The Use of Mucosal Assays in Microbicide Trials

Integrating PK/PD

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Placebo/baseline (untreated) ex vivo p24 data from:

- 17 data sets, $10^4$ TCID$_{50}$ HIV-1 BaL
- 4 Labs: Pitt, UCLA, CONRAD, Imperial
- 3 tissue types: rectal, cervical, vaginal
- 9 studies: UC781, Tenofovir, FAME01, FAME02, CHARM01, MTN013, CONRAD, MWRI01, Fox
- 700 tissue explants: 13% cervical, 72% rectal and 16% vaginal
- Coded C1-C4 (cervical), R1-R8 (rectal) and V1-V5 (vaginal).
## Comparison of Imputation Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Replace non-detectable with values....</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z (current)</td>
<td>$\frac{1}{2}$ LLOQ/LOD</td>
</tr>
<tr>
<td>A</td>
<td>Predicted from a non-linear mixed model</td>
</tr>
<tr>
<td>B</td>
<td>Predicted from (i) model of growth curve then (ii) non-linear mixed model</td>
</tr>
<tr>
<td>C</td>
<td>Predicted iteratively from model of growth curve and non-linear mixed model</td>
</tr>
</tbody>
</table>
## Comparison of Imputation Methods

<table>
<thead>
<tr>
<th>Experiment</th>
<th>&lt;500 SSI</th>
<th>≥ 500 SSI</th>
<th>Different to Z ( P &lt; 0.05 )</th>
<th>Ease of Implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>A,B and C</td>
<td>Z</td>
<td>A,B and C</td>
<td>Z-A-B-C</td>
</tr>
<tr>
<td>R2</td>
<td>A,B and C</td>
<td>Z</td>
<td>A,B and C</td>
<td>Z-A-B-C</td>
</tr>
<tr>
<td>R4</td>
<td>A,B and C</td>
<td>Z</td>
<td>A,B and C</td>
<td>Z-A-B-C</td>
</tr>
<tr>
<td>R7</td>
<td>A,B and C</td>
<td>Z</td>
<td>A,B and C</td>
<td>Z-A-B-C</td>
</tr>
</tbody>
</table>

Move forward with Method A
Rectal Ex vivo Challenge

R1
Bx n=56

R2
Bx=112

R3
Bx=9

R4
Bx=30

R5
Bx=127

R6
Bx=14

R7
Bx=144

R8
Bx=10

Rectal Curves
Bx=502
Cervical Ex vivo Challenge

Cervical Curves

- C1: Bx=28
- C2: Bx=30
- C3: Bx=24
- C4: Bx=6
- Cervical Curves: Bx=88

Graphs showing changes in Log_{10} p24 pg/mL over days.
Vaginal *Ex vivo* Challenge

<table>
<thead>
<tr>
<th>V1</th>
<th>Bx=29</th>
</tr>
</thead>
<tbody>
<tr>
<td>V2</td>
<td>Bx=30</td>
</tr>
<tr>
<td>V3</td>
<td>Bx=24</td>
</tr>
<tr>
<td>V4</td>
<td>Bx=19</td>
</tr>
<tr>
<td>V5</td>
<td>Bx=8</td>
</tr>
</tbody>
</table>

Vaginal Curve
Bx=110

Log₁₀ p24 pg/mL vs. Day for different batches (V1 to V5)
**Ex vivo Growth Across Tissue Types and Implications for Experimental Design**

### last Day Rectal p24 N

<table>
<thead>
<tr>
<th>Last Day</th>
<th>Rectal p24</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>5248</td>
<td>4</td>
</tr>
<tr>
<td>15 (R6 only)</td>
<td>1479</td>
<td>6</td>
</tr>
</tbody>
</table>

### last Day Cervical p24 N

<table>
<thead>
<tr>
<th>Last Day</th>
<th>Cervical p24</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>1318</td>
<td>19</td>
</tr>
<tr>
<td>21</td>
<td>21878</td>
<td>19</td>
</tr>
</tbody>
</table>

### last Day Vaginal p24 N

<table>
<thead>
<tr>
<th>Last Day</th>
<th>Vaginal p24</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>1514</td>
<td>24</td>
</tr>
<tr>
<td>21</td>
<td>9120</td>
<td>10</td>
</tr>
</tbody>
</table>

p24 = geometric mean cumulative p24 pg/ml.

N = no. of tissues samples needed, per treatment group, to find a one log difference in p24 to be significant ($p<0.05$) with 80% power.
Integrating PK/PD

**PD**
Determine PD endpoint (e.g. cumulative p24), log transform.

**PK**
Determine dose endpoint (e.g. concentration, Cmax, AUC), log transform.

**Integrate PK/PD**
Pair contemporaneous PK/PD measurements (same subject/time)
Linear mixed model, is slope sig?

- **yes**
  - Non-linear model, calculate % virus control, EC_{50}.
- **no**
  - No PK/PD relationship
Integrating PK/PD in Rectal Tissue: 2 steps

A Compartmental Pharmacokinetic and Pharmacodynamic Assessment of Rilpivirine LA Pre-Exposure Prophylaxis in HIV-Negative Volunteers

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