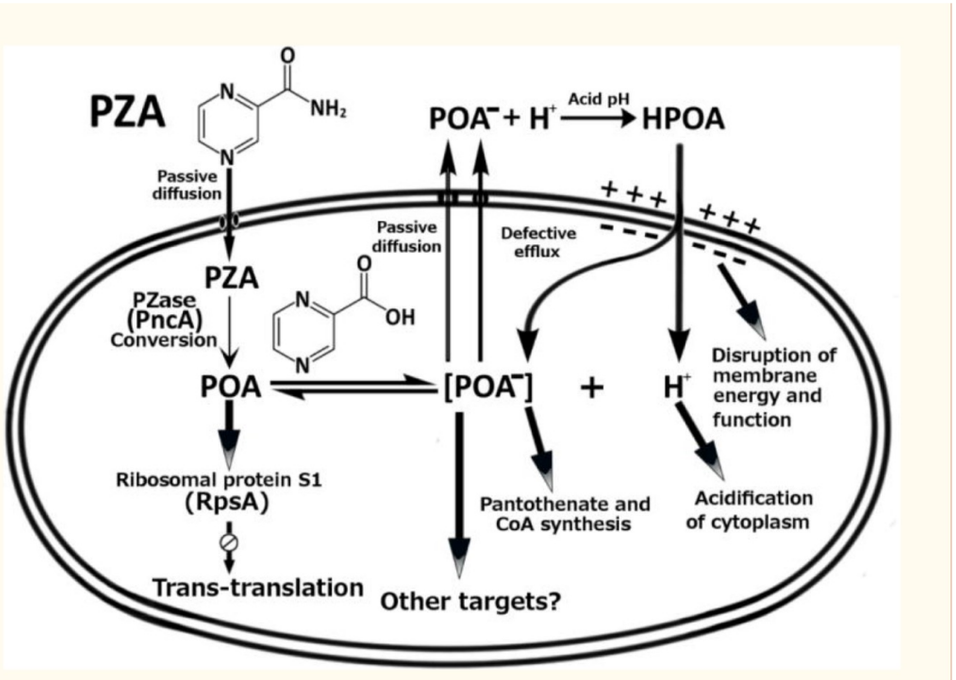


Figure 1



Short course chemotherapy

Clip slide

Short Course Chemotherapy (DOTS)

Category wise treatment regimens for tuberculosis

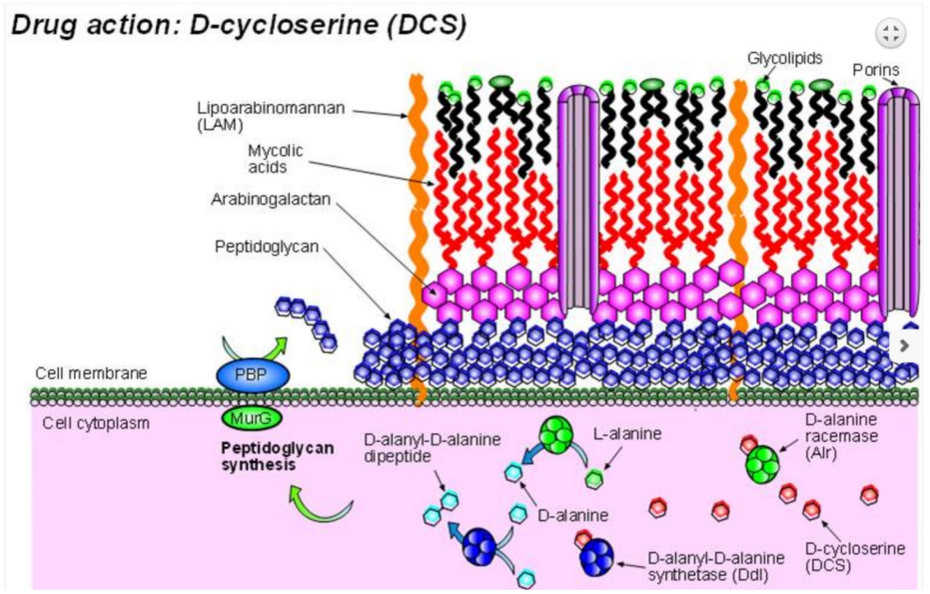
Category	*Intensive phase*	*Continuation phase*	*Duration (months)*	*Comment*
I New patient	2[$] HRZE daily	4[$] HR daily	6[$]	Optimal
	2 HRZE daily	4 HR thrice weekly	6	Acceptable if DOT ensured
	2 HRZE thrice weekly	4 HR thrice weekly	6	Acceptable if DOT ensured, and no HIV coinfection or its risk
II Previously treated patients pending DST result	2 HRZES daily + 1 HRZE daily	5 HRE daily	8	For patient with low/medium risk of MDR-TB (failure, default, etc.)
	Empirical[£] (standardized) MDR-regimen	Empirical (standardized) MDR-regimen	18–24 or till DST result	For patient with high risk of MDR-TB (failure, 2nd default, contact of MDR-TB, etc.)

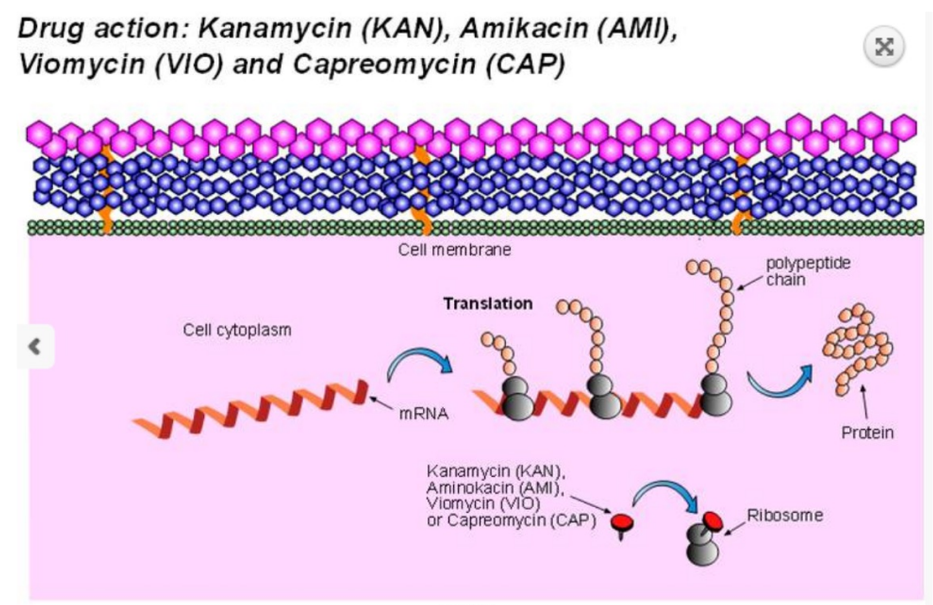
DST—Drug sensitivity testing; DOT—Directly observed therapy
H, R, Z, E, S—Standard codes for isoniazid, rifampin, pyrazinamide, ethambutol and streptomycin, respectively.
$—The neumerals indicate duration of a phase/total duration in months.
£—Empirical (Standardized) MDR regimen is country specific depending upon local data and situation (Indian regimen on p.776)

Treatment of tuberculosis: Guidelines, 4th edition (2010), WHO, Geneva.

Second line TB drugs

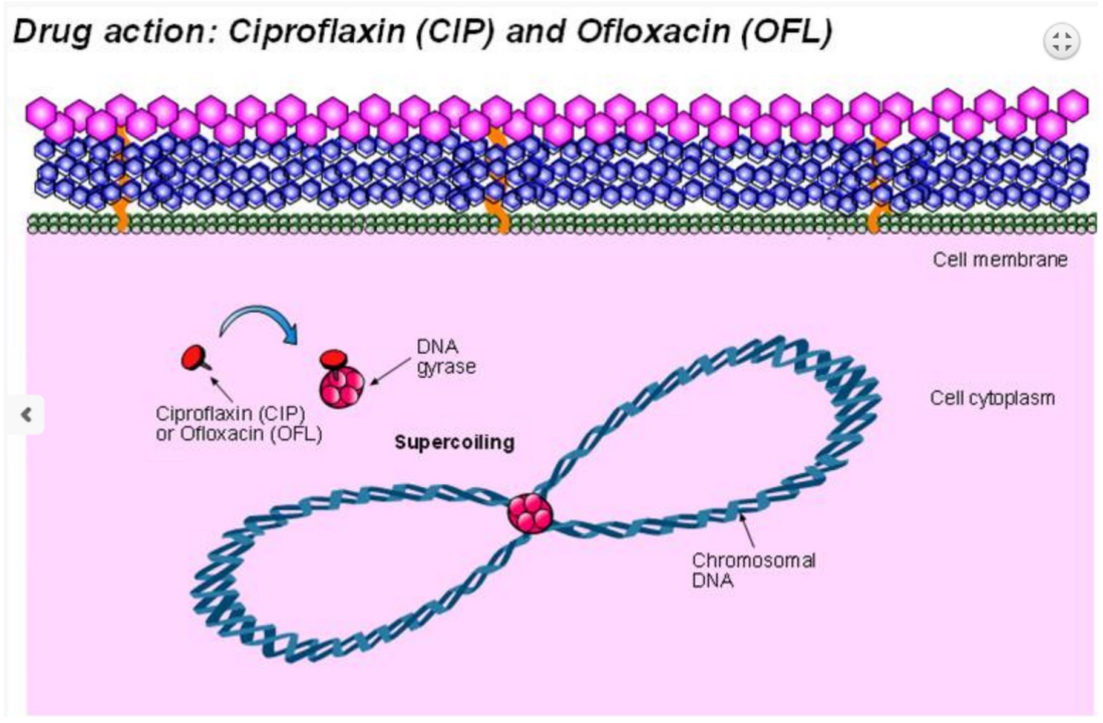
- **Cycloserine**
  - Product of Streptomycetes
  - Cell wall inhibitor blocking peptidoglycan synthesis.
  - Profound neurological side effects including depression and suicide.
- **Ethionamide**
  - Pro-drug activated by EthA
  - Similar mechanism to INH
  - GI side effects severe including nausea, diarrhea and abd pain.
- **Kanamycin, Amikacin and Capreomycin**
  - Like other aminoglycosides, disrupts protein synthesis by binding to 30S subunit of ribosome.
  - Ototoxicity



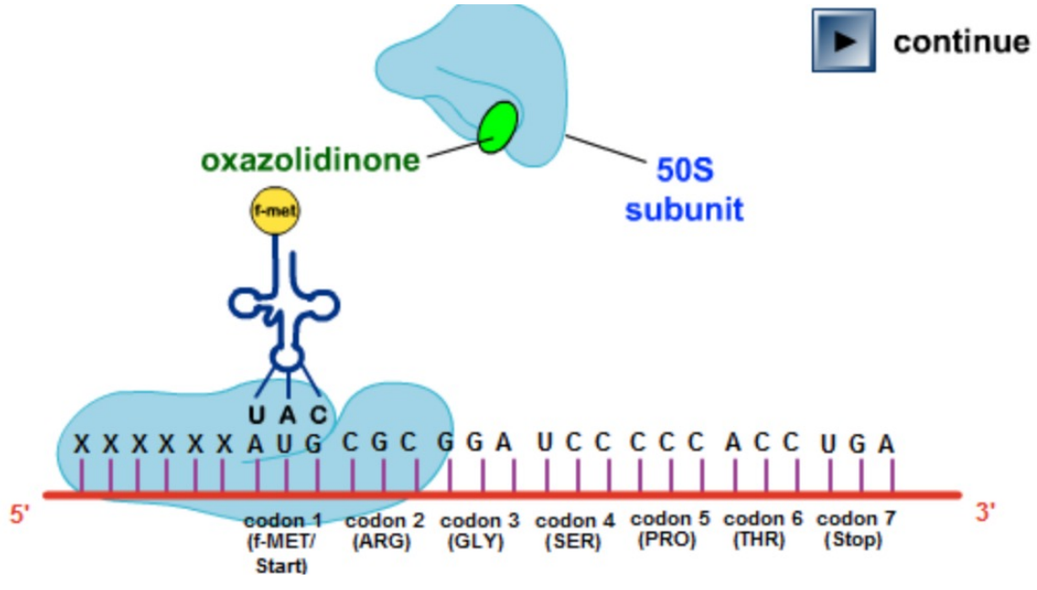


Repurposed drugs

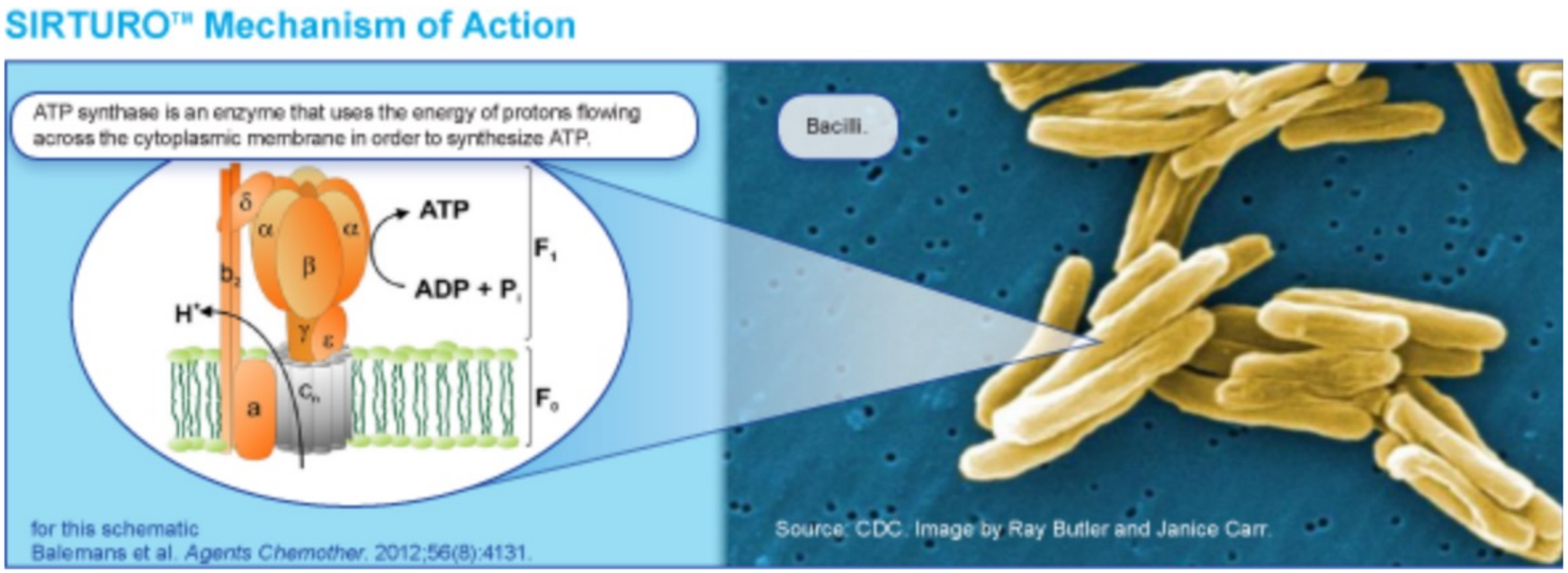
- **Fluoroquinolones**
  - Moxfoxacin, gadifloxicin etc.
  - Inhibits gyrA which effects DNA super-coiling
  - Broad-spectrum



- **Linezolid**
  - Also inhibits protein synthesis
  - Serious side effects with prolonged use.



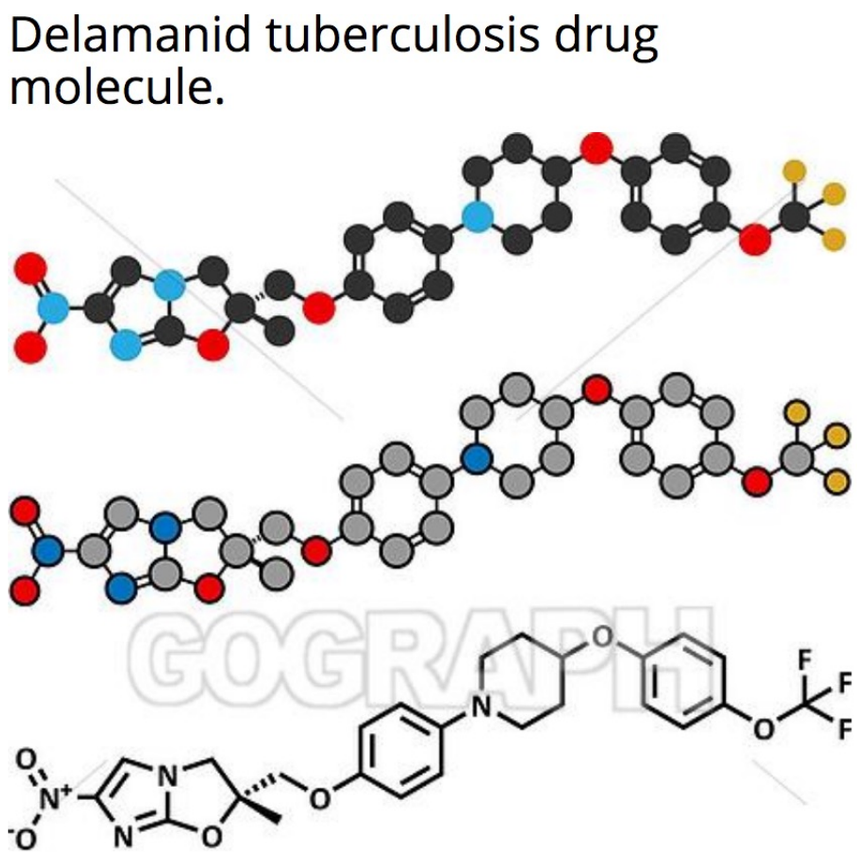
Bedaqualine



- First new TB drug in 30 years
- Blocks proton pump for ATP synthase of mycobacteria.
- Oral, daily dosing
- Side effects include QT prolongation, nausea, joint pain
- Interacts with Rif and some antiretrovirals.

Delaminid

- Nitro-dihydro-imidazooxazole derivative
- Pro-drug w activated by the deazaflavin dependent nitroreductase (Rv3547). A reactive intermediate inhibits mycolic acid production.
- Side effects also include QT prolongation.
- No interactions with antiretrovirals.



Shortened MDR regimen

FEATURES OF THE SHORTER MDR-TB REGIMEN

- Standardized shorter MDR-TB regimen with seven drugs and a treatment duration of 9-12 months
- Indicated conditionally in MDR-TB or rifampicin-resistant-TB, regardless of patient age or HIV status
- Monitoring for effectiveness, harms and relapse will be needed, with patient-centred care and social support to enable adherence
- Programmatic use is feasible in most settings worldwide
- Lowered costs (<US$1,000 in drug costs/patient) and reduced patient loss expected
- Exclusion criteria: 2nd line drug resistance, extrapulmonary disease and pregnancy.

REGIMEN COMPOSITION

4-6 Km-Mfx-Pto-Cfz-Z-$H_{high\text{-}dose}$-E / 5 Mfx-Cfz-Z-E

Km=Kanamycin; Mfx=Moxifloxacin; Pto=Prothionamide;
Cfz=Clofazimine; Z=Pyrazinamide;
$H_{high\text{-}dose}$= high-dose Isoniazid; E=Ethambutol

CHOOSING THE MDR-TB TREATMENT REGIMEN IN PATIENTS WITH CONFIRMED RIFAMPICIN-RESISTANT OR MDR-TB

CRITERIA: Do any of the following apply ?

- ✓ Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
- ✓ Exposure to ≥1 second-line medicines in the shorter MDR-TB regimen for >1 month
- ✓ Intolerance to ≥1 medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- ✓ Pregnancy
- ✓ Extrapulmonary disease
- ✓ At least one medicine in the shorter MDR-TB regimen not available in the programme

NO → **Shorter MDR-TB regimen**

Intensive phase
Duration: 4-6 months
Composition: 4 second-line drugs

Continuation phase
Duration: 5 months
Composition: 2 second-line drugs

Supported by selected first-line TB drugs

FAILING REGIMEN, DRUG INTOLERANCE, RETURN AFTER INTERRUPTION >2 MONTHS, EMERGENCE OF ANY EXCLUSION CRITERION

YES → **Individualised ("conventional") MDR/RR-TB regimens**

Intensive phase
Duration: Up to 8 months
Composition: 4 or more second-line drugs

Continuation phase
Duration: 12 months or more
Composition: 3 or more second-line drugs

Supported by selected first-line TB drugs