Knowledge gaps in HIV-TBM

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HIV = predictor of mortality in TBM: HR 2.53; 95% CI: 1.90-3.36

On ART at enrollment: 34%
Mortality on ART: 36% (n=43)  
Mortality off ART: 41% (n=93)  
p=0.42

Heemskerk D. NEJM 2016
Contributing factors to poor outcome

- Spinal complications/presentation

- Immune reconstitution inflammatory syndrome/paradoxical reaction
  - pathogenesis
  - prevention
  - management

- Hydrocephalus
Spinal involvement in HIV-associated neurological TB

• Anderson et al:
Clinical radiculomyelitis in 3% of 104 TBM patients (HIV-infected: n=1)

• Gupta et al:
Clinical radiculomyelitis in 46% of 71 TBM patients (HIV-infected: n=2)

• Candy et al:
TBM in 16% of 55 HIV-infected patients with radiculomyelitis
Retrospective review of spinal TB at IALCH

363 patients (12 yrs)

Dual infection/treatment: 44
Insufficient information: 78

Included: n=241
Definite: 48
Probable: 193
- Clinical/radiological improvement: 134
- TBM/bony TB alive at 9 months: 34
- TB elsewhere + exclusion other causes: 25

Marais S. Unpublished
## Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median/n</th>
<th>IQR/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32</td>
<td>(27-41)</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>141</td>
<td>(59)</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>31</td>
<td>(14-87)</td>
</tr>
<tr>
<td>Paraplegia</td>
<td>113</td>
<td>(47)</td>
</tr>
<tr>
<td><strong>Unable to walk</strong></td>
<td>196</td>
<td>(81)</td>
</tr>
<tr>
<td>Spine and brain involvement</td>
<td>162</td>
<td>(52)</td>
</tr>
<tr>
<td><strong>HIV infected</strong></td>
<td>192</td>
<td>(83)</td>
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<tr>
<td>- CD4 count cells/mm³</td>
<td>169</td>
<td>(100-284)</td>
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<tr>
<td>- On ART</td>
<td>102</td>
<td>(53)</td>
</tr>
<tr>
<td>Spinal symptoms on TB treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- HIV-uninfected</td>
<td>6</td>
<td>(16)</td>
</tr>
<tr>
<td>- HIV-infected</td>
<td>65</td>
<td>(34)</td>
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</tbody>
</table>
Outcome

- HIV-ass spinal TB = significant burden on health services in high TB/HIV settings
- Often occurs after initial improvement on TB treatment for TB elsewhere
- Associated with significant morbidity and poor outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median/n</th>
<th>IQR/%</th>
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</thead>
<tbody>
<tr>
<td>Duration of hospital stay (days)</td>
<td>10</td>
<td>(6-16)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>3</td>
<td>(0.01)</td>
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<tr>
<td>Follow-up at hospital</td>
<td>120</td>
<td>(50)</td>
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<tr>
<td>Duration of follow-up (months)</td>
<td>12</td>
<td>(3-25)</td>
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<tr>
<td>Followed-up for 9 months</td>
<td>71</td>
<td>(29)</td>
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<tr>
<td>Regained ability to walk</td>
<td>48</td>
<td>(46)</td>
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Paradoxical neurological TB-IRIS/paradoxical reactions

• **Paradoxical TB reactions more common in HIV:**
  - All TB: aOR = 5.05; 95% CI 1.28-19.85, p = 0.028
  - TBM: HIV+ 11/44 (25%), HIV-: 2/97 (2%) p=0.01

• **Paradoxical TB-IRIS common in high TB/HIV settings:**
  - 12% (23/190) TB-IRIS patients
  - 21% (16/75) of patients with CNS deterioration within 1 yr of starting ART
  - 47% (16/34) of TBM patients who initiated ART 2 weeks after TB treatment

• Mortality is high: 13-30%

Radiological features of neurologic TB-IRIS

Meningitis and/or tuberculoma

Focal pachymeningitis
Lumbar puncture and phlebotomy performed

TBM presentation

- Start TB treatment and prednisone (1.5 mg/kg/day)

2 weeks after TB treatment initiation

- Start antiretroviral therapy (ART)

2 weeks after ART initiation

- TBM-IRIS diagnosis
  - Prednisone reduced
  - Prednisone increased/restarted

2 weeks after TBM-IRIS diagnosis

Marais S. Clin Infect Dis 2013
CSF *M. tuberculosis* culture positivity

<table>
<thead>
<tr>
<th>Patients</th>
<th>TBM diagnosis</th>
<th>ART start</th>
<th>2 weeks post ART start</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
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**IRIS 15/16**
16 days (IQR 15-20)

**Non IRIS 6/18**
(range 4-32 days)

Relative risk of IRIS if culture positive = 9.3, 95% CI 1.4-62.2
P=0.004
CSF Neutrophil count

<table>
<thead>
<tr>
<th>TBM diagnosis</th>
<th>ART Start Day 14</th>
<th>2 weeks post ART/IRIS Day 28</th>
<th>Duration on TB treatment - days</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRIS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Non IRIS</td>
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</table>

- P=0.01
- P<0.0001
- P=0.0007
- P=0.001
- P=0.04
- P=0.01
- P=0.0001
CSF IFN-γ and TNF-α

AUC 0.91 (95% CI 0.53-0.99) p=0.02
IRIS (n=16)
Non-IRIS (n=18)
IRIS vs Culture positive Non-IRIS

Neutrophils

- Day 0 TBM Diagnosis
- Day 14 2 wks post ART

- p=0.02
- p=0.003

S100A8/A9

- Day 0 TBM Diagnosis
- Day 14 2 wks post ART

- N/S
- p=0.001
Blood transcriptomic profile in TBM-IRIS

Transcripts upregulated in TBM-IRIS

<table>
<thead>
<tr>
<th>Neutrophil-mediated immune responses</th>
<th>TBM diagnosis</th>
<th>ART initiation (2 wks after TBM diagnosis)</th>
<th>IRIS presentation (4 wks after TBM diagnosis)</th>
</tr>
</thead>
</table>

Inflammasome activation

mRNA abundance of inflammasome-related genes validated by qPCR

![Graph showing mRNA abundance](image)

21 Transcripts associated with inflammasome

![Graph showing temporal molecular distance](image)

Marais S & Lai R. J Infect Dis 2017
Conclusion

- High baseline bacillary load
- Corticosteroids was insufficient to prevent production of inflammatory mediators
- Neutrophil-dependent inflammatory responses present prior to TB treatment therapy - ? genetic predisposition (LTA4H, IL-18, TNF-α)
- Inflammasome activation during prior to ART and at time of IRIS

Narendran G. PLoS ONE 2016; Affandi JS. Dis Markers 2013
Reducing bacillary load faster with more effective regimen

• HIV patients often have malabsorption
• Low rifampicin exposure common in HIV
• Increased oral rifampicin (15 vs 10 mg/kg/day)= no survival benefit
• ? Much higher rifampicin doses ? Intravenously
• Derive and test novel combination antibiotic regimes bespoke for TBM and which can be combined with ART

Corticosteroids: ?Benefit ?Harm

Thwaites et al.
Less severe A/E's

Mayosi et al.
Increased incidence of HIV-related cancers: 0.73 vs. 0.08 p 100 py

Benefit of corticosteroids dependent on degree of immunosuppression

- Association of LTA4H genotype and outcome in HIV-uninfected TBM patients in Vietnam, but not Indonesia

Thuong NTT. J Infect Dis 2017; van Laarhoven A. J Infect Dis 2017
Survival in TBM stratified according to LTA4H genotype

- **HIV-uninfected**
- **All HIV-infected**
- **HIV-infected CD4 ≥ 150**
- **HIV-infected CD4 < 150**

Thuong NTT. J Infect Dis 2017
Prednisone effective for prevention of TB-IRIS in mild/moderate TB

Prednisone 40 mg/day for 2 weeks then 20 mg/day for 2 weeks or placebo

Relative risk = 0.70 (95%CI = 0.51 - 0.96)

Management of neurological TB-IRIS

• ? Higher doses corticosteroids
• ? Alternative agents case reports of benefit in TB-IRIS
  - Thalidomide (Anti-TNF)
  - Montelukast (Leucotriene receptor antagonist)
• ? Alternative agents approved for other indications
  - Tasquinimod (S100A9 inhibitors)
? Investigation of experimental agents
  - MCC950 (inhibits NLRP3 inflammasome activation)

Ventriculo-peritoneal shunting for hydrocephalus in TBM

“Good outcome” (GOS 4-5)
GOS 4: Moderate disability
GOS 5: Good recovery

Modified Vellore grading
1: GCS 15 - deficit
2: GCS 15 + deficit
3: GCS 9-14 ± deficit
4: GCS 3-8 ± deficit

GOS 4:
Moderate disability

GOS 5:
Good recovery

Rizvi I. J Neurol Sci 2017
### Ventrículo-peritoneal shunting for hydrocephalus in TBM according to HIV status

<table>
<thead>
<tr>
<th></th>
<th>Nadvi (South Africa)</th>
<th>Sharma (India)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients/group (n)</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Age HIV+/HIV- (years, mean±SD)</td>
<td>26±16/10±9</td>
<td>31±7/31±9</td>
</tr>
<tr>
<td>CD4: HIV (cells/mm³)</td>
<td>183±161 (mean±SD)</td>
<td>143 (26-445) (median, range)</td>
</tr>
<tr>
<td>ART prescription</td>
<td>No</td>
<td>??</td>
</tr>
<tr>
<td>Mortality HIV+/HIV- (%)</td>
<td>67/27 (p&lt;0.067) 1 month</td>
<td>67/31 Follow-up (p=0.03)</td>
</tr>
<tr>
<td>Good outcome (GOS 4 or 5) HIV+/HIV- (%)</td>
<td>27/60</td>
<td>24/65</td>
</tr>
</tbody>
</table>

Research priorities in HIV-associated TBM

• Spinal complications of TB
• Pathogenesis of neurological TB-IRIS/paradoxical reactions
  - genetics
  - neutrophils
  - Inflammasome
• Prevention/management neurological TB-IRIS/paradoxical reactions
• Management of hydrocephalus
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