Thailand’s Contribution to HIV Vaccine Research and Development

: As Part of Global Collaboration

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AIDSVACCINE Conference, BKK
Sept 13, 2011
• National Plan for AIDS Vaccine Research and Development
• Efforts for Vaccine Development
• Preparation for phase III
• The two phase IIs
• Future
HIV prevalence among female sex workers, male STD clinic patients and IDU

Source: HIV serosurveillance, Bureau of Epidemiology
1993 Thailand was chosen to be one of the potential countries for HIV vaccine R&D

• The National Plan for HIV/AIDS vaccine Development and evaluation was written with WHO GPA support

• Establishment of AIDS Vaccine Collaborating Unit at MOPH under the National AIDS Commission
• The plan was revised in 2002, 2006
• Revised National Plan 2006- to include
  - Transfer of technologies
  - Policy on communication among various partners eg. policy makers, investigators/health personnel/community leaders/volunteers/NGO/media group
  - Community involvement – community advisory board
Leading to various national and International COLLABORATIONS

• Bangkok Vaccine Evaluation Group (BVEG), TUC, US-CDC, Vaxgen Inc. 1994-2003
• Thai Aids Vaccine Evaluation Group (TAVEG) supported by MHRP 1997-now
• MOPH – TAVEG is supported by MHRP, NIH
• Thai - Japan Collaboration
• Thai Red Cross- Chulalongkorn U and Australian Collaboration
Thailand’s Efforts for developing subtype E vaccines

• 1997—Collaboration between Thailand and Japan on Research and Development of an HIV Vaccine
  BCG as a vaccine vector

• Live recombinant BCG vectors expressing HIV-1 or simian immunodeficiency virus (SIV) proteins have been reported to induce HIV-specific immune responses in animal models against a variety of antigens, such as Gag, Env, and Nef.

Prime boost immunization comprising rBCG and rVaccinia virus-DIs

- Protective immunity of r BCG/SIV Gag primed s/c and r DIs/SIV gag iv boosted against SHIV challenge showed
  - Better viral set point
  (<100 times of the control, rBCG alone or rDIs primed, rBCG boosted)

- Looking for funding support to continue

## Chulalongkorn University and TRC-ARC involvement in AIDS Vaccine

<table>
<thead>
<tr>
<th>Year</th>
<th>Type of Vaccine</th>
<th>Roles</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>DNA SEA mosaic AE/B vaccine (gag, pol, nef)</td>
<td>Immunogenic in mice with high ELISPOT IFNγ responses</td>
</tr>
<tr>
<td>2011-2012</td>
<td>DNA and MVA SEA mosaic (env or gag)</td>
<td>Will be evaluated in comparison to global mosaic DNA or MVA vaccine in non-human primates</td>
</tr>
</tbody>
</table>
Chula-initiative results Asian Mosaic AE/B: DNA Primed- Clade E vaccinia boosted: Results

VCI laboratory, Chula Medical Research Center, Chulalongkorn University

IFN$_\gamma$-ELISPOT responses of Mosaic AE/B gag

<table>
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<tr>
<th>Types of Vaccine</th>
<th>SFC / million splenocytes</th>
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<tr>
<td>Vaccinia AE</td>
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<td>Vaccinia B</td>
<td>1028, 544, 859, 1309</td>
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<tr>
<td>Mosaic gag DNA</td>
<td>430, 953, 930, 1151</td>
</tr>
<tr>
<td>Pooled peptides</td>
<td>1756, 930</td>
</tr>
</tbody>
</table>

Pooled peptides used and injection route:
- **P<0.01**
- AE ID
- AE NF
- B ID
- B NF

ID= intradermal
NF = needle free injection

Types of Vaccine

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Summary of HIV-vaccine trials in Thailand from 1993 to now—national and international collaborative efforts

<table>
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<tr>
<th>Year</th>
<th>Vaccine Construct</th>
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<tr>
<td>94</td>
<td>Modified vaccinia Ankara based vaccine</td>
</tr>
<tr>
<td>98</td>
<td>HIV-1 CM235 env/CM240 gag/pol vaccine</td>
</tr>
<tr>
<td>97</td>
<td>HIV-1 gag DNA with or without IL-12 DNA</td>
</tr>
<tr>
<td>98</td>
<td>pHis-HIV-AE (DNA) and rFPV-HIV-AE</td>
</tr>
<tr>
<td>99</td>
<td>MRKAd5 HIV-1 vaccine</td>
</tr>
<tr>
<td>00</td>
<td>ALVAC-HIV vaccine + gp 120 B/E vaccine boost</td>
</tr>
<tr>
<td>01</td>
<td>ALVAC-HIV vaccine + oligo gp 160 or gp 120 B/E vaccine boost</td>
</tr>
<tr>
<td>02</td>
<td>ALVAC-HIV vaccine + gp 120 B/E vaccine boost</td>
</tr>
<tr>
<td>03</td>
<td>AIDSVAX B/E</td>
</tr>
<tr>
<td>07</td>
<td>gp 120 alum subtype B/E (AIDSVAX B/E)</td>
</tr>
<tr>
<td>08</td>
<td>gp 120 MF 59 subtype B alone or with subtype E</td>
</tr>
<tr>
<td>09</td>
<td>gp 120 alum subtype B</td>
</tr>
<tr>
<td></td>
<td>gp 120 MF 59 subtype B</td>
</tr>
<tr>
<td></td>
<td>Peptide V3-MAPS</td>
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* The pink background is the projects which Mahidol U. involved.
Preparation for Phase III efficacy trial

- Setting up cohorts: Target population with sufficient HIV incident and assessing willingness to participate
- Monitoring/matching of circulating virus
- Assessing/looking for a suitable HIV/AIDS vaccine for advancement to phase III
- Facility and capacity:
  - Health infrastructural system
  - Laboratory capacity-safety lab and immunology lab
  - Personnel capacity/availability of in the host country
1993-2003: Trials of the first generation vaccine

National and international collaborative efforts

First generation vaccine with part of envelope proteins

* The pink background is the projects which Mahidol U. involved

Phase I/II trials

Phase III trials
Establishment of BMA Cohort (IDUs)

With the initial support from WHO and later US-CDC

Incident of 5.8 PY, Subtype E (79%), Subtype B (21%)

82.5% were willing to participate in vaccine trial
1997 three years after the national plan
Up to now for monitoring of the circulating virus

National HIV Repository and Bioinformatic Center (NHRBC) supported initially by WHO

In 2003, a new recombinant virus, combining subtype C and CRF01_AE, was reported from an HIV-1 infected Thai*
• Recombinant B,C,E has been reported
• Currently 1,765 HIV-1 nucleotide sequence of Thai viruses available in the NHRBC database
• About 200 new HIV isolates collected /year

Faculty of Medicine Siriraj Hospital, Mahidol University (Prof. Ruengpung Suttent)
• Certified by WHO to be National Laboratory of Drug Resistance and HIV Laboratory Science
• One of the international Regional Laboratories in Comprehensive antibody vaccine Immune Monitoring Consortium (CA-VIMC) under CAVD lead by Duke University –for HIV neutralizing assay

Arm Force Research Institute of Health Science: Thai-US lab similar results obtained
Data Management

1998 Up to now

- Data Management Unit (DMU) and now is BIOPHICS (Center of Excellance for Biomedical and Informatics)

Faculty of Tropical Medicine, Mahidol University

- Equipped with data-fax and manage e-CRF data base

- Training center for Bio informatics

With the support from Vaxgen Inc, MHRP, Rockefeller foundation
1998-2003 Bangkok-Vaccine Evaluation Group

- Bangkok Metropolitan Administration (BMA)
- Vaccine Trial Centre, Fac. of Tropical of Medicine, Mahidol U.
- Thai MOPH -US CDC Collaboration (TUC)
- Sponsor VaxGen
Randomized, Double-Blind, Placebo-Controlled Efficacy Trial of a Bivalent Recombinant Glycoprotein 120 HIV-1 Vaccine among Injection Drug Users in Bangkok, Thailand

Punnee Pitituttithum,1 Peter Gilbert,4 Marc Gurwith,5 William Heyward,5 Michael Martin,3 Fritz van Griensven,3 Dale Hu,5 Jordan W. Tappero,2 and Kachit Choopanya,2 for the Bangkok Vaccine Evaluation Groupa

1Department of Clinical Tropical Medicine, Mahidol University, and 2Bangkok Metropolitan Administration, Bangkok, and 3Thailand Ministry of Public Health–US Centers for Disease Control and Prevention Collaboration, Nonthaburi, Thailand; 4Statistical Center for HIV/AIDS Research and Prevention, Fred Hutchinson Cancer Research Center, Seattle, Washington; 5VaxGen, Inc., Brisbane, California; 6US Centers for Disease Control and Prevention, Atlanta, Georgia

Background. In Thailand, phase 1/2 trials of monovalent subtype B and bivalent subtype B/E (CRF01_AE) recombinant glycoprotein 120 human immunodeficiency virus type 1 (HIV-1) vaccines were successfully conducted from 1995 to 1998, prompting the first HIV-1 vaccine efficacy trial in Asia.

Methods. This randomized, double-blind, placebo-controlled efficacy trial of AIDSVAX B/E (VaxGen), which included 36-months of follow-up, was conducted among injection drug users (IDUs) in Bangkok, Thailand. The primary end point was HIV-1 infection; secondary end points included plasma HIV-1 load, CD4 cell count, onset of acquired immunodeficiency syndrome–defining conditions, and initiation of antiretroviral therapy.

Results. A total of 2546 IDUs were enrolled between March 1999 and August 2000; the median age was 26 years, and 93.4% were men. The overall HIV-1 incidence was 3.4 infections/100 person-years (95% confidence interval [CI], 3.0–3.9 infections/100 person-years), and the cumulative incidence was 8.4%. There were no differences between the vaccine and placebo arms. HIV-1 subtype E (83 vaccine and 81 placebo recipients) accounted for 77% of infections. Vaccine efficacy was estimated at 0.1% (95% CI, –30.8% to 23.8%; P = .99, log-rank test). No statistically significant effects of the vaccine on secondary end points were observed.

Conclusion. Despite the successful completion of this efficacy trial, the vaccine did not prevent HIV-1 infection or delay HIV-1 disease progression.

Thai AIDS Vaccine evaluation group
From first generation to second generation vaccine

** The pink background is the projects which Mahidol U. involved
Cohort
- Cohort of female commercial sex workers
- Cohort of sexually transmitted disease clinic users
- Cohort of military conscripts
- Cohort of factory workers

1999-2001 Community cohort in Cholburi (incident of 0.34-1.02/100PY)
and Rayong (incident 0.39/100PY) supported by MHRP
Benenson M et al, 2001
1998 onwards: Thai AIDS Vaccine Evaluation Group (TAVEG)

- Research Institute of Health Science (RIHES), Chiangmai University
- Arm Force Research Institute of Medical Science (AFRIMS) - Thai - US components
- Faculty of Medicine - Siriraj Hospital, Mahidol U.
- Vaccine Trial Centre, Faculty of Tropical Medicine, Mahidol U.

Sponsor
WRAIR MHRP
Phase III – MHRP, NIH
2003-2009 MOPH-TAVEG
• Phase III community trial-RV144

Sponsor
Phase III – MHRP, NIH
From 1998 Technology transfer and capacity Building for laboratory work by WRAIR, MHRP

- Anti HIV lab with QA - at AFRIMS
- Safety lab with QA - CAP certified at AFRIMS
- CTL assay eg. ELISPOT - at Siriraj, AFRIMS
- Thesis grant for Ph.D. students - at Siriraj & RIHES

Data Management - Establishing validating system and QA of data fax at Mahidol U.
Integrating the trial into the health care systems of the country

MOPH-District Hospital + staff
Primary health care center + staff
Village health volunteer

- **Clinical GCP compliance** teams (Mahidol U)
- Lab safety, antiHIV lab (AFRIMS-Thai, US)
  immune response (CTL, Humoral)
- Data management (Mahidol University)
- Coordinating unit-PI, MHRP
- **Trial Registry and Repository Center**
  at MOPH (>100,000 specimens were collected)
• Volunteers per month Mean, (SD) : 3,355 (1694)
• Volunteer Visits per month Mean, (SD) : 3,937 (1953)
• CRFs per month Mean (SD) : 13,804 (8127)
• QCs & Resolutions per month Mean (SD) : 1312 (786)
• Number of AEs and MedDRA coding = 24,782
Community involvement in HIV vaccine research-in general

Establishment of CAB activities

- Research Institute of Health Science, Chiangmai U (Sirisanthana T, et al) has the strongest CAB activity
- VTC, Mahidol University for Thai AIDS Vaccine Evaluation Group (TAVEG) (Pitisuttithum P, et al)
- MOPH-TAVEG (Reukknam S, et al)
RV144

- CAB
- Volunteer Relation activities- Project base-in all Phase I/II AND Phase III trials
- Volunteer network activities & Community health forum – in Phase III PB trial
Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

VE = 31.2%

5 years of efforts of various collaborations: MOPH. Mahidol U, AFRIMS-Thai US. MHRP, NIH, SP, GSID
Post and Beyond RV144
RV 144 Correlates Discovery Effort

Implications for future clinical development of this product

**Scientific Advisory Groups**

- Humoral & Innate Immunity
- Cellular Immunity
- Host Genetics
- Animal Models

**Product Development Advisory Group**

**PA H Steering Committee**

**MHRP - DAIDS Steering Committee**

**RV144 Steering Committee**

Implications for future scientific inquiry into the result and evaluation/design of other candidates and studies

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Two Phases of Correlates Discovery

- **Phase I (2010 - Present)**
  - Broad survey of innate, humoral, systems biology, genetic, and cellular assay evaluation/comparison.
  - Multiple Bab, Nab, ADCC, ADCVI approaches
  - Statistical plan

- **Phase II (May - July 2011)**
  - Case-control
  - Evaluation of a broad range of assays but with downselection of depth to optimize the statistical design

- **4000+ specimens have been shipped to Duke and University of Washington for aliquoting, final shipment and analysis**
RV144 Correlates Research: Collaborating Institutions

- 35 investigators from 20 institutions working on 32 different assays (~150 total staff)

- Cornell, Duke, Harvard, UCSC, UCI, Rush, U Mass, Northwestern, NYU, U Wash, Oxford, Kings College, Mahidol, St. George’s, U Melbourne, Scripps, IHV (U Maryland), VGTI (OSHU), MHRP, Monogram Bio, NIH (NIAID, NCI)
Summary: A244 gp120 and induced immune responses

**Antigenicity**
- Preferential binding to gD+ proteins (Mab)
- Binding to quaternary structure recognizing Mab
- A32 binding
- Similar features in prime vCP1521
- Are all pox-protein combinations equal?

**Induced Immune Responses**
- Binding antibody to V2
- Vaccine sera show blocking Ab “signature” targeting V2, V2V3, C1
- Env- and V2-specific Bab decrease after vaccination
- Monoclonal antibodies from sorted B cells are specific for V2 and other gp120 epitopes
- Cellular immune responses generated to V2

• How did these antigens affect induced immune responses?
• Were there responses that differentiate RV144 from the Vax003 trial?
• Were any of these features responsible for the observed, modest protection?


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Part of the Regional Network: AIDS Vaccine for Asia Network (AVAN)

- **AVAN’s Vision** is to develop a safe and effective HIV vaccine and ensure its access as a part of a comprehensive public health strategy for the control of new HIV infections across the region.

- An Asia-specific strategic HIV vaccine plan in alignment with the Global HIV Vaccine Enterprise was developed in 2009 in Beijing.

- The permanent secretariat was established in 2010.
• RV305- with same vaccines used in RV144 adding different boosting regimens
• RV306 –with again further boosting to maintain and antibody response
• Establishment of high risk MSM cohorts by TUC, US-CDC in BKK and MHRP in Pattaya
• Plan for another efficacy trial in high risk group
• Expanding the collaboration within the region AVAN, AAVP- North –South and South-South collaborations
The search must continue through global collaborative efforts till we get an AIDS vaccine.