The HIVIS Project, a North-South collaborative study on safety and immunogenicity of a multigene, multiclade HIV-1 plasmid DNA prime and MVA boost

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Objectives

• To optimise the immunisation schedule for HIV-1 DNA vaccine priming with HIV-1 MVA vaccine boosting in the development of HIV-1 preventive vaccine

• To develop expertise and capability to study HIV-1 vaccines in Tanzania
Immunogens in HIVIS

TANZANIA

ACD 6%
CD 6%
AC 34%
A 9%
D 6%
C 30%
7 plasmid HIV-1 DNA multigene/multiclade vaccine

Developed by Dept virology, SMI, Karolinska Inst
Produced by Vecura
MVA / CMDR

Developed by Laboratory of Viral Diseases, NIAID, NIH
Produced by Walter Reed Army Institute of Research

- Deletion II
  - MVA
  - gag protease / RTgp150 env

- Deletion III
  - mH5
  - Subtype E: CM235
  - Subtype A: CM240
Study Plan

Months

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<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>

Plasmid DNA

Recombinant MVA

HIV-genes

Phase I Stockholm

February 2005

40 volunteers

Phase I/II in Dar es Salaam, Tz

November 2006

60 volunteers (Police Officers)

Karolinska Institutet, Smittskyddsinstitutet, Södersjukhuset, US Army, Muhimbili University
HIV-1 DNA prime
Three immunizations in the deltoid muscle or the skin above

<table>
<thead>
<tr>
<th>Arm</th>
<th>Dose</th>
<th>Administration</th>
<th>Adjuvant</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1 mg</td>
<td>Id</td>
<td>-</td>
</tr>
<tr>
<td>B</td>
<td>3.8 mg</td>
<td>Im</td>
<td>-</td>
</tr>
<tr>
<td>C</td>
<td>1 mg</td>
<td>Id</td>
<td>GMCSF*</td>
</tr>
<tr>
<td>D</td>
<td>2 mg</td>
<td>Im</td>
<td>GMCSF*</td>
</tr>
</tbody>
</table>

*Leukine® (sargramostim) Berlex, 0.5 ml - 150ug
Injections

Bioject

**im**

Left arm: Env/rev, 1 inj
+/- GMCSF im

Right arm: Gag/RT, 1 inj

**id**

Left arm: Env/rev, 3 inj
+/- GMCSF sc (needle)

Right arm: Gag/RT, 2 inj

spacer
Results, in Sweden, 1

- By end of June 2006, all 38 eligible volunteers had received 3 DNA and one MVA immunizations:

- The immunizations have generally been well tolerated.
  - There were no safety laboratory abnormalities;
  - rGM-CSF was associated with influenza-like adverse events.
Results, in Sweden, 2

- **33/36 (92%)** vaccinees fullfilled the criteria of IFN-γ ELISPOT reactivity to HIV-1 peptide pools
  - Another 2 vaccinees had invalid ELISPOT results due to high background reactivity.

- **37/38 (97%)** vaccinees showed HIV-1 specific T-cell proliferative responses

- The study is still blinded.
HIV-1 DNA prime and MVA boost
IFN-g ELISPOT
33/36 positive

3 Baseline
8 2 weeks after DNA
X1 pre-MVA
X2 2 weeks after MVA

SFC/million PBMCs

Volunteer

Visit 3
Visit 8
Visit X1
Visit X2
Visit 3
Visit 8
Visit X1
Visit X2
Visit 3
Visit 8
Visit X1
Visit X2
T-cell proliferation after the MVA boost in response to AT-2-treated HIV-1 antigen (2.5 μg/ml) (J. Lifson); Stimulation index > 5 regarded as a positive test

(The mean reactivity in samples collected from 12 blood donors was 1.3 ±0.88 SI.)

C. Nilsson
In Tanzania, supportive Policies

- HIV/AIDS declared a National Emergency by the President
- The Tanzania National Framework for the conduct of HIV vaccine trials has been in place since February 2005.
Regulatory approvals

- The study protocol incorporating advice and inputs from the WHO-UNAIDS and from the African AIDS Vaccine Programme (AAVP), and largely developed by Tanzanians has already received National as well as institutional ethical clearances.

- The Tanzania’s Food and Drugs Authority (TFDA) has granted approval for the study to be conducted in Tanzania.
## Study Design in Tanzania

- Randomized, Double Blind, Placebo controlled

<table>
<thead>
<tr>
<th>Arm</th>
<th>Number</th>
<th>DNA immunization</th>
<th>MVA boost</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>20</td>
<td>DNA IM by Bioject</td>
<td>MVA $10^8$ IM</td>
</tr>
<tr>
<td>II</td>
<td>20</td>
<td>DNA ID by Bioject</td>
<td>MVA $10^8$ IM</td>
</tr>
<tr>
<td>IIIa</td>
<td>10</td>
<td>Saline IM by Bioject</td>
<td>Saline IM</td>
</tr>
<tr>
<td>IIIb</td>
<td>10</td>
<td>Saline ID by Bioject</td>
<td>Saline IM</td>
</tr>
</tbody>
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Clinical study site
Study Volunteers

• 60 VOLUNTEERS (45 men, 15 women)
  – Have 250 ready to be screened so far
• Primarily from a cohort of Police Officers’ (PO’s)
• Reasons:
  – Have had extensive contact since 1994
  – Relatively stable population, easy to follow up
  – Supportive stance from Ministry of Home Affairs & Highest Police authorities
  – Almost all have attained Secondary School Education, hence relatively better in terms of informed consent and understanding study related procedures
  – Voluntariness of participation emphasized at all levels
Workshop with Dar es Salaam Police Commanders
“BARAZA” at a Police station, Buguruni
Volunteer’s recruitment

• Formed a group of PO’s interested in HIV/AIDS prevention activities (“collaborators”)
• Conducted workshops with them and educated more on HIV/AIDS and HIV vaccine study
• Those interested invited to list their names and provide address for further contact
• Will have more educational training workshops with them for details of the study
• Those willing will be invited for screening at the site after a one to one educational session again
Study personnel, 1

- Clinical & Laboratory
  - Senior Investigators (with extensive Research experience) oversee the study
  - Younger scientists are on/have completed PhD training through Sida/SAREC funding
  - Multiple institutions
    - MUCHS
    - MNH
    - Police Force
    - University of Dar es Salaam, Sociology
  - Key personnel employed, some 100% commitment
Study Personnel, 2

• Majority trained in
  – GCP/GLP through courses facilitated by
    • WHO/AMANET/AAVP
    • IAVI
  – HIV & AIDS management
• More GCP course soon, assisted by AAVP/WHO
• Exposed (PI, Study Director, Clinical co-ordinator, Laboratory personnel) to HIV vaccine trial setting in Sweden
• In-country networking:
  – HIVIS staff visited Mbeya Medical Research Programme, involved in Phase I/II HIV vaccine trial
  – Members of TAVI
Medical & HIV care

• Availability of HIV care and treatment services at the MNH HIV clinic
  – HIVIS investigators aligned with the HIV clinic, and are of multiple sub-specialties

• The HIV clinic at MNH offers:
  – HIV counseling and testing
  – Free ARV’s
  – Co-trimoxazole prophylaxis
  – Management of OI’s

• Being at MNH, easy to handle other non-HIV related illnesses
Laboratory testing

- Safety tests at MUCHS, Tanzania
- Immunogenicity assessments mostly at MUCHS
  - T cell responses (ELISPOT, FASCIA, LPA)
- At SMI, Sweden
  - Neutralizing antibodies
  - CTL assay
  - HLA typing
- HIV strain characterization
  - Initial processing at MUCHS
  - Sequencing in South Africa (Carolyn Williamson)
    - Tagged with PhD training of a Tanzanian
Challenges

• Financial resources
  – Operating with very modest budget, while it is a tasking undertaking
  – EC extension promised
  – Availability of additional funding crucial for successful completion of the trial in Tanzania
  – Tanzanian government generally very supportive, we are exploring further ways of assistance

• Staff attrition

• Bureaucratic procedures (National & Institutional levels)
  – Need for forward planning
  – Aggressive pursuit of issues
Conclusion

- Three injections with HIV-1 plasmid DNA as prime with a single HIV-1 MVA boost are safe and gave strong IFN-gamma Elispot reactivity 2 weeks after the last injection in over 90% of healthy Swedish volunteers.
- Preparations for the conduct of a Phase I/II trial in Tanzania are at an advanced stage, and the trial is expected to start in November, 2006.
- Additional financing crucial to realise the trial to completion in Tanzania & pave the way for more trials.
HIVIS Study group
Support by EU and Sida/SAREC

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Thank you for your attention!