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 Thongcharoen
- 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

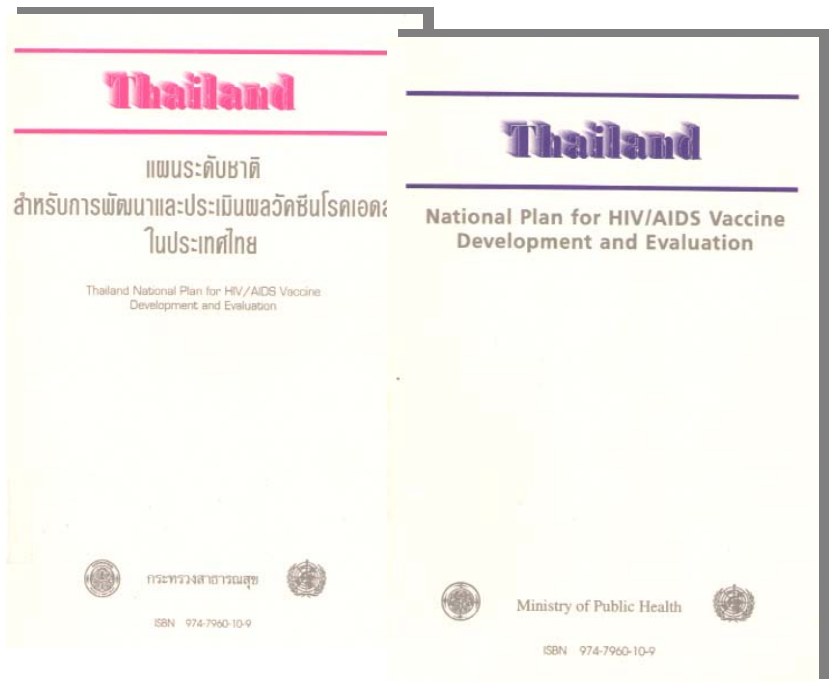
- Chairman, Subcommittee on HIV/AIDS Vaccine Development, Thai National AIDS Commission
- Fellow of the Royal Institute, Grand Palace
- Advisor, Faculty of Medicine Siriraj Hospital
- Mahidol University

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**

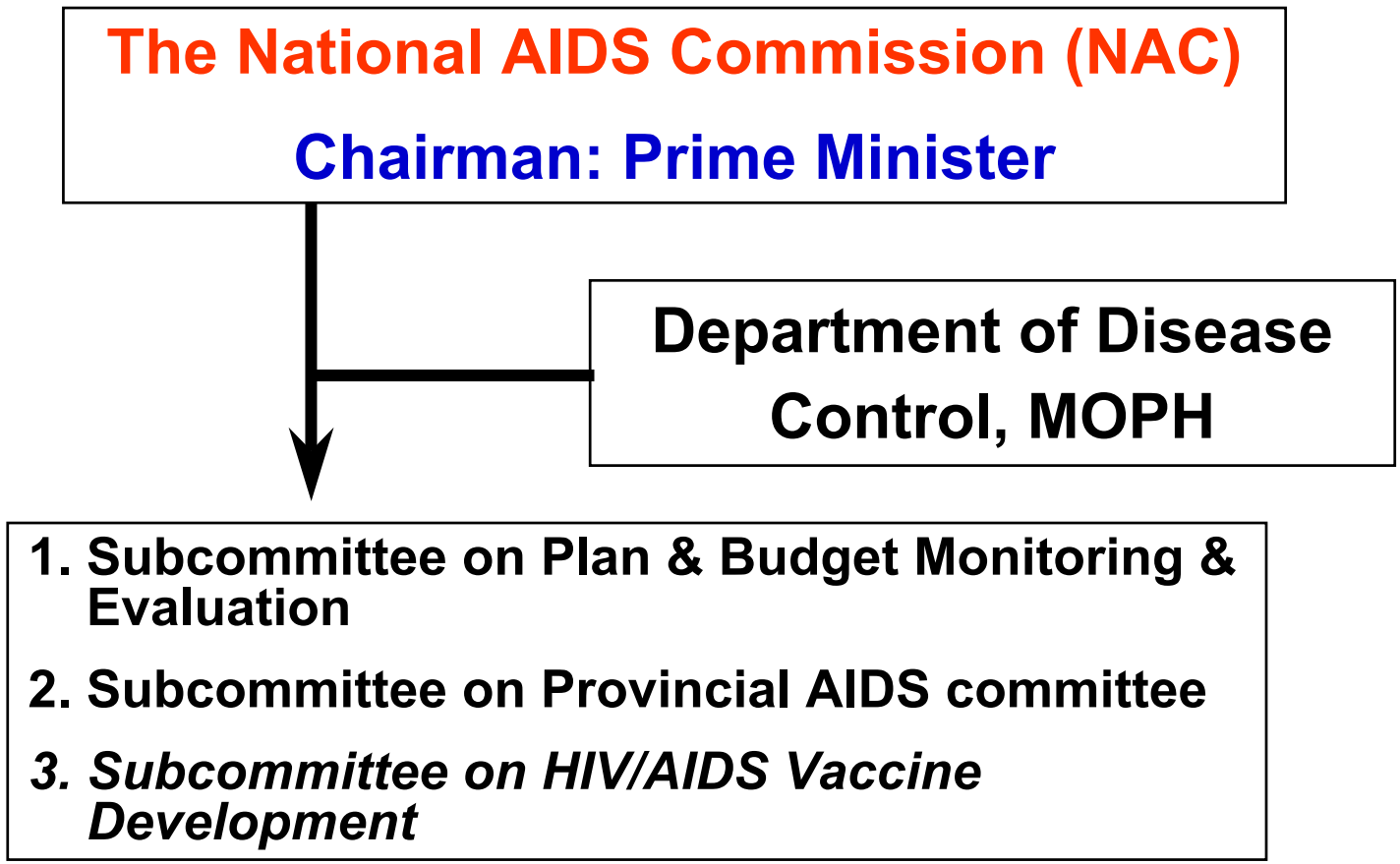
- **To develop and explain the policies and procedures for the planning, implementation, oversight, administration and evaluation of HIV/AIDS vaccine-related research activities in Thailand**

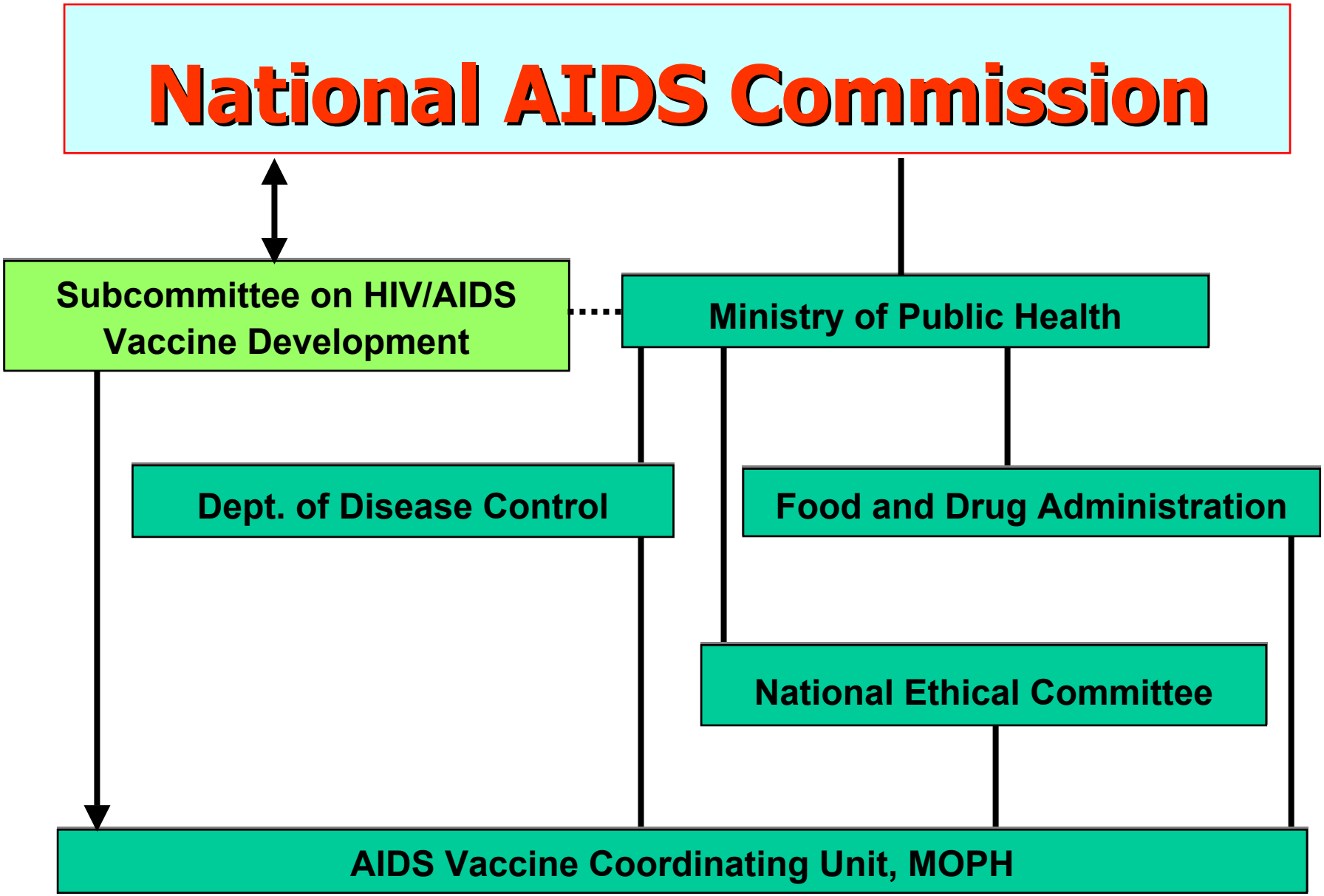
- **To facilitate the conduct of scientifically and ethically appropriate HIV/AIDS vaccine trials in Thailand**

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




National AIDS Commission
Subcommittee on HIV/AIDS Vaccine Development
Ministry of Public Health
Dept. of Disease Control
Food and Drug Administration
National Ethical Committee
AIDS Vaccine Coordinating Unit, MOPH

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

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

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
- Serologic false positive rate
  - EIA – 60%, WB – 2% (2 wk post-4th vaccination)
- Intercurrent HIV infections
  - None

Phase II Study Results: Antibody Responses (%)

		Placebo	200 mcg	600 mcg
Binding Ab	B	0	95	100
	E	0	86	96
Neut Ab	B	0	100	98
	E	0	47	71
ADCC Ab	B	11	ND	93
	E	7	ND	78

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 (%)

	gp120 E	gp120 B
Vaccinees	63	61
Placebo	7	24

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

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

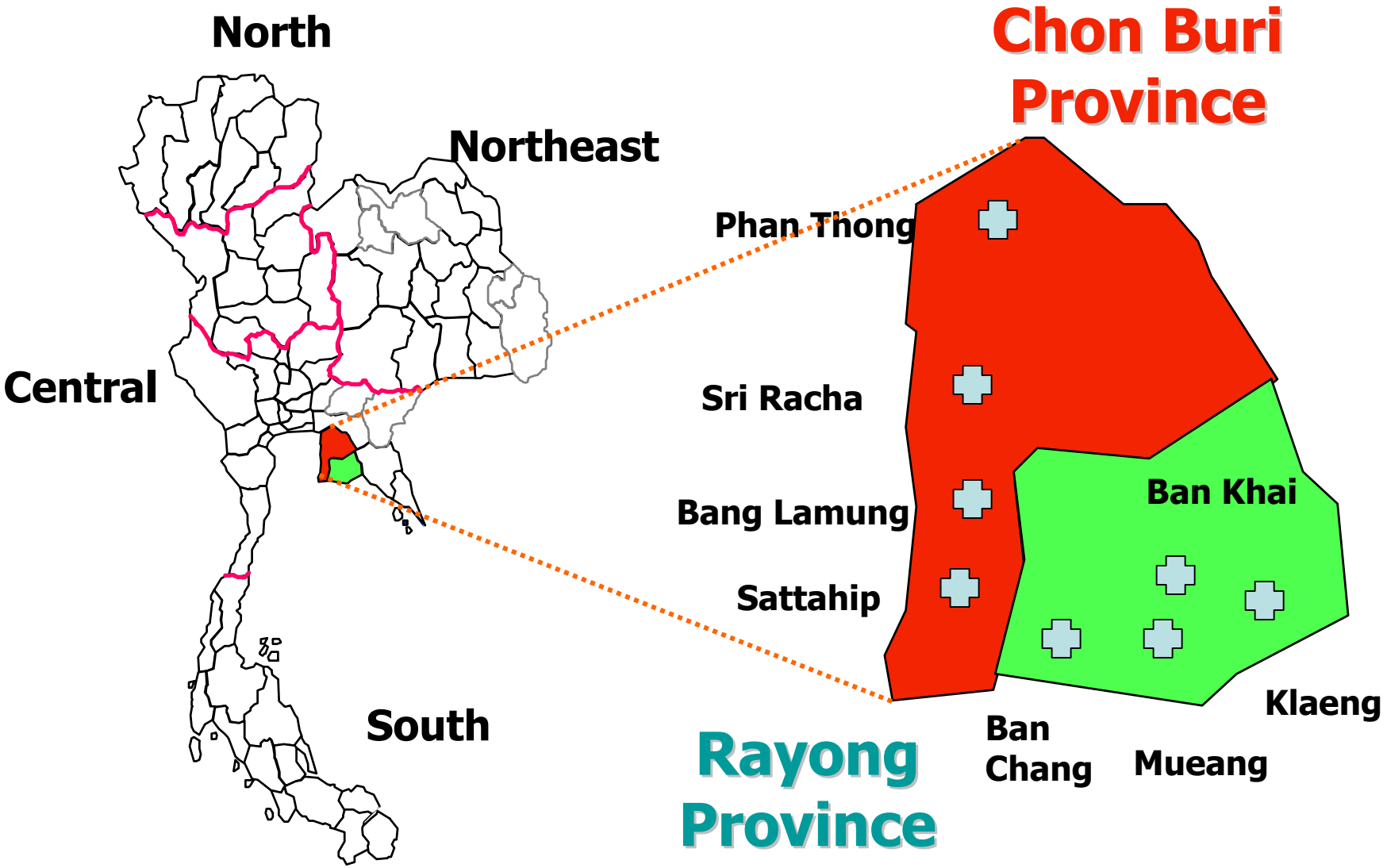
- **Incidence of HIV infection: 0.34/100 person-years (based on lower bound of 95% CI of incidence found in cohort study)**
- **Lost to follow-up: 5% per 6 months**
- **Target for enrollment: 16,000**
- **Study would have 90.8% power to detect difference between vaccine and placebo if true efficacy is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


North
Northeast
Central
South
Chon Buri Province
Phan Thong
Sri Racha
Bang Lamung
Sattahip
Ban Khai
Klaeng
Ban Chang
Mueang
Rayong Province

40 health centers and 7 district hospitals:
2 counselors each (Total personnel: ~100)

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)

- Registry
- Over 600,000 blood specimens

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**

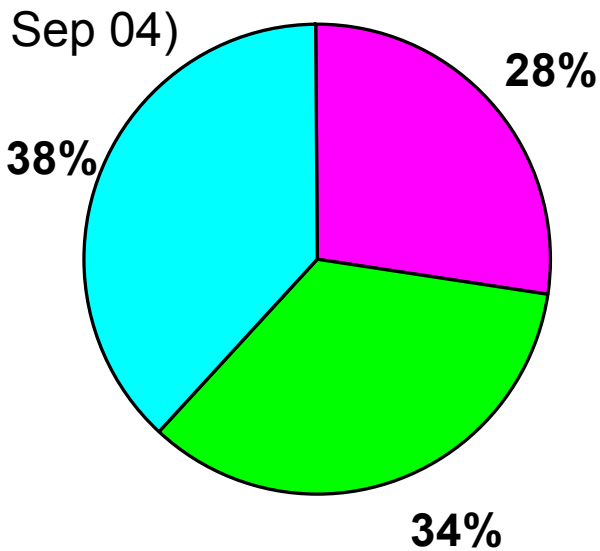
  (~200 volunteers/week)

Demographics of Participants Enrolled to Date

Gender

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

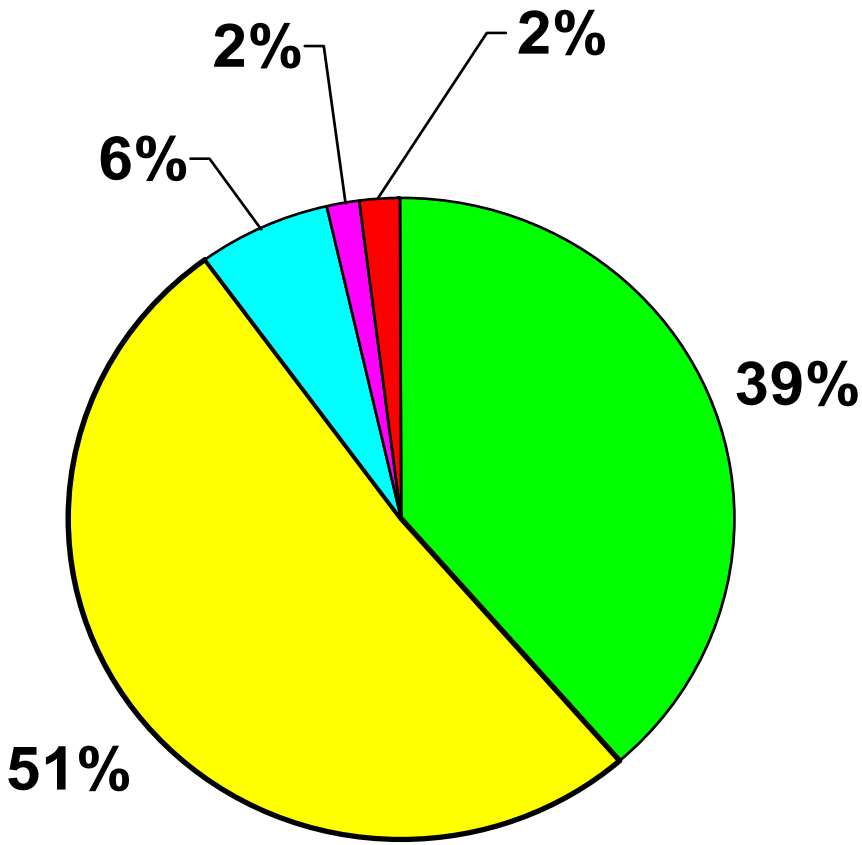
(As of 16 Sep 04)



Birth Place

- Chon Buri
- Rayong
- Other

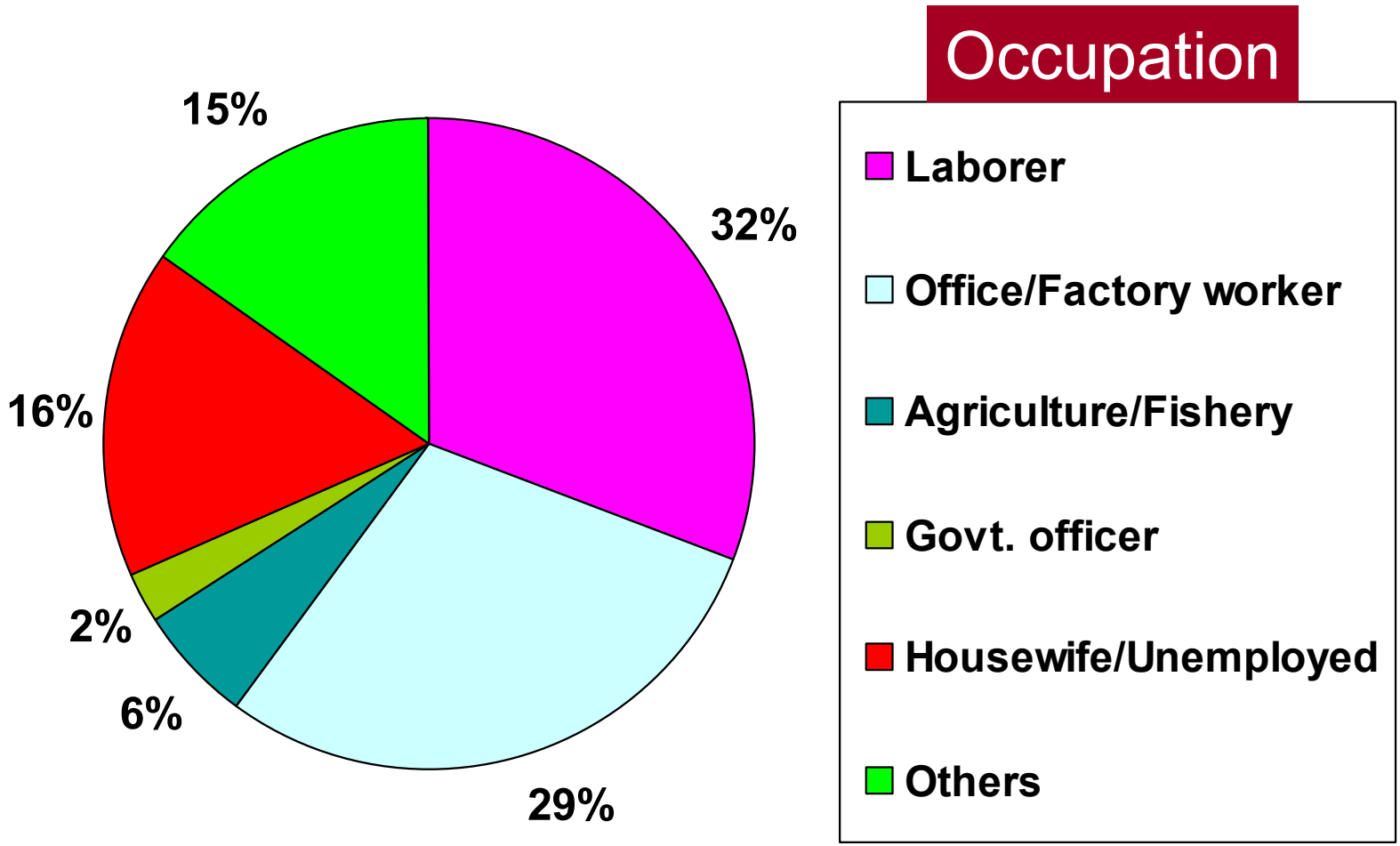
Demographics of Participants Enrolled to Date



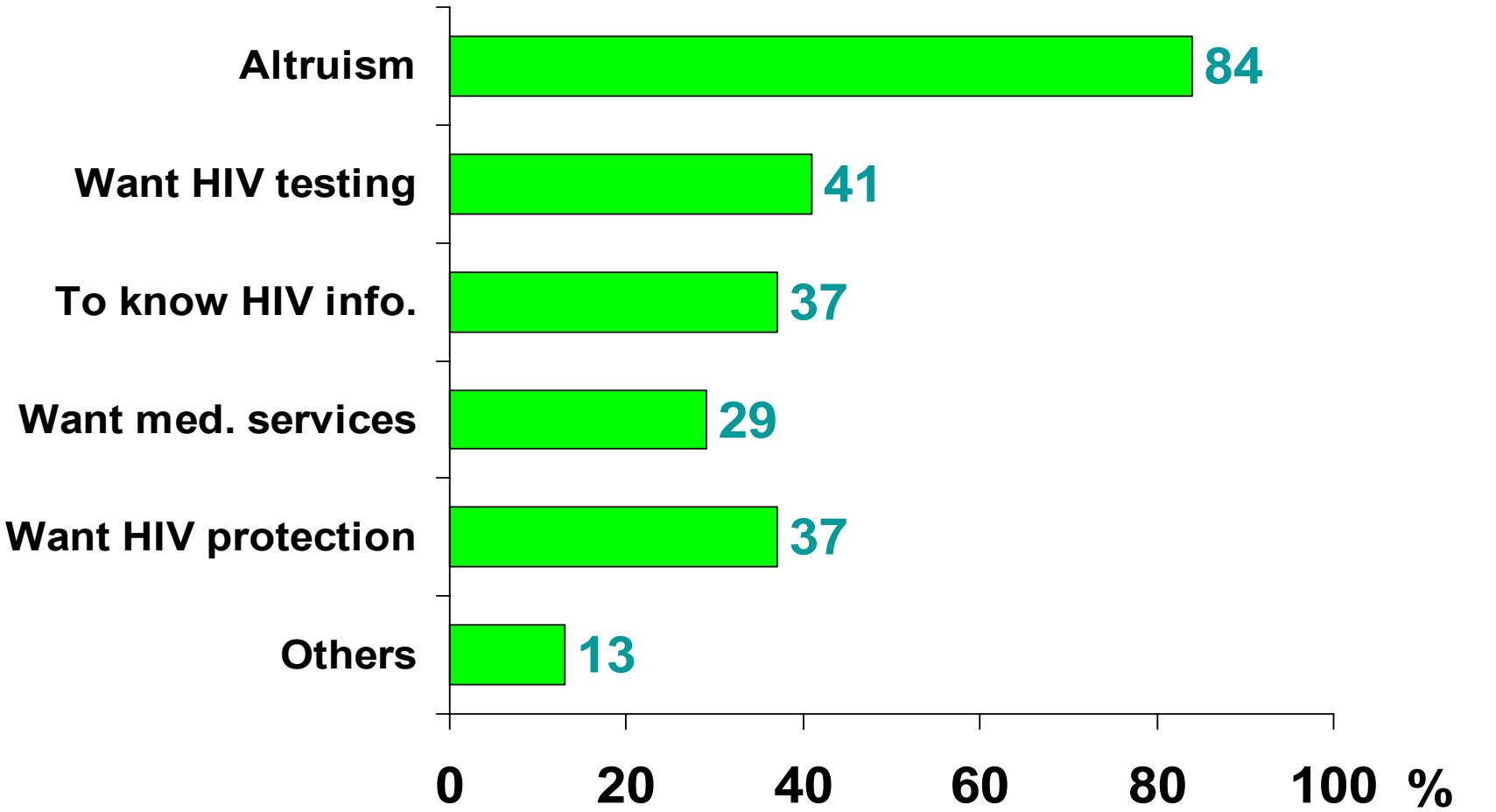
Educational level

- Primary
- Secondary
- Vocational
- Bachelor
- Other

Demographics of Participants Enrolled to Date



Motivation for Joining Trial (Screening)



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