Urine LAM in the inpatient setting: Lessons learnt from the STAMP trial

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Background – HIV/TB in inpatient settings

- Significant morbidity and mortality from HIV/TB
  - 300,000 deaths in 2017\(^1\)

- TB causes 32-67% deaths in HIV+ adults admitted to hospital in Africa\(^2\)
  - Half undiagnosed at time of death\(^2\)

- Urine-diagnostics have good diagnostic yield\(^3\)
  - Urine easily obtained
  - Disseminated TB common in advanced HIV
  - Despite imperfect sensitivity of assays

- Urine-based screening may reduce deaths and missed TB diagnoses

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1. Global Tuberculosis Report 2018
LF-LAM may be used to assist in the diagnosis of TB in HIV positive adult in-patients with signs and symptoms of TB who have a CD4 <100 cells/µL or are seriously ill.

Specific recommendation against using for screening

(conditional recommendation; low quality of evidence)
Study design

- STAMP trial: a pragmatic, multicountry randomized controlled trial

2600 UNSELECTED adult HIV+ admissions
Irrespective of TB symptoms

Exclude:
• <18 years old
• TB treatment in last 12 months
• IPT in last 6 months
• Outside follow-up area
• Admitted >48 hours
• Unable to provide consent

Standard of care arm
Sputum Xpert MTB/RIF

Intervention arm
Sputum Xpert MTB/RIF +
Urine TB-LAM and Xpert MTB/RIF

Edendale, KZN, South Africa
Zomba, Malawi
Study design

Results to medical team (masked to study arm) reported as ‘positive’, ‘negative’ or ‘not done’

Routine clinical care including decisions about TB treatment

Outcomes:
- Primary outcome: mortality risk at 56-days
- Secondary outcomes:
  - TB diagnosis (microbiological and clinical)
  - TB treatment
Results

4,788 HIV+ admissions screened for eligibility

2,600 Randomised

1,300 Standard of Care arm
Exclusions:
12 recruited twice
1 HIV-negative

1,287 included in analysis
Endpoints:
272 died (21.2%)
13 lost to follow-up (1.0%)
1,002 completed alive

1,300 Intervention arm
Exclusions:
13 recruited twice

1,287 included in analysis
Endpoints:
235 died (18.3%)
14 lost to follow-up (1.1%)
1,036 completed alive
2 withdrew

1,287 included in analysis

Endpoints:
235 died (18.3%)
14 lost to follow-up (1.1%)
1,036 completed alive
2 withdrew

Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Standard of Care</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Mean</td>
<td>39.6</td>
<td>39.7</td>
</tr>
<tr>
<td>Gender % Female</td>
<td>57.0</td>
<td>56.5</td>
</tr>
<tr>
<td>Cough % Yes</td>
<td>52.9</td>
<td>50.6</td>
</tr>
<tr>
<td>WHO TB screen % Positive</td>
<td>90.4</td>
<td>89.5</td>
</tr>
<tr>
<td>New HIV diagnosis % Yes</td>
<td>16.5</td>
<td>15.1</td>
</tr>
<tr>
<td>ART % Never</td>
<td>8.7</td>
<td>11.1</td>
</tr>
<tr>
<td>ART % On ART</td>
<td>87.0</td>
<td>84.7</td>
</tr>
<tr>
<td>Time on ART Median</td>
<td>2.9</td>
<td>2.9</td>
</tr>
<tr>
<td>BMI Mean</td>
<td>21.7</td>
<td>21.6</td>
</tr>
<tr>
<td>CD4 cell count (cells/μL) Median</td>
<td>222</td>
<td>231</td>
</tr>
<tr>
<td>% &lt; 100</td>
<td>29.5</td>
<td>28.9</td>
</tr>
<tr>
<td>Haemoglobin (g/dl) Median</td>
<td>10.4</td>
<td>10.8</td>
</tr>
<tr>
<td>&lt; 8</td>
<td>23.2</td>
<td>22.5</td>
</tr>
<tr>
<td>TB clinically suspected % Yes</td>
<td>38.5</td>
<td>39.5</td>
</tr>
</tbody>
</table>

a excludes new HIV diagnoses; b 9 missing CD4 counts; c 5 missing Hb values

Gupta-Wright et al. Lancet 2018
Results: TB diagnostic yield

Samples submitted for TB testing:
- 99.0% produced urine
- 56.9% produced sputum

- Almost all patients could provide urine samples
- Major diagnostic yield was provided by Alere LAM assay
- Few additional diagnoses provided by urine Xpert

Microbiologically confirmed TB, intervention arm (n=210)

- 41.4% (n=87) Urine LAM
- 8.6% (n=18) Sputum Xpert
- 13.8% (n=29) Urine Xpert
- 14.3% (n=30) Sputum
- 6.2% (n=13) Urine Xpert
- 3.8% (n=8) Urine

Note: 1 patient was negative on all Xpert and LAM tests but was sputum TB culture positive
## Results: inpatient TB diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>SOC n (%)</th>
<th>Intervention n (%)</th>
<th>Risk Difference*</th>
<th>p-value</th>
<th>Interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosed with TB</strong></td>
<td>192 (14.9)</td>
<td>282 (21.9)</td>
<td>7.3 (4.4, 10.2)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>TB microbiologically confirmed</strong></td>
<td>85 (6.6)</td>
<td>210 (16.3)</td>
<td>9.9 (7.5, 12.4)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>TB clinically diagnosed (empirical)</strong></td>
<td>107 (8.3)</td>
<td>72 (5.6)</td>
<td>-3.2 (-4.9, -1.4)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Treated for TB</strong></td>
<td>182 (14.1)</td>
<td>268 (20.8)</td>
<td>7.0 (4.1, 9.8)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

* adjusted by site (except for sub-group analysis by site). 29 patients missing CD4 cell counts, 5 patients missing haemoglobin, 9 patients missing clinical TB suspect at baseline data.

### Subgroup analyses (all in-patient TB diagnoses):

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>SOC n (%)</th>
<th>Intervention n (%)</th>
<th>Risk Difference (%) &amp; 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zomba, Malawi</td>
<td>68 (10.3)</td>
<td>126 (19.2)</td>
<td>8.9 (5.1, 12.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Edendale, South Africa</td>
<td>124 (19.8)</td>
<td>156 (24.7)</td>
<td>5.0 (0.4, 9.5)</td>
<td>0.035</td>
</tr>
<tr>
<td><strong>Baseline CD4 cell count, cells/μL</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.876</td>
</tr>
<tr>
<td>&lt;100</td>
<td>116 (31.1)</td>
<td>142 (38.3)</td>
<td>7.9 (1.1, 14.5)</td>
<td>0.021</td>
</tr>
<tr>
<td>≥100</td>
<td>74 (8.2)</td>
<td>137 (15.2)</td>
<td>7.0 (4.1, 10.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Baseline haemoglobin, g/l</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;8</td>
<td>58 (19.5)</td>
<td>111 (38.4)</td>
<td>18.6 (11.5, 25.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥8</td>
<td>133 (13.5)</td>
<td>171 (17.2)</td>
<td>4.1 (1.0, 7.2)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>TB clinically suspected at admission</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.323</td>
</tr>
<tr>
<td>Yes</td>
<td>143 (28.9)</td>
<td>170 (33.9)</td>
<td>4.7 (-1.1, 10.4)</td>
<td>0.11</td>
</tr>
<tr>
<td>No</td>
<td>49 (6.2)</td>
<td>111 (14.2)</td>
<td>8.0 (5.0, 11.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
## Results: mortality at 56-days

<table>
<thead>
<tr>
<th>Standard of Care [SOC]</th>
<th>Intervention</th>
<th>Risk Difference*</th>
<th>p-value</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>% (95% CI)</td>
<td></td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Intervention - SOC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>272 (21.1)</td>
<td>235 (18.3)</td>
<td>-2.8 (-5.8, 0.3)</td>
<td>0.074</td>
<td></td>
</tr>
<tr>
<td><strong>Subgroup analyses:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zomba, Malawi</td>
<td>161 (24.4)</td>
<td>137 (20.9)</td>
<td>-3.5 (-8.0, 1.0)</td>
<td>0.128</td>
</tr>
<tr>
<td>Edendale, South Africa</td>
<td>111 (17.7)</td>
<td>98 (15.5)</td>
<td>-2.2 (-6.3, 1.9)</td>
<td>0.301</td>
</tr>
<tr>
<td><strong>Baseline CD4 cell count, cells/μL</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.063</td>
</tr>
<tr>
<td>&lt;100</td>
<td>133 (35.7)</td>
<td>107 (28.8)</td>
<td>-7.1 (-13.7, -0.4)</td>
<td>0.036</td>
</tr>
<tr>
<td>≥100</td>
<td>131 (14.6)</td>
<td>127 (14.0)</td>
<td>-0.1 (-3.3, 3.1)</td>
<td>0.963</td>
</tr>
<tr>
<td><strong>Baseline haemoglobin, g/dl</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.056</td>
</tr>
<tr>
<td>&lt;8</td>
<td>116 (38.9)</td>
<td>86 (29.8)</td>
<td>-9.0 (-16.6, -1.3)</td>
<td>0.021</td>
</tr>
<tr>
<td>≥8</td>
<td>156 (15.8)</td>
<td>149 (15.0)</td>
<td>-0.9 (-4.1, 2.3)</td>
<td>0.580</td>
</tr>
<tr>
<td><strong>TB clinically suspected at admission</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.111</td>
</tr>
<tr>
<td>Yes</td>
<td>136 (27.5)</td>
<td>106 (21.2)</td>
<td>-5.7 (-11.0, -0.5)</td>
<td>0.033</td>
</tr>
<tr>
<td>No</td>
<td>136 (17.2)</td>
<td>128 (16.4)</td>
<td>-0.8 (-4.4, 2.9)</td>
<td>0.682</td>
</tr>
</tbody>
</table>

* adjusted by site (except for sub-group analysis by site). 29 patients missing CD4 cell counts, 5 patients missing haemoglobin, 9 patients missing clinical TB suspect at baseline data.
Cost-effectiveness in inpatients

- **STAMP urine screening intervention**
  - Increased life expectancy by 0.5-1.2 years
  - Cost-effective in both Malawi (ICER $450/YLS) and South Africa ($840/YLS)
  - Over 5 years, would save 51,000 years of life (Malawi) and 171,000 in SA

- **Modified STAMP intervention with LAM (no urine Xpert) is MORE cost-effective**

- **LAM implementation costs are mostly related to TB and HIV treatment costs**

Reddy et al. Lancet Global Health 2019
Urine LAM: prognostic utility in HIV/TB

- Urine LAM positivity was independent risk factor for mortality
  - Overall mortality very high (31% at 2-months)
  - LAM +ve → OR 1.7 increased mortality

- Cluster analysis identified 4 distinct clinical phenotypes in TB patients
  - Mortality differed substantially in these groups
  - Urine LAM associated with high mortality phenotype

- Urine LAM was part of simple clinical risk score for predicting HIV/TB mortality
  - ≥3 factors → 40% mortality risk
  - ≤1 factor → 13% mortality risk
  - AUC ROC 0.7, good calibration (p=0.78)
  - External validation using cohort 644 hospitalised HIV+ TB patients

Demographics factors:
1. Is the patient male? Yes: add 1 point
2. Is the patient aged 55 years or older? Yes: add 1 point

HIV factors:
3. Is the patient currently taking antiretroviral therapy? Yes: add 1 point

Clinical presentation and TB diagnosis:
4. Is the patient unable to walk unaided? Yes: add 1 point
5. Does the patient have severe anaemia (haemoglobin <8g/dL)? Yes: add 1 point
6. Is the patient positive on urine TB-LAM testing? Yes: add 1 point

Gupta-Wright et al. PLOS Med 2019
Gupta-Wright et al. Under review
Challenges to LAM implementation for inpatients

- **Diagnostic accuracy**
  - Concerns about specificity - issues around study design and reference standard
  - ? less important in inpatient settings - clinical treatment common and mortality high
  - New Fujifilm LAM assay

- **Impact on clinical outcomes**
  - 2 RCTs showing increases TB diagnosis and treatment, and likely reduces mortality

- **CD4 count testing a potential barrier to implementing WHO 2015 guidance**

- **Challenges procuring Alere LAM**

- **Training, reading and quality assurance**
  - Use of manufacturers reference card can be difficult to differentiate negative / grade 1 positive

An app to read Alere LAM assays:
- Low cost android smartphone (~$50)
- 3D printed stand
- Immediate result
- Correctly read 202/204 LAM strips (compared to 2 blinded human readers)
Conclusions

• Urine-based TB screening in HIV+ patients in inpatient settings:
  – Increased (predischarge) TB diagnosis and treatment
  – Survival benefit in ‘high-risk’ subgroups
  – Urine LAM provided most the improvement in diagnostic yield

• Urine LAM implementation in inpatient settings:
  – Cost-effective
  – Feasible with the assay being relatively inexpensive

• Urine LAM has prognostic as well as diagnostic benefits

• Challenges:
  – Several challenges to implementation, but can be overcome
  – Better assay(s) on horizon, implementing current assay will improve outcomes now, and lead to quicker adoption of newer assays once available

• Cannot be extrapolated to outpatients
Thanks

If any questions, please email ankur.gupta-wright@lshtm.ac.uk