17TH ANNUAL CONFERENCE OF THE BRITISH HIV ASSOCIATION (BHIVA)

British HIV Association BHIVA

Dr Patrick Phillips

MRC Clinical Trials Unit, London

6-8 April 2011, Bournemouth International Centre

MRC Clinical Trials Unit

Treatment-shortening trials in drug-sensitive TB

Patrick Phillips
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MRC Clinical Trials Unit
6th April 2011

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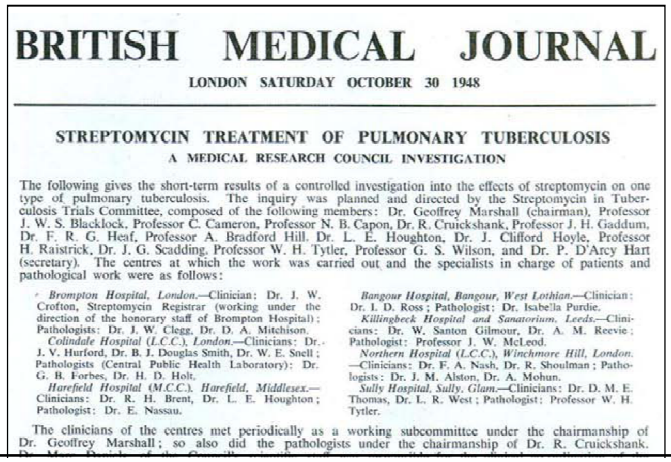
Two major breakthroughs in TB treatment

1. **1948: Streptomycin shown to be the first effective treatment for TB** (MRC, 1948)



BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gaddum, Dr. F. R. G. Heaf, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tytler, Professor G. S. Wilson, and Dr. P. D'Arcy Hart (secretary). The centres at which the work was carried out and the specialists in charge of patients and pathological work were as follows:

Brompton Hospital, London.—Clinician: Dr. J. W. Crofton, Streptomycin Registrar (working under the direction of the honorary staff of Brompton Hospital); Pathologists: Dr. J. W. Clegg, Dr. D. A. Mitchison.

Colindale Hospital (L.C.C.), London.—Clinicians: Dr. J. V. Hurford, Dr. B. J. Douglas Smith, Dr. W. E. Snell; Pathologists (Central Public Health Laboratory): Dr. G. B. Forbes, Dr. H. D. Holt.

Harefield Hospital (M.C.C.), Harefield, Middlesex.—Clinicians: Dr. R. H. Brent, Dr. L. E. Houghton; Pathologist: Dr. E. Nassau.

Bangour Hospital, Bangour, West Lothian.—Clinician: Dr. I. D. Ross; Pathologist: Dr. Isabella Purdie.

Killingbeck Hospital and Sanatorium, Leeds.—Clinicians: Dr. W. Santon Gilmour, Dr. A. M. Reevie; Pathologist: Professor J. W. McLeod.

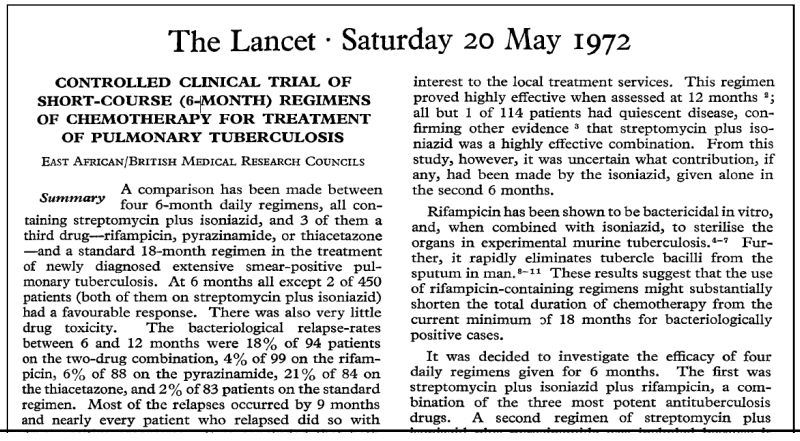
Northern Hospital (L.C.C.), Winchmore Hill, London.—Clinicians: Dr. F. A. Nash, Dr. R. Shoulman; Pathologists: Dr. J. M. Alston, Dr. A. Mohun.

Sully Hospital, Sully, Glam.—Clinicians: Dr. D. M. E. Thomas, Dr. L. R. West; Pathologist: Professor W. H. Tytler.

The clinicians of the centres met periodically as a working subcommittee under the chairmanship of Dr. Geoffrey Marshall; so also did the pathologists under the chairmanship of Dr. R. Cruickshank.

Two major breakthroughs in TB treatment

2. **1972: The addition of rifampicin and pyrazinamide shortens treatment from 18 months to 6 months** (MRC, 1972)



The Lancet · Saturday 20 May 1972

CONTROLLED CLINICAL TRIAL OF SHORT-COURSE (6-MONTH) REGIMENS OF CHEMOTHERAPY FOR TREATMENT OF PULMONARY TUBERCULOSIS

EAST AFRICAN/BRITISH MEDICAL RESEARCH COUNCILS

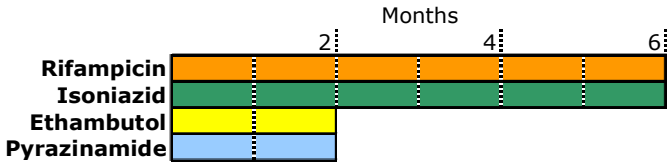
Summary A comparison has been made between four 6-month daily regimens, all containing streptomycin plus isoniazid, and 3 of them a third drug—rifampicin, pyrazinamide, or thiacetazone—and a standard 18-month regimen in the treatment of newly diagnosed extensive smear-positive pulmonary tuberculosis. At 6 months all except 2 of 450 patients (both of them on streptomycin plus isoniazid) had a favourable response. There was also very little drug toxicity. The bacteriological relapse-rates between 6 and 12 months were 18% of 94 patients on the two-drug combination, 4% of 99 on the rifampicin, 6% of 88 on the pyrazinamide, 21% of 84 on the thiacetazone, and 2% of 83 patients on the standard regimen. Most of the relapses occurred by 9 months and nearly every patient who relapsed did so with

interest to the local treatment services. This regimen proved highly effective when assessed at 12 months [2]; all but 1 of 114 patients had quiescent disease, confirming other evidence [3] that streptomycin plus isoniazid was a highly effective combination. From this study, however, it was uncertain what contribution, if any, had been made by the isoniazid, given alone in the second 6 months.

Rifampicin has been shown to be bactericidal in vitro, and, when combined with isoniazid, to sterilise the organs in experimental murine tuberculosis.[4–7] Further, it rapidly eliminates tubercle bacilli from the sputum in man.[8–11] These results suggest that the use of rifampicin-containing regimens might substantially shorten the total duration of chemotherapy from the current minimum of 18 months for bacteriologically positive cases.

It was decided to investigate the efficacy of four daily regimens given for 6 months. The first was streptomycin plus isoniazid plus rifampicin, a combination of the three most potent antituberculosis drugs. A second regimen of streptomycin plus

Standard treatment for previously untreated drug-sensitive TB



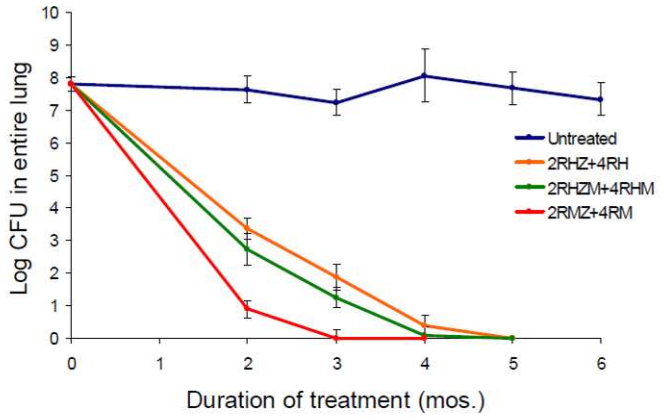
- **6-month regimen** consisting of:
  - **2-month intensive phase** of 4 drugs
  - **4-month continuation phase** of 2 drugs
- Usually given **daily throughout**
- Sometimes **2-weekly** or **3-weekly** in continuation phase.
- In trials, this 6-month regimen has **cure rate of 95%.**

6-months combination regimens are highly effective, however…

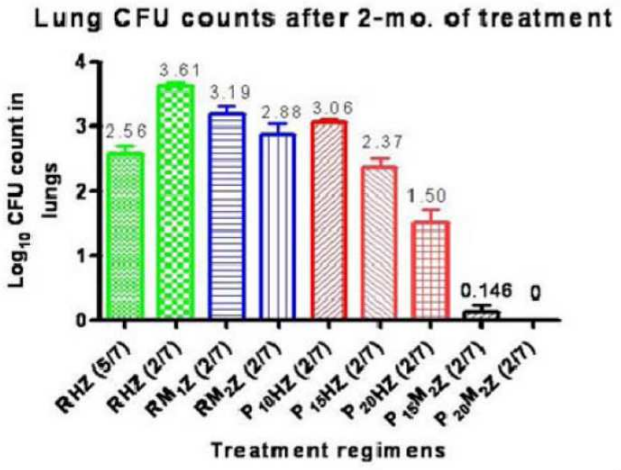
- Even with **Direct Observation of Treatment** (**DOTS**):
  - A recent report from South Africa shows a **national cure rate of only 58%** among nearly 120,000 cases of TB (Karim et al, 2009).
- Known and unknown contraindications with ART drugs
- Increasing levels of drug resistance
- **Can we shorten and simplify treatment by adding a new drug without reducing efficacy?**

Pre-clinical mouse data: Moxifloxacin

Nuermberger et al. (2003)



Pre-clinical mouse data: High-dose rifapentine (P) with moxifloxacin (M)

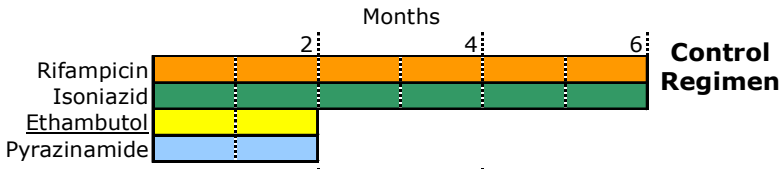


Lounis et al. (2001)

Phase III trials for new TB regimens

- Only 3 multi-centre randomised controlled trials currently ongoing
  - **OFLOTUB** (**Gatifloxacin**)
    - Results due **late 2011**
  - **REMoxTB** (**Moxifloxacin**)
    - Trial conducted by MRC CTU
    - Results due **mid 2013**
  - **RIFAQUIN** (**Moxifloxacin** and **Rifapentine**)
    - Trial conducted by MRC CTU
    - Results due **early 2013**

1. **OLFOTUB**: Gatifloxacin replacing ethambutol



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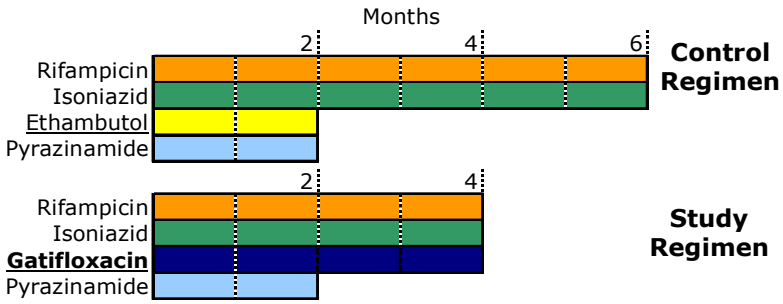


Can the replacement of **ethambutol** with **gatifloxacin** shorten treatment to **4 months**?

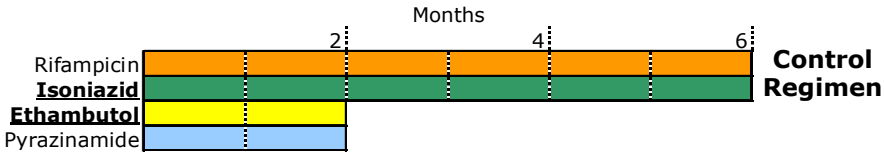
1. **OLFOTUB**: Gatifloxacin replacing ethambutol

- Sites: Sub-Saharan Africa

- Follow-up: **24 months**
- Non-inferiority design
- Recruitment stopped **October 2008**
- Sample size: **1836**

- Results due: **Late 2011**

2. **REMoxTB**: Moxifloxacin either replacing isoniazid or ethambutol



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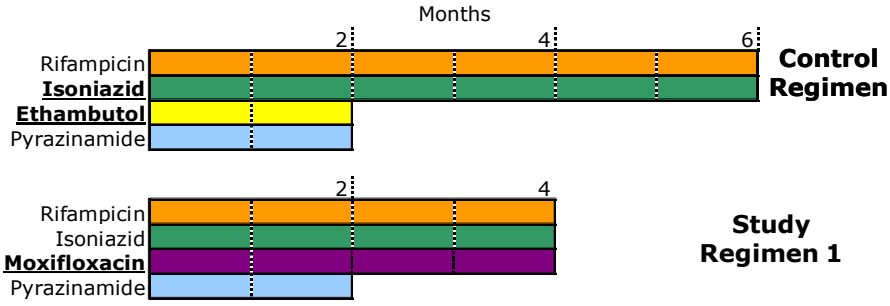

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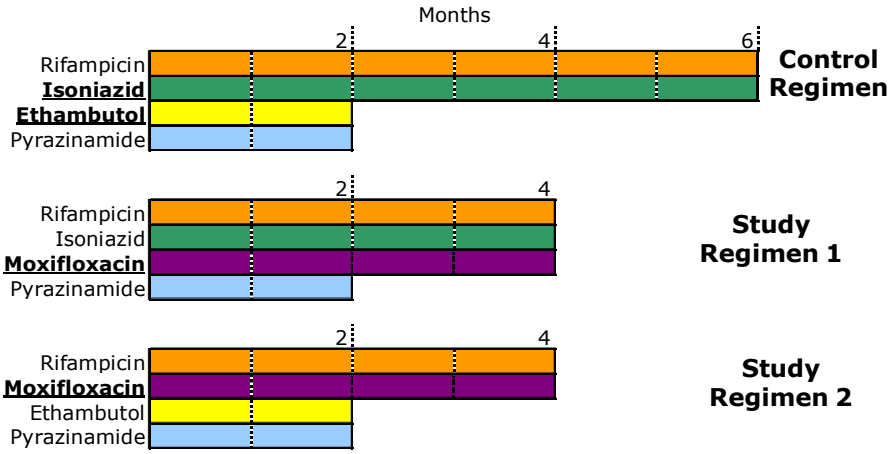


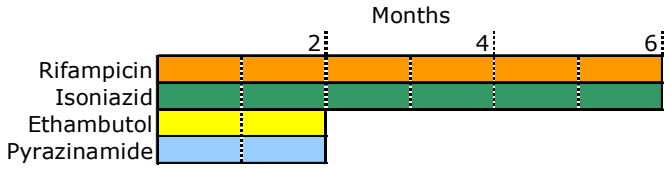
2. **REMoxTB**: Moxifloxacin (M) either replacing isoniazid (H) or ethambutol (E)

1. Can the replacement of **ethambutol** with **moxifloxacin** shorten treatment to 4 months?
2. Can the replacement of **isoniazid** with **moxifloxacin** shorten treatment to 4 months?

- Follow-up: **18 months**
- Sites: Africa, Asia and Central America
- Non-inferiority trial design
- Sample size: **1900**

- Results due: **Mid-2013**

3. **RIFAQUIN**: Intermittent dosing with moxifloxacin and high-dose rifapentine



Control Regimen

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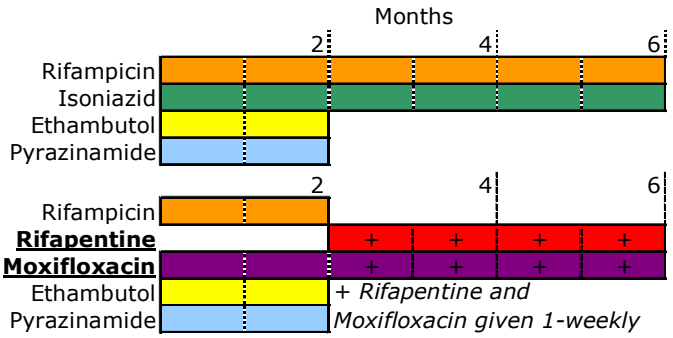

Control Regimen

Study Regimen 1

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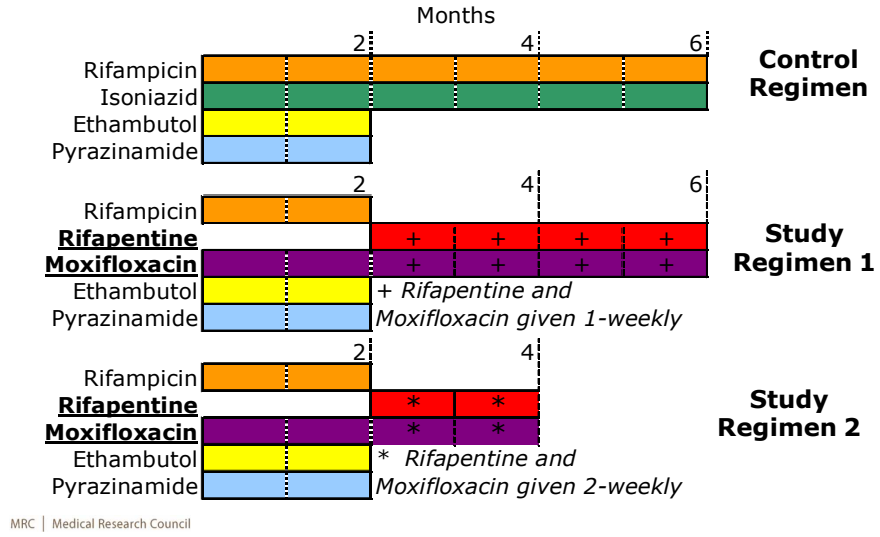

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3. **RIFAQUIN**: Intermittent dosing with moxifloxacin and high-dose rifapentine

1. Can the continuation phase of high dose **rifapentine** with **isoniazid** replaced by **moxifloxacin** by reduced to 1-weekly?
2. Can a 2-weekly continuation phase of high dose **rifapentine** with **isoniazid** replaced by **moxifloxacin** shorten treatment to 4 months?

- Follow-up: 18 months
- Sites: Southern Africa
- Non-inferiority trial design
- Sample size: **1100**
- Results due: **Early 2013**

Future planned phase III trials

- **No planned multi-centre phase III trials for drug-sensitive TB for next few years.**
- Several novel compounds currently in phase II
  - but **all targeted at MDR-TB**.

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