

# Clinical trial capacity – global needs estimate and necessary steps

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# The history of TB clinical trials: the BMRC experience

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- 1946: Initial trial assessing the value of the addition of streptomycin to bed rest
- 1948: Demonstration that emergence of drug resistance to S or PAS was greatly reduced when both drugs were combined
- 1952-1955: Exploration of treatment with INH alone and in combination with PAS or S
- 1958-1967: Search for affordable regimens led to replacing PAS with thiacetazone
- 1958--: Initiation of the policy of DOT and its later implementation in Hong Kong and Madras
- 1959: Demonstration that treatment at home was as effective as treatment in sanatorium and did not lead to increase in the rate of infection of family contacts

# The history of TB clinical trials: the BMRC experience

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- 1961--Exploration of intermittent regimens to assist implementation of full supervision
- 1970: First demonstration that inclusion of R or Z in a regimen of SH substantially reduced the relapse rate
- 1972-1974: Demonstration that the period of treatment could be shortened to 6 months by the inclusion of R and Z in the regimen
- 1976: Development of modern short course regimens by showing that sterilizing activity of Z was limited to first 2 months whereas sterilizing activity of R persisted in continuation phase
- 1977--: Demonstration of the value of intermittency in short-course regimens, particularly that thrice weekly treatment throughout was as effective as, and less toxic and expensive than daily regimens

# The history of TB clinical trials: the BMRC experience

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- Overall, from 1946-1986:
  - Over 200 regimens evaluated
  - Over 25,000 patients studied
- Drugs evaluated
  - Streptomycin
  - PAS
  - INH
  - Thiacetazone
  - Rifampin
  - Ethambutol
  - Pyrazinamide

# Current therapy for tuberculosis

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## 2HRZE/4HR

- Induction phase: 2 months  
isoniazid, rifampin,  
pyrazinamide, ethambutol
- Continuation phase: 4  
months isoniazid, rifampin
- Advantages:
  - 100% effective
  - Low relapse rate (3-4%)
  - Inexpensive
  - Universally available
  - Can be given intermittently
- Disadvantages
  - 6 months duration
  - High relapse rate (3-4%)
  - Adverse effects common
  - Interactions with HIV treatment
  - Not useful against MDR strains

# Tuberculosis drugs in development

Sponsor	Drug	Stage
Sanofi-Aventis	Rifapentine	Phase 4
Bayer/GA	Moxifloxacin	Phase 2
EU, WHO	Gatifloxacin	Phase 2
Tibotec	TMC207	Phase 2
Otsuka	Nitroimidazole	Phase 2
Global Alliance	PA-824	Phase 1
Sequella	SQ-109	Pre-clinical
Lupin	Pyrrole, LL-3858	Pre-clinical

# What are the goals of tuberculosis trials today?

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- Shorter overall treatment duration
- Lower relapse rates
- Development of regimens with fewer adverse effects, particularly less hepatotoxicity
- Development of regimens that can be given easily and safely in combination with antiretroviral therapy
- Development of regimens that are effective in treating MDR-TB

# Types of tuberculosis clinical trials

Type	Endpoint	Size	Duration of study	What is being studied?
Phase 1	Safety/tolerability	small	days-weeks	drug
PK/PD	PK/PD data; drug interactions	small	days-weeks	drug(s)
Phase 2a	EBA	small	days-weeks	drug
Phase 2b	2-month culture conversion; SSCC; time to conversion	medium	months	regimen
Phase 3	Failure/relapse	large	years	regimen
Phase 4	Detection of uncommon side effects	large	years	regimen

# What is needed to conduct TB trials now

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- Candidate drugs
- Potential study subjects
- Professional clinical trialists
- Adequate funding

# What is needed to conduct TB trials now

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- Professional clinical trials capacity: personnel
  - Physicians
  - Nurses
  - Field workers
  - Statisticians/data analysts
  - Regulatory experts
  - Site monitors
- Consortium model favored over ad hoc sites/trials (BMRC model)
  - Greater efficiency and reservoir of expertise in all areas of trial conduct
    - Regular protocol team meetings
    - Modular protocols, standardized case report forms
    - Data and statistical center
    - Standard consent form language
    - Central IRB
    - Easier collaboration with FDA, other regulatory agencies
    - GMP-compliant pharmacy

# TBTC Trials Conducted From 1995 to Date

**Study 22**  
1995-1998

**Study 23**  
1999-2003

**Study 25**  
1999-2000

**Study 24**  
1999-

**Study 26**  
2001-

**Study 27**  
2003-05

**Study 27-28PK**  
2004-

**Study 28**  
2006-

**TBTC CLINICAL TRIALS**

**ONGOING TBTC CLINICAL TRIALS**

- RBT replaces RIF in patients with HIV and HAART
- Failure/relapse rate and tolerability
- Paradoxical reactions
- RIF monoresistance
- Drug-drug interactions
- 23A: All TB drugs in S23 patients
- 23B: Nelfinavir and RBT (nested)
- 23C: Efavirenz and RBT (nested)

- 22PK all drugs in relapse vs. non-relapse patients, NAT2 genotyping
- Cavitation and 2 month culture conversion as risk factors for relapse
- RIF resistance in HIV (+) patients
- 2003 ATS/CDC recommends extended duration for H.R. pts and use of RPT in L.R. patients

- RPT dose escalation (600 mg vs. 900 mg vs. 1200 mg)
- PK evaluation
- Risk factors for relapse

- What is the best management of patients with INH resistance or intolerance?

- Evaluation of MOXI in a Phase II trial
- Can MOXI decrease infectious period and potentially shorten duration of therapy?

- Can a Phase III RTC of LTBI be accomplished?
- What is the efficacy and tolerability of a 12 dose INH/RPT weekly regimen to prevent active TB?

- What would be the effect of substituting MOXI for INH in the induction phase?

- Does RIF decrease the concentrations of MOXI?
- Is the PK of MOXI different in TB patients?

# What is needed to conduct TB trials now

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- Potential study subjects
  - General populations
    - Patients with smear positive pulmonary tuberculosis
  - Special populations
    - HIV-infected persons
    - Children
    - Patients with multidrug-resistant tuberculosis
    - Patients with extrapulmonary tuberculosis
    - Patients with smear-negative pulmonary tuberculosis

# What is needed to conduct TB trials now

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- Candidate drugs
  - More candidates available now than at any time in past 30 years
  - Several drugs with novel mechanisms
  - Trials that could be done right now
    - Higher doses of rifampin (phase 2)
    - Higher doses of rifapentine (phase 2)
    - Rifapentine with better companion drugs (i.e. moxifloxacin rather than isoniazid) (phase 2)
  - Trials that could be done soon
    - Treatment shortening with moxifloxacin (phase 3)

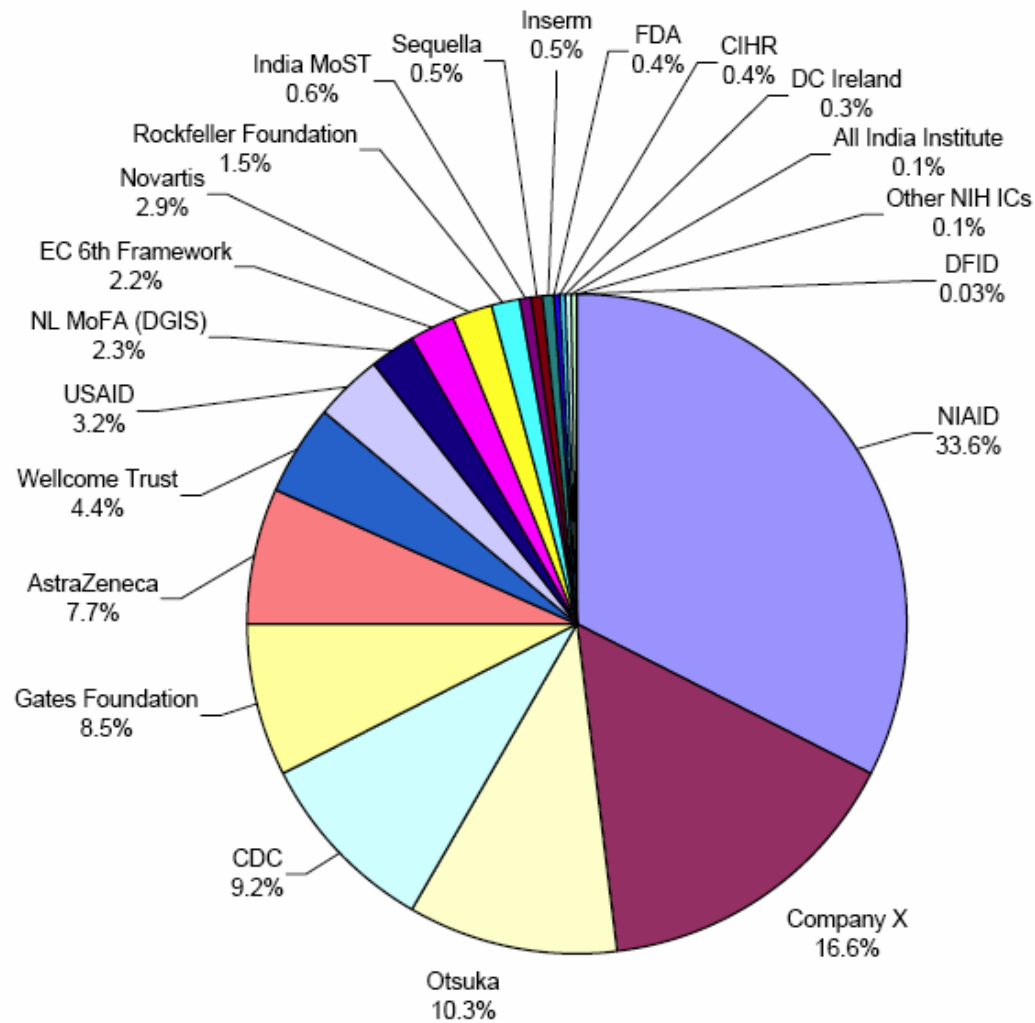
# What is needed to conduct TB trials now

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- Adequate funding
  - How much funding is needed to support TB clinical trials?

**MORE**

**Figure 6: TB Drug Research  
(Total = \$119,766,935)**

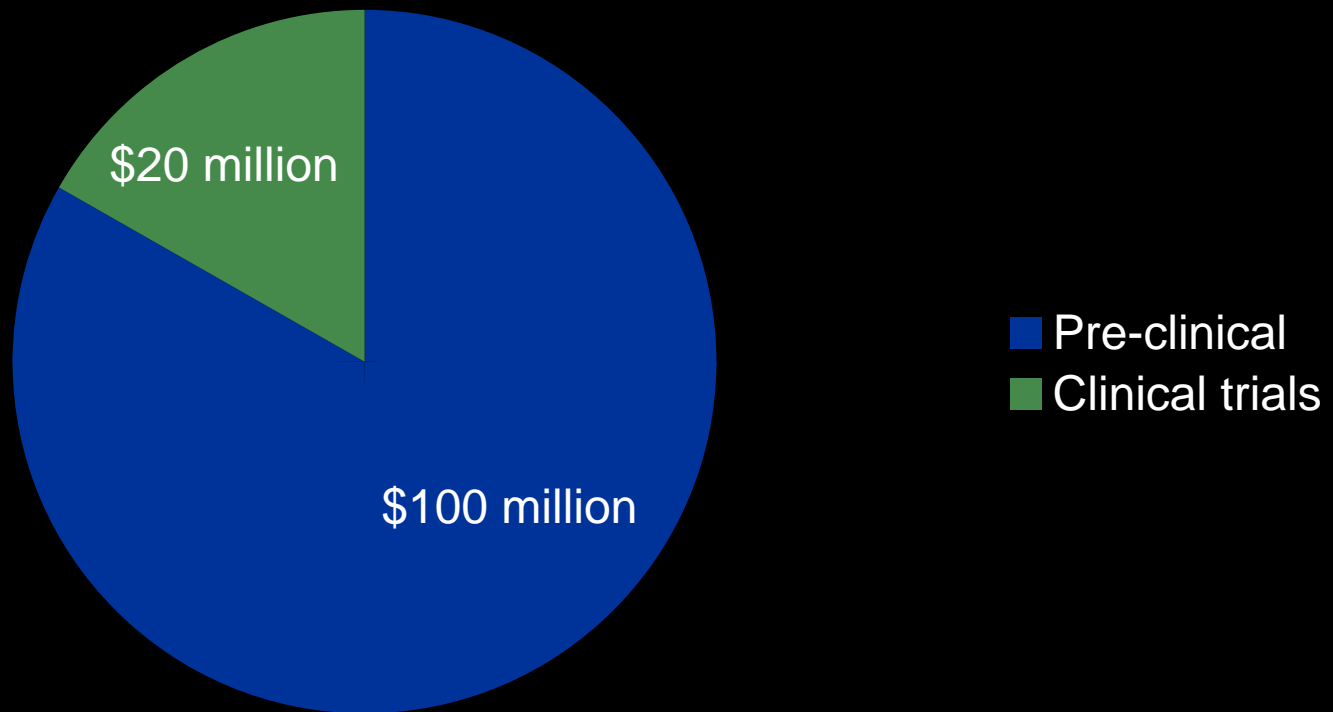


Source: Treatment Action Group, *Tuberculosis Research and Development: A Critical Analysis [2006]*

# Funding for TB clinical trials

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Total funding for TB drug research = \$120 million



Although funding for new TB drugs is ahead of that for new diagnostics and new vaccines, it is still far from sufficient. Most notably, there is no funding available to build the extensive clinical trials infrastructure needed to carry out large-scale, long-term phase II/III efficacy and post-marketing phase IV studies of new TB agents and combinations. Funds for the CDC's TB Trials Consortium (TBTC) have been cut for two consecutive years; NIH's clinical trials budget is stagnant; and the TB Alliance's new \$104 million from the Gates Foundation will support nine pre-clinical projects and identify the best of these compounds for clinical studies, and advance moxifloxacin into phase III trials. New TB drugs must address the challenges of current TB therapy by decreasing the duration and pill burden of first-line TB treatment; have manageable interactions with nevirapine and protease inhibitors; treat multi-drug-resistant (MDR) and extensively drug-resistant (XDR) TB; and treat pediatric TB disease (Syed 2006).

Source: Treatment Action Group, *Tuberculosis Research and Development: A Critical Analysis [2006]*