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

CITATION

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:

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Intensive phase – 2 month, 4 drugs</th>
<th>Continuation – 4 months, 2 drugs</th>
<th>Continuation – 6 months, 2 drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 month regimen</td>
<td>Isoniazid</td>
<td>Rifampicin</td>
<td></td>
</tr>
<tr>
<td>8 month regimens</td>
<td>Rifampicin Pyrazinamide Ethambutol / streptomycin</td>
<td>Ethambutol Isoniazid</td>
<td>Thioacetazone Isoniazid</td>
</tr>
</tbody>
</table>

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.
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, extrapulmonary 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

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Intensive phase – 2 month, 4 drugs</th>
<th>Continuation – 4 months, 2 drugs</th>
<th>Continuation – 6 months, 2 drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2EHRZ/6HE</td>
<td>2 times daily – ethambutol, isoniazid, rifampicin and pyrazinamide</td>
<td>Daily - ethambutol, isoniazid, rifampicin and pyrazinamide</td>
<td>Daily - ethambutol &amp; isoniazid</td>
</tr>
<tr>
<td></td>
<td>2(EHRZ)3/6HE 3 times weekly – ethambutol, isoniazid, rifampicin and pyrazinamide</td>
<td>2EHRZ/4HR Daily – ethambutol, isoniazid, rifampicin and pyrazinamide</td>
<td>Daily – rifampicin &amp; isoniazid</td>
</tr>
</tbody>
</table>

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
  o Failure – culture >=20 colonies at month 6 or 8 or change in treatment
  o Relapse – culture >=20 colonies at any point after end of treatment or in absence of
culture confirmation the initiation of treatment for relapse.
  o 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 sequentially entered 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

<table>
<thead>
<tr>
<th></th>
<th>2EHRZ/6HE</th>
<th>2[EHRZ]$_3$/6HE</th>
<th>2EHRZ/4HR (control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Started</td>
<td>456</td>
<td>466</td>
<td>433</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>54 (11.8%)</td>
<td>56 (12.0%)</td>
<td>50 (11.5%)</td>
</tr>
<tr>
<td>Primary analysis</td>
<td>402</td>
<td>410</td>
<td>383</td>
</tr>
<tr>
<td>Follow-up analysis</td>
<td>346</td>
<td>351</td>
<td>347</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Event rate</th>
<th>2EHRZ/6HE</th>
<th>2[EHRZ]$_3$/6HE</th>
<th>2EHRZ/4HR (control)</th>
<th>RRR (95% CI)</th>
<th>ARR (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative culture at 2 months*</td>
<td></td>
<td>365/424</td>
<td>333/433</td>
<td>335/404</td>
<td>4% (-2 to 10%)</td>
<td>0.032</td>
<td>31 (NNT to NNH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>86.1%</td>
<td>76.9%</td>
<td>82.9%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative cultures 12 months after completion of chemotherapy</td>
<td></td>
<td>290/346</td>
<td>292/351</td>
<td>316/347</td>
<td>8% (3 to 13%)</td>
<td>0.073</td>
<td>14 (8 to 42)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>83.8%</td>
<td>83.2%</td>
<td>91.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failures at end of chemotherapy</td>
<td></td>
<td>19/402</td>
<td>22/410</td>
<td>12/383</td>
<td>52% (-36 to 100%)</td>
<td>0.016</td>
<td>63 (NNT to NNH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.7%</td>
<td>5.4%</td>
<td>3.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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.

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