Indicators of therapeutic effect in FIT-06: A Phase II Trial of a DNA vaccine GTU®-Multi-HIV, in untreated HIV-1 infected participants

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Introduction

- Combination HAART has significantly decreased HIV related morbidity and mortality globally.

- Limitations of ARV HAART
  - Life long daily dosing
  - Multiple drugs with significant SE’s
  - Inability to eradicate HIV (reservoir sites, loss of functional CD4/CD8 cells)
  - High levels of patient adherence to prevent resistance/viral failure
  - Access to drugs
    - Treatment costs
    - Logistics of treatment
      - Onset of treatment, Capacity of health systems

- Therapeutic HIV vaccine research
  - Focus on HIV preventative vaccines
Therapeutic HIV Vaccines

• Immunological support for HIV infected individuals
  – Lower plasma viral load
    • ↓ sexual and mother-to-child transmission
  – Restore functional CD4 cells
    • Delay development AIDS

• Earlier therapeutic intervention in HIV infected individuals

• Cost-effective in resource constrained areas
  – ↓ ARV’s requirements
    • ↓ costs
    • ↓ SE’s
    • ↓ drug induced resistance mutations
Therapeutic Vaccine Concept

- Boost HIV immune response with strong, non pathogenic HIV antigens
- Maintain specific cellular immunity
- Slow disease progression
- Prevents viral “relapse”
- Decrease time on therapy (decreased side effects and costs)

Therapeutic HIV Vaccines

- Immune modulators
- Live-vectored
- Prime-boost combinations
- STI’s
- DNA vaccines
  - Effective in inducing cellular immunity in NHP’s
  - Failure in humans
    - Poor delivery
    - Low expression of antigens in vivo
FIT Biotech GTU® DNA HIV Vaccine

- Fusion protein of 6 different HIV genes
- Sequences derived from a specific HIV-1 B isolate, consensus (A, B, C) and phylogenetic ancestral (FGH) sequences
- Maximally represented in tandem arrayed epitope-rich regions
- Codon optimization for maximal expression
- E2 BPV promoter to enhance transcription
  - Favourable preclinical studies - mice, swine, NHP
  - Phase I study in Finland
Phase II FIT-06 Trial Design

Recruitment Wellness Clinic in Soweto South Africa (5.7 million people HIV infected & 900,000 on ARV’s)

**Enrollment characteristics (n=63):**
- untreated, chronically infected
- Age 29 yrs (range: 18-40 yrs)
- Plasma viral load > 38000 copies/ml
- CD4 cells/µl > 500

**Follow up**
- FIT-06 IM (1mg), ID (0.5 mg)
- FIT-06 IM (2mg), ID(1mg)
- Placebo IM & ID

**Primary endpoints:** safety & immunogenicity
**Secondary endpoints:** pVL, CD4 cell counts
## Local Reactogenicity

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Time point after immunisation</th>
<th>Active ID (n=21)</th>
<th>Placebo ID (n=10)</th>
<th>Active IM (n=21)</th>
<th>Placebo IM (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>Immediate</td>
<td>95.2</td>
<td>100.0</td>
<td>71.4</td>
<td>90.0</td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td>95.2</td>
<td>70.0</td>
<td>19.0</td>
<td>40.0</td>
</tr>
<tr>
<td>Bleeding at injection site</td>
<td>Immediate</td>
<td>90.5</td>
<td>80.0</td>
<td>61.9</td>
<td>80.0</td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td>4.8</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Local indurations</td>
<td>Immediate</td>
<td>95.2</td>
<td>60.0</td>
<td>9.5</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td>95.2</td>
<td>50.0</td>
<td>4.8</td>
<td>-</td>
</tr>
<tr>
<td>Persistent local edema</td>
<td>Immediately</td>
<td>95.2</td>
<td>80.0</td>
<td>4.8</td>
<td>40.0</td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td>95.2</td>
<td>70.0</td>
<td>-</td>
<td>20.0</td>
</tr>
</tbody>
</table>
## Adverse Events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Active ID (n=21)</th>
<th>Placebo ID (n=10)</th>
<th>Active IM (n=21)</th>
<th>Placebo IM (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>95.2</td>
<td>100.0</td>
<td>90.5</td>
<td>100.0</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>66.7</td>
<td>70.0</td>
<td>61.9</td>
<td>80.0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>71.4</td>
<td>60.0</td>
<td>61.9</td>
<td>70.0</td>
</tr>
<tr>
<td>Blood creatine phosphokinase increased</td>
<td>52.4</td>
<td>30.0</td>
<td>42.9</td>
<td>60.0</td>
</tr>
</tbody>
</table>
HIV-Specific CD4 and CD8 T Responses

- An increase of antigen-specific CD4 and CD8 T cells secreting TNFα was observed.
- Responses to Gag-B and/or Gag-C at V11 (week 76) and/or V13 (week 84) were observed:
  - CD4 response observed in 83% of participants
  - CD8 response observed in 67% of participants
  - CD4 and CD8 response observed in 55% of participants
# Clinical Outcomes

## Average Change in Plasma Viral Load

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Δ log(VL)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIT vs. Placebo</td>
<td>-0.31</td>
<td>0.012</td>
</tr>
<tr>
<td>ID: FIT vs. Placebo</td>
<td>-0.16</td>
<td>0.257</td>
</tr>
<tr>
<td>IM: FIT vs. Placebo</td>
<td>-0.47</td>
<td>0.001</td>
</tr>
</tbody>
</table>

## Average Change in CD4 Cell Counts

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Δ cells/uL</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIT vs. Placebo</td>
<td>+45</td>
<td>0.068</td>
</tr>
<tr>
<td>ID: FIT vs. Placebo</td>
<td>+18</td>
<td>0.514</td>
</tr>
<tr>
<td>IM: FIT vs. Placebo</td>
<td>+72</td>
<td>0.013</td>
</tr>
</tbody>
</table>

ID=Intradermal
IM=Intramuscular
ΔpVL IM immunization GTU®-MultiHIV-B

Change from baseline in log VL

- Weeks 1-12 (during first 3 vaccinations*)
  - F-06 IM: P=0.001
  - F-06 ID: P=0.022
  - Placebo: P=0.003

- Weeks 16-76 (after first 3 vaccinations*)
  - F-06 IM: P=0.350

- Weeks 80-84 (after 2 booster doses**)
  - Placebo: P=0.585

P-values versus placebo are shown.
ΔpVL IM immunization GTU®-MultiHIV-B in B*57, B*8101, B*5801

P-values versus placebo are shown.

Change from baseline in log VL

Weeks 1-12 (during first 3 vaccinations)

Weeks 16-76 (after first 3 vaccinations)

Weeks 80-84 (after 2 booster doses)
Discussion

• FIT Biotech GTU DNA vaccine is safe and well tolerated in HIV infected individuals

• GTU DNA vaccine favourably increases CD4 cell counts in untreated, chronically infected individuals

• When compared to placebo, IM immunization with vaccine had a significant impact on decreasing pVL for at least 27 months of study follow up

• Enhanced effects on pVL in participants with favorable HLA alleles types [B*57, B*8101, B*5801]
  – ID group effect

• Results provide the basis for further development of promising immunotherapies for HIV infection especially important in resource constrained areas
Acknowledgements and Thanks

• Participants

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• Presentation
  – Mart Ustav
  – Ioana Stanescu
  – Giuseppe Pantaleo
  – Kalevi Reijonen