PK/PD of first-line anti-tuberculosis drugs and concentrations associated with optimal efficacy in combination therapy regimens in adult patients

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Background: Hollow Fibers Studies-1

• PK-PD studies performed in the past by many researchers have suggested that **microbiological kill**, **post antibiotic effect** as well as **resistance suppression** of anti-TB regimens, including INH, RIF and PZA are linked to either AUC or Peak concentrations.

• Our group performed experiments of anti-TB drugs in monotherapy and in multiple drug combinations in the hollow-fiber
Pharmacokinetic Variability

INH, RIF & PZA

• PK variability significantly contributes to clinical outcomes
  – Only very high rates of missed doses (~60%) led to failure
  – No Acquired Drug Resistance (ADR) emerged because of missed doses
• Monte Carlo Simulations suggested MDR (0.68%) possible by 8 weeks despite 100% DOT
  – Attributable to PK variability

Based on the HFS model; DOT is a very poor surrogate marker and attempt to counter-measure PK variability and its effects
Thus *PK variability* is the *most proximate factor associated with failure of TB therapy and possibly responsible for emergence of drug resistance, including MDR.*
To identify drug concentration thresholds predictive of clinical outcomes in adult TB patients treated with multiple anti-TB drug combination therapy in the clinic
– used nonparametric machine-learning methods
– examined 2-month & long-term outcomes
Methods-1: Study setting

**Western Cape, SA**

- pop 5.2 M; heterogeneous ~ race/ethnic since 1652 AD
- Diverse ancestry
  - Cape Coloureds (50%)
  - Black/Africans: Bantu (30%)
  - Whites-Afrikaans (18%)
  - Asians/Indians/Malay (1%)
- TB rates
  - 917 per 100000 (all cases)
  - >9000 cases – MDR cases
  - The Brewelskloof hospital
Methods-1: study design

Clinical study and PK sampling: 142 patients

Compartmental PK analysis for each patients:
- RIF, INH & PZA

CART analysis:
- Identify, rank and select predictors
- Identify drug thresholds

INTERVENTION
Computer-aided clinical trial simulation
- 50,000 patients: Bayesian vs Standard

Cost Effectiveness Analysis
- DALYs
Methods-2 Outcomes, PKs & CART

• **Outcomes**
  – Patient followed-up for up to two years:
    • *microbiological failure; 2-month*
    • *relapse,  
    • *Death*

• **Pharmacokinetic (PK) Analysis**
  – Sampling at 9 different time points
  – Compartimental PK
    • INH, RIF & PZA
    • maximum-likelihood expectation maximization algorithm
      – Selection of # of compartments: AKAIKE Information Criteria
### Results-1: Patient Characteristics; n=142

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Estimate or Median</th>
<th>Range or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>78</td>
<td>55 %</td>
</tr>
<tr>
<td>Race/ethnicity: Mixed</td>
<td>127</td>
<td>89 %</td>
</tr>
<tr>
<td>Black</td>
<td>15</td>
<td>11%</td>
</tr>
<tr>
<td>Weight (kg): Median</td>
<td>46.00</td>
<td>28.00 – 85.50</td>
</tr>
<tr>
<td>Weight change with 2 month therapy (Median)</td>
<td>8.37</td>
<td>-11.55 – 36.84</td>
</tr>
<tr>
<td><strong>Dose and range in mg/kg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIF</td>
<td>10.90</td>
<td>7.02 – 15.79</td>
</tr>
<tr>
<td>INH</td>
<td>6.52</td>
<td>3.51 – 10.53</td>
</tr>
<tr>
<td>PZA</td>
<td>35.71</td>
<td>19.69 – 52.62</td>
</tr>
<tr>
<td>EMB</td>
<td>24.62</td>
<td>12.88 – 34.12</td>
</tr>
<tr>
<td>Received Streptomycin</td>
<td>68</td>
<td>47.89%</td>
</tr>
<tr>
<td>Prior TB therapy</td>
<td>91</td>
<td>64%</td>
</tr>
<tr>
<td>Elevated Liver function test</td>
<td>8</td>
<td>6%</td>
</tr>
</tbody>
</table>
Results-2: Variability of RIF, INH & PZA; AUC and $C_{\text{max}}$ concentrations

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CART: *nonparametric* learning approach

- Distribution free, supervised learning with pattern recognition capabilities & clinically intuitive outputs:
  - A Data driven technique (not hypothesis)
    - Identify, rank and select most important clinical predictors including PK parameters; weight, age, gender, and HIV status
    - Identify drug conc. thresholds predictive of outcomes
      - 10 fold cross-validation (142 patients)
        - Optimal tree chosen based on relative costs and parsimony
        - Hybrid modeling: additional frequentist methods used
Results-3: Sputum culture; 2\textsuperscript{nd} month

Study sample = 142 patients
- positive 15 (14%)
- negative 127 (89%)

PZA peak $\leq 58.3$: 99 pts
- pos 14 (14%)
- neg 85 (86%)

PZA peak $>58.3$: 43 pts
- pos 1 (2%)
- neg 42 (98%)

RIF peak $>6.6$: 29 pts
- pos 1 (3%)
- neg 28 (97%)

INH peak $\leq 8.8$: 57 pts
- pos 13 (23%)
- neg 44 (77%)

INH peak $>8.8$: 13 pts
- pos 0 (0%)
- neg 13 (100%)
Results-4: Long-term Outcome

Study sample = 142 pts
- good: 107 (75%)
- poor: 35 (25%)

PZA AUC > 363: 113 pts
- good: 91 (80%)
- poor: 22 (20%)

RIF AUC > 13: 40 pts
- good: 27 (67%)
- poor: 13 (33%)

RIF AUC ≥ 13: 73 pts
- good: 64 (88%)
- poor: 9 (12%)

PZA AUC ≤ 363: 29 pts
- good: 16 (55%)
- poor: 13 (45%)

INH AUC > 52: 65 pts
- good: 60 (92%)
- poor: 5 (8%)

INH AUC < 52: 8 pts
- good: 4 (50%)
- poor: 4 (50%)

INH AUC < 52: 10 pts
- good: 3 (30%)
- poor: 7 (70%)

INH AUC > 52: 30 pts
- good: 24 (80%)
- poor: 6 (20%)
### Results-5: PK Parameters in patients who developed Acquired Drug Resistance

<table>
<thead>
<tr>
<th>Patient</th>
<th>RIF Peak (mg/l)</th>
<th>RIF AUC (mg*h/L)</th>
<th>INH Peak (mg/l)</th>
<th>INH AUC (mg*h/L)</th>
<th>Treatment period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.62</td>
<td>10.83</td>
<td>0.88</td>
<td>25.36</td>
<td>First 2 months</td>
</tr>
<tr>
<td>2</td>
<td>0.81</td>
<td>7.31</td>
<td>8.6</td>
<td>30.37</td>
<td>Microbiologic failure</td>
</tr>
<tr>
<td>3</td>
<td>1.64</td>
<td>7.24</td>
<td>8.6</td>
<td>32.56</td>
<td>Relapse</td>
</tr>
</tbody>
</table>

**AUC=0 – 24 hour area under the concentration time curve**
Discussion-1

• 91% of patients with poor outcomes had at least one drug with low AUC

• All ADR had low concentrations of at least one drug

• Low PZA $c_{\text{max}}$ and PZA $A_{\text{UC}}$ accounted for 91% of all patients that were still positive at 2 months and 37% with poor long-term outcomes, respectively.
Discussion-2

2 Month Outcomes (sputum culture conversion)
1. PZA cmax
2. RIF cmax
3. INH cmax

Long-term Outcomes (failure, relapse & death)
1. PZA \text{ AUC}
2. RIF \text{ AUC}
3. INH \text{ AUC}
Conclusions

• **Pharmacokinetic variability** drives anti-tuberculosis treatment *failure* and *ADR* in patients on a first line anti-tuberculosis regimen.

• As predicted by **Hollow Fiber Systems** model; the PK/PD drivers are AUC and $C_{\text{max}}$.

• Drug concentrations are good early “**biomarkers**” of long-term outcome in patients treated with multi-drug regimens. We propose that they be used for patient care.
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   - Dr Jotam G. Pasipanodya
References


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