

## Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis

### CITATION

Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. *Lancet* 2004;364:1244-51

### BACKGROUND

The HIV epidemic, presence of rifampicin-resistance and the increased risk of severe side effects from thioacetazone amongst HIV positive individuals, lead to the change in the World Health Organisation (WHO) recommendation for treatment of Tuberculosis (TB).

Treatment for newly diagnosed smear positive TB as recommended by International Union Against Tuberculosis and Lung Disease (IUATLD) and WHO:

Regimen	Intensive phase – 2 month, 4 drugs	Continuation – 4 months, 2 drugs	Continuation – 6 months, 2 drugs
6 month regimen	Isoniazid	Rifampicin Isoniazid	
8 month regimens	Rifampicin Pyrazinamide Ethambutol / streptomycin		Ethambutol Isoniazid
			Thioacetazone Isoniazid

### RESEARCH QUESTION

In patients with newly diagnosed smear positive TB, is the bacteriological results obtained with two 8-month regimens of chemotherapy based on ethambutol and isoniazid equivalent to those of the 6-month regimen based on isoniazid and rifampicin?

### THE STUDY DESIGN

Randomised controlled trial

### STUDY SETTING

International, multicentre, centres with access to a reliable bacteriology laboratory for smear and culture examinations.

Enrolled between March 1998 and December 2003.

Ethics approval obtained

### PARTICIPANTS

Included: age 15-65 years, two sputum samples positive for tubercle bacilli on direct microscopy, less than one month previous anti-TB chemotherapy, firm home address readily accessible for visiting in case of failure to attend. Gave informed consent for study and HIV testing.

Excluded: so ill that they were thought unlikely to survive initial weeks of treatment, extra-pulmonary TB, other disease likely to prejudice response to or assessment of treatment (eg. diabetes, liver disease, nephritis, blood disorders, epilepsy, peripheral neuritis), pregnancy, psychiatric illness or alcoholism.

## INTERVENTIONS

Regimen	Intensive phase – 2 month, 4 drugs	Continuation – 4 months, 2 drugs	Continuation – 6 months, 2 drugs
2EHRZ/6HE	Daily – ethambutol, isoniazid, rifampicin and pyrazinamide		Daily - ethambutol & isoniazid
2[EHRZ] <sub>3</sub> /6HE	3 times weekly – ethambutol, isoniazid, rifampicin and pyrazinamide		
2EHRZ/4HR control	Daily – ethambutol, isoniazid, rifampicin and pyrazinamide	Daily – rifampicin & Isoniazid	

## OUTCOMES

Primary: proportion of patients with negative cultures at 2 months  
proportion with negative cultures 12 months after completion of chemotherapy

Secondary: proportion of failures at end of chemotherapy  
proportion of patients with adverse events necessitating withdrawal of their chemotherapy for 7 days or longer.  
time to unfavourable outcome by regimen

Outcome of treatment:

- Favourable – sputum culture negative provided no earlier unfavourable response
- Doubtful - < 20 colonies present of culture
- Unfavourable – failure or relapse
  - Failure – culture  $\geq 20$  colonies at month 6 or 8 or change in treatment
  - Relapse – culture  $\geq 20$  colonies at any point after end of treatment or in absence of culture confirmation the initiation of treatment for relapse.
  - Not classified as failure or relapse if culture of 20-100 colonies was followed by negative cultures and patient had not been re-treated.

**RISK OF BIAS** (Risk Scale: Low – Moderate – High)

### SELECTION BIAS: low

Allocation sequence was generated by central computer. Participating centres were supplied with a batch of sealed and serially numbered opaque envelopes, each containing the treatment card of the allocated regimen. Names of eligible patients were entered sequentially into a register to determine study number allocated and the allocated envelope to be opened. Baseline characteristics were similar.

### PERFORMANCE BIAS: low-moderate

(ie: *What else happened that may have affected the result?*)

No blinding of the patients, researchers or health care staff. Patients were admitted to hospital or attended a treatment facility for directly observed treatment for the first 2 months. Thereafter, received one month's supply to be taken under supervision of a treatment monitor.

### DETECTION BIAS: moderate

No blinding. Two sputum samples collected for smear and culture examination before treatment, at 2 month and at end of treatment. Two sputum samples for culture were collected at 3, 6 and 12 months after the scheduled end of treatment and at 24 and 30 months after start of chemotherapy. Validity and reliability of laboratory tests were not discussed.

## ATTRITION BIAS: low-moderate

	2EHRZ/6HE	2[EHRZ] <sub>3</sub> /6HE	2EHRZ/4HR (control)
Started	456	466	433
Loss to follow-up	54 (11.8%)	56 (12.0%)	50 (11.5%)
Primary analysis	402	410	383
Follow-up analysis	346	351	347

Lost to follow-up due to deaths, no results and not seen. In general loss to follow-up rates were similar for the 3 groups.

“Analysis based on intention to treat including all assessable randomised patients”

## STUDY FINDINGS

1355 randomised: Conakry 100, Cotonou 350, Henan 197, Kathmandu 285, Maputo 200, Moshi 56, Nepalgunj 99, Tianjin 68

Outcome	Event rate			RRR (95% CI)	ARR (95% CI)	NNT (95% CI)
	2EHRZ/6HE	2[EHRZ] <sub>3</sub> /6HE	2EHRZ/4HR (control)			
Negative culture at 2 months*	365/424 86.1%	333/433 76.9%	335/404 82.9%	4% (-2 to 10%)	0.032 (-0.017 to 0.081)	31 (NNT to NNH)
				7% (1 to 14%)	0.060 (0.006 to 0.114)	17 (1 to 169)
Negative cultures 12 months after completion of chemotherapy	290/346 83.8%	292/351 83.2%	316/347 91.1%	8% (3 to 13%)	0.073 (0.024 to 0.122)	14 (8 to 42)
				9% (3 to 14%)	0.079 (0.030 to 0.128)	13 (8 to 34)
Failures at end of chemotherapy	19/402 4.7%	22/410 5.4%	12/383 3.1%	52% (-36 to 100%)	0.016 (-0.011 to 0.043)	63 (NNT to NNH)
				74% (-16 to 100%)	0.023 (-0.005 to 0.051)	43 (NNT to NNH)

\* was limited to participants for whom sputum samples were collected within 2 weeks of due date – 93% each group

### Formulae:

RRR (relative risk reduction) =  $|EER - CER| / CER$

ARR (absolute risk reduction) =  $|EER - CER|$

NNT (number needed to treat) =  $1 / ARR$

## ADVERSE EVENTS

Few side effects led to an interruption of treatment.

## COMMENTS

Negative culture rates at 2 months were similar for 2EHRZ/6HE and the control. However, based on negative cultures 12 months after completion of chemotherapy both 8-month regimens were inferior to the 6-month regimen.

Prepared by: Taryn Young

E-mail: [taryn.young@mrc.ac.za](mailto:taryn.young@mrc.ac.za)

Date: 6 December 2004