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THE 49TH UNION WORLD CONFERENCE ON LUNG HEALTH

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Clinical investigation for tuberculosis
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☐ Other: ______________________________________________________
Sub-therapeutic rifampicin concentration is associated with unfavourable treatment outcomes in pulmonary tuberculosis patients on thrice weekly regimens in India

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Funding – DBT / NIH
Tuberculosis

- One of the major causes of preventable deaths in the world
- Array of powerful drugs available to ensure cure
- Cases of MDR & XDR TB increasing globally
- Are the current regimens & current doses adequate?
Drug levels & treatment outcome

- Treatment outcomes driven by multiple factors
- **Drug levels – an important determinant**
- Persistently low levels could
  - manifest as delayed smear conversion
  - provide favourable nidus for drug resistant mutants of *M. tb*
  - eventually lead to treatment failure
- **It is essential to maintain optimal drug levels**
Sub-optimal drug levels could have an adverse impact on treatment outcome

- Slow responders have RMP & INH < expected range \((\text{Emerg Infect Dis 2010})\)
- Longer time to culture conversion & treatment failures more frequent in those with drug levels below the therapeutic range \((\text{Can Respir J 2011; J Antimicrob Chemother 2014})\)
- Low RMP & INH levels preceded acquired drug resistance \((\text{J Infect Dis 2013})\)
- Modelling study - higher RMP levels associated with faster bacteriologic clearance \((\text{Clin Pharmacol Ther 2015})\)
- Low RMP levels - risk factor for poor treatment outcome \((\text{Antimicrob Agents Chemother 2017})\)
Aim

❖ To determine plasma concentrations of RMP, INH & PZA & their relationship to treatment outcomes in adult pulmonary TB patients under programmatic settings
Methods

- Sub-study of ongoing ‘C-TRIUMPh’ cohort study
- **Design:** Multi-centric Prospective Observational Study
- **Setting:** RNTCP treatment centres in Tiruvallur & BJ Medical College, Pune - India
- **Study period:** August 2014 – October 2017
- Study approved by Institutional Ethics Committee
Patients

- All consecutive patients (≥ 18 years of age)
- Newly diagnosed pulmonary TB patients
- CAT I regimens (thrice – weekly)
- Diagnosis & treatment - program guidelines
- ATT under DOT
- Willing to give informed written consent
- Not too sick or moribund
Study procedures

- Study at months 1 & 5 of ATT
- Blood at 2-hr post-dosing after direct supervision of drug admn
- RMP, INH & PZA estimated by HPLC
- Routine hematology & Clinical biochemistry testing
- Sputum at baseline – Smear, Culture & DST
- Diabetes – Either known history of DM or random blood glucose > 200mg/dl or HbA1c > 6.5%
- Patients followed up to 18 months after completion of ATT
TB treatment outcome

- Cured
- Treatment completed
- Failure
- Death
- Recurrence
TB treatment outcome

- **Favourable outcome**
  - **Cured** – consecutive negative *M. tb* during the last 2 months of ATT
  - **Treatment completed** – Absence of bacteriological evidence; absence of symptoms suggestive of TB at completion of ATT

- **Unfavourable outcome**
  - **Failure** – *M. tb* positive during last 2 months of ATT/Clinical failure
  - **Death** – all cause mortality
  - **Recurrence** – *M. tb* positive after successful completion of ATT

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Statistical evaluation

- **Mann-Whitney U test** – comparison of drug levels between patient groups
- **Z proportion test** - comparison of proportions
- **Single & multi-variable regression analysis** - to determine factors impacting drug levels
- **Single & multi-variable Poisson regression model with person-time as offset** - to identify factors associated with poor TB treatment outcome
### Patient details \( (n = 404) \)

**Values are N (%)**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong>*</td>
<td>39.5 (28 – 50)</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>260 (64.4%)</td>
</tr>
<tr>
<td><strong>BMI (kg/sqm)</strong>*</td>
<td>17.8 (15.9 – 20.3)</td>
</tr>
<tr>
<td><strong>Smokers</strong></td>
<td>134 (33.2%)</td>
</tr>
<tr>
<td><strong>Alcohol users</strong></td>
<td>183 (45.3%)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>113 (28.0%)</td>
</tr>
<tr>
<td><strong>With cavity on X-ray</strong></td>
<td>151 (45.1%)</td>
</tr>
<tr>
<td><strong>HIV sero-positive</strong></td>
<td>27 (6.7%)</td>
</tr>
</tbody>
</table>

* Median & IQR
## Plasma 2-hr drug levels

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sub-optimal cut-off (µg/ml)</th>
<th>2-hr level (µg/ml) (Median &amp; IQR)</th>
<th>Number sub-optimal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Month 1</td>
<td>Month 5</td>
</tr>
<tr>
<td>RMP</td>
<td>&lt; 8.0</td>
<td>3.6 (1.5 – 6.6)</td>
<td>4.5 (1.6 – 8.1)</td>
</tr>
<tr>
<td>INH</td>
<td>&lt; 3.0</td>
<td>5.3 (2.5 – 8.4)</td>
<td>6.2 (3.3 – 9.0)</td>
</tr>
<tr>
<td>PZA</td>
<td>&lt; 20.0</td>
<td>37.0 (27.7 – 44.9)</td>
<td>-</td>
</tr>
</tbody>
</table>
Comparison of drug levels

- **Sex** – Males & females
- **Age** – < 35 & > 35 years
- **BMI** – < 18.5 & > 18.5 kg/sqm
- **Smoking** – Yes & No
- **Alcohol intake** – Yes & No
- **Diabetes** – Yes & No
- **Smear Status** – Positive & Negative
- **Cavity on X-ray** – Present & Absent
- **HIV Status** – Positive & Negative
# Significant findings (Univariate analysis)

## Month 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>N (%)</th>
<th>2-hr RMP*</th>
<th>2-hr INH*</th>
<th>2-hr PZA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>249 (64%)</td>
<td>3.6 (1.5–6.2)</td>
<td>5.1 (2.2–8.4)</td>
<td>35.4 (26.1–42.9)</td>
</tr>
<tr>
<td>Female</td>
<td>141 (36%)</td>
<td>3.1 (1.5–6.9)</td>
<td>5.9 (3.1–8.2)</td>
<td>39.2 (29.7–51.6)</td>
</tr>
<tr>
<td>p Value</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI (kg/sqm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>185 (48%)</td>
<td>2.7 (1.2–5.7)</td>
<td>5.2 (2.2–9.0)</td>
<td>38.4 (29.0–47.2)</td>
</tr>
<tr>
<td>&gt;18.5</td>
<td>200 (52%)</td>
<td>4.3 (1.8–6.9)</td>
<td>5.4 (2.8–8.1)</td>
<td>35.9 (26.1–41.8)</td>
</tr>
<tr>
<td>p Value</td>
<td></td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>AFB Smear</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>267 (71%)</td>
<td>3.7 (1.5–6.3)</td>
<td>5.2 (2.1–8.3)</td>
<td>35.9 (23.9–44.6)</td>
</tr>
<tr>
<td>Positive</td>
<td>107 (29%)</td>
<td>3.5 (1.5–6.7)</td>
<td>5.7 (3.2–8.5)</td>
<td>37.8 (31.6–46.3)</td>
</tr>
<tr>
<td>p Value</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HIV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>365 (94%)</td>
<td>3.6 (1.5–6.5)</td>
<td>5.3 (2.5–8.1)</td>
<td>37.0 (27.6–45.0)</td>
</tr>
<tr>
<td>Positive</td>
<td>25 (6%)</td>
<td>2.6 (1.1–5.8)</td>
<td>6.1 (1.0–11.4)</td>
<td>31.9 (19.9–35.9)</td>
</tr>
<tr>
<td>p Value</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

* Median & IQR (Mann Whitney U test)
### Significant findings (Univariate analysis)
#### Month 5

<table>
<thead>
<tr>
<th>Variables</th>
<th>N (%)</th>
<th>2-hr RMP*</th>
<th>2-hr INH*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>228 (64%)</td>
<td>4.4 (1.5–7.6)</td>
<td>5.9 (3.1–8.5)</td>
</tr>
<tr>
<td>Female</td>
<td>131 (36%)</td>
<td>5.1 (2.3–8.8)</td>
<td>6.8 (3.9–11.2)</td>
</tr>
<tr>
<td><strong>p Value</strong></td>
<td></td>
<td>0.051</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Smoker</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>62 (17%)</td>
<td>4.1 (1.1–7.1)</td>
<td>5.3 (2.2–7.6)</td>
</tr>
<tr>
<td>No</td>
<td>297 (83%)</td>
<td>4.9 (1.9–8.2)</td>
<td>6.3 (3.7–9.6)</td>
</tr>
<tr>
<td><strong>p Value</strong></td>
<td></td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>HIV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>338 (94%)</td>
<td>4.6 (1.9–8.2)</td>
<td>6.3 (3.5–9.3)</td>
</tr>
<tr>
<td>Positive</td>
<td>21 (6%)</td>
<td>1.6 (1.0–5.4)</td>
<td>4.6 (2.8–8.1)</td>
</tr>
<tr>
<td><strong>p Value</strong></td>
<td></td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Median & IQR (Mann Whitney U test)
Factors influencing drug levels
Dependent variable – 2-hour RMP, INH & PZA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Variable</th>
<th>p Value</th>
<th>β</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMP</td>
<td>HIV</td>
<td>0.018</td>
<td>-1.9</td>
<td>-3.5 to -0.3</td>
</tr>
<tr>
<td>INH</td>
<td>None</td>
<td></td>
<td>0.048</td>
<td>0.015</td>
</tr>
<tr>
<td>PZA</td>
<td>Male Gender</td>
<td>&lt;0.001</td>
<td>-7.8</td>
<td>-11.9 to -3.7</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>0.048</td>
<td>-4.4</td>
<td>-8.7 to -0.03</td>
</tr>
<tr>
<td></td>
<td>Smear Positive</td>
<td>0.015</td>
<td>4.8</td>
<td>0.9 to 8.6</td>
</tr>
</tbody>
</table>
Treatment outcome

Outcome (N=404)

Favourable N=327 (81%)
  - Cured N=291 (72%)
  - Treatment Completed N=36 (9%)

Unfavourable N=77 (19%)
  - Failure N=38 (9%)
  - Recurrence N=19 (5%)
  - Death N=20 (5%)
Drug levels in favourable & unfavourable responders

* significant at 5% level

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Factors influencing treatment outcome

- **Drug levels** – RMP, INH, PZA
- **Gender** - Males & females
- **Age** – < 35 & ≥ 35 years
- **BMI** – < 18.5 & ≥ 18.5kg/sqm
- **Smoking** – Yes & No
- **Alcohol intake** – Yes & No
- **Diabetes** – Yes & No
- **Cavity on X-ray** – Present & Absent
Multiple Poisson Regression Analysis

<table>
<thead>
<tr>
<th>Factors</th>
<th>IRR (95% CI)</th>
<th>p value</th>
<th>aIRR* (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMP concentrations</td>
<td>0.81 (0.68 - 0.96)</td>
<td>0.016</td>
<td>0.75 (0.61 - 0.91)</td>
<td>0.004</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.46 (1.10 – 5.51)</td>
<td>0.029</td>
<td>2.52 (1.08 – 5.88)</td>
<td>0.032</td>
</tr>
</tbody>
</table>

An unit increase in RMP conc. of 1µg/ml, was likely to reduce the risk of unfavourable outcome by 33%

*Model adjusted for all potential confounders
Salient findings

- High proportion of patients have sub-therapeutic RMP
- Females have higher drug levels than males
- RMP & PZA levels lower in patients with HIV & TB
- HIV co-infection influences RMP levels, after adjusting for confounders
- RMP levels lower in unfavourable responders
- **Low RMP levels – significant risk factor for unfavourable outcome**
- It is important to identify patients with sub-therapeutic RMP early during ATT & consider dose enhancement
Acknowledgements

- All the patients who took part in the study
- Field investigators
- HPLC lab
- Bacteriology, Clinical Biochemistry & Hematology laboratories
- Staff at the DOTS centres
- District TB Officers
- Study funding by DBT / NIH
- ICMR
- The Union
Thank you