Témoignage
HIV associated tuberculosis: role of host directed therapies to reduce early mortality and TB-IRIS

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Rockville, MD
Host-directed therapies appear predicated on two hypotheses. TB arises because of:

1. An immune defect and thus immunostimulation is required to augment drug therapy

2. A dysregulated or even hyperinflammatory immune response, which via the induction of immune pathology
   a) antagonizes antimicrobial therapy and
   b) Causes tissue damage and morbidity

Therefore transient immunosuppression or anti-inflammatory treatment will be beneficial.
The most effective small molecule host directed therapies against tuberculosis are antiretroviral therapy and corticosteroids

Combined antiretroviral therapy

1. Reduces mortality in profoundly immunosuppressed HIV-TB patients
2. Reduces the risk of developing active TB in HIV-1 infected persons

Adjunctive corticosteroid therapy of active tuberculosis

3. Reduces short-term mortality in adults with TB meningitis
4. Reduces the death rate from TB pericarditis

Acknowledgements

Graeme Meintjes
Molebogeng Rangaka
Adrian Martineau
Anna Coussens
## Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomized double-blind placebo-controlled trial

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>667 Placebo</th>
<th>662 INH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR)</td>
<td>34 (29-40)</td>
<td>34 (30-40)</td>
</tr>
<tr>
<td>Female</td>
<td>75%</td>
<td>76%</td>
</tr>
<tr>
<td>Established on ART</td>
<td>74%</td>
<td>70%</td>
</tr>
<tr>
<td>Median days on ART (IQR)</td>
<td>189 (28-557)</td>
<td>169 (28-631)</td>
</tr>
<tr>
<td>Median CD4+ count (IQR)</td>
<td>214 (155-355) N=605</td>
<td>218 (150-373) N=587</td>
</tr>
<tr>
<td>Prior TB</td>
<td>41% N=657</td>
<td>44% N=652</td>
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</tbody>
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Rangaka M.X. *et al.* Lancet in press
Tuberculosis rate by treatment allocation

Time to TB from study entry

Placebo (n=58): 3.6 per 100 PY
(95% CI 2.8-4.7)

INH (n=37): 2.3 per 100 PY
(95% CI 1.6-3.1)

HR unadjusted = 0.63
(95% CI 0.41-0.94)

Log rank P = 0.02

Both groups on study drug for a median 12 months & both followed for a median 2.5 years

Rangaka M.X. et al. Lancet in press
Isoniazid benefit greatest in TST negative

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Isoniazid</th>
<th>HRa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Rate/100 PY</td>
<td>n</td>
</tr>
<tr>
<td>100 PY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IGRA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>261</td>
<td>3.3</td>
<td>274</td>
</tr>
<tr>
<td>Positive</td>
<td>205</td>
<td>3.9</td>
<td>184</td>
</tr>
<tr>
<td><strong>TST</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>283</td>
<td>4.1</td>
<td>269</td>
</tr>
<tr>
<td>Positive</td>
<td>202</td>
<td>2.8</td>
<td>190</td>
</tr>
</tbody>
</table>

Rangaka M.X. *et al.* *Lancet* in press
Prospective observational cohort study
660 adult HIV-infected inpatients with CD4 < 350 diagnosed with TB during admission
Baseline blood, urine and sputum investigations

Patients followed for 12 weeks

15% die

85% survive

Primary analyses

5% lost to follow-up

Investigating the pathophysiology and contribution of co-infections in fatal HIV-associated tuberculosis

Graeme Meintjes
Research questions

1. Is fatal HIV-TB associated with a sepsis syndrome caused by MTB itself resulting in major organ dysfunction and septic shock?

2. Is fatal HIV-TB associated with translocation of gram-negative bacteria and their products from the gastrointestinal tract into blood?

3. Is fatal HIV-TB associated with cytomegalovirus (CMV) viremia?

4. Is fatal HIV-TB associated with immune activation-induced apoptosis and anti-inflammatory signaling?

5. Are Rifampin, INH and PZA drug concentrations lower in hospitalized HIV-TB patients?

Graeme Meintjes
Patient diagnosed with TB and started on TB treatment

Improving on TB treatment then starts ART

Recurrence of TB symptoms and new or recurrent clinical manifestations of TB (Usually 1-4 weeks after starting ART)

Up to 40% of patients starting ART in sub-Saharan Africa are on TB treatment

Major risk factors:
- Low CD4 count
- Disseminated TB
- Short interval between TB treatment and ART

Randomized controlled trial of prednisone vs placebo

- 110 participants
- Life-threatening TB-IRIS was an exclusion
- Prednisone (or placebo) dose
  - 1.5 mg/kg/d for 2 weeks then
  - 0.75 mg/kg/d for 2 weeks
- Open-label prednisone at physician discretion if clinical deterioration/relapse

## Primary endpoint

### Cumulative number of days hospitalized and outpatient therapeutic procedures (counted as 1 additional day), ITT analysis

<table>
<thead>
<tr>
<th></th>
<th>Placebo arm N = 55</th>
<th>Prednisone arm N = 55</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total days hospitalized</td>
<td>463</td>
<td>282</td>
<td>-</td>
</tr>
<tr>
<td>Total number outpatient procedures</td>
<td>28</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td><strong>Cumulative primary endpoint (median, IQR)</strong></td>
<td>3 (0-9)</td>
<td>0 (0-3)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Preventing TB-IRIS in high-risk patients: Randomized placebo-controlled trial of prednisone (PredART trial)

Early ART (~2 weeks) reduces mortality and progression to AIDS in patients with TB and low CD4 counts, but increases the risk of paradoxical TB-IRIS.

Paradoxical TB-IRIS causes morbidity, many patients require hospitalization and it consumes health care resources.

An evidenced-based prevention strategy is required.

PredART is a randomized placebo-controlled double-blind trial to determine if addition of prednisone to the first 4 weeks of ART reduces the incidence of paradoxical TB-IRIS in HIV+ patients being treated for TB who are at high risk for TB-IRIS (CD4 <100 and starting ART within 30 days of TB treatment).

Graeme Meintjes
HIV-infected ART naive CD4 < 100 TB diagnosed n = 240

Informed consent
Randomised 1:1

Start ART + 4 weeks prednisone
Follow-up for 12 weeks (Visits at weeks 1,2,4,8 and 12)

Start ART + 4 weeks placebo
Follow-up for 12 weeks (Visits at weeks 1,2,4,8 and 12)

TB TREATMENT (and CO-TRIMOXAZOLE)

ART started within 30 days of TB treatment

Dose of prednisone/placebo: 40mg/day x 2 weeks then 20mg/day x 2 weeks
Integrated within clinic care pathway at Ubuntu HIV-TB clinic
Planned interim reviews by Data & Safety Monitoring Board
Vitamin D and tuberculosis

Per protocol analysis

Martineau et al. AJRCCM 2007; 176: 208-13
Martineau et al. Lancet 2011; 377:242-50

2.5mg cholecalciferol
Vitamin D and tuberculosis

Contribution to roadmap

• Great deal of encouragement from *in vitro* ‘pipeline’ but how to
  a. Select *in vitro* to experimental *in vivo*, and into which models?
  b. Pre-clinical to phase 1?
  c. Phase IIA/IIB

• Likely efficacy. Why prioritize in humans over vaccines and antimicrobials?

• Drug sensitive tuberculosis, in the context of a reasonable trial, gets better
  a. To demonstrate treatment shortening therefore a mighty task
  b. Exploit specific clinical circumstances
     multi-drug resistant disease?
     TB-IRIS?

• Endpoint selection remains a problem: encouragement from combined PET/CT and transcriptomic profiling

• Few facilities to test: maintaining them for IMP studies is expensive
Thank you!