The promise of TB-LAM tests
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Head of TB program

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Lipoarabinomannan (LAM)
- 17kDa glycolipid
- 60% of bacterial cell wall
- Detectable in sputum, urine and blood
- Probably adhere to plasma proteins and partly metabolized

Bułterys et al, 2019
State of the art urine LAM immunoassays

- **Commercial assays (IVD)**
  - Alere Determine TB LAM Ag
  - Fujifilm Silvamp TB LAM (2020)

- **MSD LAM Reference Platform (RUO)**
  - Lab-based quantitative test by FIND and MSD on U-plex
  - Transferred to PATH as centralized “hub for LAM research”
LAM is present in most (all) TB patients, regardless of HIV status.
Diagnostic performance of AlereLAM in HIV+

Symptomatic HIV+ patients
• Pooled sens. 42%, spec. 91%
• ↑ ~10% in-patients
• ↓ ~10% out-patients

Inverse correlation btw. CD4 cell count and LAM sensitivity

- SA township hospital, acute medical admissions, HIV+ (n=427)
- In the first 24h sputum available from 37%, urine from 99%
Comparative performance of FujiLAM and AlereLAM in HIV+ (meta analysis of 1595 patient samples from 5 cohorts SSA & Vietnam)

Stratified by CD4 cell count

<table>
<thead>
<tr>
<th>CD4 group</th>
<th>N</th>
<th>Sn [95% CI]</th>
<th>Sp [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>FujiLAM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 grp 0−100</td>
<td>677</td>
<td>87.1 [79.3 − 93.6]</td>
<td>80.5 [69.8 − 89.7]</td>
</tr>
<tr>
<td>CD4 grp 100−200</td>
<td>319</td>
<td>62.7 [52.4 − 71.9]</td>
<td>95.0 [85.6 − 99.8]</td>
</tr>
<tr>
<td>CD4 grp &gt;200</td>
<td>581</td>
<td>43.9 [34.3 − 53.9]</td>
<td>97.0 [94.9 − 98.5]</td>
</tr>
<tr>
<td>AlereLAM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 grp 0−100</td>
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<td>93.6 [89.6 − 97.0]</td>
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<tr>
<td>CD4 grp 100−200</td>
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<td>25.3 [15.8 − 34.9]</td>
<td>96.7 [89.4 − 99.9]</td>
</tr>
<tr>
<td>CD4 grp &gt;200</td>
<td>581</td>
<td>10.9 [5.2 − 18.4]</td>
<td>97.6 [93.0 − 99.7]</td>
</tr>
</tbody>
</table>

- CD4-cell dependency…but sensitivity 40-50% even at high CD4-counts and HIV-negative TB patients
- No substantial difference between in- and outpatients

Broger et al, submitted
LAM based intervention reduce mortality in PLHIV+

- Pragmatic trial Malawi and SA
- 2600 HIV+ adults, CD4 median 227 cells/ul
- Randomized to SOC or SOC + AlereLAM
- 20% all cause mortality at day 56

### Results

**CD4 <100 cells/ul (n=744)**
- 7.1% adj. risk reduction
- p=0.037

**CD4 ≥100 cells/ul (n=1801)**
- 2.8% adj. risk reduction
- p=0.074

### Additional Data

- **Post hoc 12-week mortality analysis**
- **South Africa**
- **496 HIV+, CD4 <350**

<table>
<thead>
<tr>
<th>HIV+ in-patients (n=496)</th>
<th>Died</th>
<th>AlereLAM</th>
<th>FujiLAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>101 (20%)</td>
<td>44 (44%)</td>
<td>81 (82%)</td>
</tr>
</tbody>
</table>

Gupta-Wright et al. 2018

Sossen et al. 2020
Next generation LAM test – how will we get there?

Next Generation LAM assay
Ultra sensitive (<10 pg/mL) to detect LAM in all TB patients

- Improved reagents (antibodies, antigens)
- Pre-analytical Sample Preparation
- Innovative Assay Design
Take home messages

- Urine LAM is an attractive target for a non-sputum diagnostic test

- Despite modest sensitivity, current LAM assay have a unique role in the diagnostic landscape providing rapid and cheap diagnosis to the sickest patients with the worst prognosis

- Next generation LAM tests with higher sensitivity are in the pipeline – promising outlook for use in all TB patients including EPTB and children