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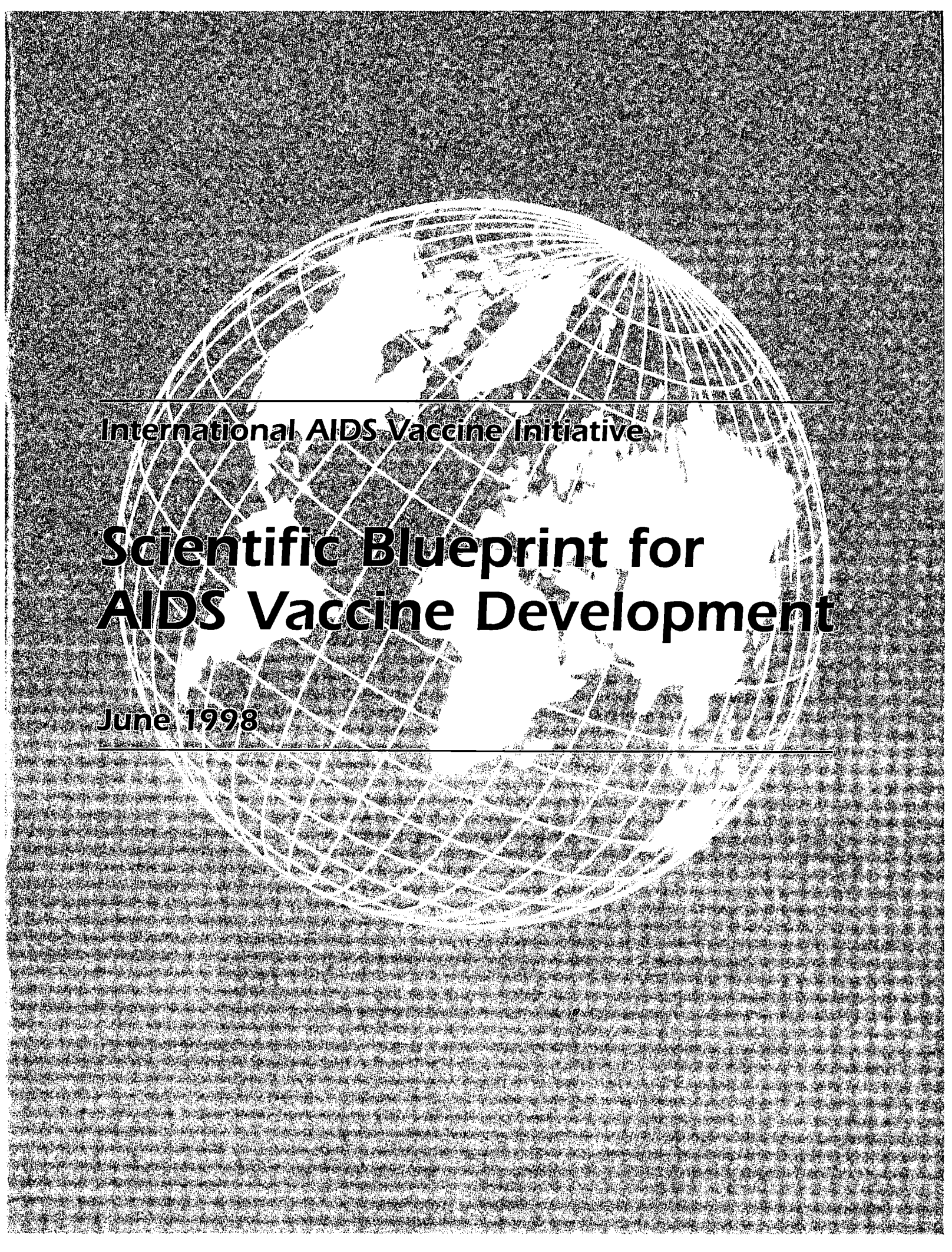


International AIDS Vaccine Initiative

Scientific Blueprint for AIDS Vaccine Development

June 1998

HIV Vaccine Research and Development Clinical Program

LTC Merlin Robb and COL Deborah Birx

Vaccine Development: Pre-clinical Research

FY98 Accomplishments:

- Firmly established limited efficacy and significant safety hazards of *nef*-deleted live attenuated vaccines using the SIV model system
- Identified a highly significant association of cervical HIV-specific IgA in protection from HIV infection in a cohort of highly exposed uninfected commercial sex workers in Thailand, and replicated these findings in a Macaque model system - providing a potential benchmark for protective immunity inducible by HIV vaccines
- Improved methods for epitope mapping lymphoproliferative responses to better explore the relationship between HLA diversity and the range of protection afforded by HIV vaccine candidates
- Successfully created infectious molecular clones from primary isolates of multiple sub-types of HIV thus providing templates with well characterized, fully functional genetic components and permitting immune assessment with full identity to the vaccine construct
- Defined the equivalence of frozen cells and fresh cells in CTL assays among HIV infected volunteers, and preliminarily in HIV uninfected vaccinees, thus permitting studies of this immune effector at remote sites in Africa and Thailand

Vaccine Development: Pre-clinical Research

FY98 Accomplishments cont.

- Evaluated several methods to optimize sensitivity of HIV CTL assays in uninfected vaccine recipients
- Developed a novel technique for measurement of neutralizing antibody using the initial cell target of sexual transmission of HIV (dendritic cells)
- Established a standard panel of primary isolates providing a reproducible range (very easy to difficult) of neutralization activity to be used to assess humoral immunogenicity across multiple vaccine products and seropositive sera
- Established the ability of DNA vaccines to prime for antibody response elicited by protein subunit boosts in the Macaque model system
- Identified that protein subunit vaccines may produce qualitatively and quantitatively different humoral responses in animal model systems depending on several variables: the source of the vaccine construct (cell line adapted virus versus primary, wild-type virus), structure of the subunit (monomer versus dimer versus multimeric structure), adjuvant and delivery system combinations

Vaccine Development: Clinical Research

FY98 Accomplishments cont.

- Initiated transitional process to advanced development for candidate vaccine approaches in human trial is Thailand
- Initiated phase I/II trial of live vector (ALVAC-HIV; vCP205) and novel glycoprotein boost and adjuvant (gp160 MN/LAI-2 in PCPP) in the United States.
- Completed pre-clinical development of a Thai-specific ALVAC + novel glycoprotein construct with industry partner (Pasteur-Merrieux-Connaught)
- Developed and received scientific approval for a protocol to conduct a comparative assessment of ALVAC-HIV prime with two different boosts (PMC or Chiron) in Thailand

Vaccine Development: Clinical Research

FY98 Accomplishments cont.

- Completed enrollment in less than five months (N=380) in a phase II trial of bivalent gp120 (Chiron Vaccines) at four clinical sites in Thailand
- Completed initial elements of a phase I plasmid HIV-DNA study in the US, demonstrating safety and immunogenicity and leading to further studies of DNA vaccines alone and in combinations
- Initiated field collaborations in Rakai, Uganda - taking advantage of a unique opportunity to develop HIV vaccines of relevance to the U.S. Military
- Enhanced laboratory capacity in Thailand necessary for vaccine development, including transition of critical CTL techniques
- Expanded field development activities in Thailand (Rayong, Chiang Mai, Chonburi) and in other international sites (Rakai, Uganda)

Overall STEP Objectives

- Between FY00-04, maintain operationally relevant national and international surveillance of HIV genotypes and recommend improvements to DOD personnel and training doctrine for prevention and control of HIV in service members (CDR Mascola)
- By FY00, transition to advanced development a test for simple and rapid forward diagnosis of HIV infection (LTC Michael)
- By FY00, provide data on the incidence of HIV infection in the mobilization base and active force By FY00, evaluate the importance of HIV genotypes in predicting HIV immunotypes necessary for inclusion in an HIV vaccine (LTC (P) McNeil, LTC Robb)
- By FY03, transition to advanced development a vaccine process to prevent HIV infection due to all genotypes of HIV-1 (A-O) (LTC (P) McNeil)
- By FY03, define the correlates of immunity to HIV (LTC Robb)
- By FY02, establish the genetic and phenotypic correlates of drug resistance as a clinical tool (Maj Wegner)

Vaccine Research & Development

Strategic Plans:

- Demonstrate improved technology sufficient to transition to field efficacy trials, candidate vaccines / approaches representing the "best" of their effector class (antibody, cellular, both), capable of protecting against multiple genotypes of HIV found worldwide. Utilize scientific data from these clinical developments to form the basis for design of improved second-generation vaccines, if necessary.
- Conduct pre-clinical research and development of new immunogens, adjuvants, and delivery systems whose discovery and design is guided by the results of scientific analyses of human vaccine trials, human observational studies evaluating correlates of transmission or disease prevention, and from animal vaccination-challenge studies. The ultimate goal of preclinical R&D is to lead to a clinical transition point for candidate products resulting in phase 0 concept studies.

Vaccine Research & Development

- Global Focus
- Critical Importance / Focus on Efficacy Trials
  - Efficacy
  - Elucidate correlate of protection
  - Validate immunogenicity assays
  - Evaluation of breakthrough
- Use efficacy design to immediately refocus 2nd/3rd generation vaccines, realizing 2nd/3rd generation efficacy studies can be done on partial efficacy platform

Vaccine Research & Development

- Purposeful, incremental advancement
- Interdependent and ***concurrent*** with basic science
- Hypothesis-testing Clinical ***Research***
- Proof-of-concept under most advantageous conditions possible

Vaccine Research & Development

- Multiple complementary vaccine approaches (evaluating specific relevant immune effector mechanisms)
- Hypothesis-testing ***clinical research***
- Select "best" candidate of each specific immune effector class (1. humoral, 2. cellular, 3. both)
- Multi-arm comparative proof-of-concept efficacy trial as a STRATEGIC GOAL
  - THIS "GOAL" MUST NOT SIGNIFICANTLY IMPEDE DEVELOPMENT TIMELINES FOR ANY CANDIDATE WHICH WOULD BE INCLUDED IN A MULTI-ARM TRIAL

Vaccine Research & Development

- Commitment to this concept should encourage concurrent vaccine R&D efforts.
- Candidate vaccines should use prevalent circulating strains to optimize the conditions for proof of concept
- Trial is designed to test "proof-of-concept", & specific concepts of protective immunity and is driven by immunologic principles and safety

Vaccine Research & Development

- More Potent Genetic (DNA) Candidates
- Novel live vectors (VEE, MVA)
- Improved delivery systems (Dendritic Cell Targeting)
- COMBINATIONS

Vaccine Research & Development

- Appropriate Candidate vaccines
  - Safe & well tolerated
  - Immunogenic
  - Antigenically relevant
- Well-characterized populations with high HIV incidence despite interventions
- Sufficient number available, informed, and willing to participate for at least 3 years
- Clinical research infrastructure with adequate lab and data management support
- Protection of human rights

Vaccine Research & Development

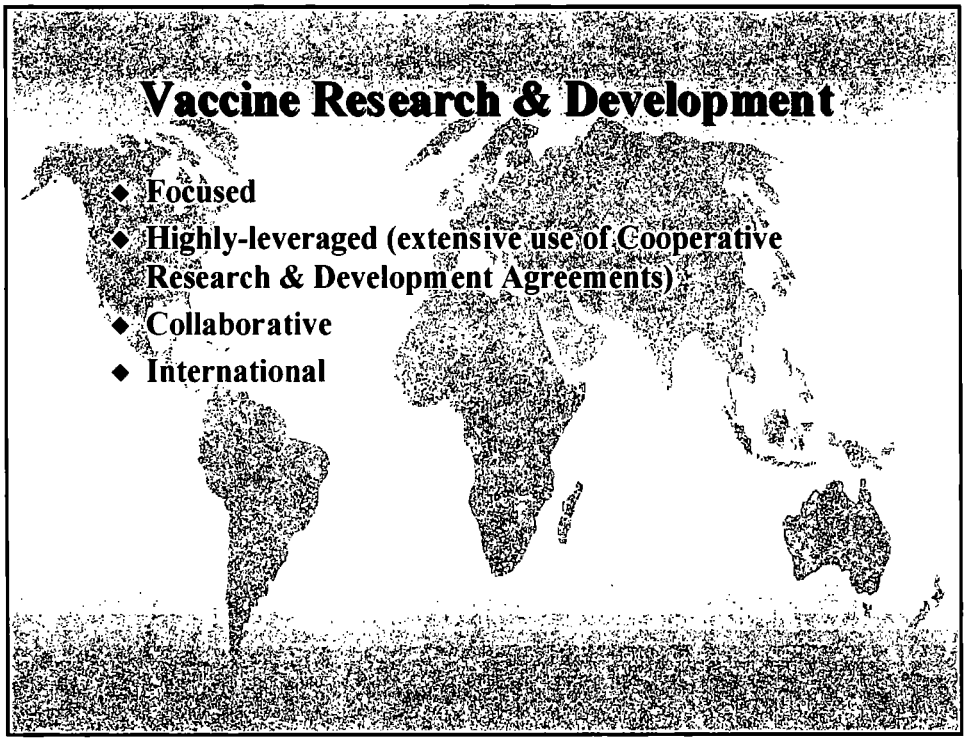
- HIV Genotyping
  - polymerase Chain Reaction
  - sequencing
  - development of typing reagents (oligonucleotides)
- Flow Cytometry
- HIV culture techniques
- Epidemiological Methods
- Data Management & Analysis
- Specimen Processing / Repository

Vaccine Research & Development

- Retroviral Diagnostics
- Humoral Assays
  - ELISA (peptide, lysates)
  - BiaCore™
  - Neutralizing Antibodies
- Cellular Assays
  - Lymphocyte Proliferation
  - T cell epitope mapping
  - Cytotoxic T lymphocytes

Vaccine Research & Development

- Focused
- Highly-leveraged (extensive use of Cooperative Research & Development Agreements)
- Collaborative
- International



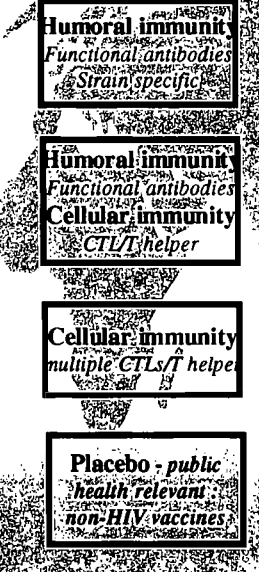
Vaccine Research & Development

Specific Tactical Methods:

- **Pre-clinical**
  - •Expand available immunogens; accelerate evaluation of combination immunogens
  - •Enhance collaboration with vaccine manufacturers, biotechs, academic inventors and international organizations (eg IAVI)
  - •Improve animal vaccination-challenge evaluation systems
  - •Define correlates of immunity
- **Clinical**
  - •Accelerate transition from preclinical to phase 0 studies in humans
  - •Transition selected clinical candidates to advanced development
  - •Maintain coordinated international development approach
  - •Maintain established infrastructure in Thailand, explore opportunities in neighboring countries
  - •Establish Rakai, Uganda as second international field site

HIV Vaccine Development Strategy

- Build trial based on plausible immune effectors of virologic control
- Select candidates that induce indicated immune responses
- Conduct head-to-head 'proof-of-concept' efficacy trial(s)



Subunit Envelope
- •Chiron Vaccines
- •PMC
- •VaxGen

Prime/Boost Strategy
- •PMC / partner

DNA/Live-vector Systems
- •WLVP
- •PMC

Vaccine Development: Clinical Research

- CLINICAL PROGRAM GOALS
  -)Establish US based phase I and II trial capability to evaluate new vaccine concepts
    -)achieve a product concept to fulfill effector arm strategy (cell mediated versus humoral versus combined)
  -)Establish an overseas phase I and II capability to evaluate promising concepts with candidate vaccines suitable for advanced development

Vaccine Development: Clinical Research

- CLINICAL PROGRAM CAPABILITIES (US)
  -)CAP certified molecular diagnostic and viral burden assessment lab on site
  -)Binding antibody and epitope mapping assays on site
  -)Neutralizing antibody assay in cell lines, PBMC and dendritic cells on site
  -)Lymphoproliferative assay, CTL and ADCC on site
  -)Statistical and data management group on site
- 5 physicians participating in clinical trail activities

Vaccine Development: Clinical Research

- CLINICAL PROGRAM CAPABILITIES (US)
- Main clinical site at main campus of WRAIR on Georgia Avenue just inside the District
- Staff includes:
- 1 MD (serves as medical monitor) 3.5 RN/Clinical Coordinator
- 2 recruiters 1 receptionist
- 2 phlebotomist 1 Pharmacist
- Studies conducted by this staff include:
- RTSS-TRAP Malaria sub-unit vaccines with challenge
- Attenuated Dengue vaccines with challenge
- Hepatitis E subunit vaccine

Vaccine Development: Clinical Research

- CLINICAL PROGRAM CAPABILITIES (US)
- Clinic activities will move to Rockville complex:
  -)increase flexibility of scheduling
  -)optimize utilization of limited MD staff
  -)increase frequency of recruitment briefings
  -)improve accessibility to volunteers
  -)provide required logistical proximity to lab complex for re-infusion protocols
- Additional clinic sites contemplated if needed

Vaccine Development:Clinical Research

RV 119 Facilitated DNA Vaccine

DNA vaccine APL 400-003: HIV-1 MN env/rev

GROUP	ROUTE	IMMUNIZATION SCHEDULE (WEEKS) NUMBER/ GROUP		0	4	8	24
		active	vehicle	DOSE µg			
I	Intramuscular	6	2	100	100	100	100
II	Intradermal	6	2	100	100	100	100
III	Intramuscular	6	2	300	300	300	300
IV	Intradermal	6	2	300	300	300	300

Vaccine Development:Clinical Research

RV 119 - Enrollment Update

- Volunteers Screened 53
- Volunteers Excluded 26
- Volunteers Currently Enrolled 16
- Drop-outs 1
- Enrolled in RV 124 7

Vaccine Development:Clinical Research

RV 119 - Reasons for Exclusion

Volunteers May Have More Than One Reason

◆ Did not return for follow-up/Not interested	6
◆ Elevated CK	5
◆ Scheduling Conflicts/unavailable for study duration	5
◆ Abnormal Immunoglobulin Levels	4
◆ Autoimmune Disease/ Increased ANA	3
◆ Doctor/Family member discouraged	2
◆ Anaphylaxis	2
◆ Hepatitis C Ab	1
◆ Psychiatric Disorder	1

Vaccine Development:Clinical Research

RV 119 Study Status

- 17 Patients Enrolled
- 1 Volunteer drop-out (moved)
- All Injections Complete (11/24/98)
- 7 Volunteers Completed Study
- Final Visit 6/4/99

Vaccine Development: Clinical Research

RV 119: ANA and anti-DS DNA

17 pts 7 pts pos ANA
63 neg tests 9 pos

P/N/P/N	1	diffuse
P/N/N/N	1	diffuse
P/P/N/N	1	speckled
N/P/N	1	speckled
N/N/P/N	1	?
N/P/N/N	1	Nucleolar
N/N/P/N	1	?

Vaccine Development: Clinical Research

FUTURE STUDIES

A. Intradermal versus Intramuscular Delivery

B. Optimize Prime Boost with DNA and ALVAC

Approach:

1. New Study to explore DNA prime / ALVAC boost

DNA prime IM plus ALVAC boost IM

DNA prime ID plus ALVAC boost IM

DNA prime ID plus ALVAC boost ID

DNA = APL 400-003 and 400-047 (env/rev and gag/pol)
ALVAC = vCP205 (env/gag/pol)

Vaccine Development: Clinical Research
FUTURE STUDIES

A. Intradermal versus Intramuscular Delivery

B. Optimize Prime Boost with DNA and ALVAC

Approach:

1. Addend current study to :

DNA boost IM as soon as possible after 12 month visit plus ALVAC boost IM 4 and 8 weeks later

DNA = APL 400-003 (env/rev)

ALVAC = vCP205 (env/gag/pol)

Vaccine Development: Clinical Research
RV 124: PMC Prime boost

Immunization Schedule

Part A Safety/Dose Escalation

Group	Subjects	gp160 Adjuvant	Months 0	1	3	6	
I	5	PCPP	25μg gp160MN/	25μg gp160MN LAI-2	25μg gp160MN LAI-2	25μg gp160MN/ LAI-2	LAI-2
II	5	PCPP	50μg gp160MN/	50μg gp160MN/ LAI-2	50μg gp160MN/ LAI-2	50μg gp160MN/ LAI-2	LAI-2
III	5	PCPP	100μg gp160MN/	100μg gp160MN/ LAI-2	100μg gp160MN/ LAI-2	100μg gp160MN/ LAI-2	LAI-2

Immunization Schedule

Part B Prime/Boost Protocol

Group	Vaccine/ Placebo	gp160 Adjuvant	Months 0	1	3	6
IV	10/2	PCPP	vCP205 + gp160 Placebo	vCP205 + gp160 Placebo	vCP205 + gp160 Placebo	vCP205 + gp160 Placebo
V	10/2	PCPP	vCP205 + gp160 Placebo	vCP205 + gp160 Placebo	vCP205 + 25µg gp160 MN/ LAI-2	vCP205 +25µg gp160 MN/ LAI-2
VI	10/2	PCPP	vCP205 + gp160 Placebo	vCP205 + gp160 Placebo	vCP205 +50µg gp160 MN/ LAI-2	vCP205 +50µg gp160 MN/ LAI-2
VII	10/2	PCPP	vCP205 + gp160 Placebo	vCP205 + gp160 Placebo	vCP205 +100µg gp160 MN/ LAI-2	vCP205 +100µg gp160 MN/ LAI-2
VIII	10/2	PCPP	vCP205 + 100µg gp160 MN/ LAI-2	vCP205 + 100µg gp160 MN/ LAI-2	vCP205 + 100µg gp160 MN/ LAI-2	vCP205 + 100µg gp160 MN/ LAI-2
IX	10/2	alum	vCP205 + gp160 Placebo	vCP205 + gp160 Placebo	vCP205 + 50µg gp160 MN/ LAI-2	vCP205 +50µg gp160 MN/ LAI-2

RV124 Protocol Summary

- A. SCREENING
- Number screened: 126
- Number enrolled: 44
- Number dropouts: 5
  - rec'd vx, Δ mind 3
  - relocation 1
  - mistaken entry 1
- Number cell lines pending: 5
- Cell lines ready, pending entry 20+

RV124 Protocol Summary

- ENROLLMENT SUMMARY
- Group 1 5 completed 4th vaccination
- Group 2 4 completed 4th vaccination, 1 in "9C"
- Group 3 5 completed 4th vaccination
- Group 4 5 completed 4th vaccination
- Group 8a 6 completed 3d vaccination, 4th vx 25 FEB 99
- Group 8b 4 completed 3d vaccination , 4th vx 8 MAR 99
- 1 completed 2d vaccination, 3d 29 JAN 99

RV124 Protocol Summary

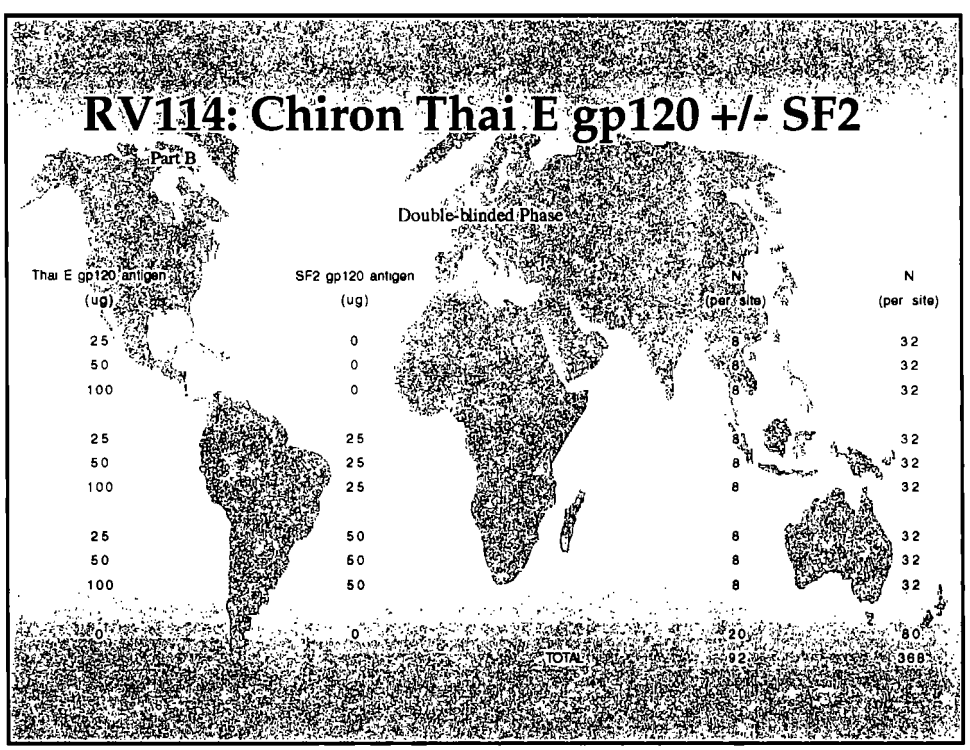
- ENROLLMENT SUMMARY
- Group 9a 5 completed 3d vaccination
- Group 9b 3 completed 3d vaccination,
- Group 9c (Gp 2 replacement) x1
- (Gp 8b replacement) x1
- 4 completed 2nd vx
- Group 7a 5 completed 2nd vaccination
- Group 7b 5 completed 2nd vaccination
- Order of groups:
- I, II, III, IV, VIII, IX, **VII, X, VI, V (underlined groups have been filled)**

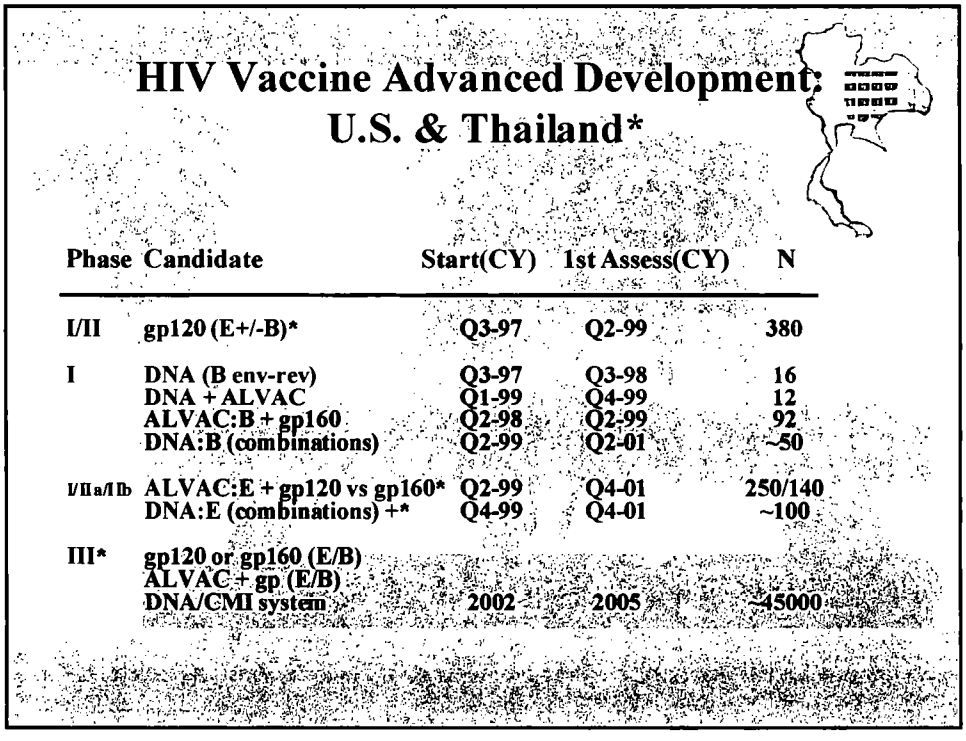
RV114: Chiron Thai E gp120 +/- SF2

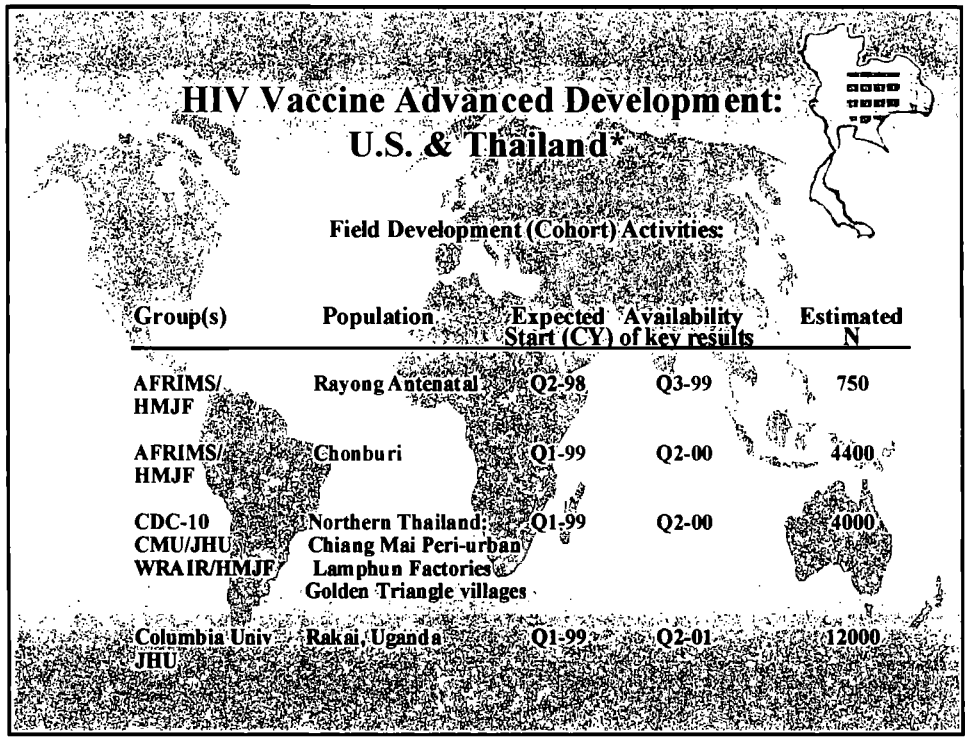
Part A

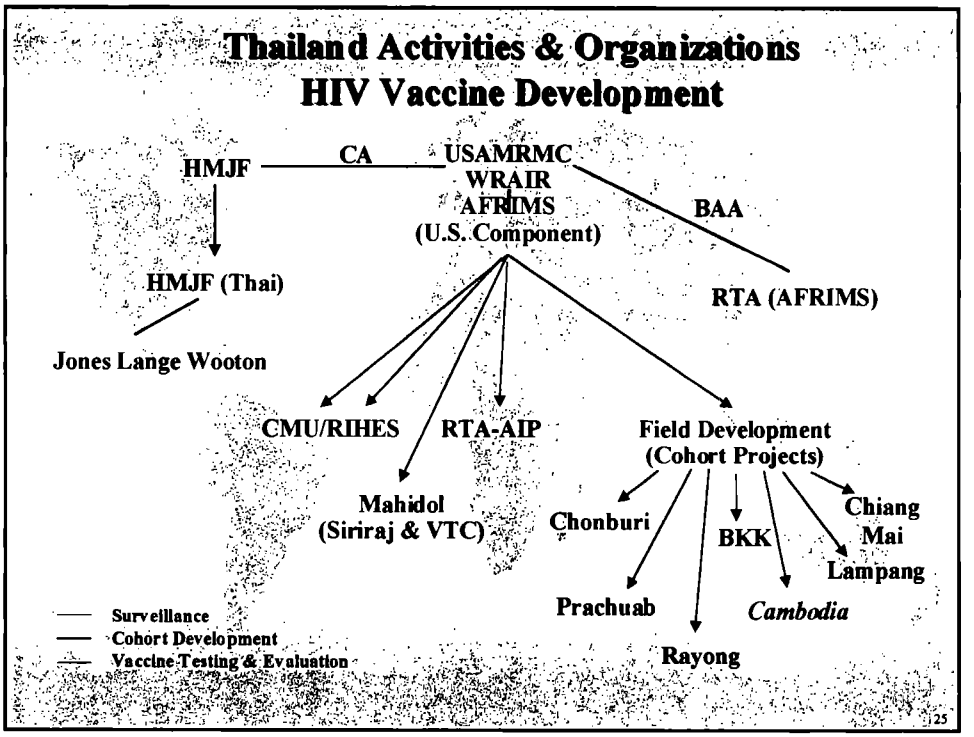
Open-label Phase

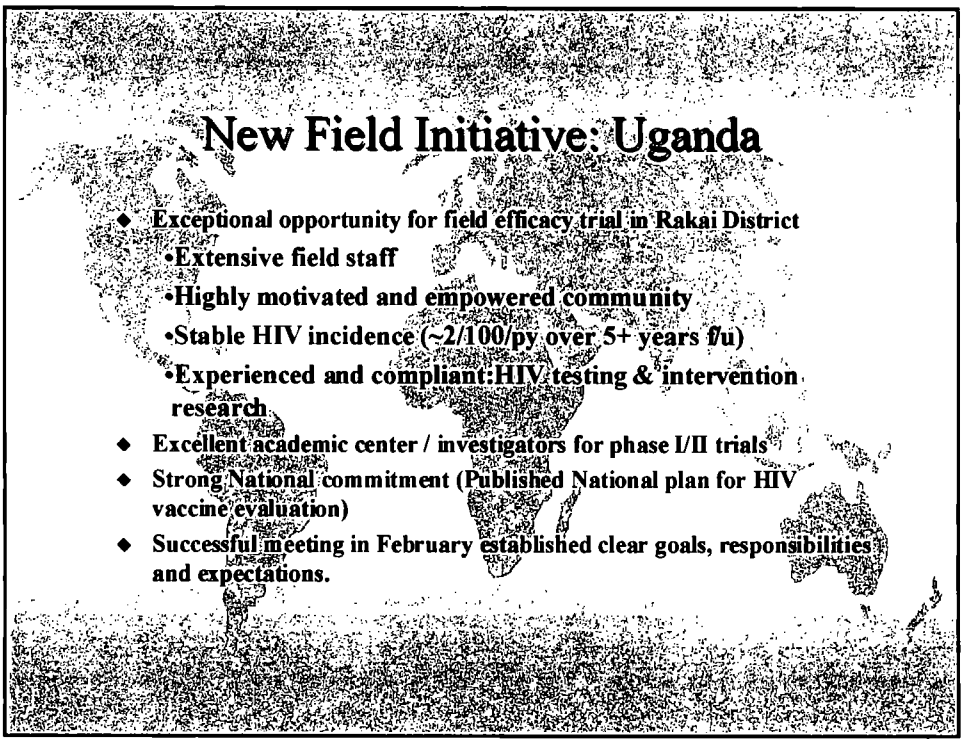
Anigen/Dose	N
Thai E gp120(25 ug)/MF59	3
Thai E gp120(25 ug)+SF2-gp120 (25 ug)/MF59	3
Thai E gp120 (100ug)/MF59	3
Thai E gp120 (100 ug)+ SF2-gp120 (50 ug)/MF59	3
	12




HIV Vaccine Advanced Development:
U.S. & Thailand*
Phase Candidate Start(CY) 1st Assess(CY) N
I/II gp120 (E+/-B)* Q3-97 Q2-99 380
I DNA (B env-rev) Q3-97 Q3-98 16
DNA + ALVAC Q1-99 Q4-99 12
ALVAC:B + gp160 Q2-98 Q2-99 92
DNA:B (combinations) Q2-99 Q2-01 ~50
I/IIa/IIb ALVAC:E + gp120 vs gp160* Q2-99 Q4-01 250/140
DNA:E (combinations) +* Q4-99 Q4-01 ~100
III* gp120 or gp160 (E/B)
ALVAC + gp (E/B)
DNA/CMI system 2002 2005 ~45000


HIV Vaccine Advanced Development:
U.S. & Thailand*
Field Development (Cohort) Activities:
Group(s) Population Expected Start (CY) Availability of key results Estimated N
AFRIMS/ HMJF Rayong Antenatal Q2-98 Q3-99 750
AFRIMS/ HMJF Chonburi Q1-99 Q2-00 4400
CDC-10 CMU/JHU WRAIR/HMJF Northern Thailand: Chiang Mai Peri-urban Lamphun Factories Golden Triangle villages Q1-99 Q2-00 4000
Columbia Univ JHU Rakai, Uganda Q1-99 Q2-01 12000


Thailand Activities & Organizations
HIV Vaccine Development
HMJF
CA
USAMRMC
WRAIR
AFRIMS
(U.S. Component)
BAA
HMJF (Thai)
RTA (AFRIMS)
Jones Lange Wooton
CMU/RIHES
RTA-AIP
Field Development
(Cohort Projects)
Mahidol
(Siriraj & VTC)
Chonburi
BKK
Chiang
Mai
Lampang
Prachuab
Cambodia
Rayong
Surveillance
Cohort Development
Vaccine Testing & Evaluation
25


New Field Initiative: Uganda
Exceptional opportunity for field efficacy trial in Rakai District
•Extensive field staff
•Highly motivated and empowered community
•Stable HIV incidence (~2/100/py over 5+ years f/u)
•Experienced and compliant:HIV testing & intervention research
Excellent academic center / investigators for phase I/II trials
Strong National commitment (Published National plan for HIV vaccine evaluation)
Successful meeting in February established clear goals, responsibilities and expectations.

Vaccine Development: Clinical Research

Preparation for HIV Vaccine Testing in the Rakai Project, Uganda: An Integrated Community HIV Epidemiological Research (CHER) and Molecular Epidemiological Research (MER) Project.

- The study is divided broadly into two distinct but integrated elements;
- Community HIV Epidemiological Research (CHER) and
- Molecular Epidemiological Research (MER) Project

Vaccine Development: Clinical Research

CHER is a population-based cohort study to :

- 1) determine the prevalence and incidence of HIV in Rakai District and
- 2) assess knowledge and attitudes to HIV vaccines
- 3) CHER also serves as the mechanism to identify subjects for enrollment into MER

Vaccine Development: Clinical Research

MER is an evaluation of HIV-1 seroconverters and matched seronegative controls identified through CHER and from a recently completed study. The purpose of MER is to establish the following;

- 1) the distribution of HIV-1 genetic subtypes in the region,
- 2) the distribution of HIV burden during the first months or years after infection
- 3) the presence and character of recombinant forms of HIV,
- 4) the incidence and prevalence of malaria, its drug susceptibility pattern and influence on HIV specific viral regulation, and
- 5) the incidence and prevalence of sexually transmitted diseases and estimate their influence on acquisition of HIV and viral regulation.

- The latter two study components (#4 and#5) will include a sample of HIV negative persons matched for age, sex and village

Press Conference Sponsored by UNAIDS

VACCINE ETHICS

Monday, June 29, 1998

Peter Piot, Executive Director, UNAIDS, announced the development of a new set of ethical guidelines designed to protect the rights of participants in international HIV vaccine trials. The need to create a new set of guidelines became urgent following the recent announcement of a large-scale HIV vaccine trial in the U.S.

The guidelines were developed by UNAIDS following a nine-month consultative process involving 200 people from 30 countries. Ruth Macklin, Chair, UNAIDS Ethical Review Committee, presented highlights of the new guidelines:

- It is appropriate and ethical to conduct vaccine trials in developing countries simultaneously with or prior to trials in developed countries.
- Decisions regarding the appropriate level of medical treatment for participants in vaccine trials should be made through a collaborative process. Participating countries need to consider the highest attainable standard of care within the context of their own realities.
- An appropriate standard of counseling and other HIV preventive measures must be provided.
- Individual informed consent must be obtained. Measures must be taken to ensure that individuals truly understand information and freely give consent. The informed consent process should be monitored by an ethical review committee.

Community participation and involvement should be present from the earliest stage of trial design and continue throughout the study.

The guidelines will be published later this year.

<u>Selected Questions & Answers</u>

Why is it acceptable now to do trials in developing countries simultaneously with or prior to those in developed countries?
A significant amount of capacity building has taken place in developing countries both in terms of scientific skill and infrastructure. Mechanisms for human rights protection and ethical review also now exist in developing countries. Paternalism and protectionism are not appropriate today, rather collaboration must occur.

Are the new guidelines legally binding?
No, as with other international guidelines, there is no mechanism for enforcement. Yet researchers will violate the guidelines at their own peril since ethical review groups will be monitoring trials.

How will efficacy be measured?
Vaccine trials should be double blind, placebo-controlled studies. Efficacy will be measured by the number of infections in the control arm versus the vaccine arm. The use of a placebo design in a vaccine trial is likely to become an ethical issue in the future.

At the conference, vaccines seem to be receiving a great deal of attention. Yet less than 10% of the Division of AIDS budget is earmarked for vaccine research and development.
President Clinton expressed his commitment to a vaccine in less than 10 years. The hope is that the U.S. and the world will make vaccine development a priority.

Jan Harrington
Constellation

UNAIDS
UNICEF • UNDP • UNFPA
UNESCO • WHO • WORLD BANK

Joint United Nations Programme on HIV/AIDS

UNDER EMBARGO UNTIL 14.45 GMT
Geneva, 29 June 1998

NEW ETHICAL GUIDELINES ON HIV VACCINE RESEARCH PAVE THE WAY FOR LARGE-SCALE INTERNATIONAL TRIALS OF HIV VACCINES

The recent announcement of large-scale vaccine trials has created an urgent need to draw up a new set of ethical guidelines designed to protect the rights of those taking part in international vaccine trials. The Joint United Nations Programme on HIV/AIDS (UNAIDS) today announced the development of such guidelines which, although not legally binding, are expected to set a new gold standard for ethical criteria in HIV vaccine trials.

The new ethical guidelines have been drawn up to complement the current International Ethical Guidelines for Biomedical Research Involving Human Subjects, which were produced by the Council for International Organizations of Medical Science (CIOMS) and the World Health Organization in 1993. When the existing guidelines were drafted, the contributors did not anticipate the special problems that would arise today with the start of the first-ever Phase III trials of an HIV vaccine, involving thousands of volunteers.

The guidelines have been developed by UNAIDS as a result of a nine-month consultative process involving 200 people from 30 countries. A key element of this process was a series of community workshops in Brazil (Ouro Preto), Thailand (Bangkok), and Uganda (Entebbe), each with representatives from a wide range of countries. The guidelines were then discussed last week at a two-day meeting in Geneva, involving over 80 participants. They included people living with HIV/AIDS, vaccine researchers, and experts in the field of law, medical ethics, and public health, as well as representatives of national HIV/AIDS programmes, the pharmaceutical industry, and international and other organizations.

Speaking at the 12th World AIDS Conference, currently being held in Geneva, Dr Peter Piot, Executive Director of UNAIDS, pointed out that with 16,000 new infections now occurring every day, the development of an HIV vaccine was a major priority for the world community. The guidelines, he said, were intended to ensure that ethical considerations were given due consideration in the development of a new vaccine. They heralded a new era

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of cooperation and capacity-building between countries. "Paternalism and resource imbalance should be replaced by empowerment in decision-making and equality in partnership between sponsors and hosts of scientific research", he added.

The new guidelines reinforce the need to obtain individual informed consent, and deal with more difficult ethical issues including the need to ensure an appropriate standard of counselling and other HIV preventive measures, and to provide treatment and care for people who become infected during the course of the trial.

A key proposal is that once a vaccine is proved to be safe and effective, the obligation to make the vaccine widely available should be the joint responsibility of all the agencies involved in sponsoring the trials, including the pharmaceutical manufacturers, research agencies, national and international organizations.

One of the most difficult ethical issues to resolve was the appropriate level of medical treatment that should be made available to treat participants who become HIV-infected. Is there an ethical obligation to provide expensive antiretroviral drugs which are not available to the rest of the population or that may not be available once the trial ends? The consensus reached suggests that participating countries need to consider the highest attainable standards of care within the context of their own realities.

Dr Peter Piot said those taking part in the trials should be among the first to benefit from the availability of a vaccine. "Those taking the risks of HIV vaccine development should be the first to realize the benefit. So all populations worldwide who have participated in vaccine research should have some form of early and preferential access."

The guidelines will be published later this year.

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UNAIDS both mobilizes the responses to the epidemic of its six cosponsoring organizations and supplements these efforts with special initiatives. Its purpose is to lead and assist an expansion of the international response to HIV on all fronts: medical, public health, social, economic, cultural, political and human rights. UNAIDS works with a broad range of partners – governmental and NGO, business, scientific and lay – to share knowledge, skills and best practice across boundaries.

For more information, please contact Anne Winter, UNAIDS, Geneva (+41 22) 791.4577, Andrew Caddell, UNAIDS, Geneva (+41 22) 791.3387, UNAIDS Desk at the Palexpo Media Centre (+41 22) 761.2708, Denny Lee, UNAIDS, New York (+1 212) 880.5288. You may also visit the UNAIDS Home Page on the Internet for more information about the programme (http://www.unaids.org).

UNAIDS
UNICEF • UNDP • UNFPA
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Joint United Nations Programme on HIV/AIDS

UNAIDS NEWS CONFERENCES

MONDAY, JUNE 29

12.30 to 1.30 p.m."Mother-to-Child Transmission of HIV"
Swissair Centre, Geneva Room 2

Dr. Peter Piot will chair a news conference with the participation of:

- Dr. Bernard Kouchner, Secretary of State for Health for France
- Dr. David Alnwick, Chief of Health Section, UNICEF
- Mr. Peter Young, Vice-President, Glaxo-Wellcome
- Dr. Awa-Marie Coll-Seck, Director, Policy, Strategy and Research for UNAIDS
- Dr. Thierry Mertens, Director, Office of HIV/AIDS and Sexually Transmitted Diseases, WHO

4.45 to 5.45 p.m. "Vaccine Ethics and Vaccine Trials in Developing Countries"
Swissair Centre, Geneva Room 2

- Dr. Peter Piot, Executive Director, UNAIDS
- Professor Barry Bloom, Howard Hughes Medical Institute, Albert Einstein College of Medicine, New York and Chair, UNAIDS Vaccine Advisory Committee
- Professor Ruth Macklin, Head, Division of Philosophy and History of Medicine, Albert Einstein College of Medicine, New York, and Chair, UNAIDS Ethical Review Committee

20, avenue Appia • CH-1211 Geneva 27 • Switzerland • Tel: (+4122) 791.3666 • Fax: (+4122) 791.4187 • e-mail: UNAIDS@WHO.CH

Thought you might want to cc this to PACHA research.

Todd

COPIES TO
RESEARCH SUBC

program announcement issued: oct. 2, 1998

AmFAR
AIDS RESEARCH

due: nov. 4, 1998

SPECIAL TARGETED REQUEST FOR PROPOSALS:
HIV VACCINE DEVELOPMENT

research grant support for projects in

The American Foundation for AIDS Research (AmFAR) is pleased to announce the availability of special targeted-research grant support for awards of $75,000 to $150,000, including not more than 20% for indirect costs, for projects in **HIV Vaccine Development**.* These projects will have a one-year period of performance, with the possibility of renewal for a second year of work. Collaboration among applicants and within existing research projects is strongly encouraged by the Foundation. You are invited to submit a pre-application Letter of Intent for projects that fall within the areas described below. A limited number of full applications will be solicited from submitted Letters of Intent.

* **Requests exceeding $75,000 will be considered only for projects involving collaboration between two separate research groups. These research groups may be at the same or separate institutions.**

The American Foundation for AIDS Research (AmFAR) is the nation's leading nonprofit organization dedicated to the support of AIDS research (both basic-biomedical and clinical research), AIDS prevention, and the advocacy of sound AIDS-related public policy. Since 1985, AmFAR has invested nearly $150 million in support for its programs, primarily through grants to 1,745 research teams.

TARGETED RESEARCH TOPICS

AmFAR is seeking applications for HIV vaccine research projects in areas which are relevant to the development of a successful vaccine to prevent HIV infection. Applications for basic research are encouraged. Applications for clinical trials will not be considered. However, small hypothesis testing studies in animals and humans will be considered.

AmFAR invites Letters of Intent for research projects in the following areas.

- **Development of new or novel approaches for an HIV vaccine to enhance the qualitative and quantitative cellular and antibody responses, either systemically or in relevant mucosal areas. Approaches may include, for example, the use of novel adjuvants or cytokines in conjunction with HIV antigens, or the evaluation of new or not well-studied targets for developing protective immunity.**

- **Studies of the mechanisms of HIV antigen presentation and processing that will result in improved methods for enhancing the cellular and antibody responses to HIV antigens. This may include studies with novel vectors.**

- **Studies on the structure and characterization of HIV antigens that will enhance understanding of immunogenicity, for example, glycosylation of HIV antigens.**

- **Small well-characterized hypothesis-testing studies that will lead to an increased understanding of the requirements for protective immunity.**

due date for your letter of intent

Please submit the original and 8 copies (9 total) of the Letter of Intent document as described on the attached Cover Sheet form. The Cover Sheet form must be used for all pre-application submissions. Letters of Intent that arrive late, are unsigned, lack sufficient copies, are incomplete, or exceed page limitations will not be reviewed. Faxed copies or e-mail will not be accepted. Awards will be announced in April 1999. Letters of Intent are due no later than **5:00 pm, Wednesday, November 4, 1998**, at the address below:

American Foundation for AIDS Research
Grants Department
120 Wall Street, 13th Floor
New York, NY 10005-3209

Additional Letter of Intent application forms can be requested in writing, by telephone to 212-806-1696, or by faxing your written request to 212-806-1601. Letter of Intent application forms can also be downloaded from our website (http://www.amfar.org). All requests for additional applications must specifically mention this RFP.

Further information on the scope of this RFP may be obtained by contacting: American Foundation for AIDS Research, Program Office, 120 Wall Street, 13th Floor, New York, NY, 10005 (tel: 212-806-1696 • fax: 212-806-1601 • vaccines@amfar.org).

Targeted Research Grants are intended to satisfy a variety of needs in investigations related to HIV and AIDS. A Targeted Research Grant is generally made to cover the costs of such items as salaries for professional and technical personnel, equipment, supplies, travel, publications, limited laboratory construction or alteration, and other miscellaneous items. The maximum amount for a Research Grant is U.S. $150,000 of which not more than 20% of the awarded amount may be used for institutional indirect costs.

PREPARING A LETTER OF INTENT

To be eligible to be considered for solicitation of an application, investigators must first submit a Letter of Intent. A Letter of Intent consists of 9 collated sets (an original and 8 copies) of the following documents in the order listed:

1. **Cover Page** — completely filled out including the research topic assignment code.

2. **Abstract** — a not more than 200 word peer-language description of the proposed one-year research plan.

3. **Description/Research Plan** — three pages or less, including references and figures, typed in no smaller than a 12 point font, which must provide a one-year research plan which should include background and rationale, preliminary studies, specific aims, experimental design and procedures to be used and data analysis. Please relate specific aims to long-term objectives. Discuss new methodologies, if any.

4. **Relevance Description** — a maximum one page document which addresses the direct relevance of the proposed research to HIV vaccine development.

5. **Biographical Sketch** — of the investigator, not more than two pages in length including not more than 15 references to relevant and/or recent publications.

SPECIAL NOTES

Unsolicitated Applications — The Foundation does not accept unsolicited grant applications. A Letter of Intent (LOI) pre-application must be submitted and approved prior to submission of a grant application.

Duplication — When requests for the support of a project are submitted to more than one granting agency, AmFAR support cannot be accepted in duplication of other support.

Authority for Making Grants — AmFAR seeks to encourage and promote research of the highest quality. Therefore, all grant applications are peer-reviewed by AmFAR's Scientific Advisory Committee, a voluntary body whose members include experts in the various fields of AIDS research supported by AmFAR. The Scientific Advisory Committee makes its recommendations to the Board of Directors, which makes all awards.

Review of Applications and Letter of Intent — Each submission is peer-reviewed by the Foundation's Scientific Advisory Committee. The Committee evaluates:

- **scientific merit of the proposal**
- **relevance of the research to the control of the epidemic or benefit to patients with AIDS or related conditions**
- **qualifications, experience and productivity of the investigator(s)**
- **facilities available.**

Full applications will be solicited from investigators whose LOIs are accepted after final review by the Foundation's Scientific Advisory and Science Policy Committees. A limited number of applications for each program are solicited for a grant cycle.

Applications and Letters of Intent must be received in the Foundation's New York office no later than 5:00 p.m., on deadline dates specified in the RFP and/or the application instructions, to allow for preparation by staff and review by the Scientific Advisory Committee and the Board of Directors. Applications that are received late, are unsigned, have insufficient copies, or exceed page limitations will not be accepted and will be returned.

Applications rejected by the Foundation will not be reconsidered.

Confidentiality of Information — In processing and reviewing applications, the Foundation will do its best to not disclose confidential or proprietary information contained in submitted proposals. However, the Foundation has no mechanisms for maintaining or guaranteeing the confidentiality of information and, as a Not-For-Profit Public Benefit Corporation, does not have the financial resources to (a) sustain liability for disclosure of information, or (b) institute mechanisms to maintain the confidentiality of information. Submission of an application is deemed acceptance of this provision.

Source of Funds — Funds available to the Foundation are obtained principally from private donations.

To whom Grants are Made — Grants are awarded only to national or international not-for-profit institutions. Grant applications will not be accepted from for-profit entities. A grant is not made to an individual investigator. Accordingly, applications must bear the signature of an official authorized to sign for the applicant institution. If two or more institutions are collaborating on a single grant application, one institution should be designated as the lead institution. The application should be signed by an authorized official of the lead institution. Applicant organizations must submit proof of not-for-profit status.

In awarding such grants, the Foundation does not assume any responsibility for the conduct of the investigation or the acts of the investigators, since both are under the direction and control of the grantee institution and subject to its medical and scientific policies. Personnel, compensated in full or in part with funds from a Foundation grant, shall not be considered to be employed by the Foundation, but to be employed by the grantee institution.

Members of the Foundation's Board of Directors are not eligible as investigators in Foundation-supported research.

Members of the Foundation's Scientific Advisory Committee are eligible, provided they comply with the Foundation's policies regarding the avoidance of conflicts of interest.

Applicants need not be American citizens and there are no restrictions as to age, color, creed, gender, handicap, marital status, medical condition, national origin, parental status, political affiliation, race, religion, or sexual orientation.

Requests for information about AmFAR granting programs, inclusion on program announcement mailings and other grant related inquires should be submitted in writing via fax (212-806-1601), e-mail (grants@amfar.org), or mailed to:

American Foundation for AIDS Research (AmFAR)
Grants Department
120 Wall Street, 13th Floor
New York, NY 10005-3209

for official use only

AmFAR
AIDS RESEARCH

TARGETED RESEARCH GRANT

RESEARCH ASSIGNMENT CODE*
(Select one only. See below)

TITLE OF APPLICATION (do not exceed 52 typewriter spaces)

APPLICANT ORGANIZATION

PRINCIPAL INVESTIGATOR

Name	Degree / Social Security Number
Position Title	Telephone Number / Fax Number
Department	Street, Building, Room
Subdivision	City, State, Zip
Signature	Date

letter of intent cover sheet

*** RESEARCH ASSIGNMENT CODES**

Please enter the research assignment code immediately preceding these research areas in the appropriate space above when submitting your pre-application. Use one Research Assignment Code only.

VAC1 — Development of new or novel approaches for an HIV vaccine to enhance the qualitative and quantitative cellular and antibody responses, either systemically or in relevant mucosal areas. Approaches may include, for example, the use of novel adjuvants or cytokines in conjunction with HIV antigens, or the evaluation of new or not well-studied targets for developing protective immunity.

VAC2 — Studies of the mechanisms of HIV antigen presentation and processing that will result in improved methods for enhancing the cellular and antibody responses to HIV antigens. This may include studies with novel vectors.

VAC3 — Studies on the structure and characterization of HIV antigens that will enhance understanding of immunogenicity, for example, glycosylation of HIV antigens.

VAC4 — Small well-characterized hypothesis-testing studies that will lead to an increased understanding of the requirements for protective immunity.

A Letter of Intent document consists of the original and 8 (total of 9) collated and stapled sets of the following assembled in the order indicated below:

1. **Cover Page** — completely filled out including the research topic assignment code.

2. **Abstract** — a not more than 200 word peer-language description of the proposed one-year research plan.

3. **Description/Research Plan** — three pages or less, including references and figures, typed in no smaller than a 12 point font, which must provide a one-year research plan which should include background and rationale, preliminary studies, specific aims, experimental design and procedures to be used and data analysis. Please relate specific aims to long-term objectives. Discuss new methodologies, if any.

4. **Relevance Description** — a maximum one page document which addresses the direct relevance of the proposed research to HIV vaccine development.

5. **Biographical Sketch** — of the investigator, not more than two pages in length including not more than 15 references to relevant and/or recent publications.

NOTE: Submission of a letter of intent (LOI) is not a guarantee of eligibility to submit a full application. The LOI pre-application review process is highly competitive. Only a limited number of LOIs will be approved.

Letters of Intent (original & 8 copies) must be received
at the address below by 5:00 P.M. Wednesday, November 4, 1998.

NO SUBMISSIONS BY FAX OR E-MAIL WILL BE ACCEPTED.

American Foundation for AIDS Research (AmFAR)
Grants Department
120 Wall Street, 13th Floor
New York, NY 10005-3902

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