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Inter TB

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Standard treatment

2HRZE/4RH

lasts 6 months

H = isoniazid R = rifampicin

Z = pyrazinamide E = Ethambutol

Aims in drug development

- Shorter current 6 months treatment
- Reduce frequency of dosage
- Activity against resistant disease (MDR, XMDR)

New drugs in clinical testing

Fluoroquinolones

Ofloxacin, levofloxacin,
gatifloxacin, moxifloxacin

Diarylquinoline TM207

Johnson & Johnson, Tibotec

Nitroimidazoles

- PA824

Global Alliance

- OPC67683

Otsuka

Diamine SQ109

Sequella

Problems with new drugs

- High plasma binding
- Insoluble —→ poor absorption
- Cell wall targets
- Inhibitors of genes. Inefficient against dormant bacilli

New drug development faces many problems and will take many years.

What can we do now?

How do current drugs work?

	Period during which drugs kill TB	Prevention of drug-resistance
Rifampicin	Entire 6 months	All drugs prevent resistance to other drugs
Pyrazinamide	Initial 2 months only	
Isoniazid	Initial 2-5 days only	
Ethambutol	None	
Methods:	1) Old clinical trials	2) Response of patients with initial resistance

Initial isoniazid (H) resistance in clinical trials

Regimen	Initial H-resistance	Total patients	Failure %	Relapse %
SHRZ/TH	Sens.	928	0.4	8
	Res.	67	16	31
EHRZ/EH	Sens.	420		10
	Res.	35		31
SHRZ/RH	Sens.	1223	0	5
	Res.	61	0	8
EHRZ/RH	Sens.	190		4
	Res.	23		4

Can we improve current drugs?

Effects of increasing dose size

Isoniazid	Already at dose size with maximal effect
Pyrazinamide	Increased dose → liver toxicity
Ethambutol	Risk of optic toxicity
Rifampicin Rifapentine	Increase in dose size should speed up killing of TB

Current priorities

Test higher doses of rifamycins

Develop fluoroquinolones