Ongoing trials on empiric TB treatment for PLHIV: prospects and challenges for policy recommendation

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WHO/HQ
Definition of empiric treatment

- No official definition but two possible versions:
  - TB treatment based on clinical suspicion or perceived high risk of TB without bacteriological confirmation (but after TB investigations)
  - TB treatment initiation in peripheral facilities exclusively based on clinical suspicion (before TB investigations) for seriously sick patients (current WHO guidelines definition).

- Also known as presumptive treatment
Current WHO recommendations on empiric TB treatment for PLHIV in resource limited settings

• In peripheral health facilities in HIV-prevalent settings, clinicians should initiate empiric anti-TB treatment early in patients with serious illness thought to be due to extrapulmonary tuberculosis.

• Every effort should then be made to confirm the diagnosis of tuberculosis afterwards.

• Empiric treatment should be stopped only if there is bacteriological, histological or strong clinical evidence of an alternative diagnosis.
Autopsy studies among PLHIV showing percentage of TB diagnosis

- Cox, 2012* (Uganda) 50%
- Wong, 2012* (S Africa) 69%
- Some, 2013* (Kenya) 52%
- Kilale, 2013 (Tanzania) 55%

* Among PLHIV receiving ART

What is the safety, tolerability, efficacy and impact of empiric TB treatment on TB mortality in people with advanced HIV infection, either before or soon after initiation of antiretroviral therapy?
The key policy and program questions

- Is empiric TB treatment beneficial to prevent mortality in PLHIV with advanced disease?
- What are the clinical predictors to select PLHIV for empiric treatment?
- Can it be given by clinical officers/nurses?
Prospective cohort study among 800 PLHIV in Brazil
Median follow up – 2.8 years
(Albuquerque et al, BMC Public Health, 2014)

Inclusion criteria: (1) age ≥18 yrs (2)cough of any duration (3) AFB or culture negative or not done
Empiric TB treatment was given to 171 PLHIV (21.4%)
The trials

- **Prevention of early Mortality by Presumptive Tuberculosis (PROMPT)**

- **Reducing Early Mortality and Early Morbidity by Empiric Tuberculosis Treatment Regimens (REMEMBER)**

- **Systematic empirical vs. Test-guided Anti-tuberculosis Treatment Impact in Severely immunosuppressed HIV-infected adults (STATIS)**

- **TB Fast track cluster randomize trial**
# The clinical trials

<table>
<thead>
<tr>
<th>Study sites</th>
<th>PROMPT</th>
<th>REMEMBER</th>
<th>STATIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gabon, Mozambique, Uganda,</td>
<td>Brazil, Haiti, India, Kenya, Malawi, Peru,</td>
<td>Cambodia, Cote d’Ivore, Uganda, Viet Nam</td>
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<tr>
<td></td>
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<td>SA, Tanzania, Zimbabwe</td>
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<tr>
<td>CD4 count</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Age (years)</td>
<td>18-60</td>
<td>≥ 13</td>
<td>≥18</td>
</tr>
<tr>
<td>Arm 1</td>
<td>TB treatment followed by ART</td>
<td>ART and TB treatment</td>
<td>TB treatment followed by ART</td>
</tr>
<tr>
<td>Arm 2</td>
<td>ART only</td>
<td>ART only</td>
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</tr>
<tr>
<td>Primary endpoint</td>
<td>All cause mortality at 24 week</td>
<td>Mortality at 24 weeks</td>
<td>Mortality and occurrence of invasive bacterial infections at 24 weeks</td>
</tr>
</tbody>
</table>

**CD4 count**:  
- **<50** for PROMPT
- **<50** for REMEMBER
- **<100** for STATIS

**Age (years)**:  
- **18-60** for PROMPT
- **≥13** for REMEMBER
- **≥18** for STATIS

**Arm 1**:  
- TB treatment followed by ART
  - PROMPT
  - REMEMBER
  - STATIS

**Arm 2**:  
- ART only
  - PROMPT
  - REMEMBER
  - STATIS

**Primary endpoint**:  
- All cause mortality at 24 week
  - PROMPT
- Mortality at 24 weeks
  - REMEMBER
- Mortality and occurrence of invasive bacterial infections at 24 weeks
  - STATIS
The clinical trials

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<td><strong>Secondary outcomes</strong></td>
<td><strong>CD4 cell, causes and time to death, viral suppression, safety and tolerability, treatment adherence, drug resistance, cost-effectiveness, quality of life</strong></td>
<td><strong>CD4 cells, TB incidence, safety and tolerability, viral suppression, IRIS, cost-effectiveness, drug resistance</strong></td>
</tr>
<tr>
<td><strong>Suspected TB</strong></td>
<td><strong>Included but smear positive and negative cases excluded</strong></td>
<td><strong>Excluded</strong></td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>44 (terminated)/340</td>
<td>851</td>
</tr>
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</table>
Screened: n=163

Eligible: n=44

Consent withdrawal: n=1

Enrolled: n=43

ART only treatment: n=20
  Died: n=2

ART+TB treatment: n=23
  Died: n=4

Challenges:
- Insufficient recruitment
- Clinicians are eager to treat than randomize
- Disruption by Xpert MTB/RIF introduction
- 329 adverse events

PROMPT Trial
PROMPT trial: causes of Death

**Arm 1**: ART only
- Subject 1. Chronic Diarrhea
- Subject 2. Viral Meningoencephalitis

**Arm 2**: ART + TB treatment
- Subject 1. Acute Gastroenteritis
- Subject 2. Anaemia, Hypokalemia, Hyponatremia
- Subject 3. Study drug Induced Hepatotoxicity
- Subject 4. Renal Failure
Impact of three empirical anti-tuberculosis treatment strategies for people initiating antiretroviral therapy

A. Van Rie,* D. Westreich,* I. Sanne‡‡

(Pragmatic: putting all PLHIV with < 100 CD4 on empiric TB treatment)

6-25% deaths and 11-57% incident TB averted
Numbers receiving TB treatment will increase (Van Rie et al, 2014)

SOC = standard of care (observed)

SOC = standard of care (observed)

NNT to avert 1 death
Pragmatic – 21
REMEMBER – 19
PROMPT – 13

NNT to prevent 1 TB case
Pragmatic - 8
REMEMBER - 7
PROMPT - 6
TB Fast Track cluster randomised trial in South Africa

- HIV+, CD4<150
- TB symptom screen; urine LAM; BMI; Hb

High probability TB
LAM +, Hb<10; BMI<18.5 [or smear /Xpert pos]

Start TB treatment, then ART

Medium probability TB
symptomatic; LAM negative; Hb>10, BMI>18.5

CXR, antibiotics, sputum culture & review within 1w

Follow up at 6m for vital status

Low probability TB
no TB symptoms, LAM negative; Hb>10; BMI>18.5

Start ART

- Nurse-based
- Pragmatic
- Routine care
- 24 clusters
Summary

• Key policy and programme questions on empiric TB treatment as an intervention are being answered

• However, gap still remains in generating evidence for the current WHO recommendation:

  “In peripheral health facilities in HIV-prevalent settings, clinicians should initiate empiric anti-TB treatment early in patients with serious illness thought to be due to extrapulmonary tuberculosis”

  (Recommendation based on expert opinion)
Acknowledgement

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