Recent Advances in TB Vaccine Clinical Research: prospects and challenges

Ann M. Ginsberg, MD, PhD | 4 March 2019
WHO-CROI HIV/TB Research Meeting
Seattle, WA
TB Is #1 Infectious Killer - 10M new cases in 2017

Deaths in 2017

- TUBERCULOSIS: 1.6M
- HIV/AIDS: 940K
- Co-infection: 300K

Source: WHO Global TB Report 2018
2018 – A Year of Unprecedented Progress

➢ Now is the time to accelerate TB vaccine development
H4:IC31 and BCG revaccination
Phase II Prevention of Infection Trial

Clinical Trial Sites:
SATVI and DTHF/Emavundleni
Prevention of Infection as an Early POC Trial for Go/NoGo Decision-making

Reduce sample size by:

- Selecting high risk study population: IGRA (-) adolescents/adults at high risk of infection
  - ~8x the risk of TB disease in the same population
- Reducing statistical power of the study
  - As this is POC, consider power less than 90%. A reasonably powered study could have power >70%.
  - Increased risk that you will fail to find a significant result, even if one does exist (i.e., false negative)
- Increasing alpha: Type 1 error rate of 10% (1-sided)
  - Increases chance of having a statistically significant result when one does not exist (i.e., false positive)
  - Less likely to ‘miss’ a true signal

CAVEAT: Prevention of infection might only occur in the 90% of persons infected with *M.tb* who will never develop TB disease anyway.
Proof of Concept:
Phase 2 Prevention of Infection study to evaluate safety, efficacy and immunogenicity

3 Study Arms:
- H4:IC31 (IM, 2 doses, 56 days apart)
- BCG revaccination (ID, 1 dose; SSI BCG)
- Placebo (saline; IM, 2 doses, 56 days apart)

Population:
- QFT*-negative adolescents (12–17 yrs)
- Western Cape, South Africa (SATVI/EMA)
- High risk of infection (~10% per year)
  - Defined as QFT conversion from + to -

Design:
- Randomized (1:1:1)
- Placebo-controlled
- Partially blinded

Study Size:
N=990 (330/arm)

*QFT = QuantiFERON Gold In-Tube interferon gamma release assay
POI Trial Results and Conclusions

• Both H4:IC31® and BCG revaccination appeared safe and immunogenic
  ➢ Population: healthy, M.tb-uninfected, high risk of TB adolescents in Western Cape
• Neither vaccine showed statistical significance in preventing initial infection (initial QFT conversion)
• BCG revaccination: statistically significant prevention of sustained QFT conversion (increased clearance or control of infection; VE: 45.4%; p=0.01)
• H4:IC31: not statistically significant prevention of sustained QFT conversion at 95% confidence level (VE: 30.5%; p=0.08)
• Biobank created and analysis plan being developed for discovery of candidate correlates of risk and/or protection
First POI Trial: Conclusions and Next Steps (H4:IC31 and BCG revaccination in high risk adolescents)

BCG Revaccination
- Statistically significant prevention of sustained infection
- Confirm then/and evaluate in Prevention of TB Disease trial
- Potential correlates of protection discovery

H4:IC31
- First signal of any protection against TB infection or disease in humans by a subunit vaccine
- Suggests benefit of studying other subunit vaccines
- Not being further developed

POI Trial Design
- Is feasible and may be useful tool for decision-making.
- Should be validated in a Prevention of Disease trial
M72/AS01E Phase IIb Prevention of Disease Trial

Results of the primary analysis
M72/AS01\textsubscript{E} candidate vaccine (M72)

To induce a robust Th1 CD4\textsuperscript{+} T cell response against Mtb antigens

**Antigens selection**

[Skeiky, 1999; Dillon, 1999; Al-Attiyah 2004]

- Lymphoproliferation - IFN-γ production
  - + Healthy PPD +
  - + TB patients
  - × PPD -
- No IL-10 production in TB patients

**Mtb antigens**
PepA (Mtb32A) and PPE18 (Mtb39A)

**Adjuvant system**
AS01\textsubscript{E}

*S: QS-21: Quillaja saponaria Molina, fraction 21; Licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation.

\textsuperscript{*}QS-21: Quillaja saponaria Molina, fraction 21; Licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation.
Clinical Phase I/II experience

Safety and immunogenicity assessed in a broad range of populations

MTB-001: Ph 1 FTIH
Adults PPD-USA(1)

TB-002: Ph I
Adults PPD-Belgium(2)

TB-004: Ph I/II
Adults PPD+ Switzerland(3)

TB-005/008: Ph I/II
Adults PPD-Belgium (4)

TB-009: Ph II
Adults PPD+ Philippines (5)

TB-010: Ph II
Adults PPD +/- South Africa (6)

TB-011: Ph I/II
Adults HIV+/ART+ Switzerland (7)

TB-012: Ph II
Adolescents South Africa (8)

TB-013: Ph II
Infants (±EPI) The Gambia(9)

TB-014: Ph II
Adults HIV+/- ±ART India(10)

TB-015: Ph I
Adults PPD-
Belgium (11)

TB-017: Ph II
Adults with TB disease
Taiwan & Estonia (12)


M72/AS01\textsubscript{E} candidate vaccine

Goal: induce a robust Th1 CD4+ T cell response against Mtb antigens

Clinical safety and immunological profiles to date

- Generally well tolerated although higher reactogenicity observed in patients with active tuberculosis
- High seroconversion rate & long lasting humoral response
- Poly-functional CD4 Th1 cells (IFN\textsubscript{\gamma}, TNF\textsubscript{α}, IL-2+)
  - 3 years persistence*
- CD8 Th1 cells
- IL-17-expressing CD4 T cells
- T cell responses in lung

Phase IIb Study design

- **Subjects**
  - HIV negative healthy adults (18 - 50 years)
  - Negative sputum by PCR (Xpert MTB/RIF)
  - Mtb-infected: positive by QuantiFERON

- **Design**
  - Double-blind, randomized (1:1)
  - M72/AS01_E or Placebo
  - 2 doses 1 month apart

- **TB cases determination by**
  - Active follow-up every 2 months either by calls, home visits or SMS
  - TB symptoms and bacteriological confirmation
    - By PCR and/or MGIT culture

- **3 years follow up**
  - Primary analysis at year 2
  - LSLV November 2018
Study participants

- Screened: n=8,336
- Enrolled: n=3,575
- Total Vaccinated: n=3,573
- Not Vaccinated: n=2
- ATP Efficacy: n=3,283
- Not ATP Efficacy: n=290

Trial sites:
- KEMRI
- CIDRZ
- Zambart
- SATVI
- TASK
- CIDRI
- Aurum Inst.
- Tembisa
- Klerksdorp
- BePart
- Setshaba
- PHRU

Figure adapted from Van Der Meeren et al, presented at IDWeek, October 2018, San Francisco CA, Abstract 70677
http://www.idweek.org
Van Der Meeren et al., NEJM, 2018
## Vaccine efficacy for all case definitions (ATP)

### Sputum sampling and HIV status

<table>
<thead>
<tr>
<th>Sputum sampling</th>
<th>Site</th>
<th>HIV status</th>
<th>Sputum positivity by PCR/culture</th>
<th>TB disease cases</th>
<th>Vaccine efficacy against TB disease (90% CI) unadjusted Cox regression model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total M72 Placebo</td>
<td>p-value</td>
</tr>
<tr>
<td>1 Before treatment onset</td>
<td>P</td>
<td>-</td>
<td>At least 1</td>
<td>32 10 22</td>
<td>54 0.042</td>
</tr>
<tr>
<td>2</td>
<td>P</td>
<td>-</td>
<td>At least 2</td>
<td>22 5 17</td>
<td>70 0.017</td>
</tr>
<tr>
<td>3</td>
<td>P</td>
<td>-</td>
<td>At least 1 PCR</td>
<td>24 7 17</td>
<td>58 0.051</td>
</tr>
<tr>
<td>4</td>
<td>P</td>
<td>-/+</td>
<td>At least 1</td>
<td>41 16 25</td>
<td>35 0.174</td>
</tr>
<tr>
<td>5</td>
<td>Any</td>
<td>-/+</td>
<td>Any *</td>
<td>44 17 27</td>
<td>36 0.144</td>
</tr>
<tr>
<td>6</td>
<td>Any</td>
<td>-</td>
<td>Any*</td>
<td>44 17 27</td>
<td>29 0.225</td>
</tr>
</tbody>
</table>

*Van Der Meeren at al., NEJM, September 25, 2018*

P: Pulmonary – PCR by Xpert MTB/RIF™ - * Clinician has diagnosed TB and subject was treated
Study participants

- Screened: n=8,336
  - Enrolled: n=3,575
    - Total Vaccinated: n=3,573
      - ATP Efficacy: n=3,283
      - Not ATP Efficacy: n=290
    - Screening failure: n=4,761
  - Not vaccinated: n=2

Trial sites:
- KEMRI
- CIDRZ
- Zambart
- SATVI
- TASK
- CIDRI
- Aurum Inst.
- Tembisa
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http://www.idweek.org

Van Der Meeren et al., NEJM, 2018

ATP: According To Protocol
### Kaplan-Meier (ATP cohort for efficacy)

<table>
<thead>
<tr>
<th>Time</th>
<th>VE (case definition 1, ATP)</th>
<th>%</th>
<th>LL 90%CI</th>
<th>UL 90%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period1 (≤ 1.12 years)</td>
<td>39.0</td>
<td>-42.5</td>
<td>73.9</td>
<td></td>
</tr>
<tr>
<td>Period2 (&gt; 1.12 years)</td>
<td>66.5</td>
<td>13.3</td>
<td>87.0</td>
<td></td>
</tr>
</tbody>
</table>

**Differential vaccine effect by time?**

- Incipient TB not excluded at baseline?
- Repeated exposure boosts VE?

Figure adapted from Van Der Meeren et al, presented at IDWeek, October 2018, San Francisco CA, Abstract 70677

[http://www.idweek.org](http://www.idweek.org)

Van Der Meeren et al., NEJM, 2018
Higher vaccine efficacy in ≤ 25 year olds?

Pre-specified sub-group analyses by age

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Group</th>
<th>N</th>
<th>n</th>
<th>T (year)</th>
<th>Person-year rate</th>
<th>VE (case definition 1, ATP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Person-year rate</td>
<td>VE (case definition 1, ATP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25 years</td>
<td>M72AS01e</td>
<td>705</td>
<td>2</td>
<td>1599.77</td>
<td>0.1</td>
<td>84.4</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>724</td>
<td>13</td>
<td>1616.66</td>
<td>0.8</td>
<td>45.7</td>
</tr>
<tr>
<td>&gt;25 years</td>
<td>M72AS01e</td>
<td>918</td>
<td>8</td>
<td>2107.25</td>
<td>0.4</td>
<td>10.2</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>936</td>
<td>9</td>
<td>2130.77</td>
<td>0.4</td>
<td>-99.6</td>
</tr>
</tbody>
</table>

Does repeated exposure boost VE? Is more recent infection better controlled by vaccine?

Unadjusted Cox model at different levels of baseline covariates (ATP cohort for efficacy)
Ancillary biobank study

- Samples obtained from 99% of the M72 clinical POC trial participants
- Discovery of candidate correlates of risk and protection

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 37</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBMC/plasma</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Whole Blood cell count</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Intracellular RNA</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

NCT02097095
Conclusions and next steps

- M72/AS01E prevented TB disease in Mtb-infected adults
  - Efficacy of 54% [CI90% 14-75%, p=0.04] - primary endpoint met
  - Secondary endpoint met (VE of 58%; p=0.05)
  - Acceptable safety profile
- More research is warranted
  - End of study analysis
  - IAVI Biobank – correlates discovery
- Next steps under discussion with stakeholders and funders
Proof of Concept Study Acknowledgments

Study participants and their communities

Investigators and their teams

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* Aeras TB vaccine clinical program was recently transferred to IAVI
TB Vaccine R&D Has Turned a Corner

- First demonstration that a vaccine can protect Mtb-infected adults from developing TB disease
- Proof of concept that a subunit vaccine (2 Mtb antigens plus adjuvant) can protect against TB disease
- New use for old vaccine - protect high risk, uninfected populations from Mtb infection with BCG revaccination
- Opportunity to discover correlates of protection and increase understanding of protective human immune responses
- Human efficacy data to inform optimization and use of preclinical models

➢ Leverage results to accelerate development through delivery
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Thank you