Infant HIV-1 Vaccine Development

Tomáš Hanke
University of Oxford
Building Capacity for Infant HIV-1 Vaccine Clinical Trial Centres in Nairobi, Kenya and Fajara, The Gambia

Hanke

Flanagan (Rowland-Jones)

Jaoko

John-Stewart

Reilly

Joseph

UNIVERSITAT DE BARCELONA
Objectives

1. To build capacity for infant HIV-1 vaccine trials at two sites in Africa

2. To carry out 2 HIV-1 vaccine clinical trials in infants born to
   HIV-1-negative mothers (The Gambia)
   HIV-1-infected mothers (Kenya)

3. To construct a novel Investigational Medicinal Product under GLP
   BCG.HIVA
Unacceptably high number of infants gets infected with HIV-1 through their mother’s breast milk.

The best solution is development of a safe, accessible, prophylactic paediatric vaccine against breast milk transmission (and a vaccine for adults to decrease infection of mothers).
To induce protective responses against breast milk transmission, i.e. at birth, we proposed a vaccine regimen consisting of

At birth

**BCG.HIVA prime** – **MVA.HIVA boost**

BCG is a TB vaccine  MVA is a smallpox vaccine

MVA85A as a boost for BCG is in two phase IIb trials in RSA and Senegal

Such strategy may provide a basis for a life-long protection against HIV-1, which can be maintained by enhancing boosts later in life

As the first step towards the infant BCG.HIVA-MVA.HIVA regimen, we decided to test

The safety and immunogenicity **MVA.HIVA** (the boost vaccine) in 20-week-old infants

** Its compatibility with other childhood vaccines (EPI or KEPI)

No safety data on **BCG.HIVA** from humans
The Vaccine MVA.HIVA

The Vector MVA
Modified vaccinia virus Ankara (MVA)
Non-replicating attenuated poxvirus used as a smallpox vaccine
GOOD BOOSTER, weak primer

The immunogen HIVA (designed 1999)
Consists of HIV-1 Gag p24/p17 capsid subunits of consensus African clade A
coupled to a string of overlapping T killer cell epitopes

Hanke and McMichael 2000 Nat Med 6: 951
MVA.HIVA had been used, and found safe and immunogenic in 375 adult volunteers in the North and South.

<table>
<thead>
<tr>
<th>Trial/Vaccine</th>
<th>Site</th>
<th>Subjects</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAVI 001</td>
<td>Oxford</td>
<td>18 healthy HIV-1-negative</td>
<td>S/I</td>
</tr>
<tr>
<td>IAVI 002</td>
<td>Nairobi</td>
<td>18 healthy HIV-1-negative</td>
<td>S/I</td>
</tr>
<tr>
<td>IAVI 003</td>
<td>Oxford</td>
<td>8 healthy HIV-1-negative</td>
<td>S/I</td>
</tr>
<tr>
<td>IAVI 004</td>
<td>Nairobi</td>
<td>20 healthy HIV-1-negative</td>
<td>S/I</td>
</tr>
<tr>
<td>IAVI 005</td>
<td>IAVI 001+MVA.HIVA</td>
<td>9 healthy HIV-1-negative</td>
<td>S/I</td>
</tr>
<tr>
<td>IAVI 006</td>
<td>Oxford/London</td>
<td>119 healthy HIV-1-negative</td>
<td>S/I, DNA dose</td>
</tr>
<tr>
<td>IAVI 008</td>
<td>Nairobi</td>
<td>10 healthy HIV-1-negative</td>
<td>S/I</td>
</tr>
<tr>
<td>IAVI 009</td>
<td>Entebbe</td>
<td>50 healthy HIV-1-negative</td>
<td>S/I, no. of primes</td>
</tr>
<tr>
<td>IAVI 010</td>
<td>Nairobi/London</td>
<td>114 healthy HIV-1-negative</td>
<td>S/I, MVA dose &amp; route</td>
</tr>
<tr>
<td>IAVI 011</td>
<td>Cape Town/London</td>
<td>111 healthy HIV-1-negative</td>
<td>S/I, MVA dose &amp; route</td>
</tr>
<tr>
<td>IAVI 016</td>
<td>Oxford</td>
<td>24 healthy HIV-1-negative</td>
<td>S, more detailed I</td>
</tr>
<tr>
<td>Ther 001</td>
<td>Oxford</td>
<td>10 HIV-1-infected/HAART</td>
<td>S/I</td>
</tr>
<tr>
<td>Ther 002</td>
<td>Oxford</td>
<td>10 HIV-1-infected/HAART</td>
<td>S/I</td>
</tr>
<tr>
<td>Ther 003</td>
<td>Oxford</td>
<td>10 HIV-1-infected/HAART</td>
<td>S/I</td>
</tr>
</tbody>
</table>

*Hanke et al. 2007 J Gen Virol 88: 1*

MVA is a week prime, but a good boost
Need a stronger primer than DNA
1 Capacity Building
The Sukuta Health Centre was substantially redesigned and refurbished, significantly increasing capacity and efficiency. Staff on the site have been trained in GLP, GCP, data and project management and 2 students enrolled into Masters/PhD programmes.
Capacity Building in Kenya

We have established of an Infant HIV-1 Vaccine Clinical Trials Centre at the Department of Paediatrics and Child Health at the University of Nairobi, which includes new equipment and specimen repository. Staff activities and training include laboratory, GCP, and data and project management. 4 students enrolled into Masters studies.
2 PedVacc001 and 002 Infant HIV-1 Vaccine Clinical Trials
**PEDVACC001 - Sukuta, The Gambia**

An Open Randomized Phase I Study Evaluating Safety and Immunogenicity of a Candidate HIV-1 Vaccine, MVA.HIVA, Administered to Infants Born to HIV-1/2-Uninfected Mothers

**Population:**
Plan: N = 48
24 healthy infants who have received all Expanded Programme on Immunization (EPI) vaccines to date randomized to MVA.HIVA
24 healthy infants who have received all EPI vaccines to date randomized to no treatment

**Description of Investigational Product/ Intervention:**
1 low dose of $5 \times 10^7$ pfu of MVA.HIVA administered intramuscularly at week 20 of age

**Objectives:**
**Primary:**
Safety and immunogenicity of MVA.HIVA vaccine in 20-week-old healthy Gambian infants born to HIV-1/2-uninfected mothers.

**Secondary:**
Gross impact of MVA.HIVA on the immunogenicity of EPI vaccines (DTP, HiB, HepB, and OPV) when administered at 20 weeks (4 weeks after the last EPI vaccines) to infants, who have had BCG vaccine within the first 4 weeks of life.
Enhance existing capacity for Infant Vaccine Clinical Trials in Sukuta, The Gambia.
**Population:**
Plan: N = 72 mostly breastfeeding infants
36 healthy infants who have received all Kenyan EPI (KEPI) vaccines to date randomized to MVA.HIVA
37 healthy infants who have received all KEPI vaccines to date randomized to no treatment

**Description of Investigational Product/Intervention:**
1 low dose of 5x10^7 pfu of MVA.HIVA administered intramuscularly at week 20 of age

**Objectives:**
**Primary:**
Safety and immunogenicity of MVA.HIVA vaccine in 20-week-old healthy Kenyan infants born to HIV-1-infected mothers.

**Secondary:**
Comparison of responses to certain KEPI vaccines (DTP, HiB, HepB, and OPV) between MVA.HIVA and unvaccinated controls
Build capacity for Infant HIV-1 Vaccine Clinical Trials Centre in Nairobi, Kenya
Primary endpoints:
MVA.HIVA vaccine was well tolerated in 20-week old infants with no SAE

There we no vaccine-elicited responses detected in ex vivo IFN-γ ELISPOT assay in PV001 and PV002

In cultured IFN-γ ELISPOT assay

PV001: statistically significant differences between the unvaccinated and vaccinated infant groups were found: P9 at 1 week and P1&P2 at 8 weeks post-vaccination

PV002 cultured IFN-γ ELISPOT assays are on going

Secondary endpoints:
MVA.HIVA did not interfere with antibody induction by EPI or KEPI
**PV001 immunogenicity in cultured IFN-γ ELISPOT assay**

<table>
<thead>
<tr>
<th>Age of study infants</th>
<th>16w</th>
<th>19w</th>
<th>20w</th>
<th>21w</th>
<th>28w</th>
<th>36w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study visit</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Bleeding schedule</td>
<td>-1w</td>
<td>+1w</td>
<td>+8w</td>
<td>+16w</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative to study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>product administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Group 1 (n=24)**
  - EPI
  - Bleed
  - MVA.HIVA
  - Bleed
  - Bleed
  - Bleed
  - EPI
  - ESP

- **Group 2 (n=24)**
  - EPI
  - Bleed
  - Bleed
  - Bleed
  - Bleed
  - EPI
  - ESP

**HIV-1 gag**

- p24
- p17

**CTL epitopes**

- Pool 1
- Pool 2
- Pool 3
- Pool 4
- Pool 9
- Pool 90 (1+2+3+4)
This slide was removed by the presenter because it contained unpublished data
This slide was removed by the presenter because it contained unpublished data
This slide was removed by the presenter because it contained unpublished data
3 Construction of Novel IMP
Successful construction of GLP BCG.HIVA\textsuperscript{CAT}
PedVacc Conclusions

All planned outcomes achieved

Enhanced capacity at two sites
  New equipment was purchased
  Staff trained in laboratory, GCP, data and project management
  6 students enrolled into Masters/PhD programmes.
Substantial networking was facilitated by setting up strong North-North, North-South and particularly South-South collaborations regarding data and project management, assay design and methodology.

Two clinical trials carried to the highest ethical standards
  100% retention of infants in both trials
  Vaccine was well tolerated
  Vaccine was marginally immunogenic in a small number of infants
  Vaccine did not interfere with EPI

A new strategy for constructing safer (lysine auxotroph) rBCG has been developed
Future Directions for Infant Vaccine

Novel Immunogen

Novel Delivery
The Biggest Challenge to Both T- and B-Cell Vaccine Development Are

HIV-1 Diversity and Escape
HIVconsv – Immunogen Based on Conserved Regions of the HIV-1 Proteome

The 14 most highly conserved regions of HIV-1 proteins

Létourneau et al., PLoS ONE 2007
Targeting HIV-1 Where It Hurts

- Clade Consensus: to reflect variation within clades
- Alternating 4 major clades: to ensure equal clade representation
- Mutations in these regions are likely associated with fitness loss
- Altering natural (unprotective) hierarchy of epitope responses
- Can be deployed in Africa, Asia, Europe, America; it is universal
Vaccine Modalities Delivering HIVconsv

Plasmid DNA

DREP/VREP
Semliki Forest virus replicons

SLP
adjuvanted peptides

ChAdV-63
attenuated chimp adenovirus

BCG
AERAS
Joan Joseph

MVA
attenuated poxvirus

HAdV-5
STEP trial

Synthetic gene - Humanized codons

Gag  Pol  Vif  Env  Epitopes
HIV-CORE002
Healthy, Low-Risk Volunteers Oxford, UK

March 2011 – August 2012
Extension to bleed at 1 and 2 years

D – DNA.HIVconsv; M – MVA.HIVconsv; C – ChAdV63.HIVconsv
This slide was removed by the presenter because it contained unpublished data
This slide was removed by the presenter because it contained unpublished data.
This slide was removed by the presenter because it contained unpublished data
This slide was removed by the presenter because it contained unpublished data
This slide was removed by the presenter because it contained unpublished data
Future Directions for Pediatric Vaccines

New immunogen that better addresses HIV-1 diversity and escape
HIVconsv – conserved regions of HIV-1

Dual MVA.HIVconsv.85A
MVA85A is a TB vaccine currently in two efficacy trials in Africa as a boost to BCG

The second-generation vaccine platforms

BCG.HIVconsv prime – MVA.HIVconsv.85A boost

BCG+ChAdV63.HIVconsv prime - MVA.HIVconsv.85A boost

BCG prime – MVA.HIVconsv.85A boost (control arm)

Grant application to FP7 is on hold

+ Early passive protection?
Acknowledgements PedVacc

UNIV OF OXFORD
Tomáš Hanke
Antony Black
Nicola Borthwick

THE GAMBIA UNIT
Katie Flanagan
(Sarah Rowland-Jones)
Muhammed Afolabi
Jorjoh Ndure
Vivat Thomas
David Parker
Jenny Mueller
& the study team

UNIV OF NAIROBI
Walter Jaoko/
Grace John-Stewart
Barbara Payne
Christine Gichuhi
Irene Njuguna
Moses Mundia
James Osanya
Amos Thairu
Elizabeth Obimbo
Ruth Nduati
Dorothy Mbori-Ngacha
Dalton Wamalwa
& the study team

KAROLINSKA INSTITUTE
Marie Reilly

UNIV OF WASHINGTON
Grace John-Stewart
Gwen Ambler

DMEC COMMITTEE
Frances Gotch (co-C), Glenda Grey (co-C), Maria Grazia Valsecchhi, Laura Guay, Aggrey Wassuna, Eduard Sanders

TSC COMMITTEE
Pontiano Kaleebu (C), Clive Gray, Stephen Howie, James Berkley

We thank all the mother and infant volunteers for making these trials possible
ACKNOWLEDGEMENTS

HIV-CORE002

UNIVERSITY OF OXFORD
LAB AND TRIAL

NICOLA BORTHWICK
BEATRICE ONDONDO
TINA AHMED
GENEVIEVE CLUTTON
SULTAN ABDUL-JAWAD
ALICE MBEWE-MVULA
ANNIE ROSE
UMAR EBRAHIMSA
EMMA-JO HAYTON
ANNE BRIDGEMAN
ANDREW McMICHAEL
LUCY DORRELL

UNIVERSITY OF OXFORD
CLINICAL BIOMANUFACTURING
FACILITY

ELEANOR BERRIE
SARAH MOYLE
CATHY OLIVEIRA
ALISON CROOK
EMMA BOLAM
ADRIAN HILL

CBMF

OKAIROS

ALFREDO NICOSEIA
ROBERTO CORTESE
STEFANO COLLOCA
VIRGINIA AMMENDOLA

IAVI

PETER HAYES
JILL GILMOOUR
JOSEPHINE COX
PAT FAST
WAYNE KOFF

LOS ALAMOS NATIONAL
LABORATORY

BETTE KORBER

MRC Medical Research Council