Phase III Clinical Trial of Prime-Boost HIV Vaccine Combination in HIV-Negative Thai Adults

VRBPAC Briefing
23 September 2004
Speakers

- Perspective from Thai National AIDS Commission
  - Prof Dr Prasert Thongcharooen
- Background and study results
  - LTC Arthur Brown
- Phase III study design and status
  - Dr Supachai Rerks-Ngarm
Collaborative Research towards Preventive HIV Vaccine

- HIV collaboration between U.S. and Thai Armies
  - Since 1991, focus on preventive vaccine
- Collaboration expanded to universities and vaccine manufacturers
- Creation of the Thai AIDS Vaccine Evaluation Group (TAVEG)
- Thai Ministry of Public Health (MOPH)
  - National HIV Vaccine Development Plan in 1993
HIV Vaccine Research & Development in Thailand

Professor Emeritus Dr. Prasert Thongcharoen

- Chairman, Subcommittee on HIV/AIDS Vaccine Development, Thai National AIDS Commission
- Fellow of the Royal Institute, Grand Palace
- Advisor, Faculty of Medicine Siriraj Hospital
- Mahidol University
Presentation Overview

- Thailand National plan for HIV/AIDS vaccine development
- Government commitment
- Independent technical and scientific review of protocols and research proposals
- Development of infrastructure and training
National Plan for HIV/AIDS Vaccine Development and Evaluation

- Developed by Thai MOPH and research scientists with GPA/WHO collaboration

- Approved by NAC and launched in 1993 placing HIV vaccine research and development on the “fast track”

- Aimed at research and development of safe, effective, affordable and accessible HIV vaccines for the Thai people at the earliest possible date
National Plan for HIV/AIDS Vaccine: Objectives

- To develop a comprehensive, well-coordinated, long-term strategy for the evaluation of the safety, immunogenicity and efficacy of preventive, therapeutic and perinatal HIV/AIDS vaccines in Thailand

- To develop and explain the policies and procedures for the planning, implementation, oversight, administration and evaluation of HIV/AIDS vaccine-related research activities in Thailand

- To facilitate the conduct of scientifically and ethically appropriate HIV/AIDS vaccine trials in Thailand
National Plan for HIV/AIDS Vaccine: Infrastructure and Research Activities

- Establish virological and immunological HIV expertise
- Strengthen clinical (GCP) and laboratory facilities (GLP) for Phase I, II and III trials
- Develop epidemiological and intervention research studies required for cohort development
- Conduct social and behavioral research
- Establish appropriate data management systems
- Establish the National Specimen Repository
Commitment and Support

The National AIDS Commission (NAC)

Chairman: Prime Minister

Department of Disease Control, MOPH

1. Subcommittee on Plan & Budget Monitoring & Evaluation
2. Subcommittee on Provincial AIDS committee
3. Subcommittee on HIV/AIDS Vaccine Development
National Plan for HIV/AIDS Vaccine: Subcommittee on Vaccine Development

- To identify and prioritize research activities related to HIV/AIDS vaccine evaluation
- To provide coordination for all HIV/AIDS vaccine-related activities in Thailand
- To provide scientific and technical review of all HIV/AIDS vaccine-related research protocols and proposals
Scientific and Technical Review of Proposals and Protocols

- To be submitted to the Subcommittee on HIV/AIDS Vaccine Development and reviewed for technical value before the research can be implemented.

- The Subcommittee ensures that vaccine protocols meet appropriate regulatory requirements.

- Upon the request of the Ministry of Public Health, the research proposals and protocols would also be reviewed by the WHO/UNAIDS Steering Committee on Vaccine Development, by an independent review group in Thailand, and when applicable, by other funding agencies and the investigators’ host institutions.
### Summary of HIV Vaccine Clinical Trials in Thailand 1994 - 2004

<table>
<thead>
<tr>
<th>Year</th>
<th>Phase</th>
<th>Candidate Vaccine</th>
<th>Volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>I</td>
<td>V3 octameric peptide</td>
<td>24</td>
</tr>
<tr>
<td>1995</td>
<td>I/II</td>
<td>rgp 120 B (MN)</td>
<td>30</td>
</tr>
<tr>
<td>1995</td>
<td>I/II</td>
<td>rgp 120 B (SF2)</td>
<td>52</td>
</tr>
<tr>
<td>1996</td>
<td>I</td>
<td>HIV-1 Immunogen</td>
<td>30 (HIV+ve)</td>
</tr>
<tr>
<td>1997</td>
<td>II</td>
<td>HIV-1 Immunogen</td>
<td>297 (HIV+ve)</td>
</tr>
<tr>
<td>1997</td>
<td>II</td>
<td>rgp 120 B/E (SF2/CM235)</td>
<td>380</td>
</tr>
<tr>
<td>1998</td>
<td>II</td>
<td>rgp 120 B/E (MN/A244)</td>
<td>90</td>
</tr>
<tr>
<td>1999</td>
<td>III</td>
<td>rgp 120 B/E (MN/A244)</td>
<td>2,545</td>
</tr>
<tr>
<td>2000</td>
<td>I/II</td>
<td>ALVAC vCP1521 + rgp 120 B/E</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ALVAC vCP1521 + rgp160 E</td>
<td>70</td>
</tr>
<tr>
<td>2000</td>
<td>I/II</td>
<td>ALVAC vCP1521 + rgp 120 B/E</td>
<td>133</td>
</tr>
<tr>
<td>2003</td>
<td>I/II</td>
<td>MRKAd-5 gag B</td>
<td>87</td>
</tr>
<tr>
<td>2003</td>
<td>III</td>
<td>ALVAC vCP1521 + rgp 120 B/E</td>
<td>16,000</td>
</tr>
</tbody>
</table>
Summary

National Plan for HIV/AIDS vaccine established in 1993 has led to:

- Development of appropriate local research, clinical infrastructure and training
- Independent scientific and technical review and selection of appropriate vaccine candidates and research proposals
- Sustained government support and commitment
Background and Phase II Study Results

VRBPAC Briefing
23 September 2004

LTC Arthur Brown, MD, MPH
U.S. Army Medical Materiel Development Agency
Fort Detrick, MD
Content

- Background
- Phase II study
- Advancing to Phase III
- Summary
Collaborative Research towards Preventive HIV Vaccine

- Research and capacity
  - Focus on virology, diagnostics, epidemiology, prevention education, and disease course
  - Infrastructure and capacity building

- Vaccines and trials
  - Tailored to local E & B strains
  - TAVEG tested four candidates in more than 700 subjects
Phase II Study Results
[Ref: JID 190: 702, 2004]

- Double-blind, placebo-controlled
- Vaccine candidates
  - ALVAC vCP1521 (Env, Gag-protease)
  - AIDSVAX B/E (monomeric rgp120)
  - Prime, with ALVAC IM at 0, 4, 12 and 24 weeks
  - Boost, with AIDSVAX IM at 12 and 24 weeks
- Three groups
  - 200 microgram boost
  - 600 microgram boost
  - Placebo
- Healthy adults, HIV EIA non-reactive
Phase II Study Results

- **Subjects**
  - 133 enrolled and 122 vaccinated

- **Safety and tolerability**
  - No vaccine-related serious adverse events
  - No severe local/systemic reactogenicity

- **Sero logic false positive rate**
  - EIA – 60%, WB – 2% (2 wk post-4th vaccination)

- **Intercurrent HIV infections**
  - None
# Phase II Study Results: Antibody Responses (%)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>200 mcg</th>
<th>600 mcg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding Ab</td>
<td>B</td>
<td>0</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>0</td>
<td>86</td>
</tr>
<tr>
<td>Neut Ab</td>
<td>B</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>0</td>
<td>47</td>
</tr>
<tr>
<td>ADCC Ab</td>
<td>B</td>
<td>11</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>7</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND: not done
Phase II Study Results:
HIV-Specific CD8 CTL Activity

- **Vaccine:**
  - Detection from post-2nd vaccination to 6 months post-4th vaccination
  - Cumulative frequency of 23%
  - Cross-clade activity

- **Placebo:**
  - Consistently negative
Phase II Study Results: Lymphocyte Proliferative Responses (%)

<table>
<thead>
<tr>
<th></th>
<th>gp120 E</th>
<th>gp120 B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinees</td>
<td>63</td>
<td>61</td>
</tr>
<tr>
<td>Placebo</td>
<td>7</td>
<td>24</td>
</tr>
</tbody>
</table>
Advancing to Phase III: Critical Factors

- Program decision regarding vaccine candidates:
  - Should induce humoral and cellular (CD4 helper and CD8 cytolytic) immune responses
  - Should match locally circulating HIV subtypes
Advancing to Phase III: Critical Factors

- Requirements re. vaccine candidates:
  - Safe and well tolerated
  - Immunogenicity comparable to candidate B constructs (ALVAC-HIV vCP205 and gp120 B studies)

- Requirements re. potential cohort:
  - Characterized, including HIV incidence and follow-up
Advancing to Phase III: Protocol Development

- Joint agreement among U.S. and Thai Governments, academia and manufacturers.
- Ten institutional and regulatory reviews.
- Presented to advisory committees:
  - Thai (National AIDS Commission)
  - U.S. (‘Baltimore’ Committee)
  - International (WHO-UNAIDS)
- Presented at meetings:
  - Thai national AIDS meetings
  - Barcelona International AIDS Conference
Advancing to Phase III: Sponsorship and Leadership

- **Sponsorship**
  - Office of the Surgeon General, U.S. Army (IND holder and funder)
  - Division of AIDS, NIAID, NIH (funder)

- **Executing Authority**
  - Thailand Ministry of Public Health

- **Principal Investigator**
  - Dr. Supachai Rerks-Ngarm

- **Multiple Collaborators**
In summary, this phase III study is founded upon …

- A decade of preparedness and capacity building
- Supportive scientific and clinical data
- A unique partnership among academia, governments and industry
Phase III Clinical Trial of Prime-Boost HIV Vaccine Combination in HIV-Negative Thai Adults

Briefing to VRBPAC, 23 Sep 2004

Dr. Supachai Rerks-Ngarm
Principal Investigator

Department of Disease Control
Ministry of Public Health, Thailand
A Phase III Trial of Aventis Pasteur Live Recombinant ALVAC-HIV (vCP1521) Priming With VaxGen gp120 B/E (AIDSVAX® B/E) Boosting in HIV-Uninfected Thai Adults

Primary Objective:

- To determine whether immunization with ALVAC-HIV (vCP1521) boosted by AIDSVAX® B/E gp120 B/E protects Thai volunteers from HIV infection

Secondary Objectives:

- To determine the effect of immunization on viral load after inter-current infection
- To determine the effect of immunization on CD4 cell count after inter-current infection
- To confirm the safety of this vaccine combination
- To evaluate whether participation is associated with behavior change increasing risk of HIV infection
Design

- Community-based, randomized, double-blind, placebo-controlled (vaccine to placebo 1:1)
- Vaccines:
  ALVAC-HIV (vCP1521) at 0, 4, 12, 24 weeks
  AIDSVAX® B/E at 12 and 24 weeks
- Volunteers, HIV negative, 20-30 years of age
- Follow-up for 3 years post-vaccination
Study Assumptions and Power

- Incidence of HIV infection: 0.34/100 person-years (based on lower bound of 95% CI of incidence found in cohort study)
- Lost to follow-up: 5% per 6 months
- Target for enrollment: 16,000
- Study would have 90.8% power to detect difference between vaccine and placebo if true efficacy is 50% or greater
Clinical Trial Features

- Women: test for pregnancy
- Reactogenicity evaluated for 72 hr post-vaccination
- Assessment of AEs and provision of risk reduction education at vaccine and follow-up visits
- Behavioral risk assessment at baseline and every 6 months
Clinical Trial Features

- HIV tested during screening, at week 24 and then every 6 months, with standard pre- and post-test counseling
- Plasma collected/stored at baseline and q 6 months; PBMCs at baseline, 6, 12 and 42 months
- Will utilize local health centers to enhance follow up of volunteers during post-immunization phase
A Phase III Trial of Aventis Pasteur Live Recombinant ALVAC-HIV (vCP1521) Priming With VaxGen gp120 B/E (AIDSVAX® B/E) Boosting in HIV-Uninfected Thai Adults
A Phase III Trial of Aventis Pasteur Live Recombinant ALVAC-HIV (vCP1521) Priming With VaxGen gp120 B/E (AIDSVAX® B/E) Boosting in HIV-Uninfected Thai Adults

47 Screening Sites

40 health centers and 7 district hospitals: 2 counselors each (Total personnel: ~100)
A Phase III Trial of Aventis Pasteur Live Recombinant ALVAC-HIV (vCP1521) Priming With VaxGen gp120 B/E (AIDSVAX® B/E) Boosting in HIV-Uninfected Thai Adults

8 Clinical Sites

7 district hospitals and 1 STD clinic

Personnel per site
Counselors: 10
Nurse Coordinators: 2
Site Physicians: 2
Clinical Research Co’s: 5
Pharmacy Nurses: 2
Research Assistants: 3
(Total personnel: ~200)
A Phase III Trial of Aventis Pasteur Live Recombinant ALVAC-HIV (vCP1521) Priming With VaxGen gp120 B/E (AIDSVAX® B/E) Boosting in HIV-Uninfected Thai Adults

- Registry
- Over 600,000 blood specimens
A Phase III Trial of Aventis Pasteur Live Recombinant ALVAC-HIV (vCP1521) Priming With VaxGen gp120 B/E (AIDSVAX® B/E) Boosting in HIV-Uninfected Thai Adults

Vaccine Distribution Center, Chon Buri
Current Status

- Screening started **29 Sep 2003**
- First vaccination **20 Oct 2003**
- Site by site initiation: all sites enrolling **Feb 2004**
- Enrollment as of 19 Sep 2004:
  - 9,384 volunteers screened
  - 5,587 volunteers enrolled
  (~200 volunteers/week)
A Phase III Trial of Aventis Pasteur Live Recombinant ALVAC-HIV (vCP1521) Priming With VaxGen gp120 B/E (AIDSVAX® B/E) Boosting in HIV-Uninfected Thai Adults

Demographics of Participants Enrolled to Date

**Gender**

- Male: n=3,142 (58%)
- Female: n=2,300 (42%)

**Birth Place**

- Chon Buri: 28%
- Rayong: 34%
- Other: 38%

(As of 16 Sep 04)
Demographics of Participants Enrolled to Date

- 39% Primary
- 51% Secondary
- 2% Vocational
- 2% Bachelor
- 2% Other
A Phase III Trial of Aventis Pasteur Live Recombinant ALVAC-HIV (vCP1521) Priming With VaxGen gp120 B/E (AIDSVAX® B/E) Boosting in HIV-Uninfected Thai Adults

Demographics of Participants Enrolled to Date

**Occupation**

- Laborer: 32%
- Office/Factory worker: 15%
- Agriculture/Fishery: 16%
- Govt. officer: 6%
- Housewife/Unemployed: 2%
- Others: 29%
Motivation for Joining Trial (Screening)

- **Altruism**: 84%
- **Want HIV testing**: 41%
- **To know HIV info.**: 37%
- **Want med. services**: 29%
- **Want HIV protection**: 37%
- **Others**: 13%
A Phase III Trial of Aventis Pasteur Live Recombinant ALVAC-HIV (vCP1521) Priming With VaxGen gp120 B/E (AIDSVAX® B/E) Boosting in HIV-Uninfected Thai Adults

Trial Oversight

- Pharmacovigilance Committee
- External monitoring by CRO (Quintiles Inc.)
- Data and Safety Monitoring Board
  - Chair Dr. Walter Dowdle
  - International membership
  - Meeting planned for every 6 months
  - Interim meeting in July 2004
Conclusions

DSMB comments

- Commended PI on professional conduct of trial
- No safety concerns identified
- Enrollment rate to be carefully monitored
- Recommended continuation of trial

Thank You