**FOIA Number:** 2018-0756-F

# FOIA MARKER

**This is not a textual record. This is used as an administrative marker by the William J. Clinton Presidential Library Staff.**

---

**Collection/Record Group:** Clinton Presidential Records

**Subgroup/Office of Origin:** National AIDS Policy Office

**Series/Staff Member:** Kristine Gebbie

**Subseries:**

---

**OA/ID Number:** 3772

**FolderID:**

---

**Folder Title:**
Meeting with St. Louis University 1/7/94

| Stack: | Row: | Section: | Shelf: | Position: |
|---|---|---|---|---|
| S | 66 | 5 | 5 | 3 |

**CONFIRMED Kristine Gebbie Interviews on January 7**
**(updated Jan. 6 at 5 p.m.)**

*(This is the only interview in the early morning. This is confirmed.)*
**7:17 a.m.---(From Hotel)** Ms. Gebbie calls KMOX-AM radio for a taped phone (not live as we originally planned) interview from 7:20-7:25 a.m. Ms. Gebbie should ask for John Angelides at (314) 444-3234.

(From Dr. Robert Belshe's office at SLU)

**9 a.m.**--Reporter Bill Allen, *St. Louis Post-Dispatch*

**9:15 a.m.**--Jenny Slosar--*West County Journals*

**9:30 a.m.**--KTVI-TV Channel 2 (ABC)

**9:45 a.m.**--KSDK-TV Channel 5 (NBC)

**10 a.m.**--Tour of research labs and meet researchers and vaccine study participants. Media will videotape/photograph this session.

**10:45 a.m.**--KMOV-TV Channel 4 (CBS)

**11 a.m.**--Roger Schleuter or Doug Kaufman, *Belleville News-Democrat* (Ill. paper)

**11:15-11:30 a.m.**--Andrea Murray, KWMU-FM Radio

*11:30 a.m.--Must leave for Learning Resources auditorium for noon presentation at Grand Rounds.*

**Ms. Gebbie:

KMOX Radio decided to do a taped interview at 7:15 a.m. on Friday for use later in the day instead of the live interview we originally told you about. If you have any questions about media interviews for Friday, you can beep our office at 469-8245 at any hour tonight or tomorrow morning before 8 a.m. Marie Dilg will answer the beeper.

Kristine M. Gebbie Itinerary

This is the final proposed schedule for Ms. Kristine M. Gebbie's visit to St. Louis University on January 6 and 7.

| | |
|---|---|
| **January 6** | Ms. Gebbie arrives in St. Louis. Plans with Dr. Joan Hrubetz. |
| **January 7** | |
| 7:17 a.m. | Ms. Gebbie calls KMOX-AM radio for taped interview from 7:20 to 7:25 a.m. Ms. Gebbie is requested to call John Angelides at (314) 444-3234. |
| 7:30 a.m. | Ms. Gebbie meets Dr. Belshe and Dr Patricia Fast (NIAID) for breakfast at the Cheshire Inn. After breakfast they depart for Dr. Belshe's office at St. Louis University Hospital. |
| 9:00 a.m. | Ms. Gebbie participates in four 15-minute, one-on-one interviews with reporters on the suggested topics of national AIDS policy and St. Louis community efforts for diagnosis and treatment of AIDS. (Note: SLU community relations staff will coordinate timing of interviews.) |
| 10:00 a.m. | Ms. Gebbie will tour HIV vaccine center and research labs. She will meet research staff and HIV vaccine study volunteers from the community. This is also a photo/video opportunity for the media. |
| 10:45 a.m. | Ms. Gebbie participates in three additional one-on-one interviews as needed. |

-more-

| | |
|---|---|
| 11:30 a.m. | Move to auditorium across the street where next presentation takes place. We are hopeful time will permit a few minutes relaxation in private for light refreshments for Ms. Gebbie. |
| Noon | Ms. Gebbie will make a presentation at Grand Rounds for about 200 internal medicine faculty and special guests, including Dr. William Powderley, the AIDS clinical trials principal investigator at Washington University School of Medicine, and other area researchers. The subject of this talk will be National AIDS Policy. (Dr. Hrubetz will introduce Ms. Gebbie.) |
| 1 p.m. | Ms. Gebbie attends sit-down lunch with Dr. Belshe, VIP guests from state and local health agencies; and top university officials. |
| 2 p.m. | Ms. Gebbie will make a community presentation, including guests from city and county health departments; health organizations; the AIDS foundation and other AIDS community-based programs; city and county boards of education; and health care providers to AIDS patients throughout the St. Louis area. This presentation will focus on how St. Louis has responded to the need for collaboration and is a model city where work on AIDS research and treatment is concerned. Suggested title is "Community Efforts for Diagnosis and Treatment of AIDS" and the suggested length of this talk is 30 minutes long plus another 30 minutes for questions and answers. (Dr. James Kimmey will introduce Ms. Gebbie.) |
| 3 p.m. | Reception for all attendees with time to conclude any interviews not taken care of earlier. |
| 3:15 p.m. | Ms. Gebbie meets with local AIDS group . |
| 3:45 p.m. | Ms. Gebbie departs St. Louis University Health Sciences Center for the airport. |

# CITY OF ST. LOUIS
# DEPARTMENT OF HEALTH & HOSPITALS

## FACSIMILE TRANSMITTAL SHEET

DATE: 1/6 TIME: 9:45

[✓] Immediate No. of Pages to Follow: 8

[ ] Priority

[ ] Routine

To: Kristine Gebbie, RN, MN

From: William Kincaid, MD

Message:

Confirmation Phone Number: 314/658-1054
Facsimile Number: 314/658-1017
Equipment Type: Ricoh - Model 550

*City of Saint Louis*
**DEPARTMENT OF HEALTH AND HOSPITALS**
**DIVISION OF HEALTH**
OFFICE OF THE HEALTH COMMISSIONER
634 N. Grand - P.O. Box 14702
St. Louis, Missouri 63178
(314) 658-1054

FREEMAN R. BOSLEY, JR.
MAYOR

WILLIAM L. KINCAID, M.D., M.P.H.
HEALTH COMMISSIONER

January 5, 1994

Kristine M. Gebbie, R.N., M.N.
National AIDS Policy Coordinator
Executive Office of the President
750 17th Street, N.W. Suite 1060
Washington, D.C 20500

Dear Kristine:

Your visit to St. Louis on Friday could not be more appropriately timed. The National Condom Campaign commercials have received some press and electronic media coverage in St. Louis.

As you know, St. Louis is a very midwestern and conservative town. The condom message is raising some of the expected objections. We feel the promotion of condom use is an extremely important public health problem in the St. Louis area not only because of the AIDS epidemic but also because of the ongoing gonorrhea and syphilis epidemics in St. Louis. Over the last two years, St. Louis has had a dramatic rise in the number of syphilis cases. We are currently number one in the nation in the rate of syphilis cases for cities over 200,000 residents. Over 90% of those affected are African-American and the victims are equally split between males and females. We have had over forty cases of congenital syphilis and one child has died.

Our current concern is that this syphilis epidemic is a harbinger of an even larger AIDS epidemic in our community. The AIDS virus is much more easily spread in those who have open sores.

We feel that the message of condom use is extremely important. Some of this data is depicted in graphic form and several graphs, charts and summary pages are enclosed. We have had a difficult time getting the media to focus on the syphilis epidemic. Please feel free to emphasize the syphilis epidemic and condom use.

I look forward to seeing you on Friday.

Sincerely,

Bill

William L. Kincaid, M.D., M.P.H.
Director of Health and Hospitals
City of St. Louis

WLK/jk
Enclosure

# Bullet Points

## Syphilis Epidemic—City of St. Louis, MO

- **The City of St. Louis and the County Health Departments have set up a SYPHILIS TASK FORCE to deal in a coordinated way with the epidemic.**
  - The Role of Public Health
    St. Louis Metropolitan Syphilis Task Force
    Public Information
    Educate Health Professionals
    Facilitate Access to Primary Care
    Increase Screening Activities
    Coordinate Activities
  - Public Health Approach to Sexually Transmitted Diseases
    Education to Prevent Infection
    Early Treatment
    Individual Contact Tracing
    Screening High Risk Persons
    Cluster Investigations
- **Average age of syphilis patients is 29. 56% of the cases occur in ages from 20 to 39. (Gonnorrhea has an average age of 19.)**
- **Minorities are disproportionately affected. 90% of cases occur in African Americans.**
- **Males and females are equally likely to get syphilis.**
- **Lack of insurance and access to primary care services is a major problem in the St. Louis area, particularly the City.**
  - Despite the fact that the County has three times the population, the City accounts for 80% of the cases in the City/County area.
  - 85% of all cases in the City are diagnosed at the St. Louis Health Department.
- **The dramatic increase in City cases has made he rate of syphilis infection higher now than at the end of World War II when penicillin was first widely available. The occurrence of this epidemic is an indication of how dysfunctional our health care system has become. Focusing on quick and expensive "fixes" instead of lower cost and longer term prevention and primary care.**

William L. Kincaid, MD, MPH
Department of Health and Hospitals

❒ **SUMMARY: The syphilis epidemic is largely a young heterosexual minority event. The Task Force has moved to increase the traditional services to identify and treat those affected with syphilis.**

- Dissemination of information about the epidemic and responsible sexuality, promoting the consistent and correct use of condoms, and limiting the number of sexual partners are high priorities.
- PREVENTING NEW INFECTIONS IS OUR GREATEST CHALLENGE. Many of the changes in personal behavior that will reduce the risk of syphilis will also reduce the risk of AIDS.

Very few public health problems occur in isolation. The approach to one often influences and is influenced by that of others.

Community involvement in these common solutions are often the best. We have tried to link our solutions here to community participation, but we have much still to learn and teach each other about out common problems.

Finding ways to encourage participation by public and private providers in programs and policies that promote personal and institutional responsibility is health care reform.

William L. Kincaid, MD, MPH
Department of Health and Hospitals

Syphilis Summary
1993 Year to Date
27 Nov

Jan 3 to Nov 27, 1993

# Syphilis St Louis Metropolitan Area

## Total Cases

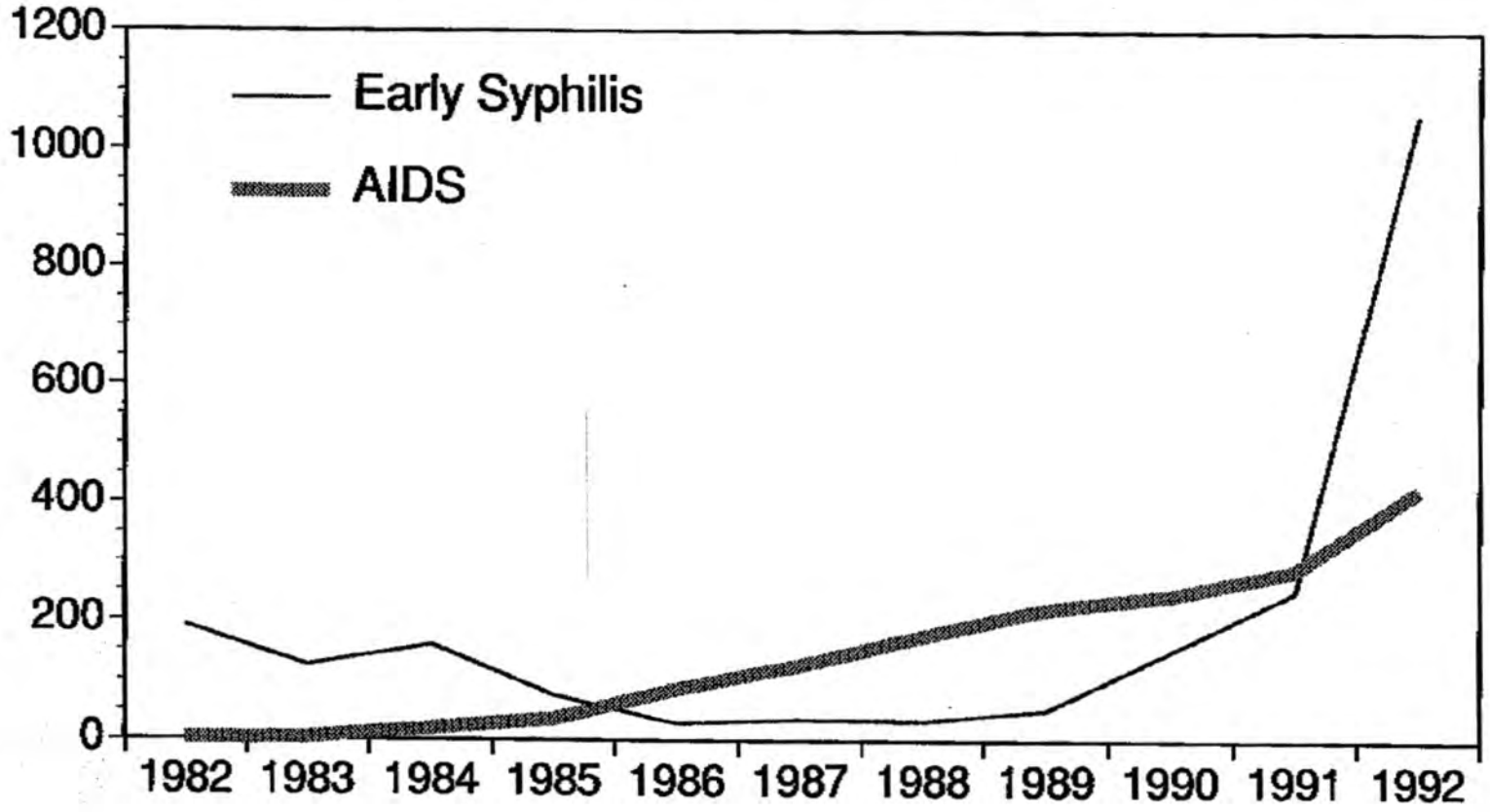
| City | County | Total |
|---|---|---|
| 1283 | 329 | 1612 |
| 79.6% | 20.4% | 100.0% |

| | Numbers of Cases | | | Percentages | | |
|---|---|---|---|---|---|---|
| | City | County | CI+CO | Ci +Co | City | County |
| Asian/PI | 1 | | 1 | 0.1% | 0.1% | |
| Black | 1193 | 299 | 1492 | 92.6% | 93.0% | 90.9% |
| Unknown | 11 | 2 | 13 | 0.8% | 0.9% | 0.6% |
| White | 78 | 28 | 106 | 6.6% | 6.1% | 8.5% |
| Total | 1283 | 329 | 1612 | 100.0% | 100.0% | 100.0% |

| | | | |
|---|---|---|---|
| Congenital | 48 | 8 | 56 |
| | 85.7% | 14.3% | |

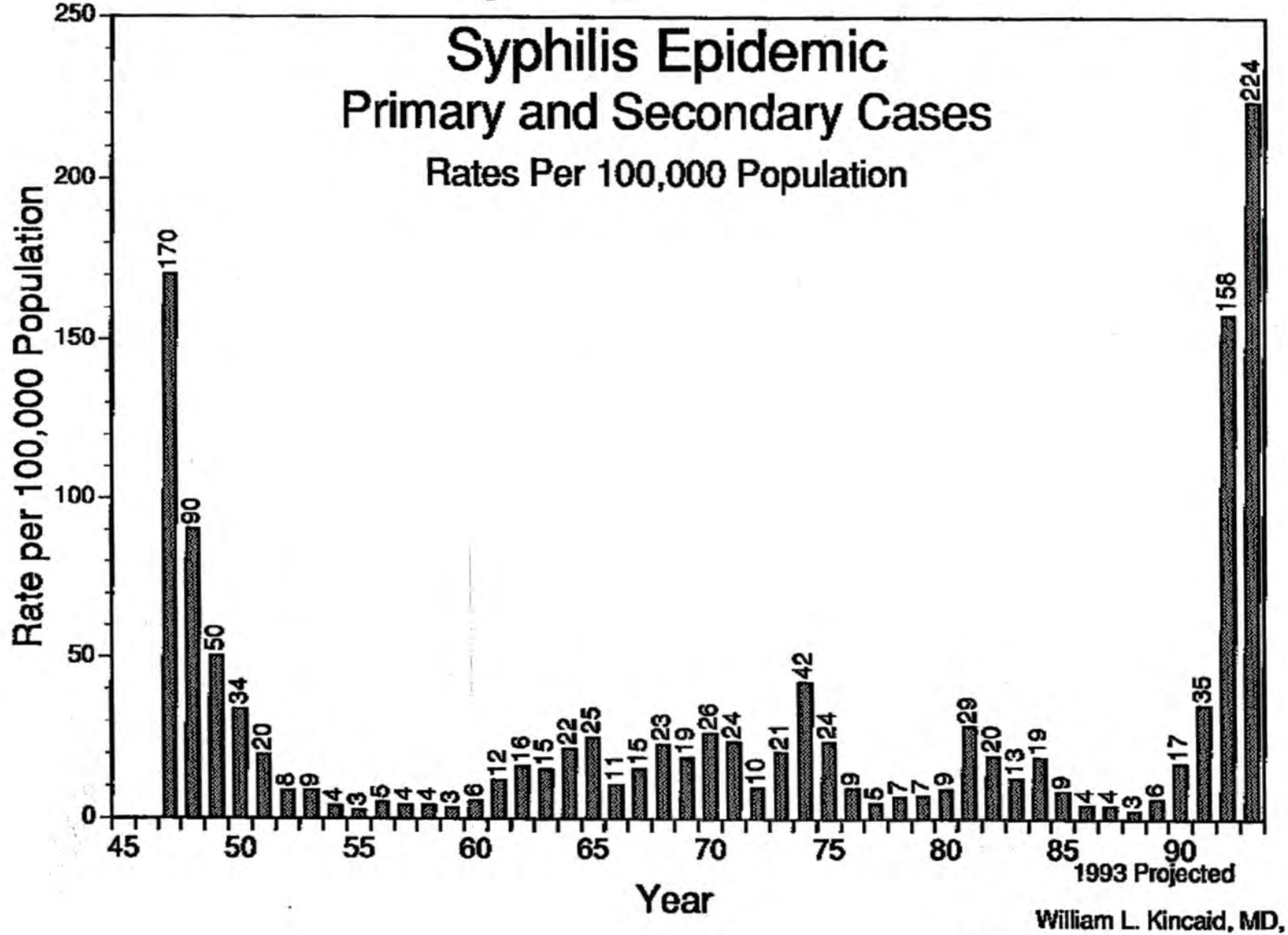
Department of Health and Hospitals

# Early Syphilis Cases and AIDS Cases By Year of Diagnosis St. Louis Metropolitan Area, 1982-1992




City of St. Louis
Department of Health and Hospitals

# City of St. Louis




William L. Kincaid, MD, MPH
Department of Health and Hospitals
City of St. Louis

1/5/94

## St. Louis Syphilis Epidemic Synopsis

The City of St. Louis has been experiencing a syphilis epidemic which began in mid-year 1991 and continues today. Between 1991 there were a total of 188 early cases of syphilis reported in the City of St. Louis. For the first 10 months of 1993 there were 1,141 cases of early syphilis reported. During 1992 the City of St. Louis had the highest primary and secondary syphilis rates per 100,000 population of cities with population of over 200,000. Since the numbers for 1993 are higher than 1992 it is very likely the City of St. Louis will be number one during 1993. Along with the increase in early syphilis morbidity there has been a tremendous increase in the number of congenital syphilis cases in the City of St. Louis. During the 1980's there were fewer than ten cases of congenital syphilis in the City of St. Louis. During 1993 there have been greater than 50 cases of congenital syphilis reported in the City. This syphilis epidemic is symptomatic of the community's continuing problem in the area of sexually transmitted diseases. In order to deal with the STD problem we have been making the following recommendations.

- When having sex use condoms.
- Reduce the number of sexual partners preferably to one.
- Be tested for syphilis or other sexually transmitted diseases if you are sexually active.
- Seek medical attention if you are sexually active and have an unexplained sore on your genitals or mouth, or a rash on other parts of your body.
- Have screening tests during the first and third trimesters of pregnancy.
- Be aware that if you have syphilis or another sexually transmitted disease and have un-protected sex you are at a much greater risk of contracting AIDS.

LK/bh

SAINT LOUIS UNIVERSITY
HEALTH SCIENCES CENTER

SCHOOL OF MEDICINE

3635 Vista Ave. at Grand Blvd.
St. Louis, MO 63110-0250
314/577-8795 FAX 314/771-1945

**Department of Surgery**
**Division of Neurological Surgery**

Kenneth R. Smith, Jr., M.D.
David C. Crafts, M.D.
Kong Woo Peter Yoon, M.D.
Francis S. Walker, M.D.
Paul E. Stohr, M.D.

Richard D. Bucholz, M.D.
Image Guided/Stereotactic Surgery

Thomas Pittman, M.D.
Pediatric Neurosurgery

Robert J. Bernardi, M.D.
Spinal Neurosurgery

January 25, 1994



Ms. Kristine Gebbe
200 Independence Avenue SW #725 H
Washington, DC 20201

Dear Kris,

Please accept my apologies for being so tardy in writing to thank you for your wonderful visit to St. Louis. It was a real pleasure for me and Marjorie personally. It was a great occasion for Saint Louis University to have you return to your former work site along the Mississippi.

I hope you were pleased with the progress we are making in our vaccine program at Saint Louis University and in our AIDS program in St. Louis in general which seems fairly good, although I am sure we have room for improvement as noted by some of the patients and patient advocates at the late afternoon meeting.

Thank you very much for the information about your friend in Portland who Scott Clark can contact about doing some work with AIDS prevention.

We are all proud of the great contributions you are making in the AIDS effort in the Clinton administration, and hope to meet you again soon in Washington or St. Louis or some other spot. Please let Marjorie and me know if there is anything any of us in the Smith or Clark families can do to help with the AIDS effort.

Please keep up your good work. I am sure you will accomplish a great deal in helping fight this dread disease.

Best wishes,

Sincerely,

Ken & Marji

Kenneth R. Smith, Jr., M.D.

KRS:dla

St. Louis U
lot for community
meeting.

Health Center
Mrs. Bernice Green Clinic Coordinator
1206 North 9th St.
St. Louis, MO 63106

Attn: John M. Silva
Executive Director
6313 Michigan
St. Louis, MO 63111

Tim Massmann, RN, BSN, MUS
Ambulatory Care Supervisor
1027 S. Vandeventer
St. Louis, MO 63110

Grace Hill Neighborhood Health Center
Attn: Ville Appoo Koenig
Director of Primary Care
2500 Hadley
St. Louis, MO 63106

Grace Hill Neighborhood Health Center
Attn: John Brewer, MD
Medical Director
2500 Hadley
St. Louis, MO 63106

People's Health Centers
Betty Jean Kerr
Executive Director
7319 Manchester
St. Louis, MO 63143

People's Health Centers
Marilyn Billingsly
Medical Director
7319 Manchester Road
St. Louis, MO 63143

Soulard Health Center
Liz Jones, RN
Director
2028 S. 12th
St. Louis, MO 63104

St. Louis Comprehensive Health Center
Myrtle Hillard Davis
President
5471 Martin Luther King Drive
St. Louis, MO 63112

St. Louis Comprehensive Health Center
Ann Streak, MD
Medical Director
5471 Martin Luther King Drive
St. Louis, MO 63112

Watertower Health Center
Janet Davis, RN
Executive Director
4308 N. Grand
St. Louis, MO 63107

Courtney
Jeanetta Hegwood, RN
Director of Nursing
1717 Biddle
St. Louis, MO 63106

Florence Hill Health Center
Carol Horton, RN
Clinical Nurse Manager
5541 Riverview
St. Louis, MO 63120

Homer G. Phillips
Shirley Marks, RN
Clinical Nurse Manager
2601 N. Whittier
St. Louis, MO 63113

Max C. Starkloff
Greta Chitwood, RN
Clinical Nurse Manager
2220 Lemp
St. Louis, MO 63104

St. Louis Regional Medical Center
William Smiley, MD
5535 Delmar
St. Louis, MO 63112

Joan Fiock, RN
Public Health Administrator
School of Social Services
634 N. Grand
St. Louis, MO 63103

St. Louis Regional Medical Center
Herman Ferrell, MD
Medical Director
5535 Delmar
St. Louis, MO 63112

St. Louis Regional Medical Center
Sherman McCoy, CEO
5535 Delmar
St. Louis, MO 63112

St. Louis Regional Medical Center
Leona Young, Vice President
Ambulatory Care
5535 Delmar
St. Louis, MO 63112

Hopewell Center
Dr. Amanda Murphy
Director
3322 Olive
St. Louis, MO 63103

St. Louis Mental Health Center
Diane McFarland
Director
1508 S. Grand
St. Louis, MO 63104

Meramec Tower Bldg.
Dr. Alpha Fowler-Bryan
Director
111 S. Meramec
Clayton, MO 63105

South County Health Center
Jane Hutchinson
Medical Director
177 Kingston
Lemay, MO 63125

John C. Murphy Family Health Center
Connie Brooks, RN
Administrator
6065 Helen Ave.
Berkeley, MO 63134

North Central County Health Center
Linda Fisher, MD
Medical Director
6150 Natural Bridge
Pine Lawn, MO 63120

Freeman Bosley, Jr.
Mayor of St. Louis
City Hall, Room 200
Tucker & Market Streets
St. Louis, MO 63103

Lloyd Jordan
Chief of Staff
City Hall, Room 200
Tucker & Market Streets
St. Louis, MO 63103

Marie Jeffries
Director of Operations
City Hall, Room 200
Tucker & Market Streets
St. Louis, MO 63103

Tim Person
Executive Assistant
City Hall, Room 200
Tucker & Market Streets
St. Louis, MO 63103

Mark Utterback
Executive Director
4579 Laclede Ave., Suite 309
St. Louis, MO 63108

Michael Luntar
Direct Services
4579 Laclede Ave., Suite 309
St. Louis, MO 63108

Judge Susan Block
7101 Stanford
University City, MO 63130

Mr. James F. Metzler
4463 S. Thirty-Eighth St.
St. Louis, MO 63116

Rev. Earl E. Nance, Jr.
4205 West Sacremento Ave.
St. Louis, MO 63115

Mrs. Renni Shuter
6240 McPherson Ave.
St. Louis, MO 63130

Mrs. Paula V. Smith
4287 Holly Ave.
St. Louis, MO 63115

| Post-it™ Fax Note 7671 | Date 1/3/94 | # of pages ▶ 3 |
|---|---|---|
| To Steve Lee | From Dan Hope | |
| Co./Dept. | Co. St. Louis Univ. | |
| Phone # | Phone # (314) 577-8014 | |
| Fax # (202) 632-1096 | Fax # | |

John Holste
AIDS Foundation of St. Louis
214 South Central
St. Louis, MO 63105 50

Northside AIDS Outreach
Josephine Ingram
3540 Marcus
St. Louis, MO 63115 2

Liam Gannon
3854 Juniata Apt. A
St. Louis, MO 63116

✓ William Kincaid, MD, MPH
Health Commission
City of St. Louis Health Division
634 N. Grand
St. Louis, MO 63103

PAWS/STL
Liz Human
3952 S. Grand
St. Louis, MO 63118

Rev. Paul Kidner
St. Louis Abbey
500 South Mason Rd.
St. Louis, MO 63141

✓ Don Conners, PAC
Metro AIDS
634 N. Grand
St. Louis, MO 63103

Rhonda West
407 Larkhill Court
St. Louis, MO 63119

Rodney Wilson
1023 A. Eiler
St. Louis, MO 63111

John Thompson ~~-~~ Deryck McGinley
Metro AIDS
634 N. Grand
St. Louis, MO 63103

Jim Thomas
4526 Shenandoah
St. Louis, MO 63110

Jim Thomas - Chair Person
c/o Gay & Lesbian News Telegraph
P.O. Box 14229-A
St. Louis, MO 63178

Bethany Place-Belleville
Carol Baltosiewich
224 West Washington St.
Belleville, IL 62220 10

Richard Westcott Jr.
5335 Delmar Blvd. Apt. 3C
St. Louis, MO 63112

Kim A. Marley
1041 Allen Ave.
St. Louis, MO 63104

Care and Counseling
Gail Zink
12145 Ladue Rd.
St. Louis, MO 63141 12

Jan Judy
616 Vassar
St. Louis, MO 63130

Don Kleinschmidt
2234 Hickory
St. Louis, MO 63104

Lynn Cooper
✓ Doorways, The Interfaith AIDS Residence
5335 Delmar Blvd.
St. Louis, MO 63112

Mr. Eddie G. Davis,
President
4303 East Fairfax Ct.
St. Louis, MO 63113

Arnell Joiner
#8 Lewis Place
St. Louis, MO 63113

lanned Parenthood of the St. Louis Region
aula Gianino
415 Manchester Ave.
t. Louis, MO 63143 12

Mr. William Purdy
Vice President
6256 Kinsey Pl.
St. Louis, MO 63109

Mrs. Hattie R. Jackson
4453 Laclede Ave.
St. Louis, MO 63108

American Red Cross
Al Shom
4050 Lindell Blvd.
St. Louis, MO 63108 5

Ms. Robbyn G. Stewart
Secretary
810 Ann Ave.
St. Louis, MO 63104

Mr. William J. Kuehling
1036 Blendon Pl.
St. Louis, MO 63117

St. Louis Effort for AIDS
Carol Wibbenmeyer
5622 Delmar Blvd., Suite 104E
St. Louis, MO 63112 32

Mr. Thomas M. Nolan
Corresponding Secretary
2647 Russell Blvd.
St. Louis, MO 63104

Dr. John P. Mahoney
3535 Victor St.
St. Louis, MO 63104

Genevieve Mosblech
AIDS Project
625 North Euclid Ave.
St. Louis, MO 63108 2

Dr. Albert E. Bender, Sr.
6150 Kingsbury Pl.
St. Louis, MO 63112

Dr. David J. Mahan
Superintendent of Schools
St. Louis Public Schools
911 Locust St.

SAINT LOUIS UNIVERSITY
HEALTH SCIENCES CENTER

3635 Vista Ave. at Grand Blvd.
P.O. Box 15250
St. Louis, MO 63110-0250
314/577-8014
FAX 314/268-5151

Department of Community Relations

January 5, 1993

Kristine M. Gebbie
National AIDS Coordinator
750 17th St. NW, Suite 1060
Washington, DC 20503

Dear Ms. Gebbie:

On behalf of St. Louis University Health Sciences Center, we are proud to host your visit on Friday, January 7.

We have arranged for a room at the Cheshire Inn on Thursday. Your confirmation number there is 9141. Dr. Joan Hrubetz will pick you up at the airport on Thursday night and take you to dinner.

The university also will arrange to pick up your air fare. Please provide us with an original invoice as soon as possible.

We all look forward to a busy and productive day on Friday.

Sincerely,

Sandra A. Wallick

Sandra A. Wallick
Executive Director Community Relations
Saint Louis University Health Sciences Center

P.S. On a more personal note, you were the first person I met at the medical center. Back in the mid-1970s you gave me a tour of the hospital construction site.

# Human trials of experimental AIDS vaccines

**Patricia E. Fast and Mary Clare Walker**

AIDS 1993, 7 (suppl 1):S147–159

**Keywords: AIDS, HIV-1, HIV vaccines, vaccine clinical trials.**

## Introduction

A vaccine against HIV-1 has several potential uses. In a prophylactic setting, it could be given to uninfected individuals to protect them against HIV disease. Protection could occur by one of three mechanisms: (1) 'sterilizing immunity' might completely prevent infection, (2) the immunity induced by the vaccine might limit viral replication or destroy infected cells, so that a transient, subclinical infection would be followed by clearance of the virus, or (3) a vaccinated individual might become permanently infected, but viral replication might be limited and onset of disease delayed or prevented. A reduction in free or cell-associated virus might reduce the likelihood that the vaccinated individual would transmit the virus by sexual contact, by blood and blood products, or to infants during gestation or at birth. Alternatively, in a therapeutic setting, vaccination might be initiated after virus infection is established, with the goal of slowing disease progression or preventing transmission.

It is difficult to conceive a mechanism other than neutralizing antibodies that might produce sterilizing immunity. Studies in chimpanzees, in which neutralizing antibody was induced by active immunization with HIV envelope antigens (M. De Wilde and C. Bruck, personal communication, 1992) [1] or in which polyclonal [2] or monoclonal [3] antibody with neutralizing activity was administered passively, support the notion that neutralizing antibody can be protective. However, humans will repeatedly encounter swarms of HIV-1 virions that vary widely in their antigenic structures; it is unlikely that the entire inoculum will be neutralized before even a few cells become infected. In some experiments, macaques vaccinated against simian immunodeficiency virus (SIV) became infected, but viral burden and disease were reduced [see A. Schultz and S-L. Hu, this volume, for review]. Vaccines that induce cell-mediated immunity as well as antibody may be more likely to eradicate infected cells or to prevent or delay disease in the face of infection. There is, to date, no evidence in animal models for efficacy of postinfection therapeutic vaccination.

During the past year, there has been a considerable increase in the number of clinical trials of candidate HIV-1 vaccines (only active immunization approaches will be discussed here). We will describe ongoing trials, briefly outline the results presented to date, and discuss obstacles to developing an effective AIDS vaccine and some newer approaches that may help to solve them. For brevity, trials in healthy volunteers who are not infected with HIV-1 will be called 'prophylactic' trials, while trials involving immunization of volunteers who are infected with HIV-1 will be called 'therapeutic', to denote their ultimate intent. However, it should be understood that there are no trials underway that will show prophylactic efficacy — such trials would have to enroll thousands of individuals at high risk for HIV-1 infection.

## Candidate HIV-1 vaccines

To date, more than 20 candidate AIDS vaccines have been entered into clinical trials to assess their safety and immunogenicity (Table 1). Most are composed of recombinant proteins, and most are based on the envelope glycoprotein precursor, gp160, or on the glycoprotein gp120. These 'subunit' vaccines are called rgp160 or rgp120 to indicate their production in recombinant expression systems. Epitopes or segments of the envelope protein that are recognized by antibodies or T lymphocytes, especially the V3 loop or principal neutralizing domain [27–32], which includes epitopes recognized by both antibodies and T cells [32–35], will be key components of prototype peptide vaccines. Two experimental vaccines made from HIV envelope peptides conjugated to protein carriers have been tested in small trials (A. Rubinstein and S.J. Cryz, Jr, personal communication, 1992) [15], and V3 peptide is one of two vaccines to be used in a French trial (J-L. Excler, personal communication, 1992).

From the Vaccine Research and Development Branch, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA.

Requests for reprints to: Dr P.E. Fast, Vaccine Research and Development Branch, Division of AIDS, NIAID, NIH, Solar Building, Room 2B-06, 6003 Executive Boulevard, Bethesda, MD 20892, USA.

ISBN 1-870485-74-2 ISSN 0269-9370

**Table 1.** AIDS vaccine candidates undergoing evaluation in experimental trials.

| Vaccine candidate | Expression system/ production method | HIV strain | Adjuvant or delivery system | Vaccine developer | Reference |
|---|---|---|---|---|---|
| **Envelope proteins/peptides** | | | | | |
| rgp160 | Baculovirus/insect | LAI* | Alum | MicroGeneSys | [4,5] |
| rgp160 | Monkey kidney/vaccinia | LAI* | Alum + DOC | ImmunoAG | [6,7] |
| rgp160 | Mammalian | MN/LAI | Alum or IFA | Pasteur–Mérieux–Connaught (Transgène) | [8] |
| rgp160 | Mammalian | LAI | IFA | A. Burney, Université Libre de Bruxelles | [9,10] |
| Env 2–3 | Yeast | SF2 | MF59 +/– MTP-PE | Chiron/Biocine | [11] |
| rgp120 | Chinese hamster ovary | SF2 | MF59 +/– MTP-PE | Chiron/Biocine | [12] |
| rgp120 | Chinese hamster ovary | LAI | Alum | Genentech | [1,13] |
| rgp120 | Chinese hamster ovary | MN* | Alum | Genentech | [13,14] |
| V3–PPD | Purified protein derivative-coupled V3 peptide | MN | – | Swiss Serum & Vaccine Institute | (A. Rubinstein & S.J. Cryz jr, 1992†) |
| V3 | Synthetic peptide | MN | Alum or IFA | Pasteur–Mérieux–Connaught (Transgène) | (H-L. Excler, 1992†) |
| Mixed Env peptides | Synthetic peptide | LAI | ISA724 | A. Burney, Université Libre de Bruxelles | [9,10] |
| Mixed Env peptides | KLH carrier, synthetic | MN, RF, IIIB | Alum | Yokahoma City University, Japan | [15] |
| V3–MAPS | MAPS carrier, synthetic | LAI | Alum | United Biomedical, Inc. | [16,17] |
| **Core protein/peptides** | | | | | |
| HGP-30 | Synthetic p17 peptide | – | Alum | Viral Technologies, Inc. | [18] |
| Ty.p24.VLP | Portion p17/p24 + yeast transposon product | LAI | Alum | British Bio-technology, Ltd | [19] |
| rp24 | Synthetic peptide | LAI | Alum | MicroGeneSys | [20] |
| **Recombinant poxvirus** | | | | | |
| vac–gp160 | Recombinant vaccinia | LAI | – | Bristol–Myers–Squibb/Oncogen | [21] |
| vac–gp160 | Recombinant vaccinia | LAI | – | C. Béaud, Institut Jacques Monod, Paris, France | [9,10] |
| CP–gp160 | Recombinant canarypox | MN | – | Pasteur–Mérieux–Connaught (Virogenetics) | (E. Paoletti & J. Tartaglia, 1992†) [22] |
| **Whole inactivated HIV-1** | | | | | |
| Whole inactivated HIV | β-propiolactone and γ-irradiation inactivation | HZ321 | IFA | Immune Response Corporation | [23,24] |
| **CD4 as immunogen** | | | | | |
| Recombinant CD4 | Synthetic protein | – | IFA | Biogen | (N. Letvin, 1992†) |
| **Anti-idiotype approach** | | | | | |
| Anti-gp120 | Immunoglobulin | – | SAF | IDEC | [25] |
| Anti-CD4 idiotype (IO74) | Monoclonal antibody | – | Alum | Immunotech SA | [26] |

*Similar vaccine candidates based on other viral strains may soon be available. †Personal communication. LAI, group of HIV isolates that includes LAV, IIIB and BRU; DOC, deoxycholate; IFA, incomplete Freund's adjuvant; KLH, keyhole limpet hemocyanin; MAPS, multiple antigen presentation system; Ty, yeast retrotransposon; VLP, virus-like particle. Addresses for vaccine developers: MicroGeneSys, Meriden, Connecticut, USA; ImmunoAG, Vienna, Austria; Pasteur–Mérieux–Connaught, Lyon, France; Chiron, Emeryville, California, USA; Biocine, Emeryville, California, USA; Genentech, South San Francisco, California, USA; Swiss Serum & Vaccine Institute, Berne, Switzerland; United Biomedical, Inc., Hauppage, New York, USA; Viral Technologies, Inc., Alexandria, Virginia, USA; British Bio-technology Ltd, Oxford, England, UK; Bristol–Myers–Squibb, Wallingford, Connecticut, USA; Oncogen, Seattle, Washington, USA; Immune Response Corporation, San Diego, California, USA; Biogen, Boston, Massachusetts, USA; IDEC, La Jolla, California, USA; Immunotech, Marseille, France.

Trials of recombinant poxviruses containing the gp160 gene of HIV-1 in man have introduced a novel approach to human immunization — sequential use of two different vaccines. Priming with the live vector is followed by boosting with recombinant envelope protein or peptide [9,10,36–40]. Vaccines that include part or all of the core (Gag) proteins of HIV-1 include virus-like particles, made by introducing a portion of Gag into the yeast retrotransposon Ty [19], as well as a 30 amino-acid peptide of HIV p17, HGP-30 [18], and Jonas Salk's whole inactivated HIV-1 virus (WTV), which is depleted of gp120 [23,24].

Three experimental vaccines contain neither proteins nor peptides derived from HIV. One therapeutic trial is using recombinant human soluble CD4 as an immunogen to induce antibodies that will block binding of HIV-1 to CD4, its receptor on the cell surface (N. Letvin, personal communication, 1992). In the second non-HIV experimental vaccine, antibodies directed against anti-gp120-antibodies are being administered as immunogens to induce anti-idiotypic antibodies that will recognize the CD4 binding site of gp120, the structure that binds to CD4 on the surface of cells [25]. The third trial also aims to induce anti-idiotype antibodies that will recognize the CD4-binding domain of gp120, using antibodies directed against CD4 [26].

To increase their immunogenicity, vaccines are formulated with adjuvants. Although most incorporate alum (aluminum phosphate or aluminum hydroxide),

the whole inactivated HIV vaccine is formulated in incomplete Freund's adjuvant (IFA) [24]. Trials in France will compare IFA and alum (J-L. Excler, personal communication, 1992). The two rgp120 vaccines of Biocine are formulated in a microfluidized oil-in-water emulsion, MF-59 [41]. These have been tested with and without the addition of muramyl tripeptide-phosphatidylethanolamine (MTP-PE), a synthetic analog of muramyl dipeptide (MDP), which is an immunostimulatory peptide derived from mycobacterial cell walls [41]. A related adjuvant, Syntex adjuvant formulation (SAF) with or without MDP, is used in the IDEC anti-idiotypic vaccine [25].

## Phase I/II trials in uninfected volunteers

Trials of HIV candidate vaccines in uninfected volunteers have now taken place in several countries, including the United States, the United Kingdom, France, Switzerland and Japan (Table 2). The size of these trials has ranged from a handful to 128 volunteers. We will define as Phase I the first test of a vaccine, or a trial involving 25 individuals or less, while further tests in up to 100 or more low-risk volunteers will be called Phase I/II. In the United States, most of the trials have been sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), through the Intramural Laboratory of Immunoregulation or the AIDS Vaccine Evaluation Group (AVEG), supported by the extramural Division of AIDS. The AVEG is a consortium of five academic groups, which recruit, immunize and monitor the volunteers and perform certain immunologic evaluations. Additional standardized immunologic assessments are performed at the Central Immunology Laboratory at Duke University (Durham, North Carolina, USA) and data are collected and analyzed by the AVEG Data Co-ordination and Analysis Center. Independent trials have been performed at San Francisco General Hospital.

Selection and counseling of healthy uninfected volunteers for the trials is critical for the success of clinical AIDS vaccine research. Volunteers in the AVEG Phase I trials, men and women from 18 to 60 years of age with no identifiable risk of HIV infection, are warned that there is no evidence that the vaccine will protect them against infection with HIV, and that it could theoretically make them more susceptible to infection. The importance of avoiding high-risk behavior is emphasized at each visit. Volunteers are also counseled that appearing to be HIV-positive may cause difficulty with obtaining medical or life insurance, enlisting in the armed forces, or traveling. The volunteers are given a tamper-proof identification card and a hot-line telephone is maintained to assist them. NIAID has requested the co-operation of the major insurance associations in the United States to prevent discrimination against its volunteers. A similar program is being organized independently in California. Recruitment procedures in several of the other trials have been similar, but with variations: women have been excluded from the British trials [48], and psychosocial screening by letter and formal questionnaire has been used in France [52].

The frequent misunderstanding among members of the public that some of these vaccines might 'cause' AIDS must be dispelled. The vaccines tested to date in seronegative volunteers cannot cause HIV infection, although they could conceivably predispose to infection if the volunteer engages in high-risk activities.

### Safety of HIV candidate vaccines in uninfected volunteers

The HIV-1 candidate vaccines may cause side-effects typical of vaccines in general, including local pain and tenderness, low-grade fever and minor systemic symptoms, some of which also occur in placebo recipients. In general, these have been mild and the vaccines well tolerated; no hematologic, renal, hepatic or neurologic toxicity has been reported [5,9,10,15,36,40,42,44–51,53–56]. The safety profile of the vaccine appears identical to that of the parent smallpox vaccine [50,51]. When MTP-PE is included, some volunteers have experienced more severe malaise and fever, occasionally leading to 1 or 2 days of missed work or school [46]. To date, no serious illness has been attributed to an HIV candidate vaccine. There has been concern that gp120 or gp160 might cause immune suppression or loss of CD4 cells through binding to CD4 on lymphocytes; however, CD4 cells have remained stable in vaccines and lymphocyte blastogenic responses to mitogens and recall antigens, such as tetanus toxoid, have been unimpaired [10,42,46,48,49,53–57].

### Immunogenicity of HIV candidate vaccines in uninfected volunteers

By the end of 1991, the results of Phase I trials had been published for three vaccines based on envelope proteins (baculovirus-produced rgp160 [5], rgp120 produced in yeast [56], and live recombinant vaccinia containing the gp160 gene [50]), for a vaccine based on Gag, HGP-30 [18], and for the complex immunization approach of Zagury *et al.* [9]. These reports were updated and data from several additional trials presented at the Keystone Symposium on Prevention and Treatment of AIDS, at the VIII International Conference on AIDS in Amsterdam, and at the 1991 and 1992 Conferences on Advances in AIDS Vaccine Development in Marco Island, Florida and Chantilly, Virginia, respectively.

Two gp160 vaccines, both produced from LAI strains of HIV-1 and adjuvanted with alum, have been tested using a schedule of 0, 1, 6 and 12 months [42,44]. Antibody production was dose-dependent; titers after immunization with 40 or 80 μg of the MicroGeneSys vaccine were low [5,58], while either 160 or 640 μg

**Table 2.** Current clinical trials of AIDS vaccine candidates in uninfected volunteers.

| Candidate vaccine | HIV strain | Vaccine developer | Phase | Trial site(s) | Reference |
|---|---|---|---|---|---|
| **Envelope proteins** | | | | | |
| rgp160 | LAI | MicroGeneSys | I/II | NIAID (AVEG) | [5,42] |
| rgp160 | LAI | MicroGeneSys | I | NIAID (LIR) | [43] |
| rgp160 | LAI | ImmunoAG | I/II | NIAID (AVEG) | [44] |
| rgp160 | MN/LAI | Pasteur–Mérieux–Connaught | I/II | PMSV/ANRS | (J-L. Excler, 1992*) |
| rgp120 | LAI | Genentech | I | NIAID (AVEG) | [45] |
| rgp120 | MN | Genentech | I | NIAID (AVEG) | (R. Belshe, 1992*) |
| rgp120 (Env 2–3) | SF2 | Biocine | I | NIAID (AVEG) | [46] |
| rgp120 (CHO) | SF2 | Biocine | I/II | UCSF | [47] |
| rgp120 (CHO) | SF2 | Biocine | I/II | NIAID (AVEG) | (B. Graham, 1992*) |
| **Virus-like particles** | | | | | |
| Ty.p24.VLP | LAI | British Bio-technology Ltd | I | St Mary's Hospital Medical School, London | [48] |
| **Peptides** | | | | | |
| Mixed envelope peptides on keyhole limpet hemocyanin carrier | LAI, MN, RF | Yokohama City University Japan | I | Yokohama City Univerity Japan | [15] |
| V3 loop conjugated to purified protein derivative | MN | Swiss Serum & Vaccine Institute (SSVI) | I | SSVI, Berne | (A. Rubinstein & S.J. Cryz Jr*, 1992) |
| HGP-30 | LAI | Viral Technologies, Inc. | I | SFGH/UCSF | [49] |
| V3-MAPS | LAI | United Biomedical, Inc. | I | NIAID (AVEG) | (G. Corse, 1993*) |
| **Vectors** | | | | | |
| Vaccinia–gp160 | LAI | Bristol–Myers–Squibb/Oncogen | I/II | University of Washington | [50] |
| Vaccinia–gp160 | LAI | Bristol–Myers–Squibb/Oncogen | I/II | NIAID (AVEG) | [51] |
| Canarypox–gp160 | MN | Pasteur–Mérieux–Connaught (Virogenetics) | I | PMSV/ANRS | (J-L. Excler, 1992*) |
| **Vaccine combinations** | | | | | |
| Vaccinia–gp160 plus subunit rgp160 | LAI | Bristol–Myers–Squibb/ Oncogen; MicroGeneSys | I | NIAID (AVEG) | [38,40] |
| Vaccinia–gp160 plus Vaccinia–gp160 | LAI | Bristol–Meyers–Squibb/ Oncogen; MicroGeneSys | I | University of Washington | [39] |
| Vaccinia–gp160 plus subunit rgp120 (yeast or mammalian cell produced) | LAI/SF2 | Bristol-Myers Squibb/ Oncogen; Biocine | I/II | NIAID (AVEG) | (L. Corey, 1992*) |
| Vaccinia–gp160 plus subunit gp160 plus 3 envelope peptides | LAI | G. Béaud, Institut Jacques Monod Paris, France A. Burney, Université Libre de Bruxelles | I | Hôpital Saint-Antoine, Paris, France | [9,10,36] |
| Canarypox–gp160 plus V3 peptide | MN/LAI | Pasteur–Mérieux–Connaught (Virogenetics, Transgène) | I | PMSV/ANRS | (J-L. Excler, 1992*) |
| rgp160 plus V3 peptide | MN/LAI | Pasteur–Mérieux–Connaught (Transgène) | I | PMSV/ANRS | (J-L. Excler, 1992*) |

*Personal communication. LAI, group of HIV isolates that includes LAV, IIIB and BRU; NIAID, National Institute of Allergy and Infectious Diseases; LIR, Laboratory of Immunoregulation; AVEG, AIDS Vaccine Evaluation Group of AIDS Vaccine Clinical Trials Network: Johns Hopkins University, St Louis University, University of Rochester, University of Washington, Vanderbilt University (former members: Baylor University and University of Maryland); PMSV, Pasteur Mérieux Serums et Vaccins; ANRS, Agence Nationale de Recherches sur le SIDA; SFGH, San Francisco General Hospital; UCSF, University of California at San Francisco. Addresses for vaccine developers: MicroGeneSys, Meriden, Connecticut, USA; ImmunoAG, Vienna, Austria; Pasteur–Mérieux–Connaught, Lyon, France; Chiron, Emeryville, California, USA; Genentech, South San Francisco, California, USA; Biocine, Emeryville, California, USA; British Bio-technology Ltd, Oxford, England, UK; Swiss Serum & Vaccine Institute, Berne, Switzerland; Viral Technologies, Inc., Alexandria, Virginia, USA; United Biomedical, Inc., Hauppage, New York, USA; Bristol–Myers–Squibb, Wallingford, Connecticut, USA; Oncogen, Seattle, Washington, USA; Immune Response Corporation, San Diego, California, USA.

of the antigen induced strong antibody responses as measured by binding assays, including Abbott enzyme-linked immunosorbent assay (ELISA), Western blots or enzyme immunoassays (EIA) using the immunogen [42]. The ImmunoAG rgp160, tested at 12.5 and 50 μg (a lower dose range) also induced binding antibody in a dose-dependent manner [44]. Both immunogens induced anamnestic responses, but the antibody titers waned over a period of months. Type-specific neutralizing antibody was detected in some vaccinees after

the third or fourth immunization, particularly at the higher doses, but titers were usually low [5,42,44]. Both of the rgp160 vaccine candidates induced cellular immune responses [53–55,59–62]. Stimulation of volunteer's peripheral blood lymphocytes *in vitro* with rgp160 induced lymphoproliferation before humoral antibody was detectable. Following immunization with low doses of either vaccine, significant lymphocyte proliferation responses were noted in some volunteers within 2–4 weeks, although humoral responses were weak or undetectable until after the second immunization [53–55,61]. Both rgp160 vaccines induced circulating precursors for CD4+ cytotoxic T lymphocytes (CTL), which were restricted by class II major histocompatibility antigens [59,60,62]; the significance of this finding with respect to protection from infection is unknown.

Two trials have evaluated live recombinant vaccinia–gp160. *In vitro* lymphocyte proliferative responses were detected following vaccination [37,50,51]. Little antibody is produced after one or two vaccinations. Circulating CD4+ CTL precursors were detected in one of the two vaccinees tested [62]. However, a vigorous response was induced when volunteers primed with vaccinia–gp160 were boosted with MicroGeneSys rgp160; all volunteers produced binding antibody within 2 weeks [37,39,40,63]. Unlike recipients of the rgp160 protein alone, more than half of the vaccinees produced neutralizing and syncytium-inhibiting antibody [37–40]. The effect of the priming was most pronounced when (1) volunteers had never been vaccinated against smallpox [37–40], (2) at least 6 months had elapsed between priming with vaccinia–gp160 and boosting with rgp160 [38,40], and (3) volunteers received two priming doses of vaccinia–rgp160 (B. Graham, personal communication, 1992).

The prime–boost combination induced a strong cellular immune response. Most volunteers developed T-cell memory, as measured by lymphoproliferative responses to gp160, which persisted for at least 1 year following vaccination [9,37,39,40,64]. CD4+ CTL precursors were detected in the peripheral blood of some of the volunteers [62]. However, the vaccine combination also induced persistent circulating precursors of CD8+, MHC class I-restricted CTL in some of the volunteers. CD8+ CTL were detected after *in vitro* stimulation with gp160-expressing poxvirus vectors (K. Weinhold, personal communication, 1992), Epstein–Barr virus vectors expressing gp160 [65], whole inactivated HIV [64] or autologous HIV-infected macrophages (J. McElrath, personal communication, 1992). Picard *et al.* [10,36] have also reported the *in vitro* generation of CD8+ CTL, restricted by MHC class I antigens, after immunization with vaccinia–gp160 and/or subunit immunogens.

Data from three trials of rgp120 vaccines have been reported this year. Genentech rgp120 (IIIB) was injected (100 or 300 μg) at months 0, 1 and 8, mimicking the schedule that previously led to protection of two chimpanzees from intravenous challenge with HIV-$1_{IIIB}$ given 2 weeks after boosting [1]. The humans responded much like the chimpanzees; after the third inoculation with 300 μg rgp120, neutralizing antibody was observed in nine out of 10 volunteers; antibodies that bound to V3 loop peptide and blocked the binding of CD4 to gp120 were also induced [45]. Most volunteers who received 300 μg Genentech rgp120 showed strong *in vitro* proliferative responses to IIIB rgp120 produced in either a mammalian or a baculovirus expression system [66]. CD4+ CTL were also induced in some of the vaccinees [62].

The yeast-produced rgp120, Env 2–3, was administered in an oil-in-water emulsion, MF59, with or without an immunomodulator, MTP-PE. With a vaccine dose of 30 μg, the MTP-PE dose was increased from 0 to 100 μg/dose; 100 μg vaccine was given in MF59 alone. Syncytium-inhibiting and/or neutralizing antibodies were evident in a few volunteers after the second dose of antigen, and in most after the third immunization [46]. There was no clear evidence of a dose–response relationship for either the rgp120 or the MTP-PE [46]. The relationship of the MTP-PE to the quality and duration of the antibody response requires further study. No data on cell-mediated immune responses to this vaccine candidate have been reported. Preliminary results of studies of mammalian-cell produced rgp120 derived from the same HIV genome, SF2, formulated in the same adjuvant, showed an improved neutralizing antibody response (B. Graham, personal communication, 1992) [47].

A small number of individuals were immunized with a mixture of peptides conjugated to keyhole limpet hemocyanin (KLH) [15]. The peptides included parts of the V3 loop [32,33], including peptides encoding a CTL epitope [34]. They reportedly produced both binding and neutralizing antibodies and their peripheral blood mononuclear cells responded to the peptides *in vitro* by proliferation.

Two trials in which normal volunteers were immunized against core antigens were reported in 1992. HGP-30, a peptide derived from p17, conjugated to KLH, was used to immunize subjects in a San Francisco study [49,57]. Antibody formation was demonstrated, but no neutralizing antibody was detected. T-cell proliferative responses were variable and occurred in only a few volunteers. Four out of 11 volunteers were reported to have positive CTL responses [57]. In London, a p24-virus-like particle vaccine (p24 VLP or Ty-*gag*), adjuvanted with alum, was given to 16 volunteers at doses of 100 or 500 μg intradermally followed by 500 μg intramuscularly [48]. Low titers of antibody were observed until the fourth dose (first intermuscular dose). T-cell proliferative responses were demonstrated, but no CTL were observed [67].

Trials that have started recently for which no data are yet available include the AVEG trials of Genentech rgp120 MN, Biocine SF2 rgp120 (CHO), and recombinant vaccinia–gp160, followed by boosting with rgp120 vaccine based on a different viral strain, and two French trials using either recombinant canarypox (to be boosted with rgp160) or rgp160 (to be boosted with V3 loop peptides) (J.L. Excler, personal communication, 1992). A small trial of V3 loop peptide conjugated to purified protein derivative (PPD) is underway in Switzerland (A. Rubinstein and S.J. Cryz, Jr, personal communication, 1992).

## Obstacles to development of a prophylactic vaccine

HIV-1 is a formidable foe, which presents many obstacles to the development of an efficacious prophylactic vaccine. Relatively little is known about immune responses that can protect against this virus because there is no convalescent state. The only known immune mechanism for the prevention of infection by a pathogen is specific antibody [68]. Antiviral antibodies can react with the virus itself or with viral proteins on the surface of infected cells. In the case of HIV-1, only the envelope glycoproteins are expressed in quantity on the surface of both intact virions and infected cells. Limitation or clearance of viral infection is usually effected by CD8+ CTL, which are restricted by MHC class I antigens [68]. In individuals infected by HIV-1, such CTL responses to HIV-1 envelope, Gag, reverse transcriptase, Nef and Vif have been detected [69–74]. Various methods of antigen presentation may select different types of immune responses, while a live attenuated retrovirus or live recombinant vaccine may induce both T-cell responses and antibodies, a soluble subunit vaccine rarely induces CD8+ CTL unless presented in a special adjuvant or delivery system (see M. Clerici in this volume, for review).

An increasingly large proportion of HIV-1 transmission is sexual, and occurs across mucosal membranes. It is therefore possible that an efficacious prophylactic vaccine will have to induce HIV-1-specific mucosal immunity, such as anti-HIV antibodies of the secretory immunoglobulin (Ig) A type.

The diversity of the sequence coding for HIV proteins, particularly envelope proteins [32,75], is another obstacle to AIDS vaccine development. Recent studies with polyclonal and monoclonal antibodies have demonstrated that antibodies directed against three or more regions of the envelope can cross-react with many viral strains [76–79]; antibodies specific for different regions of the envelope may act synergistically to neutralize HIV [80]. With the exception of antibodies directed against the crown of the V3 loop [76], broadly cross-reactive anti-HIV antibodies are often directed against discontinuous epitopes, which are more likely to be present in glycosylated recombinant envelope proteins produced in mammalian systems than in denatured or non-glycosylated proteins made in prokaryotic expression systems [12,77]. The extent to which such epitopes are found in envelope proteins produced in insect expression systems is controversial (J. Moore, personal communication, 1992) [81].

Certain epitopes on HIV proteins may mimic host proteins (N. Roberts, Jr, personal communication, 1992) [82]. Such cross-reactions could theoretically induce autoimmune disease, but there is no evidence that HIV candidate vaccines induce pathologic processes. Molecular mimicry might also explain the rather poor immunogenicity of HIV envelope proteins; alternatively, the heavy glycosylation of the envelope glycoproteins may mask their antigenicity [83].

## Approaches to developing a prophylactic vaccine

Clinical trials that will address several of the obstacles to development of an effective HIV vaccine may begin within the next year. Simple but potentially important variables, such as dose and schedule of immunization, are being addressed with current vaccines. The combination of two vaccines, live vector and purified recombinant protein is being explored further with recombinant vectors based on two poxviruses (vaccinia and canarypox) in France and the United States, using a variety of different subunits to boost. Live vectored vaccines based on other viruses or bacteria are being developed, some of which could be administered orally to induce mucosal immunity (Table 3). A multivalent recombinant vaccinia has been shown to induce CD8+ CTL as well as antibody in animals [94]. Comparative adjuvant experiments already underway on a large scale in the SIV model in Europe (G. Hunsmann, personal communication, 1992) and the United States (M. Murphy-Corb, personal communication, 1992), are planned for clinical trials within the next year. In addition to inducing antibody responses, vaccines based on peptides may induce cytotoxic lymphocytes, provided the match of peptide to HLA type is correct [34]. The components of multivalent peptide vaccines could be changed rapidly to reflect a changing epidemic; and one or more peptide vaccines may enter trials within 1992–1993. Thus several of the outstanding problems, including magnitude and duration of functional immune responses and the response to viral variation, will be variously addressed in clinical trials planned for the next year.

Table 3. Some AIDS vaccine candidates in development.

| Vaccine prototype | Expression system/ production method | Viral strain | Adjuvant or delivery system | Vaccine developer | Reference |
|---|---|---|---|---|---|
| **Envelope proteins/peptides** | | | | | |
| rgp160 | Mammalian | LAI | Oil/water, 3-deacyl monophosphoryl Lipid A | SmithKline Beecham | [84] |
| rgp120 | Drosophila | LAI | Oil/water, 3-deacyl monophosphoryl Lipid A | SmithKline Beecham | [84] |
| V3-MAPS | Synthetic | Multiple | Alum | United Biomedical, Inc. | [16,17] |
| T1-SP10(A) | Synthetic | Multiple | IFA or alum | B. Haynes, Duke University | [85,87] |
| MN-PND-Toxin A conjugate | Synthetic peptide/ *Pseudomonas aeruginosa* | MN | – | Swiss Serum & Vaccine Institute | (S.J. Cryz Jr, 1992†) |
| Env-PND-Gag-HGP-30 conjugate | Synthetic, peptide | LAI | Cholera toxin B | Alpha-1 Biomedicals | [88] |
| Ty-VLP-Env peptides | Yeast | Multiple | Alum | British Bio-technology Ltd | [89] |
| CLTB-28, CLTB-32, CLTB-36, CLTB-37 | Synthetic chimeric V3-p24 gag peptides | MN | – | Connaught Laboratories | [90] |
| Four-helix bundle of Env and Gag peptides | Synthetic | – | – | NPO Vector, Kolsovo | [91] |
| Peptide tertiary structural templates | Synthetic | Multiple | To be determined | A. Komoriya and S. Shinagawa CBER, FDA | [92] |
| **Particle/virus-like** | | | | | |
| HBcAg-V3 particles | *Escherichia coli* | BH10 | – | A. von Brunn, Max von Pettenkofer-Institut | [93] |
| HIV-Env, Gag, Pol pseudovirions* | Mammalian/vaccinia | LAI | Alum | Therion Biologics | [94] |
| HIV-Env, Gag, Pol pseudovirions* | Mammalian (Vero) | LAI and MN | – | Connaught Laboratories | [95] |
| Gag-V3 virus-like particles | Baculovirus/ insect cells | LAI | – | Universität Regensburg | [96] |
| **Inactivated virus** | | | | | |
| Whole inactivated HIV-1 | Betapropiolactone BEI, formaldehyde inactivation | LAI, IIIB | Digitonin | Retroscreen Ltd/ISI | [97] |
| Whole inactivated HIV-2 | Triton or formalin inactivation | HIV-2 | IFA, alum, RIBI adjuvant, ISCOMS | National Bacteriological Laboratory, Sweden | [98] |
| **Live vector** | | | | | |
| TBC-3B | Attenuated recombinant vaccinia | LAI | – | Therion Biologics | [94] |
| NYVAC | Attenuated recombinant vaccinia | LAI | – | Pasteur-Mérieux-Connaught (Virogenetics) | (E. Paoletti & J. Tartaglia, 1992†) [22] |
| Adenovirus-HIV | Recombinant adenovirus | LAI | – | Wyeth-Ayerst | [99] |
| Poliovirus-HIV | Recombinant poliovirus | LAI | – | | [100,101] |
| Salmonella-HIV | Recombinant salmonella | HIV-2 | – | | [102] |
| BCG-HIV | Recombinant BCG | LAI | – | Medimmune, Inc. | [103] |
| BCG-HIV | Recombinant BCG | LAI | – | | [104] |
| **Other approaches** | | | | | |
| Inactivated autologous cells expressing HIV antigens | Transduction of MuLV-HIV-1 Env, Gag, or Pol constructs into human fibroblasts or B-lymphocytes | Multiple | – | Viagene, Inc. | [105] |
| HIV expression vector-coated 1.0 μm gold particles | Non-expressed DNA | Multiple | Particle acceleration device | Agracetus | [106] |

*Lacks some regulatory sequences. †Personal communication. HBcAG, hepatitis B core antigen; BCG, bacille Calmette–Guérin; MuLV, murine leukemia virus; LAI, group of HIV isolates that includes LAV, IIIB and BRU. IFA, incomplete Freund's adjuvant. Addresses for vaccine developers: SmithKline Beecham, Rixensart, Belgium/Philadelphia, Pennsylvania, USA; United Biomedical, Inc., Hauppage, New York, USA; Swiss Serum & Vaccine Institute, Berne, Switzerland; Alpha-1 Biomedicals, Bethesda, Maryland, USA; British Bio-technology Ltd, Oxford, England, UK; Connaught Laboratories, Willowdale, Ontario, Canada; NPO Vector, Kolsovo, Novosibursk region, Russia; CBER (Center for Biologics Evaluation and Research), FDA (Food and Drug Administration), Bethesda, Maryland, USA; Max von Pettenkofer-Institut, Munich, Germany; Universitat Regensburg, Regensburg, Germany; Retroscreen Ltd, London, UK; Therion Biologics, Cambridge, Massachusetts, USA; Pasteur-Mérieux-Connaught, Lyon, France; Wyeth-Ayerst Laboratories, Radnor, Pennsylvania, USA; Medimmune, Inc., Gaithersburg, Maryland, USA; Viagene, Inc., San Diego, California, USA; Agracetus, Inc., Middleton, Wisconsin, USA.

Table 4. Current clinical trials of AIDS vaccine candidates in HIV-infected individuals.

| Candidate vaccine | HIV strain | Vaccine developer | Phase | Trial site(s) | Reference |
|---|---|---|---|---|---|
| **Envelope proteins** | | | | | |
| rgp160 | LAI | MicroGeneSys | I | NIAID (LIR) | [107] |
| | | | I/II | NIAID (ACTG) | [108] |
| | | | I/II | WRAIR | [109,110] |
| | | | I/II | McGill University, Montreal | [111] |
| | | | I/II | NBL, Stockholm | [112] |
| | | | II | WRAIR & multicenter collaboration | [110] |
| rgp160 | LAI | ImmunoAG | I/II | NIAID (AVEG, ACTG) | (D. Schwartz, 1992*) |
| rgp120 | LAI | Genentech | I | WRAIR | [113] |
| rgp120 (Env 2–3) | SF2 | Biocine | I | NIAID (AVEG) | (L. Corey, 1992*) |
| | | | I/II | VIRx | (D. Chernoff, 1992*) |
| rgp120 (CHO) | SF2 | Biocine | I | VIRx | (D. Chernoff, 1992*) |
| **Whole killed virus** | | | | | |
| Whole inactivated HIV-1, without envelope | HZ321 | Immune Response Corporation/ Immunization Products Ltd | I/II | Multicenter | [24] |
| **Vaccine combinations** | | | | | |
| Vaccinia–gp160 plus gp160 subunit plus fixed vaccinia–gp160 infected autologous cells | LAI | G. Béaud, Institut Jacques Monod A. Burney, Université Libre de Bruxelles | I | Hôpital Saint-Antoine, Paris | [114] |
| gp160 plus p24 | LAI | MicroGeneSys | I | Southern New England Community Consortium Greenwich, Connecticut | [20] |
| **Anti-idiotype antibodies** | | | | | |
| Anti-gp120 idiotype | – | IDEC | I | Multicenter | (J. Merritt, 1992*) |
| Anti-CD4 idiotype (IOT4a) | – | Immunotech SA | I | Medical School of Hanover, Germany | [26] |
| **Cellular antigens** | | | | | |
| Soluble CD4 | – | Biogen | I | Harvard University, Boston (N. Letvin) | (N. Letvin, 1992*) |

*Personal communication. LAI, group of HIV isolates that includes LAV, IIIB and BRU. NIAID, National Institute of Allergy and Infectious Diseases; LIR, Laboratory of Immunoregulation; ACTG, AIDS Clinical Trials Group; AVEG, AIDS Vaccine Evaluation Group; WRAIR, Walter Reed Army Institute of Research; NBL, National Bacteriological Laboratory, Sweden. Addresses for vaccine developers: MicroGeneSys, Meriden, Connecticut, USA; ImmunoAG, Vienna, Austria; Genentech, South San Francisco, California, USA; Biocine, Emeryville, California, USA; Immune Response Corporation, San Diego, California, USA; Immunization Products Ltd, Horsham, Pennsylvania, USA; IDEC, La Jolla, California, USA; Immunotech, Marseille, France; Biogen, Boston, Massachusetts, USA; ViRx, San Francisco, California, USA.

## HIV vaccine therapy trials

Several pilot, uncontrolled trials have been reported, and incremental data on immunization with recombinant HIV envelope proteins to augment the immune responses of individuals already infected with HIV-1 have become available in the past year (Table 4). Two trials, neither of which contains placebo controls, will provide preliminary information about the combined use of rgp160 and zidovudine [110] or p24 [20]. In addition, immunogenicity and safety data on the use of whole inactivated (envelope-depleted) HIV have been presented [24]. All of these trials have been reassuring with respect to safety; CD4 counts have not been lowered by the vaccines, as theoretical considerations of apoptosis and/or viral activation had suggested, and appear to be stabilized in some trials [107–113], although data from uncontrolled trials must be regarded with great caution. There is evidence of new antibody formation to some epitopes (G. Smith, personal communication, 1992) [108–113,115], increased T-cell memory [35,108–113,116], and increased cytotoxic T-cell activity [108,116]. As previously noted, uninfected volunteers respond differently to rgp160 after priming with recombinant vaccinia [38–40]; it is possible that the responses of HIV-infected individuals, who have been immunologically primed by the virus infecting them, differ from those of uninfected volunteers. The dose required for maximal antibody response to rgp160 in HIV-infected volunteers [108,111] may be less than that required in uninfected volunteers [5,42].

Complete information about the effects on viral burden (proviral and replicating) and confirmation of the intriguing preliminary observations of Redfield *et al.* [110] on increased responses, including neutralization, to autologous viral strains, are awaited with great

interest. Individuals immunized with whole inactivated virus or with rgp160 have a dose-dependent delayed-type hypersensitivity response (DTH) to intradermal injections of the vaccine product [24,116]. The relationship of these immune responses and surrogate markers to the ultimate well-being of the individual will be difficult to assess; most of the trials have enrolled subjects with relatively high CD4 counts, in whom progression to AIDS or death may be many years away, so definitive answers will require years of follow-up of the entire vaccinated cohort in double-blind, randomized studies. Two trials have enrolled individuals with low T-cell counts [20,24], and further elucidation of the relationship of T-cell counts to ability to respond to vaccine will be critical in planning future trials.

Three things seem clear from these therapeutic vaccine trials: (1) new immune responses can be mounted by most HIV-infected individuals against experimental HIV vaccines; (2) in the short term, these vaccines do not appear to cause harm; and (3) in the short term, no dramatic improvement in CD4 cell counts or viral burden has been demonstrated. Since the majority of HIV replication probably takes place in lymphoid organs, rather than in circulating peripheral blood mononuclear cells [117], and since immune manipulations may alter lymphocyte or monocyte recirculation patterns [118], any alterations in viral burden measured in peripheral blood mononuclear cells and any changes in circulating CD4 cell counts must be interpreted cautiously. Ultimately the health and well-being of the vaccinated individuals will be the critical outcome to be measured.

Additional products entered into AVEG therapeutic Phase I trials during the past year include Env 2–3 (Biocine), with and without zidovudine, and rgp160 (ImmunoAG). The AIDS Clinical Trials Group (ACTG) plans an extensive Phase I comparison of several vaccines, as well as a trial of one vaccine over a wider range of CD4 counts. Additional, larger trials are now being planned. Large-scale, multicenter trials are underway to test the Salk Whole Inactivated HIV-1 Vaccine, MicroGeneSys rgp160, and Genentech rgp120(MN) in HIV-infected volunteers.

## Pediatric and perinatal trials

Phase I trials in which a small number of HIV-infected pregnant women will be vaccinated with recombinant envelope products to determine safety and immunogenicity are also being planned. Presently, pregnant women are excluded from all therapeutic trials of AIDS vaccines. If such vaccines are immunogenic during pregnancy and safe for both mother and fetus, one or more efficacy trials could be undertaken with two goals: to prevent transmission of HIV infection from mother to infant, and to slow or stop the decline in immune function that the mother may undergo during pregnancy [119–121]. This approach, if successful, would offer hope to the many women who are first diagnosed as HIV-infected when they become pregnant.

HIV candidate vaccines will also be tested in infants and children in trials planned by the ACTG. Phase I trials will evaluate recombinant envelope vaccine candidates for safety and immunogenicity in two populations: children known to be infected with HIV, and newborn infants of HIV-positive mothers. The onset of disease is more rapid in some children than in adults; eventual efficacy trials of vaccine therapy in infants might reveal real clinical benefit within a small number of years. In interpreting these trials, however, one must bear in mind that a vaccine might benefit the children who experiences 'slow' disease onset (i.e., 2–10 years) without benefiting those who, for unknown reasons, are destined to succumb rapidly to HIV infection [120,121]. Vaccination of newborns, some of whom probably become infected at birth, might prevent infection or disease completely, but it appears likely that additional passive immunization would be required, as in the effective active-plus-passive immunization of newborns against hepatitis B [122].

## Conclusion

A variety of HIV vaccines are now being evaluated in Phase I/II prophylactic trials. The vaccines appear to be safe. Although we do not know which immune responses will be protective, researchers have been encouraged by the induction of neutralizing antibody either by a combined regimen of vaccinia–gp160 priming followed by rgp160 boosting or by immunization with gp120 alone in more than half the volunteers. Similarly, the recent demonstration of CD8+ CTL in recipients of the combined recombinant vaccinia–gp160 plus rgp160 regimen suggests that more than one functional response can be induced. It appears likely that the duration, breadth and magnitude of responses to immunization must be improved before an efficacy trial will be feasible. A variety of strategies, including addition of novel adjuvants [123,124], new combinations of vaccines, new vector and peptide vaccines will probably enter clinical trials within the next year.

Therapeutic vaccine trials have yielded tantalizing hints that disease stabilization may be possible, but final conclusions must await therapeutic trials that evaluate end-points of disease onset and death, as well as surrogate markers, blind. Children, pregnant women and newborn infants at risk will soon be vaccinated, in an attempt to prevent perinatal transmission, allow access to therapy trials by pregnant women, and prevent or delay pediatric AIDS.

## Acknowledgements

We thank our many colleagues for generously allowing us to cite their unpublished work, including that presented at the Advances in AIDS Vaccine Development meetings of 1991 and 1992. We thank Sharon Chambers for prompt, efficient and accurate secretarial assistance.

## References

1. BERMAN PW, GREGORY TJ, RIDDLE L, *ET AL.*: Protection of chimpanzees from infection by HIV-1 after vaccination with recombinant glycoprotein gp120 but not gp160. *Nature* 1990, 345:622–625.
2. PRINCE AM, HOROWITZ B, SHULMAN RW, *ET AL.*: Apparent prevention of HIV infection by HIV immunoglobulin given prior to low-dose HIV challenge. In *Vaccines 90.* Edited by Brown F, Lerner RA, Chanock RM, Ginsberg H. Cold Spring Harbor: Cold Spring Harbor Press; 1990:347–351.
3. EMINI EA, SCHLEIF WA, NUNBERG JH, *ET AL.*: Prevention of HIV-1 infection in chimpanzees by gp120 V3 domain-specific monoclonal antibody. *Nature* 1992, 355:728–730.
4. COCHRAN MA, ERICSON BL, KNELL JD, *ET AL.*: Use of baculovirus recombinants as a general method for the production of subunit vaccines. In *Vaccines 87.* Edited by Ginsberg H, Brown F, Lerner RA, Chanock RM. Cold Spring Harbor: Cold Spring Harbor Press; 1987:384–388.
5. DOLIN R, GRAHAM B, GREENBERG S, *ET AL.*: Safety and immunogenicity of an HIV-1 recombinant gp160 candidate vaccine in humans. *Ann Intern Med* 1991, 114:119–127.
6. FUERST TR, EARL PL, MOSS B: Use of a hybrid vaccinia virus-T7 RNA polymerase system for expression of target genes. *Mol Cell Biol* 1987, 7:2538–2544.
7. BARRETT N, MITTERER A, MUNDT W, *ET AL.*: Large-scale production and purification of a vaccinia-derived HIV-1 gp160 and analysis of its immunogenicity. *AIDS Res Hum Retroviruses* 1989, 5:159–171.
8. KIENY M-P, RAUTMANN G, SCHMITT D, *ET AL.*: AIDS virus Env protein expressed from a recombinant vaccinia virus. *Bio/Technol* 1986, 4:790–795.
9. ZAGURY D, BERNARD J, CHEYNIER R, *ET AL.*: A group-specific anamnestic immune reaction against HIV-1 induced by a candidate vaccine against AIDS. *Nature* 1988, 332:728–731.
10. PICARD O, ACHOUR A, BERNARD J, *ET AL.*: A 2-year follow-up of an anti-HIV immune reaction in HIV-1 gp160-immunized healthy seronegative humans: evidence for persistent cell-mediated immunity. *J Acquir Immune Defic Syndr* 1992, 6:539–546.
11. STEIMER KS, VAN NEST G, DINA D, BARR PJ, LUCAW PA, MILLER ET: Genetically engineering human immunodeficiency virus envelope glycoprotein gp120 produced in yeast is the target of neutralizing antibodies. In *Vaccines 87.* Edited by Ginsberg H, Brown F, Lerner RA, Chanock RM. Cold Spring Harbor: Cold Spring Harbor Press; 1987:236–241.
12. HAIGWOOD NL, NARA PL, BROOKS E, *ET AL.*: Native but not denatured recombinant human immunodeficiency virus type 1 gp120 generates broad-spectrum neutralizing antibodies in baboons. *J Virol* 1992, 66:172–182.
13. LASKY LA, GROOPMAN JE, FENNIE CW, *ET AL.*: Neutralization of the AIDS retrovirus by antibodies to a recombinant envelope glycoprotein. *Science* 1986, 233:209–212.
14. BERMAN PW, MATTHEWS TJ, RIDDLE L, *ET AL.*: Neutralization of laboratory and clinical isolates of HIV-1 by antisera raised against a monovalent subunit vaccine [abstract]. *J Cell Biochem* 1992, suppl 16E:15.
15. OKUDA K, INAMI S, KANEKO T: Strong synergistic effects of polyvalent vaccine for human immunodeficiency virus (HIV-1) infection. *VIII International Conference on AIDS/III STD World Congress.* Amsterdam, July 1992 [abstract PoA2425].
16. WANG CY, LOONEY DJ, LI ML, *ET AL.*: Long-term high-titer neutralizing activity induced by octameric synthetic HIV-1 antigen. *Science* 1991, 254:285–288.
17. WALFIELD A, LI ML, HOSEIN B, *ET AL.*: High-titer neutralization for multiple HIV-1 isolates elicited by branched immunogens. *VIII International Conference on AIDS/III STD World Congress.* Amsterdam, July 1992 [abstract PoA2233].
18. GOLDSTEIN AL, NAYLOR PH, SARIN PS, *ET AL.*: Progress in the development of a p17-based HIV vaccine: safety and potential efficacy of the HGP-30 synthetic peptide vaccine in humans. *VII International Conference on AIDS.* Florence, June 1991 [abstract MA1342].
19. ADAMS SE, DAWSON KM, GULL K, KINGSMAN SM, KINGSMAN AJ: The expression of hybrid HIV:Ty virus-like particles in yeast. *Nature* 1987, 329:68–70.
20. BUCK G, CROOK S, BUCHANAN S, DIAMOND M, SMITH G, VOLVOVITZ F: A Phase I/II study of the toxicity, immunogenicity and efficacy of recombinant gp160 and p24 vaccines (Vax3yn) in HIV-infected individuals regardless of CD4+ cell count. *VIII International Conference on AIDS/III STD World Congress.* Amsterdam, July 1992 [abstract TuB0562].
21. HU SL, KOSOWSKI SG, DALRYMPLE JM: Expression of AIDS virus envelope in recombinant vaccinia viruses. *Nature* 1986, 320:537–539.
22. TARTAGLIA J, COX WI, TAYLOR J, *ET AL.*: Highly attenuated poxvirus vectors. *AIDS Res Hum Retroviruses* 1992, 8:1445–1447.
23. SALK J: Prospects for the control of AIDS by immunizing seropositive individuals. *Nature* 1987, 327:473–476.
24. TURNER JL, SLADE HB, TRAUGER RJ, *ET AL.*: Double-blind, placebo-controlled dose-ranging study of Salk immunogen in incomplete Freund's adjuvant in asymptomatic patients with early human immunodeficiency virus infection. *VIII International Conference on AIDS/III STD World Congress.* Amsterdam, July 1992 [abstract PoB3043].
25. KANG C-Y, NARA P, CHAMAT S, *ET AL.*: Anti-idiotype monoclonal antibody elicits broadly neutralizing anti-gp120 antibodies in monkeys. *Proc Natl Acad Sci USA* 1992, 89:2546–2550.
26. SUTOR G-C, TRIESSNAR J, JURKIEWICH E, *ET AL.*: Anti-CD4 idiotype vaccination of HIV+ volunteers. *VIII International Conference on AIDS/III STD World Congress.* Amsterdam, July 1992 [abstract PoB3042].
27. PUTNEY SD, MATTHEWS TJ, ROBEY WG, *ET AL.*: HTLV-III/LAV neutralizing antibodies to an *E. coli*-produced fragment of the virus envelope. *Science* 1986, 234:1392–1395.
28. HO DD, SARNGADHARAN MG, HIRSCH MS, *ET AL.*: Human immunodeficiency virus neutralizing antibodies recognize several conserved domains on the envelope glycoproteins. *J Virol* 1987, 61:2024–2028.
29. RUSCHE JR, JAVAHERIAN K, MCDANAL C, *ET AL.*: Antibodies that inhibit fusion of human immunodeficiency virus-infected cells bind a 24 amino-acid sequence of the viral envelope, gp120. *Proc Natl Acad Sci USA* 1988, 85:3198–3202.
30. PALKER TJ, CLARK ME, LANGLOIS AJ, *ET AL.*: Type-specific neutralization of the human immunodeficiency virus with antibodies to *env*-encoded synthetic peptides. *Proc Natl Acad Sci USA* 1988, 85:1932–1936.
31. JAVAHERIAN K, LANGLOIS AJ, MCDANAL C, *ET AL.*: Principal neutralizing domain of the human immunodeficiency virus type 1 envelope protein. *Proc Natl Acad Sci USA* 1989, 86:6768–6772.
32. LAROSA GJ, DAVIDE JP, WEINHOLD K, *ET AL.*: Conserved sequence and structural elements in the HIV-1 principal neutralizing domain. *Science* 1990, 249:932–935.
33. BERZOFSKY JA, BENSUSSAN A, CEASE KB, *ET AL.*: Antigenic peptide recognized by T lymphocytes from AIDS viral envelope-immune humans. *Nature* 1988, 334:706–708.
34. TAKAHASHI H, COHEN J, HOSMALIN A, *ET AL.*: An immunodominant epitope of the human immunodeficiency virus envelope glycoprotein gp160 recognized by class I major histocompatibility complex molecule-restricted murine cytotoxic T lymphocytes. *Proc Natl Acad Sci USA* 1988, 85:3105–3109.
35. WAHREN B, ROSEN J, SANDSTRÖM E, MATTHESON T, MODROW S, WIGZELL H: HIV-1 peptides induce a proliferative response in lymphocytes from infected persons. *J Acquir Immune Defic Syndr* 1989, 2:448–456.

36. PICARD O, LACHGAR A, ACHOUN A, *ET AL*: Anti-HIV active immunization. Evidence for persistent cell-mediated immunity after a 2-year follow-up. *VIII International Conference on AIDS/III STD World Congress* Amsterdam, July 1992 [abstract MoA0024].

37. COREY L: Phase 1 trials of subunit gp160 vaccines: a current summary [abstract]. *J Cell Biochem* 1992, suppl 16E:9.

38. GRAHAM BS, BELSHE R, CLEMENTS ML, *ET AL*: Determinants of antibody (AB) response in volunteers primed with Vac-Env and boosted with rgp160. *VIII International Conference on AIDS/III STD World Congress* Amsterdam, July 1992 [abstract MoA0013].

39. MCELRATH J, PETERSON E, DRAGAVON J, *ET AL*: Combination prime-boost approach to HIV vaccination in seronegative individuals: enhanced immunity with additional subunit gp160 protein boosting. *VIII International Conference on AIDS/III STD World Congress* Amsterdam, July 1992 [abstract MoA0027].

40. GRAHAM BS, MATTHEWS TJ, BELSHE RB, *ET AL*: Augmentation of HIV-1 neutralizing antibody by priming with gp160 recombinant vaccinia and boosting with rgp160. *J Infect Dis* 1993 (in press).

41. VAN NEST GA, STEIMER KS, HAIGWOOD NL, BURKE RL, OTT G: Advanced adjuvant formulation for use with recombinant subunit vaccines. In *Vaccines 92*. Edited by Brown F, Chanock R, Ginsberg HS, Lerner R. Cold Spring Harbor: Cold Spring Harbor Laboratory Press; 1992:57–62.

42. KEEFER M, BELSHE R, CLEMENTS ML, *ET AL*: Safety and immunogenicity of a baculovirus-derived HIV-1 IIIB recombinant gp160 vaccine (VacSyn). *VIII International Conference on AIDS/III STD World Congress* Amsterdam, July 1992 [abstract PoA2228].

43. VASUDEVACHARI MB, UPPELMAN KW, KOVACS J, YEH C-K, LANE HC, SALZMAN NP: Envelope specific antibodies in the saliva of individuals vaccinated with recombinant HIV-1 gp160. *J Acquir Immune Defic Syndr* 1992, 5:817–821.

44. BELSHE R, CLEMENTS ML, DOLIN R, *ET AL*: Safety and immunogenicity of fully glycosylated rgp160 IIIB vaccine in low-risk volunteers. *VIII International Conference on AIDS/III STD World Congress* Amsterdam, July 1992 [abstract PoA2432].

45. CLEMENTS ML, BELSHE R, DULIEGE AM, *ET AL*: Safety and immunogenicity of IIIB rgp120/HIV-1 vaccine in seronegative volunteers. *VIII International Conference on AIDS/III STD World Congress* Amsterdam, July 1992 [abstract MoA0026].

46. DOLIN R, COREY L, GRAHAM B, *ET AL*: Safety and immunogenicity of an HIV vaccine candidate, Env 2,3, in combination with MTP-PE/MF59. *VIII International Conference on AIDS/III STD World Congress* Amsterdam, July 1992 [abstract PoA2226].

47. CHERNOFF D, KAHN J, SINANGIL F, *ET AL*: Phase I dose escalation MTP-PE study of an HIV-1 gp120 vaccine in seronegative adults. *VIII International Conference on AIDS/III STD World Congress* Amsterdam, July 1992 [abstract MoA0025].

48. WEBER J, KENNEDAY A, CALLOW D, ZIGMOND A, CHEINGSONG-POPOV R: A Phase I study of the safety and immunogenicity of Ty.p24 VLP in healthy volunteers. *VIII International Conference on AIDS/III STD World Congress* Amsterdam, July 1992 [abstract PoA2240].

49. KAHN J, COLEMAN R, STITES D, *ET AL*: A Phase I study of HGP-30, a 30 amino-acid subunit of HIV p17 synthetic peptide analogue subunit vaccine in seronegative subjects. *VIII International Conference on AIDS/III STD World Congress* Amsterdam, July 1992 [abstract PoB3057].

50. COONEY EL, COLLIER AC, GREENBERG PD, *ET AL*: Safety of and immunological response to a recombinant vaccinia virus vaccine expressing HIV envelope glycoprotein. *Lancet* 1991, 337:567–572.

51. GRAHAM BS, BELSHE RB, CLEMENTS ML, *ET AL*: Vaccination of vaccinia-naive adults with HIV-1 gp160 recombinant vaccinia (HIVAC-1e) in a blinded, controlled, randomized clinical trial. *J Infect Dis* 1992, 116:244–252.

52. SOLTEYRAND Y, PIALOUX G, LINARD F, *ET AL*: Selection of volunteers for trials of HIV vaccines: problems and methods. *VIII International Conference on AIDS/III STD World Congress* Amsterdam, July 1992 [abstract PoB3041].

53. KEEFER MC, BONNEZ W, ROBERTS NJ JR, DOLIN R, REICHMAN RC: Human immunodeficiency virus (HIV-1) gp160-specific lymphocyte proliferative responses of mononuclear leukocytes from HIV-1 recombinant gp160 vaccine recipients. *J Infect Dis* 1991, 163:448–453.

54. GORSE GJ, BELSHE RB, NEWMAN FK, FREY SE AND THE NIAID AIDS VACCINE CLINICAL TRIALS NETWORK: Lymphocyte proliferative responses following immunization with human immunodeficiency virus recombinant gp160. *Vaccine* 1992, 10:383–388.

55. GORSE G, BELSHE R AND THE AIDS VACCINE CLINICAL TRIALS NETWORK: Lymphocyte proliferation following vaccination with fully glycosylated gp160. *VIII International Conference on AIDS/III STD World Congress* Amsterdam, July 1992 [abstract PoB3038].

56. WINTSCH J, CHAIGNAT C-L, BRAUN DG, *ET AL*: Safety and immunogenicity of a genetically engineered human immunodeficiency virus vaccine. *J Infect Dis* 1991, 163:219–225.

57. COLEMAN R, STITES D, SCILLIAN J, *ET AL*: The development of cytotoxic T lymphocytes (CTL) in subjects immunized with HGP-30, a 30 amino-acid subunit of HIV p17 core protein [abstract]. *J Cell Biochem* 1992, suppl 16E:60.

58. VISCIDI R, ELLERBECK E, GARRISON L, *ET AL*: Characterization of serum antibody responses to recombinant HIV-1 gp160 vaccine by enzyme immunoassay. *AIDS Res Hum Retroviruses* 1990, 6:1251–1256.

59. ORENTAS RJ, HILDRETH JEK, OBAH E, *ET AL*: Induction of CD4+ human cytolytic T cells specific for HIV-infected cells by a gp160 subunit vaccine. *Science* 1990, 248:1234–1237.

60. HAMMOND SA, BOLLINGER RC, STANHOPE PE, QUINN TC, CLEMENTS ML, SILICIANO RF: Comparative clinical analysis of human immunodeficiency virus type 1 (HIV-1)-specific CD4+ and CD8+ cytotoxic T lymphocytes isolated from seronegative humans immunized with candidate HIV-1 vaccines. *J Exp Med* 1992, 176:1531–1542.

61. CLERICI M, TACKET CO, VIA CS, *ET AL*: Immunization with subunit immunodeficiency virus vaccine generates stronger T-helper cell immunity than natural infection. *Eur J Immunol* 1991, 21:1345–1349.

62. SILICIANO RF, CALLAHAN K, LIU AY, HAMMOND S, STANHOPE PE: The role of HIV-1-specific T cells in the pathogenesis and prevention of AIDS [abstract]. *J Cell Biochem.* 1992, suppl 16E:9.

63. FREY SE, GORSE GJ, NEWMAN FK, BELSHE RB, NIAID AIDS VACCINE CLINICAL TRIALS NETWORK: Anti-gp160 enzyme and the linked immunosorbent assay antibody responses to a combination human immunodeficiency virus vaccine regimen [abstract]. *Clin Res* 1991, 39:727A.

64. EL-DAHER N, KEEFER MC, REICHMAN RC, DOLIN R, ROBERTS NJ JR: Persisting HIV-1 gp160-specific human T-lymphocyte responses after receipt of vaccine recombinant and purified subunit HIV-derived envelope vaccines [abstract]. *AIDS Res Hum Retroviruses* 1993 (in press).

65. HAMMOND SA, OBAH E, STANHOPE P, *ET AL*: Characterization of a conserved T-cell epitope in HIV-1 gp41 recognized by vaccine-induced human cytolytic T cells. *J Immunol* 1991, 146:1470–1477.

66. SCHWARTZ D, CLEMENTS ML, BERMAN P, *ET AL*: Safety and immunogenicity of Genentech IIIB rgp120/HIV-1 [abstract]. *AIDS Res Hum Retroviruses* 1993 (in press).

67. MARTIN S, WEBER J, ROITT I, MATEAR P, JONES K, VYAKARNAM A: Recombinant HIV-1 Gag p24-Ty virus-like particles (VLPs) induce HIV-1 p24-specific T helper cells in seronegative volunteers vaccinated with these particles. *VIII International Conference on AIDS/III STD World Congress* Amsterdam, July 1992 [abstract PoA2194].

68. ADA GL: Vaccines. In *Fundamental Immunology*, 2nd edn. Edited by Paul WE. New York: Raven Press Ltd; 1989:985–1026.

69. WALKER BD, CHAKRABARTI S, MOSS B, *ET AL*: HIV-specific cytotoxic T lymphocytes in seropositive individuals. *Nature* 1987, 328:345–348.

70. PLATA F, AUTRAN B, PEDROZA-MARTINS L, *ET AL*: AIDS virus-specific cytotoxic T lymphocytes in lung disorders. *Nature* 1987, 328:348–351.

71. KOENIG S, EERL P, POWELL D, *ET AL*: Group-specific, major histocompatibility complex class I-restricted cytotoxic responses to human immunodeficiency virus 1 (HIV-1) envelope proteins by cloned peripheral blood T cells from an HIV-1-infected individual. *Proc Natl Acad Sci USA* 1988, 85:8638–8642.

72. RIVIERE Y, TANNEAU-SALVADORI F, REGNAULT A, *ET AL*: Human immunodeficiency virus-specific cytotoxic responses of seropositive individuals: distinct types of effector cells mediate killing of targets expressing Gag and Env proteins. *J Virol* 1989, 63:2270–2277.

73. WALKER BD, FLEXNER C, PARADIS TJ, *ET AL*: HIV-1 reverse transcriptase is a target for cytotoxic T lymphocytes in infected individuals. *Science* 1988, 240:64–66.

74. KOUP RA, SULLIVAN JL, LEVINE PH, *ET AL*: Detection of major histocompatibility complex class I-restricted, HIV-specific cytotoxic T lymphocytes in the blood of infected hemophiliacs. *Blood* 1989, 73:1909–1914.

75. MYERS G, KORBER B, BERZOFSKY J, SMITH RF, PAVLAKIS GN: *Human Retroviruses and AIDS 1991*. Los Alamos: Los Alamos National Laboratory; 1991.

76. ZOLLA-PAZNER S, KARWOWSKA S, XU J-Y, BUCHBINDER A, GORNY MK: Type-specific and group-specific antibodies to HIV: the decline and fall of an oversimplified concept [abstract]. *J Cell Biochem* 1992, suppl 16E:7.

77. STEIMER KS, HAGWOOD NL: Importance of conformation in the neutralizing antibody responses to HIV-1 gp120. *Biotech Therapeut* 1990–1991, 2:63–89.

78. PURTSCHER M, GRUBER G, TRKOLA A, JUNGBAUER A, KATINGER H: Human monoclonal antibodies against HIV-1 in a long-term *in vitro* neutralization study. *VIII International Conference on AIDS/III STD World Congress*. Amsterdam, July 1992 [abstract PoA2422].

79. TILLEY SA, HONNEN WJ, RACHO ME, HILGARTNER M, PINTER A: Very broadly neutralizing human monoclonal antibody against the CD4-binding site of HIV-1 gp120. *VIII International Conference on AIDS/III STD World Congress*. Amsterdam, July 1992 [abstract TuA0505].

80. POTTS B, WU Y, FIELD K: Potency and broadness of neutralization of HIV-1 by α-V3 MAbs is enhanced by synergy with CD4 and cell killing with α-CD3 MAbs. *VIII International Conference on AIDS/III STD World Congress*. Amsterdam, July 1992 [abstract MoA0043].

81. BERKOWER I, MURPHY D, SMITH CC, SMITH GE: A predominant group-specific neutralizing epitope of human immunodeficiency virus type 1 maps to residues 342 to 511 of the envelope glycoprotein gp120. *J Virol* 1991, 65: 5983–5990.

82. GOLDING H, ROBEY FA, GATES FT III, *ET AL*: Identification of homologous regions in human immunodeficiency virus I gp41 and human MHC class II β domain. I. Monoclonal antibodies against the gp41-derived peptide and patient's sera react with native HLA class II antigens, suggesting a role for autoimmunity in the pathogenesis of acquired immune deficiency syndrome. *J Exp Med* 1988, 167:914–923.

83. LEE T-H, LEE CN, LEE WR, CHENG YL, LIN HL, ESSEX M: Potential of selectively deglycosylated HIV-1 gp120 as a more effective vaccine antigen. *VIII International Conference on AIDS/III STD World Congress*. Amsterdam, July 1992 [abstract MoA0010].

84. FRANCOTTE J, BRUCK C, DE WILDE M, *ET AL*: Analysis of the serological response of rhesus monkeys immunized with HIV-1 recombinant envelope proteins. *VII International Conference on AIDS*. Florence, June 1991 [abstract MA1356].

85. PALKER TJ, MATTHEWS TJ, LANGLOIS A, *ET AL*: Polyvalent human immunodeficiency virus synthetic immunogen comprised of envelope gp120 T-helper cell sites and B-cell neutralization epitopes. *J Immunol* 1989, 142:3612–3619.

86. HART MK, WEINHOLD KJ, SCEARCE RM, *ET AL*: Priming of anti-human immunodeficiency virus (HIV) CD8+ cytotoxic T cells *in vitro* by carrier-free HIV synthetic peptides. *Proc Natl Acad Sci USA* 1991, 88:9448–9452.

87. HART MK, PALKER TJ, MATTHEWS TJ, *ET AL*: Synthetic peptides containing T- and B-cell epitopes from human immunodeficiency virus envelope gp120 induce anti-HIV proliferative responses and high titers of neutralizing antibodies in rhesus monkeys. *J Immunol* 1990, 144:2677–2685.

88. NAYLOR PH, KIRKLEY JE, SARIN PS, WANG SS, GOLDSTEIN AL: HIV envelope–Gag peptide constructs and formulations to induce mucosal immunity as prototype for an AIDS vaccine. *VIII International Conference on AIDS/III STD World Congress*. Amsterdam, July 1992 [abstract PoA2247].

89. HILL-PERKINS MS, LAYTON GT, COLE JS, *ET AL*: Immune responses to HIV-1 epitopes presented as hybrid Ty-VLPs. *VIII International Conference on AIDS/III STD World Congress*. Amsterdam, July 1992 [abstract PoA2223].

90. SIA C, MATTHEWS T, CHANG P, BOLOGNESI D, KLEIN M: Construction of synthetic HIV vaccine candidates. *VIII International Conference on AIDS/III STD World Congress*. Amsterdam, July 1992 [abstract WeD1039].

91. EROSHKIN A, KARGINOVA EA, KRAVCHENKO VV, *ET AL*: Design of four-helix-bundle protein as a candidate in anti-HIV vaccine. *VIII International Conference on AIDS/III STD World Congress*. Amsterdam, July 1992 [abstract PoA2221].

92. KOMORIYA A, SHINAGAWA S: Design and synthesis of conformationally constrained peptide tertiary structural templates (PTST) for AIDS vaccine development. *VIII International Conference on AIDS/III STD World Congress*. Amsterdam, July 1992 [abstract PoA2235].

93. VON BRUNN A, EBERLE J, REICHHUBER C, *ET AL*: The principal neutralizing determinant (V3) of HIV-1 elicits a high HIV-1-specific antibody response upon expression on HBcAg particles. *VIII International Conference on AIDS/III STD World Congress*. Amsterdam, July 1992 [abstract PoA2231].

94. HESSELTON RM, MAZZARA GP, PANICALI D, SULLIVAN JL: HIV-specific immune response in rabbits immunized with HIV-like particles and recombinant vaccinia virus. *VIII International Conference on AIDS/III STD World Congress*. Amsterdam, July 1992 [abstract MoA0045].

95. ROVINSKY B, CAO S-X, JAMES O, *ET AL*: Genetically engineered HIV-like particles containing chimeric MN/LAI envelope glycoproteins can induce cross-neutralizing antibodies recognizing the IIIB and MN isolates. *VIII International Conference on AIDS/III STD World Congress*. Amsterdam, July 1992 [abstract WeD1041].

96. WAGNER R, WANNER G, FLEISBACH H, MOOROW S, NIEDRIG M, WOLF H: Recombinant HIV-gp120/core particles: an HIV candidate vaccine. *VIII International Conference on AIDS/III STD World Congress*. Amsterdam, July 1992 [abstract PoA2232].

97. RACE E, STEPHENS D, DAVIS D, FREZZA P, OXFORD J: The development of a whole inactivated HIV vaccine: immunogenicity studies. *VIII International Conference on AIDS/III STD World Congress*. Amsterdam, July 1992 [abstract PoA2413].

98. BIBERFELD G, PUTKONEN P, THORSTENSSON R, ALBERT J, NORRBY E: HIV-2 vaccines [abstract]. *J Cell Biochem* 1992, suppl 16E:10.

99. CHANDRA PK, NATUK RJ, MASON BB, *ET AL*: High-level expression of the envelope glycoprotein of the human immunodeficiency virus type 1 in presence of *rev* gene using helper-independent adenovirus type 7 recombinants. *Virology* 1990, 175:535–574.

100. EVANS DJ, MCKEATING J, MEREDITH JM, BURKE KL: An engineered poliovirus chimaera elicits broadly reactive HIV-1 neutralizing antibodies. *Nature* 1989, 339:385–388.

101. BURKE KL, ALMOND JW, EVANS DJ: Antigen chimeras of poliovirus. *Prog Med Virol* 1991, 38:56–68.

102. AGGARWAL A, SADOFF J, MARKHAM P, GALLO R, FRANCHINI G: Induction of cytotoxic T lymphocytes against HIV-2 in mice immunized with recombinant *Salmonella typhimurium*. *VIII International Conference on AIDS/III STD World Congress*. Florence, June 1991 [abstract MA1036].

103. STOVER CK, DE LA CRUZ VF, FUERST TR, *ET AL*: New use of BCG for recombinant vaccines. *Nature* 1991, 351:456–460.

104. ALDOVINI A, YOUNG RA: Humoral and cell-mediated immune responses to live recombinant BCG–HIV vaccines. *Nature* 1991, 351:479–482.

105. WARNER JF, ANDERSON CG, LAUBE L, *ET AL*: Induction of HIV-specific immune responses using retroviral vectors. *VIII International Conference on AIDS/III STD World Congress*. Amsterdam, July 1992 [abstract PoB3462].

106. HAYNES J, FULLER D, EISENBRAUN M: Induction of HIV-specific immune responses in mice following epidermal delivery of

an HIV expression vector via accell gene delivery technology. *VIII International Conference on AIDS/III STD World Congress.* Amsterdam, July 1992 [abstract PoA2227].

107. KOVACS JA, EASTER ME, DAVEY R, *ET AL*: Safety and immunogenicity of recombinant gp160, a candidate AIDS vaccine. *XXX International Conference on Antimicrobial Agents and Chemotherapy.* Atlanta, October 1990 [abstract 495].
108. VALENTINE F, KATZENSTEIN D, HASLETT P, *ET AL*: A randomized, controlled study of immunogenicity of rgp160 vaccine in HIV-infected subjects. *VIII International Conference on AIDS/III STD World Congress.* Amsterdam, July 1992 [abstract TuB0561].
109. REDFIELD RR, BIRX DL, KETTER N, *ET AL*: A Phase I evaluation of the safety and immunogenicity of vaccination with recombinant gp160 in patients with early human immunodeficiency virus infection. *N Engl J Med* 1991, 324:1677–1684.
110. REDFIELD R, BIRX D, VAHEY M, *ET AL*: HIV vaccine therapy: Phase I safety and immunogenicity using gp160. *VIII International Conference on AIDS/III STD World Congress.* Amsterdam, July 1992 [abstract TuB0563].
111. TSOUKAS C, SAMPALIS J, GOLD P, *ET AL*: Specific active immunotherapy in asymptomatic HIV disease using recombinant gp160. *VIII International Conference on AIDS/III STD World Congress.* Amsterdam, July 1992 [abstract TuB0560].
112. BRATT G, ERICKSSON L, SANDSTRÖM E, GILLIAM G, HINKULA J, WAHREN B: A study of gp160 vaccine in healthy HIV carriers with and without zidovudine. *VIII International Conference on AIDS/III STD World Congress.* Amsterdam, July 1992 [abstract PoB3036].
113. BIRX D, JOHNSON S, AMMAN A, *ET AL*: Immunogenicity and safety of rgp120 (LAI) in early-stage HIV-positive patients. *VIII International Conference on AIDS/III STD World Congress.* Amsterdam, July 1992 [abstract TuB0564].
114. PICARD O, GIRAL P, DEFER MC, *ET AL*: AIDS vaccine therapy: Phase I trial. *Lancet* 1990, 336:179–182.
115. BISELLI R, LOOMIS LD, DEL BONO V, BURKE DS, REDFIELD RR, BIRX DL: Vaccine therapy with gp160: effect on human anti-gp120 antibody spectrotype. *VIII International Conference on AIDS/III STD World Congress.* Amsterdam, July 1992 [abstract MoA0011].
116. KATZENSTEIN D, VALENTINE F, KUNDU SK, HASLETT P, SMITH G, MERIGAN TC: Delayed-type hypersensitivity reactions to intradermal gp160 in HIV-infected individuals immunized with gp160. *VIII International Conference on AIDS/III STD World Congress.* Amsterdam, July 1992 [abstract PoA2192].
117. PANTALEO G, GRAZIOSI C, BUTINI L, *ET AL*: Lymphoid organs function as major reservoirs for human immunodeficiency virus. *Proc Natl Acad Sci USA* 1991, 88:9838–9842.
118. SHIMIZU Y, SHAW S, GRABER N, *ET AL*: Activation-independent binding of human memory T cells to adhesion molecule ELAM-1. *Nature* 1991, 349:799–802.
119. BIGGAR RJ, PAHWA S, MINKOLF H, *ET AL*: Immunosuppression in pregnant women infected with human immunodeficiency virus. *Am J Obstet Gynecol* 1989, 161:1239–1244.
120. MOFENSON LM, BURNS DN: Passive immunization to prevent mother-infant transmission of human immunodeficiency virus: current issues and future directions. *Pediatr Infect Dis J* 1991, 10:456–462.
121. UKWU H, GRAHAM BS, LAMBERT JS, WRIGHT PF: Perinatal transmission of HIV-1 infection and immunization strategies for prevention. *Obstet Gynecol* 1992, 80:458–468.
122. COMMITTEE ON INFECTIOUS DISEASES, AMERICAN ACADEMY OF PEDIATRICS: Hepatitis B. In *Report of the Committee on Infectious Diseases.* Edited by Peter G, Lepow ML, McCracken GH, Phillips CF. Elk Grove Village: American Academy of Pediatrics; 1991:238–255.
123. EDELMAN R: An update on vaccine adjuvants in clinical trial. *AIDS Res Hum Retroviruses* 1992, 8:1409–1411.
124. ALVING CR, GLASS M, DETRICK B: Summary: adjuvants/clinical trials working group. *AIDS Res Hum Retroviruses* 1992, 8:1427–1430.

National Institute of Allergy and Infectious Diseases

# HIV/AIDS Vaccines

Despite education and treatment advances, experts project a worsening of the human immunodeficiency virus (HIV) crisis through the year 2000. HIV infection and AIDS death rates will continue to mount worldwide. In the United States, the tally of AIDS cases will escalate, particularly among women and minorities. If present trends continue, numbers of new infections will remain relatively stable in Europe and North America but will increase in parts of Latin America, Africa and, most markedly, in Asia.

Developing safe and effective vaccines to curb the human and economic costs of the HIV/AIDS pandemic has become an international health priority. To help reach this goal, the National Institute of Allergy and Infectious Diseases (NIAID), which spearheads federal funding for biomedical research on HIV/AIDS for the National Institutes of Health (NIH), has intensified its HIV vaccine research program.

This fact sheet summarizes NIAID's approach to developing HIV/AIDS vaccines. It describes the challenges facing vaccine researchers and the Institute's response, including basic and clinical research initiatives and advance planning for efficacy trials of the most promising candidate vaccines. Throughout the fact sheet scientific terms common to vaccine research have been printed in **boldface** type and defined.

## *NIAID'S HIV VACCINE PROGRAM--A BALANCED STRATEGY*

NIAID's Division of AIDS (DAIDS) directs the HIV vaccine research program. Institute staff meet regularly with scientific, public health and community advisors to review the priorities and operation of the program.

The program has two main thrusts: 1) foster basic research on the structure and function of HIV, vaccine formulations, vaccine delivery systems and laboratory studies of vaccine performance, and 2) promptly evaluate promising candidate vaccines in animal models and, if warranted, in humans.

Although traditional investigator-initiated research grant forms the foundation for HIV/AIDS vaccine research, NIAID supports several special initiatives to accomplish specific research objectives. These include the following:

- ***National Cooperative Vaccine Development Groups*** **(NCVDGs)** represent the core HIV vaccine discovery and development effort sponsored by NIAID. Teams of scientists from industry, academia and government collaborate to develop and test novel experimental HIV vaccine concepts in the laboratory and in animal models.

- ***AIDS Cooperative Adjuvant Groups*** conduct multidisciplinary research exploring the mechanisms of action of **adjuvants**, substances that can be combined with a vaccine to increase the type, strength or duration of immune response elicited. The groups also develop new adjuvant formulations and evaluate vaccine-adjuvant combinations in relevant animal models.

- The ***NIAID AIDS Vaccine Clinical Trials Network*** conducts trials in humans to determine the safety of and immune responses stimulated by experimental HIV vaccines (**Phase I** and **Phase II** trials). The network includes a specimen bank, immunology laboratories and a data analysis center.

- ***Primate research laboratories*** answer HIV-vaccine-related questions by testing HIV and HIV-like vaccines in chimpanzees and monkeys.

- ***Master Contracts for Preclinical HIV Vaccine Development*** provide flexible resources that can support various tasks in the preclinical development of the most promising HIV vaccine candidates. These resources include vaccine production, preclinical evaluation of vaccines in nonhuman primates and the development of biological and chemical substances called **reagents** for use in comparative vaccine studies.

- The ***HIV Variation Project*** examines the rates and magnitudes of genetic and immunologic changes in HIV and related retroviruses and their consequences for vaccine design.

In addition, NIAID's nationwide university-based and community-based clinical trials programs conduct trials of candidate therapeutic HIV vaccines.

**Planning for Efficacy Trials**

Inevitably, promising HIV candidate vaccines suitable for large-scale testing of their effectiveness will be identified. The Institute is laying the groundwork for such **Phase III** trials in the United States and abroad to ensure that no delay in starting these trials occurs.

NIAID ***Preparation for AIDS/HIV Vaccine Evaluations*** (**PAVE**) grants already support collaborative studies to develop baseline data for determining the feasibility of conducting HIV vaccine trials in international settings and to develop capabilities at these sites to conduct HIV vaccine efficacy trials. Eight awards have been made to domestic investigators and their collaborating international sites.

PAVE investigators as well as domestic contractors are collecting field data on virus strains being transmitted, rates of new infections and the prevalence of sexually transmitted disease and other potential co-factors of HIV transmission from various populations in the United States and abroad at high risk for HIV infection.

Institute staff assist public health and government officials, community members, scientists and others affiliated with potential trial sites to resolve numerous legal, practical and ethical issues

that attend planning for efficacy trials. These concerns include vaccine cost and delivery, liability issues, and training of medical personnel and conduct of trials at potential overseas sites.

To prepare for such trials, NIAID has established the ***HIV Vaccine Efficacy Trials Network*** **(HIVNET)**, which consists of the following:

- **A domestic HIV/AIDS vaccine efficacy trials master contractor** will subcontract with clinical sites to evaluate the efficacy of candidate HIV vaccines in U.S. populations.
- An **international HIV/AIDS vaccine efficacy trials master contractor** will subcontract with clinical sites to support trials in international populations.
- **A statistical and data coordinating center** contract will provide statistical and data management support for the domestic and international trials.
- **A laboratory** contract will provide specialized testing for the domestic and international trials.
- **A specimen repository** contract serves the domestic and international trials.

## *CHALLENGES IN DESIGNING HIV VACCINES*

The ideal HIV vaccine would be inexpensive, easy to store and to administer, and elicit strong, appropriate immune responses that confer long-lasting protection against both bloodborne and mucosal (sexual) exposure to multiple HIV subtypes. However, the following describes some reasons this ideal has not been easy to achieve.

### What Constitutes Immune Protection?

Researchers face unprecedented scientific obstacles in trying to develop effective vaccines for HIV. The easiest way to design an effective vaccine is to know what immune responses protect against the specific infection and construct a vaccine that stimulates those responses. Although scientists have found clues about these so-called **correlates of immunity** or **correlates of protection** for HIV, they have not been able to precisely identify them. Unlike other viral diseases for which successful vaccines have been made, recovery from HIV infection has not been documented. Therefore, researchers have no human model of protection to guide them when constructing candidate HIV vaccines. *Indeed, whether a natural protective state against HIV can exist remains unknown.*

However, now that the pandemic has matured, long-term HIV survivors and others provide ample evidence that some people appear better able than others to resist HIV infection or the development of AIDS. Much of this information has come from extended studies of people at high-risk for HIV. The "resisters" can be grouped as follows: 1) those who maintain healthy levels of CD4+ T cells, a crucial immune cell and HIV's main target, for seven to 10 years or more after becoming infected; 2) individuals who lose a significant proportion of CD4+ T cells but apparently

remain healthy; and 3) people who appear to escape infection despite repeated exposure to the virus.

To determine if genetic or biologic factors affect the body's response to HIV exposure and infection, NIAID-funded investigators and others are comparing long-term HIV survivors with people who quickly became infected or sick. Leading areas of research include genetics, individual variations in the immune response and exposure to or infection by less deadly variants of HIV. Any patterns found in the data may help decode what contributes to protective immunity against HIV.

**Immune Responses**

The ability to stimulate immune responses is called **immunogenicity**. Two main types of immunity exist: humoral immunity and cellular immunity. **Humoral (antibody-mediated) immunity** refers to protection provided by the products of one type of white blood cell called a **lymphocyte**. These products, custom-made proteins known as **antibodies**, circulate in body fluids, primarily blood and lymph. **B lymphocytes (B cells)** produce antibodies in response to a specific foreign invader like HIV or a vaccine.

Several different antibodies can be generated. So-called **binding antibodies** simply attach to some part of HIV and may or may not have antiviral effects. **Functional antibodies** are binding antibodies that actually do something. For example, one type--**neutralizing antibodies**--inactivates HIV or prevents it from infecting other cells.

Scientists have identified HIV's **V3 loop** as important for stimulating neutralizing antibodies. The V3 loop is part of **gp120** (glycoprotein 120), a major protein found on the surface or **envelope** of HIV. Thus, gp120 and its parent protein, **gp160**, form the basis of many **recombinant subunit vaccines**, so-called because they are genetically engineered and contain only pieces of the virus.

The second type of immunity, **cellular (cell-mediated) immunity**, refers to activities of **T lymphocytes**. **Cytotoxic T lymphocytes (CTLs)**, nicknamed **killer T cells**, directly destroy HIV-infected cells. A subset called **CD8+ CTLs (CD8+ T cells)** bear **CD8 receptors** on their surfaces and kill cells that are producing HIV. CD8+ T cells most likely are critical to protection against HIV.

**Regulatory T cells**, another component of cellular immunity, direct both antibody- and cell-mediated immune responses, much like a conductor leading a symphony orchestra. The chief regulatory T cell, the **helper T cell**, also is HIV's main target. The virus attaches to the cell through a **receptor** on the cell's surface called **CD4**. Hence, helper T cells also are called **CD4+ T cells**. A subset of helper T cells, **memory T cells**, are evoked on first exposure to an invading organism. The name "memory" reflects their function, which is to create a criminal record file on that virus or microorganism. If the virus enters the body again, memory T cells will quickly stir the immune system into action. The most common way to measure memory T cells is by a test called the **T lymphocyte proliferation assay**, which indicates the strength of such cell responses to HIV.

To be effective, an HIV vaccine may have to stimulate a third type of immunity, **mucosal immunity**. Immune cells lining the mucous membranes of the genital tract and other HIV portals into the body produce special immune responses.

NIAID's ***Correlates of HIV Immune Protection*** project will characterize immune responses in selected HIV vaccines enrolled in Phase III efficacy trials and compare those immune responses that are protective with those that are not.

**HIV Strain Variation**

HIV continually evolves as a result of genetic mutation and recombination. Thus, researchers must estimate the significance of **strain variation** within individuals and among populations when developing AIDS vaccines. Usually a person is not infected with more than one HIV strain. But once HIV infection becomes established, the virus undergoes changes, and many **variants** of one HIV strain may arise within an infected person. Whenever a drug or immune response destroys one variant, a distinct but related one can emerge. Also, certain variants may thrive in specific tissues or become dominant in an individual because they replicate faster than others. Any of these changes may yield a virus that can escape immune detection.

The envelope regions of many HIV **isolates**, the viruses taken from patients, have been genetically analyzed and compared. Based on this information, scientists have grouped HIV isolates into at least five **subtypes** or **clades**, each about 30 percent different from any of the others. Successful vaccines for other viruses have had to protect against only one or a limited number of virus strains.

The first AIDS vaccines made were based on the **LAI** strain (also known as **IIIB** and **LAV**). Subsequently, LAI has been shown to be unlike most strains found in infected people. Newer vaccines have been based on the **SF-2** and **MN** isolates, which are the same subtype as **LAI** but better represent HIV strains isolated from North Americans and Europeans.

A preventive vaccine will need to generate immune responses that protect *noninfected* individuals from all the different clades of HIV to which they may be exposed. Conserved regions of HIV genes that may exist in more than one clade would be desirable to find. A cocktail vaccine of several proteins or peptides from different HIV strains may be the most effective way to invoke broad-based immunity.

NIAID's ***HIV Variation Project*** comprises several collaborative research projects aimed at solving vaccine development problems related to HIV's genetic diversity. Part of the project is conducted in collaboration with the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO). These studies investigate the rate and magnitude of genetic variation in HIV and related retroviruses and explore the impact of this variation on strategies for developing HIV vaccines. The project includes a laboratory that uses state-of-the-art technology to determine the genetic sequences of many HIV specimens. A separate laboratory will be established to assess the immunologic significance of genetic variation.

Another component of the HIV Variation Project is the ***HIV Sequence Database and Analysis Unit*** at New Mexico's Los Alamos National Laboratory, which compiles and analyzes genetic sequences of HIV variants contributed by various laboratories.

**HIV Transmission Complicates Protection**

Unlike most other viruses, *HIV can be transmitted and can exist in the body not only as free virus but also in infected cells.* Thus, a vaccine against HIV may be required to stimulate the two main types of immunity. Humoral immunity uses antibodies to defend against free virus. Cellular immunity directly or indirectly results in the killing of infected cells by immune cells. A major unanswered question is how important each type of immunity is to protection from HIV. Data on long-term HIV survivors and those generated from animal model and human clinical trials of experimental HIV vaccines may offer clues to the answer.

Another factor complicates the attempt to define HIV protection. Of all the HIV transmissions worldwide, 80 percent occur sexually, according to the WHO. *Thus, an effective HIV vaccine also may have to stimulate mucosal immunity.* Immune cells found in the lining of the respiratory, digestive and reproductive tracts and in nearby lymph nodes provide the first line of defense against HIV and other infectious organisms. Unfortunately, relatively little is known about how the mucosal immune system works.

NIAID has increased its commitment to research that enables scientists to learn how HIV and other pathogens elude the defenses of mucosal cells and the immune-modulating proteins, called cytokines, that they stimulate. Specifically, the ***Cooperative Mucosal Immunology Group for Investigations on AIDS Vaccines*** supports investigator-initiated research on methods to stimulate and evaluate mucosal immune responses to simian immunodeficiency virus (SIV) and HIV, and uses this information to design new vaccines that will protect from mucosal exposure to HIV. Animal models are being developed to explore novel strategies for vaccination and for mucosal challenge with HIV. The investigators also are developing tests, reagents and technology to evaluate specific, protective immune responses induced by HIV vaccines in animal and human volunteers.

**Immune System Breakdown**

Perhaps the most difficult challenge vaccine researchers face is that *the major target organ of HIV is the immune system itself.* HIV infects the key CD4+ T cells that regulate the immune response, modifying or destroying their ability to function. After infection, HIV incorporates its genetic material into that of the host cell. There the virus can hide indefinitely until the cell receives an activation signal and makes new viruses. Other cells act as HIV reservoirs, harboring intact viruses that may remain undetected by the immune system.

Understanding how HIV disease evolves, especially during early infection, is a high priority for the Institute. Scientists at NIAID and elsewhere have shown that no true period of biological latency exists in HIV infection. After entering the body, the virus rapidly disseminates, homing to the lymph nodes and related organs where it replicates and accumulates in large quantities. Paradoxically, the filtering system in these lymphoid organs, so effective at trapping pathogens and initiating an immune response, may help destroy the immune system by infecting the steady stream of CD4+ T cells that travel there in response to HIV infection.

The study of early HIV infection is an area of investigation where basic research in immunology, epidemiology studies of long-term survivors and animal model and human clinical trials

all can contribute to a greater understanding of the immune system breakdown and ways vaccines may be designed to prevent or slow down the progress of HIV disease.

NIAID's ***AIDS Vaccine Reagent Project*** is a contract effort to provide large quantities of reagents for comparative immunologic studies. These reagents also will be used in preclinical vaccine development, adjuvant development and standardized immunologic assessments of clinical samples from volunteers in vaccine trials.

In addition, the Institute's ***Antibody Serologic Project*** identifies and standardizes panels of monoclonal antibodies to characterize specific components of HIV and SIV. This project, a collaborative effort between NIAID and WHO, involves investigators from around the world.

**Adjuvants and Other Immune Enhancers**

Because of safety concerns, most candidate HIV/AIDS vaccines are made from one or more pieces of HIV rather than the whole virus. These new-generation vaccine candidates contain no intact live virus and thus stimulate less potent immune responses than traditional vaccines made from live-weakened or whole-inactivated viruses.

To augment the immune responses elicited by these and other vaccines, scientists use adjuvants. Currently, only one adjuvant--**alum**--is incorporated into vaccines licensed for use in humans by the U.S. Food and Drug Administration (FDA). Alum, first described in 1926, increases the strength of antibody responses generated by the vaccine **antigen**.

An adjuvant may work well with several different experimental vaccines. Thus, FDA licenses for human use the vaccine formulation, or the antigen-adjuvant combination, rather than the adjuvant alone. Experimental adjuvants can increase the type, strength and durability of immune responses evoked by an experimental vaccine. For example, some vaccine antigen/adjuvant combinations can induce cell-mediated immune responses, even if the vaccine antigen by itself does not. Some adjuvants also stimulate mucosal immunity.

NIAID-funded scientists are evaluating a panel of promising adjuvants in monkeys to help identify the suitable candidates to incorporate in experimental human HIV vaccines. In 1993, NIAID began the first Phase I HIV vaccine adjuvant trials in humans. Various adjuvants paired with two different vaccine candidates are being compared to determine the best vaccine formulations to pursue.

A different way to enhance immune responses to HIV is the **prime-boost** vaccine strategy. Researchers first ready or prime the immune systems of volunteers with a **live vector vaccine**, a bacterium or virus that has been genetically engineered to contain a gene for an HIV protein such as gp160 but that cannot infect the person with HIV or cause disease. The best studied vector is **vaccinia virus**, formerly used to immunize against smallpox. Vaccinia transports the foreign HIV gene into the body. There, the HIV gene makes a protein that the body perceives as foreign, stimulating production of protective antibodies. Later, the volunteers receive booster shots of a recombinant vaccine made from the same HIV protein.

By itself, a gp160-containing vaccinia virus vaccine stimulates memory T cells but few antibodies. The prime-boost combination, however, can stimulate a strong cellular immune response--including persistent killer CD8+ T cells--as well as antibodies that neutralize the virus or inhibit formation of syncytia, giant cells formed when HIV-infected cells fuse with non-HIV-infected cells.

Because of concerns that a vaccinia-based vaccine might cause serious vaccinia infection in some people who have compromised immune systems, such as people with HIV who have not been exposed to either smallpox or the vaccine, other vector vaccines also are being developed and evaluated. One candidate made from a canarypox virus that closely resembles vaccinia is in clinical trials. Canarypox virus does not grow in human cells and therefore should be much safer. Another example of a vector under development for HIV vaccines is *Salmonella*, bacteria that infect the human gut.

**Animals Model Studies - Imperfect But Important**

Animal model studies can answer critical questions that may pose undue risk to humans or cannot be answered using computer modeling or laboratory tests. For example, animals can be inoculated with an experimental vaccine and then challenged with HIV to test the vaccine's effectiveness--a study that would be unethical to conduct in humans.

Although chimpanzees can be infected with HIV, they have not yet been observed to develop disease. Moreover, they are expensive to maintain.

Most large-animal AIDS research is conducted with macaque monkeys. They can be infected with SIV, a retrovirus similar to HIV that causes an AIDS-like disease. The genetic and physical structures of SIV differ enough from those of HIV, however, that extrapolating the results of SIV experiments to humans must be done carefully.

Despite *the lack of an ideal animal model*, important information has been obtained from both monkeys and chimpanzees. Experiments in both primates have demonstrated the feasibility of developing a protective vaccine. Moreover, two new animal models--infection of pigtail macaques with HIV and of rhesus macaques with a chimeric SIV-HIV virus--may become valuable alternatives to chimpanzees for evaluating candidate HIV vaccines.

In late 1992, NIAID-funded investigators first reported results from their experiments with a live-attenuated SIV vaccine made by deleting the SIV *nef* gene. The vaccine demonstrated durable protection against high intravenous doses of a lethal SIV different from that used in the vaccine. These findings provide hope that safe and effective human HIV vaccines can be developed.

NIAID's ***SIV Vaccine Evaluation Units*** (SIV VEUs) evaluate vaccine concepts in the SIV model. The units permit standardized and directly comparable evaluations of various SIV vaccine candidates. NIAID's ***Chimpanzee Unit***, operated through an interagency agreement with the National Cancer Institute, is used to prepare chimpanzee stocks and to evaluate candidate vaccine concepts and products in chimpanzees.

In addition, NIAID's ***Immunology Laboratory Support for Assessment of AIDS Vaccines in Primates*** develops and standardizes cellular and serologic immunology tests to assess responses to SIV and HIV vaccines in the SIV VEU, Chimpanzee Unit and NCVDG laboratories. This standardization permits the direct comparison of candidate vaccines evaluated in independent laboratories and facilitates selection of the most promising vaccine designs.

## *CLINICAL RESEARCH*

Important immunologic targets on HIV and on infected cells have been identified. For example, scientists now know that gp120 contains the cell attachment site called CD4. For these reasons, vaccines based on genetically engineered HIV envelope proteins--gp160 and one of its cleavage products, gp120--have been the most well-studied to date. Approximately 25 experimental HIV vaccines are currently in various stages of human testing around the world. Vaccine approaches in development or in clinical trials include the following:

- ***subunit vaccine*** - a piece of HIV, such as the envelope proteins gp160 or gp120, produced by genetic engineering.
- ***recombinant vectors*** - a live bacterium or virus such as vaccinia (used in the smallpox vaccine) that can transport into the body a gene that makes an HIV protein.
- ***vaccine combinations*** - use of a recombinant vector vaccine to induce cellular immune responses followed by booster shots of a subunit vaccine to stimulate antibody production.
- ***peptide vaccine*** - chemically synthesized portions of HIV proteins (peptides) known to stimulate immunity.
- ***virus-like particle vaccine*** - a non-infectious HIV look-alike that retains all or part of the HIV envelope but only some of the interior components.
- ***anti-idiotype vaccine*** - antibodies generated against antibodies to the virus.
- ***naked DNA vaccine*** - direct injection of genes coding for HIV proteins.
- ***whole-inactivated virus vaccine*** - HIV that has been inactivated by chemicals, irradiation or other means so it is not infectious.
- ***live-attenuated virus vaccine*** - live HIV from which one or more apparent disease-promoting genes of the virus have been deleted.

### Stages of Human Testing

After an experimental vaccine has performed well in preclinical safety tests, it must successfully complete three stages of testing in people before development into a licensed product.

A **Phase I** trial is the first setting in which an experimental HIV vaccine is given to people. Such a trial enrolls about 20 to 80 non-HIV infected volunteers at low risk of HIV infection. A Phase I trial primarily seeks information on safety, usually assessing any vaccine-related side effects by comparing the vaccine with an inactive **placebo** or **control** that looks like the test product. At this stage, researchers try to determine the maximum useful dose that can be tolerated without compromising safety. A Phase I trial also can provide preliminary data on the vaccine's immunogenicity. If the vaccine elicits neutralizing antibodies, scientists can study how these react against HIV strains from the same or other clades to determine the potential breadth of protection. A Phase I trial may last one to two years.

Once Phase I trials show an experimental HIV vaccine to be well-tolerated, it then can advance into **Phase II** trials. These trials enroll more people, up to a few hundred, and often include some volunteers at higher risk for acquiring HIV. Researchers gather data about safety and immune responses, asking more sophisticated questions that such larger trials allow. Optimally, the trials are **randomized** and **double-blind**, meaning that volunteers are assigned at random to a study group and that neither the health care workers nor the patients know what preparations the patients receive. Phase II trials usually last one to two years.

The most promising candidate vaccines move into **Phase III** or **efficacy** trials, enrolling large numbers of non-HIV-infected people at high risk for acquiring the virus. A Phase III trial usually is designed to ensure the collection of enough data on safety and effectiveness to support a license application, if warranted. The vaccine may be tested against a placebo or a vaccine such as hepatitis B of known potential benefit to the study population. An efficacy trial can involve thousands of volunteers and therefore takes much longer, at least four years, to complete.

**Clinical Trials of Preventive HIV Vaccines**

In August 1987, NIAID opened the first clinical trial of an experimental HIV vaccine at the NIH Clinical Center in Bethesda, Md. This safety trial eventually enrolled 138 noninfected healthy volunteers. The gp160 subunit candidate vaccine tested caused no serious adverse effects.

From the first trial until May 1993, about two dozen preventive HIV vaccine trials have been initiated worldwide. These Phase I trials seek information on the vaccine's safety and preliminary information on its ability to stimulate immune responses.

NIAID's AIDS Vaccine Clinical Trials Network is the largest cooperative HIV vaccine clinical trials group in the United States. Between 1988 and December 1993, more than 1,300 men and women have participated in preventive HIV vaccine trials conducted at its five medical center sites located in Seattle, Baltimore, St. Louis, Nashville and Rochester, N.Y.

To date, all the vaccine candidates tested have been well-tolerated, generally producing only mild side effects typical of most vaccines. The most thoroughly tested candidates stimulate production of antibodies, although levels decrease within a relatively short period of time. Initial formulations and dosages of these vaccines produced few or low levels of neutralizing antibodies and rarely elicited cytotoxic T cells, which are invoked through cell-mediated immunity to kill HIV-infected cells. With the newer protocols that have increased vaccine dosages, changed immunization

schedules, tested experimental adjuvants, and used recombinant proteins shaped more like those of native HIV, more promising data have begun to emerge.

In December 1992, NIAID launched the first Phase II preventive HIV trial worldwide. Earlier trials enrolled noninfected people at low risk of HIV infection and primarily sought data on safety. The Phase II trial includes noninfected volunteers with a history of high-risk behavior--injection drug use, multiple sex partners or sexually transmitted diseases. Participants are counseled repeatedly to avoid any behavior that puts them at risk of HIV infection. The trial will help determine if these distinct populations, representative of people likely to be enrolled in large-scale efficacy trials, respond differently to the vaccines. The trial also will gather more detailed data on the safety and ability of the vaccines to stimulate immune responses.

As experimental HIV vaccines continue to grow in number and kind, clinical trials are expected to yield more valuable information about the relative effects of different vaccine formulations and different methods of delivery on the immune response.

The ***NIAID AIDS Vaccine Clinical Trials Network*** includes the following:

- The five ***AIDS Vaccine Evaluation Units (AVEUs)*** [known collectively as the ***AIDS Vaccine Evaluation Group (AVEG)***], are located at research centers throughout the United States, conduct phase I and II clinical trials of candidate HIV vaccines in low-risk and high-risk HIV-seronegative volunteers.

- The ***Central Immunology Laboratory*** provides state-of-the-art evaluation of humoral and cellular immune responses of vaccines in AVEG trials. Samples from the AVEUs are evaluated using standardized tests, permitting the comparison of responses in different individuals and to different candidate vaccines.

- The ***Data Coordinating and Analysis Center*** provides a central facility for collecting and analyzing data from the trials conducted by the AVEUs.

- The ***Data and Safety Monitoring Board*** periodically reviews data from AVEG studies.

- The ***Immunology Laboratory Support for Assessment of Mucosal Immune Responses Induced by AIDS Vaccines*** evaluates human mucosal immune responses to candidate vaccines in standardized tests, permitting the comparison of responses in volunteers at different AVEUs and in volunteers who receive different candidate vaccines.

**Therapeutic Vaccines--A New Strategy**

Traditionally, vaccines are used prophylactically, that is, to prevent infection. Experimental HIV vaccines also are being tested as possible treatments. The goal of **therapeutic vaccination** is to boost the immunity of an HIV-infected person to prevent or slow further development of disease.

As of early 1993, NIAID and other sponsors had initiated more than a dozen therapeutic HIV vaccine trials worldwide, including some larger more advanced trials. So far, the vaccine candidates

being tested seem to be well tolerated, but longer follow-up is needed to generate more data for interpretation.

Most therapeutic HIV vaccine trials have enrolled people who are HIV-infected but otherwise healthy and free of AIDS symptoms. In the first half of 1993, NIAID launched the first trials in the world to test therapeutic HIV vaccines in three additional populations: pregnant HIV-infected women and infants born to them, and asymptomatic HIV-infected infants and children. Early 1993 also marked the opening of the first NIAID therapeutic HIV vaccine trial to include people with more advanced HIV disease.

***FUTURE DIRECTIONS***

Although the challenges are daunting, scientists remain optimistic that safe and effective HIV vaccines can be developed. Basic researchers have made tremendous strides in understanding how HIV causes disease, recently describing how throughout the long symptomless period of HIV infection, the virus gradually ravages the lymph nodes and related organs, a process imperceptible by the patient who generally feels well during this time.

Moreover, novel ways to present HIV proteins to the immune system continue to be designed and tested, as do new antigen/adjuvant vaccine formulations. A growing number and variety of experimental vaccines are entering clinical tests in primates and humans, and more trials are exploring whether changing immunization schedules, increasing booster doses or using a combination vaccine strategy can stimulate stronger, more durable immune responses. Together, progress in basic and clinical research is moving scientists closer toward identifying products suitable for large-scale HIV vaccine efficacy trials.

###

NIAID, a component of NIH, supports research on AIDS, tuberculosis and other infectious diseases as well as allergies, immunology and transplantation. NIH is an agency of the U.S. Public Health Service, U.S. Department of Health and Human Services.

Prepared by:
Office of Communications
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland 20892

Public Health Service
U.S. Department of Health and Human Services

**January 1994**

National Institute of Allergy and Infectious Diseases

# News from NIAID

FOR RELEASE:
Sunday, Oct. 10, 1993

NATIONAL INSTITUTES OF HEALTH
Laurie K. Doepel
(301) 402-1663

## NIAID HIV VACCINE TRIALS UPDATE

The National Institute of Allergy and Infectious Diseases (NIAID) sponsors clinical trials of experimental vaccines made to prevent or to treat HIV disease. 1993 has been a productive year: NIAID has launched many new clinical investigations, a record number of people have entered into trials and important results have begun to emerge. This document highlights significant clinical trials initiated since the spring of 1993, as well as key research findings.

The AIDS Vaccine Evaluation Group (AVEG), which conducts Phase I and II clinical trials of experimental vaccines to prevent HIV infection, is the backbone of NIAID's HIV vaccine clinical trials effort. AVEG comprises five university-based clinical trial sites, support laboratories and a statistics and data analysis center. Between Feb. 2, 1988, and Sept. 1, 1993, AVEG initiated 19 trials and enrolled 1,312 volunteers. One-third of these volunteers, about 60 per month, enrolled in 1993.

Although AVEG primarily focuses on vaccines to prevent HIV disease, the group has initiated a few investigations in HIV-infected individuals. Some of these studies are conducted jointly with NIAID's AIDS Clinical Trials Group (ACTG), a nationwide clinical research network for testing AIDS therapies. ACTG carries out most NIAID-funded trials examining the therapeutic potential of candidate HIV vaccines. The Institute's Terry Beirn Community Programs for Clinical Research on AIDS also has recruited 137 of the several hundred people in a Phase II collaborative study with the Walter Reed Army Institute of Research investigating whether or not an experimental HIV vaccine benefits people infected with the virus.

NIAID announced several significant HIV/AIDS vaccine trials in the last year:

- the first Phase II preventive HIV vaccine trial worldwide (Dec. 1, 1992; AVEG 201);
- the first Phase I preventive trial in the United States of an experimental vaccine made from a chemically synthesized protein fragment, or peptide, of HIV (Feb. 12, 1993, AVEG 011);
- the first trials of candidate HIV vaccines in asymptomatic HIV-infected children between 1 month and 12 years old (Mar. 30, 1993, ACTG 218);
- the first trials of candidate AIDS vaccine in pregnant HIV-infected women who have few or no symptoms (May 5, 1993; AVEG 102/ACTG 234 and AVEG 104/ACTG 235).

Separate updates describing these studies are available from NIAID's Office of Communications.

(more)

**NIAID Opens First Comparative Vaccine Adjuvant Trials**

NIAID has begun the first clinical trials comparing the ability of several novel adjuvants to enhance the potency of candidate AIDS vaccines. Adjuvants are substances added to vaccines in an attempt to increase the type, strength or duration of immune responses they elicit.

Since 1926, the only adjuvants incorporated into human vaccines licensed in the United States have been aluminum salts, generically known as alum. Alum can increase the magnitude of antibody responses provoked by a vaccine but generally does not induce cytotoxic T cell responses. The latter are thought to be important to HIV immunity because they help kill HIV-infected cells.

A pair of separate Phase I trials, begun in June 1993 and expected to last 18 months, will identify the adjuvants that induce the most robust immune responses from two promising experimental AIDS vaccines. The trials also will provide the first information about how well humans tolerate these novel vaccine/adjuvant formulations.

The vaccine being tested in each trial contains a recombinant form of one part of HIV-1, the gp120 surface protein, thought to be important for stimulating immunity. Monkey studies of similar subunit vaccines--tailor-made using new tools of molecular biology and genetic engineering--have shown that such vaccine constructs are potentially safer but that they perform more poorly than expected compared with conventional vaccines for other diseases made from weakened or inactivated whole viruses such as measles or polio.

The gp120 vaccines are undergoing evaluation in NIAID's only Phase II trial of preventive HIV vaccines. Earlier studies of these same vaccines indicate that both are safe and that they stimulate similar immune responses, including neutralizing antibodies that laboratory tests show inactivate HIV and neutralize laboratory strains of the virus somewhat different from the strains used to make the respective vaccines. Furthermore, antibodies to the vaccines appear to persist in the circulation for months. Although these findings are encouraging, novel adjuvants may optimize protective immune responses and, by generating stronger, potentially more effective immune responses, allow smaller doses of the vaccines to be used.

The adjuvant trial AVEG 015 compares seven different immunogen/adjuvant formulations against alum alone given as a placebo control. Each formulation contains 50 µg of the immunogen, recombinant gp120 (rgp 120) based on HIV's SF-2 strain, made by Biocine (Emeryville, Calif., a joint venture of Chiron and CIBA-GEIGY). These adjuvants are:

- Aluminum hydroxide (alum)
- Monophosphoryl lipid A (MPL; Ribi ImmunoChem Research, Inc., Hamilton, Mont.)
- Liposome-encapsulated MPL with alum (liposomes made by Washington, D.C. researchers at the Walter Reed Army Research Institute)
- MF59 (Biocine)
- MF59 plus MTP-PE (Biocine)
- SAF/2 (Biocine)
- SAF/2 plus MDP (Syntex Corp., Palo Alto, Calif.)

(more)

what rgp120-adjuvant combination each volunteer receives. A primary immunization is followed by boosters at two and six months.

The second study, AVEG 016, is comparing different dosages of rgp120 MN strain (Genentech, Inc., South San Francisco) formulated with varied amounts of the adjuvant QS-21, a detergent-like substance made by Cambridge Biotech (Worcester, Mass.) from the bark of the South American soap bark tree.

Each of the 80 participants in the double-blind trial, healthy noninfected men and women at low risk of HIV infection, receives a primary vaccination and boosters at one and six months or one and 10 months. Three different doses of rgp 120, each combined with 50 or 100 μg of QS-21, are being tested in 68 volunteers. Some formulations also include alum. These participants will be compared with those twelve who receive just the QS-21 with or without alum.

**Trial Tests Safety of HIV Vaccines in Neonates at Risk for HIV Infection**

The ACTG is evaluating the safety and immune-stimulating ability of two experimental HIV vaccines in babies born to HIV-infected mothers. The babies, younger than 3 days old, are at risk for HIV infection, but their HIV status is unknown.

The Phase I trial, known as ACTG 230, is enrolling 120 infants at selected ACTG sites. The first babies enrolled in the trial are receiving low doses of Genentech's gp120 MN vaccine with alum or Biocine's gp120 SF-2 vaccine with the experimental adjuvant MF59. If three-fourths of the newborns in these low-dose groups show no signs of serious toxicity, the investigators will proceed to test a bigger dose in other infants. Similar criteria must be met before a third group of infants receives an even higher dosage of vaccine.

The study, which opened in mid-July, is expected to take two years to complete. The infants will be randomly assigned to either of two schedules of four shots given over a period of five months.

**Vaccine Uses Bird Virus as Shuttle for HIV Gene**

In May, AVEG investigators began a Phase I trial of ALVAC-gp160, a live recombinant vaccine made by inserting the gene for HIV's gp160 MN coat protein into a canarypox virus. The vaccine, made by Virogenetics of Albany, N.Y., a subsidiary of Pasteur Merieux-Connaught Laboratories in Swiftwater, Pa, is being tested in uninfected adults at low risk for HIV infection. The trial is expected to be completed in late 1994.

AVEG and other scientists have been evaluating live recombinant vaccines based on a vaccinia virus (the vaccine used against smallpox) that has been modified to make copies of the HIV gp160 surface protein. Results from these trials indicate that antibody- and cell-mediated immune responses can be stimulated by priming with the vaccinia construct and boosting with a recombinant subunit

vaccine containing gp160. Although no serious adverse reactions to vaccinia virus recombinants have been observed in these trials, concerns have been raised about the potential for an inadequately weakened vaccinia to cause infection.

Unlike vaccinia virus, canarypox virus does not replicate in mammalian cells. However, like vaccinia, the canarypox virus can accommodate large amounts of foreign DNA in its genome and can infect mammalian cells and use them to produce foreign proteins. This virus also does not need refrigeration and is relatively inexpensive to produce. Live viruses such as vaccinia and canarypox generally elicit strong immune responses, and their use may increase the response to the HIV proteins made by the vaccines.

The new Phase I study, AVEG 012, was designed to complement trials of the vaccine already under way in France. One vaccination schedule in the AVEG trial calls for a second priming immunization at two months rather than one month. Also, half of the volunteers will receive two booster shots of ALVAC-gp160 rather than two booster doses of a vaccine containing gp160 antigen alone.

The trial has two parts. Initially, 10 volunteers who have received smallpox vaccinations and 10 who have not are being given ALVAC-gp160 to determine if immunity conferred by smallpox vaccination interferes with the immune response to the canarypox vaccine. The eight other volunteers, five of whom will be vaccinia-immune, are receiving a control vaccine. The control is ALVAC-RG, a recombinant canarypox virus vaccine for rabies that has caused no serious side effects in animals or in humans.

If the initial dosage of ALVAC-gp160 is well tolerated, 40 additional vaccinia-immune volunteers will be enrolled in a test of a higher dose of ALVAC-gp160. They will be similarly divided at random to the different schedules of primary immunizations and the different type of booster shots. An additional 10 people will receive the control ALVAC-RG vaccine.

**Therapeutic Vaccine Trial Enrolls People with More Advanced Disease**

Most studies of therapeutic HIV vaccines enroll HIV-infected individuals with relatively intact immune systems as indicated by CD4+ T-cell counts above 500/mm$^3$ of blood. In one of the first HIV vaccine trials in people with more advanced HIV disease, NIAID-supported researchers are investigating how immune competence and antiviral treatment affect the response to therapeutic HIV vaccines.

ACTG 209 is a Phase I/II trial testing the safety and therapeutic potential of Genentech's rgp120 MN vaccine in people with CD4+ T cell levels between 50 and 500/mm$^3$. The trial began in March 1993 and has enrolled or screened the 168 HIV-infected individuals needed for the study. The individuals are stratified by CD4 count into four groups.

Participants with 350 to 500 CD4+ T cells/mm$^3$ have been split into two groups. The first group--those with no prior ddI or ddC treatment who tolerated two to 12 months of 500 to 600 mg

zidovudine (AZT) daily immediately prior to study entry--are receiving either 600 µg/month of vaccine or placebo control, alum adjuvant, in addition to a daily dose of 600 mg of AZT. The second group--those with 350 to 500 CD4+ T cells/mm$^3$ and no history of antiretroviral therapy, or less than one month of therapy three or more months ago--is receiving 600 µg of the vaccine per month.

Volunteers with 200 to 349 CD4+ T cells/mm$^3$ and the same history of retroviral drug treatment as those in the first group are receiving the same treatment as that group. Individuals in the fourth group, those with 50 to 199 CD4+ T cells/mm$^3$ and a minimum of two months previous therapy with AZT, ddI or ddC, are receiving either 600 µg/month of vaccine or alum control plus their current daily dose of antiretroviral therapy.

All participants receive two 300-µg immunizations into the muscle each month for six months. Periodically, the investigators look for any changes in measurable virus, CD4+ T-cell count, specific immune responses and disease progression. Follow-up will last six months after the last immunization.

**Vaccine Trials In Search of Recruits**

Individuals interested in volunteering for HIV vaccine trials can find out which ones are recruiting by calling 1-800-TRIALS-A, the AIDS Clinical Trials Information Service hotline, weekdays between 9:00 am. and 7:00 p.m. Eastern time. Spanish-speaking personnel can assist callers. The following NIAID-sponsored trials currently need more volunteers.

***HIV-infected pregnant women with few or minor disease symptoms:***

*AVEU 102/ACTG 234* - A Phase I trial of the MicroGeneSys rgp160 vaccine and alum in pregnant women infected with HIV. Potential volunteers must have few or no symptoms and CD4+ T cell counts of 400/mm$^3$ or more. Volunteers should enroll early after conception to receive the first immunization between the fourth and sixth month of pregnancy. Although coordinated through the AVEU, this trial is being conducted only at Yale University in New Haven, Conn.

*AVEU 104/ACTG 235* - A Phase I trial of Genentech's rgp120 MN vaccine with alum adjuvant. Same criteria as for AVEU 102. Trial being conducted at all AVEU sites and the University of California at San Francisco pediatric AIDS Clinical Trials Unit.

*ACTG 233* - This new Phase I trial is testing Biocine's yeast-derived rgp120 SF-2 vaccine in the same population as AVEU 102. Volunteers are being recruited through five ACTG sites in Philadelphia, Miami, New York City, New Orleans and Worcester.

***Noninfected healthy men and women at higher risk for HIV infection:***

*AVEU 201* - A Phase II study of Genentech and Biocine rgp120 vaccines. Enrollment near complete, but heterosexuals between 16 to 28 years old who have multiple sex partners or are otherwise practicing high risk sexual behavior are still needed. Also recruiting heterosexuals between 18 and 60 whose partners are HIV-infected and who do or do not practice safer sex.

***HIV-infected children:***

*ACTG 218* - A Phase I clinical trial to evaluate the safety and immunogenicity of recombinant envelope proteins (MicroGeneSys gp160 IIIb, Genentech rgp120 MN and Biocine rgp120 SF-2) in children 1 month or older with asymptomatic HIV infection.

***Neonates born to HIV-infected mothers:***

*ACTG 230* - A Phase I trial to evaluate the safety and immunogenicity of two recombinant subunit vaccines (Genentech rgp120 MN and Biocine rgp120 SF-2) in newborns up to 3 days old who are born to HIV-infected mothers but whose HIV status is unknown.

# # #

Bill Kincaid list of participants in community meeting.
Each one called by me.

# CITY OF ST. LOUIS
# DEPARTMENT OF HEALTH & HOSPITALS

## FACSIMILE TRANSMITTAL SHEET

**DATE:** 12-28-93 **TIME:** 4:30

[X] **Immediate** **No. of Pages to Follow:** 3

[ ] **Priority**

[ ] **Routine**

**To:**
Steve Lee

**From:**
Don Conner
Metro AIDS
634 N. Grand

**Message:**

**Confirmation Phone Number: 314/658-1054**
**Facsimile Number: 314/658-1017**
**Equipment Type: Ricoh - Model 550**

P.1

DEC 28 '93 04:28PM HEALTH COMMISSIONER

# Metropolitan St. Louis AIDS Program

St. Louis County
Department of Community Health and Medical Care
Alpha Fowler Bryan, M.D., Director

City of St. Louis
Department of Health and Hospitals
William L. Kincaid, M.D., M.P.H., Director

**M E M O R A N D U M**

Highest rate syphilis
of 256,000.
90%

TO: Steve Lee
National AIDS Policy Office

FROM: Don Conner, PA-C
Metro St. Louis AIDS Program

SUBJECT: Participant List for Kristine Gebbie Meeting

DATE: December 28, 1993

| | |
|---|---|
| Dr. William Kincaid | Health Commissioner<br>City of St. Louis<br>634 N. Grand, Suite 410<br>St. Louis, MO 63103 |
| Dr. Alpha Fowler-Bryant | Director<br>St. Louis County Health Dept.<br>121 Meramec<br>St. Louis, MO 63105 |
| Dr. Linda Fisher | Chief Medical Officer<br>St. Louis Dept. of Health<br>121 Meramec St.<br>Clayton, MO 63105 |
| Lynn Cooper, D. Min. | Executive Director<br>Doorways<br>P.O. Box 4652<br>St. Louis, MO 63108 |
| Mark Sanford | President<br>Blacks Assisting Blacks Against AIDS<br>1307 Washington, Suite 400<br>St. Louis, MO 63103 |

634 North Grand Boulevard, Room 436, St. Louis MO 63103 Phone 658-1159
6065 Helen Avenue, St. Louis County, MO 63134 Phone 522-6410, ext. 6143

| | |
|---|---|
| Beth Meyerson, M. Div. | Director of Client Services<br>St. Louis E.F.A.<br>5622 Delmar 104E<br>St. Louis, MO 63112 |
| Deborah McGruder | Title I Grants Manager<br>Metro St. Louis AIDS Program<br>634 N. Grand, Suite 436<br>St. Louis, MO 63103 |
| Eileen Nickisch | Missouri Department of Health<br>#2 Campbell Plaza<br>St. Louis, MO 63139 |
| Don Conner | Program Manager<br>Metro St. Louis AIDS Program<br>634 N. Grand, Suite 436<br>St. Louis, MO 63103 |
| Richard Wescott<br>5535 Delmar, Apt. C<br>St. Louis, MO 63112 | Affected Community |
| Helena Henry-Hatch<br>6242 North Drive #1E<br>U. City, MO 63130 | Affected Community |
| Prudence Brungard<br>6233 Northwood Ave. #2W<br>St. Louis, MO 63105 | Affected Community |
| Bill Dotson | Program Manager<br>St. Louis C.O.R.R. Program<br>634 N. Grand, Suite 444<br>St. Louis, MO 63103 |
| Marcos Williams<br>3851 Lindell #36<br>St. Louis, MO 63108 | Affected Community |
| Colleen Wilson<br>2347 Wittemore Pl.<br>St. Louis, 63104 | Affected Community |
| Rudi Nickens<br>1314 Boland Pl.<br>St. Louis, MO 63117 | Affected Community |
| Dr. Morton Singer | 11040 Manchester Pl.<br>St. Louis, MO 63122 |

| | |
|---|---|
| Josephine Ingram | Northside AIDS Outreach<br>3540 Marcus Ave.<br>St. Louis, MO 63115 |
| Lynn Emrick<br>916 S. Church St.<br>Belleville, Ill 62220 | Affected Community |
| Cawood Bebout<br>101 S. Hanley, 16th Fl.<br>St. Louis, MO 63105 | Affected Community |
| Sarah Simms<br>6904 Corbitt Ave.<br>St. Louis, MO 63130 | Affected Community |

# OFFICE OF COMMUNICATIONS

**National Institute of Allergy and Infectious Diseases**

**DATE: 1/5/94** **TIME: 6:00**

**TO: Steve Lee**

**ORGANIZATION: Kristine Gebbie's office**

**FAX #: 202-632-1096**

**NO. OF PAGES, INCLUDING COVER SHEET:**

**FROM: Laurie K. Doepel**
**NIAID Office of Communications**
**National Institutes of Health**
**9000 Rockville Pike**
**Bldg. 31, Room 7A50**
**Bethesda, MD 20892**

**(301) 402-1663 (PRESS)**
**(301) 496-5717 (ALL OTHERS)**
**FAX #: (301) 402-0120 or (301) 402-3573**

**Steve:**

**Lois Ford Long from St. Louis U. Community Relations asked that I send you some background info on AIDS/HIV vaccine research. Please let me know if you need anything else. FYI, Dr. Patricia Fast, the co-author of one of these papers, will be in St. Louis for this event. She's chief of the Clinical Research Section, Vaccine Research and Development Branch, Division of AIDS, NIAID.**

***National Institute of Allergy and Infectious Diseases***

**National Institutes of Health**
**U.S. Public Health Service**

# NIAID AIDS VACCINE EVALUATION UNITS

Dr. Mary Lou Clements
Johns Hopkins University
Center for Immunization Research
Hampton House, Room 125
624 North Broadway
Baltimore, MD 21205

Contact: Karen Charron
Tel. (410) 955-7283

Dr. Robert Belshe
St. Louis University
School of Medicine
3635 Vista Ave., FDT-8N
St. Louis, MO 63110

Contact: Carol Berry
Tel. (314) 577-8649

Dr. Ray Dolin
University of Rochester
Medical Center
Box 689, 601 Elmwood Ave.
Rochester, NY 14642

Contact: Shirley Erb
Tel. (716) 275-5871

Dr. Lawrence Corey
University of Washington
School of Medicine
c/o Pacific Medical Center
1200 12th Ave. S., 9th floor
Seattle, WA 98144

Contact: David Berger
Tel. (206) 326-4179

Dr. Peter Wright
Dr. Barney Graham
Vanderbilt University
Division of Infectious Diseases
Medical Center N., Room A3310
Nashville, TN 37232-2605

Contact: Lois Wagner
Tel. (615) 343-2437

Prepared by:
NIAID Office of Communications
National Institutes of Health
Bethesda, MD 20892

**February 1993**

N I A I D

AIDS VACCINE EVALUATION GROUP

## SUMMARY/DESCRIPTION OF PROTOCOLS

| PROTOCOL | VACCINE | ADJUVANT | MANUFACTURER | DOSAGES | SCHEDULE (months) | ACCRUAL COMPLETED |
|---|---|---|---|---|---|---|
| 002, A, B | Live recombinant vaccinia-gp160 IIIB<br>and<br>Baculovirus expressed-rgp160 IIIB | –<br><br>Alum | Bristol-Myers-Squibb/Oncogen<br><br>MicroGeneSys | $10^7$, $10^8$, or $10^9$ pfu/ml<br><br>160, 640 µg | 0, 2<br><br>>12 or 2 | 102 |
| 003, A, B | Baculovirus expressed-rgp160 IIIB [VaxSyn] | Alum | MicroGeneSys | 40, 80, 160, 640 µg | 0, 1, 6 (and 12 or 18) | 128 |
| 004, A, B | Mammalian cell expressed rgp160 IIIB | Alum and DOC (Deoxycholate) | IMMUNO-AG | 12.5, 50, 200 µg | 0, 1, 6 (12 and 18) or 0, 1, 2, 3, 4, 5 | 115 |
| 005A, B, C | Yeast derived rgp120 SF-2 [ENV 2-3] | MTP-PE in MF59 | Chiron/Biocine | 30, 100 µg | 0, 1, 6 (and 12) | 78 |
| 006<br><br>[Rollover] | Mammalian cell expressed rgp120 IIIB<br><br>rgp120 IIIB or MN | Alum<br><br>Alum | Genentech<br><br>Genentech | 100, 300 µg<br><br>300 µg | 0, 1, 8<br><br>(13, 20) | 28 |
| 007A, B, C | Mammalian cell expressed rgp120 SF-2 | MTP-PE in MF59 | Chiron/Biocine | 15, 50 µg rgp120 0, 50 µg MTP-PE | 0, 1, 6 or 0, 1, 2, 3, 4 | 63 |
| 008 | Live vaccinia gp160 IIIB + Chiron ENV 2-3 SF-2 or rgp120 SF-2 | MF59 | Bristol-Myers-Squibb/Oncogen<br>Chiron/Biocine | $10^8$ pfu/ml<br><br>50 or 100 µg | 0, 8, 12 | 56 |

EMMES CORP., Potomac, Md.
10/93

AIDS VACCINE EVALUATION GROUP

## SUMMARY/DESCRIPTION OF PROTOCOLS - *continued*

| PROTOCOL | VACCINE | ADJUVANT | MANUFACTURER | DOSAGES | SCHEDULE (months) | ACCRUAL COMPLETED |
|---|---|---|---|---|---|---|
| 009 | Mammalian cell expressed rgp120 MN ± rgp120 IIIB | Alum | Genentech | 100, 300, 600 µg | 0, 1, 6, 12 | 57 |
| 010 | Live vaccinia gp160 + rgp120 SF-2 or rgp120 IIIB or rgp120 MN or rgp160 MN | MF59 Alum Alum DOC/Alum | Bristol-Myers-Squibb/Oncogen Chiron/Biocine Genentech Genentech IMMUNO-AG | $10^9$ pfu/ml 50 µg 600 µg 600 µg 200 µg | 0, (4), 8, 12 | 56 |
| 011 | HIV-1 MN octameric V3 peptide (SynVac) | Alum | UBI | 20, 100, 500 µg | 0, 1, 6 | 36 |
| 012A | ALVAC vCP125 HIV-1 gp160 MN live canarypox | | Connaught/ Pasteur Merieux | ALVAC gp160 MN $10^8$ $TCID_{50}$ | 0, 2 ,6, 12 | 28 |
| 012B | ALVAC vCP125 HIV-1 gp160 MN live canarypox | | Connaught/ Pasteur Merieux | ALVAC gp160 MN $10^7$ $TCID_{50}$ | 0, 1, 6, 12 or 0, 2, 6, 12 | 50 |
| 013A | Mammalian cell expressed rgp160 MN | Alum and DOC | IMMUNO-AG | 200 µg | 0, 1, 6 or 0, 2, 8 | 24 |

AIDS VACCINE EVALUATION GROUP

## SUMMARY/DESCRIPTION OF PROTOCOLS - *continued*

| PROTOCOL | VACCINE | ADJUVANT | MANUFACTURER | DOSAGES | SCHEDULE (months) | ACCRUAL COMPLETED |
|---|---|---|---|---|---|---|
| 015 | Mammalian cell expressed rgp120 SF-2 | • Alum<br>♦ Monophosphoryl Lipid A (MPL)<br>■ Alum-adsorbed liposomes w/MPL<br>✓ SAF-m with and without MDP<br>o MF59 with and without MTP-PE | Chiron/Biocine<br>• Superfos/as<br>♦ RIBI<br>■ WRAIR<br>✓ Biocine<br>o Ciba-Geigy | 50 µg | 0, 2, 6 | 110* |
| 016 | rgp120 MN | QS21 with and without Alum | Genentech | 0, 100, 300, or 600 µg rgp120<br>0, 50, or 100 µg QS21 | 0, 1, 10 or 0, 1, 6 | 80* |
| 201 | Mammalian cell expressed rgp120 SF-2 or rgp120 MN | MF59<br>Alum | Chiron/Biocine<br>Genentech | 50 µg<br>600 µg | 0, 1, 6 and 12 or 18 | 360* |

* In Progress

## SUMMARY/DESCRIPTION OF PROTOCOLS - *continued*

| PROTOCOL | VACCINE | ADJUVANT | MANUFACTURER | DOSAGES | SCHEDULE (months) | ACCRUAL COMPLETED |
|---|---|---|---|---|---|---|
| **HIV-1 ENVELOPE** | | | | | | |
| 101 | Mammalian cell expressed rgp160 IIIB | Alum and DOC (Deoxycholate) | IMMUNO-AG | 50 µg | 0, 1, 2, 3, 4, 5 | 55 |
| 102 | Baculovirus expressed-rgp160 IIIB [VaxSyn] | Alum | MicroGeneSys | 640 µg | 5 monthly injections during pregnancy; (and 3, 6, 9, 12 months post partum) | 24* |
| 103, A, B | Yeast-derived rgp120 SF-2 [ENV 2-3] | MTP-PE in MF59 | Chiron/Biocine | 0, 30 µg ENV 2-3 0, 10, 50, 100 µg MTP-PE | 0, 1, 4 (7,10) | 53 |
| 104 | Mammalian cell expressed rgp120 MN | Alum | Genentech | 300 µg | 5 monthly injections during pregnancy; (and 3, 6, 9, 12 months post partum) | 24* |

* In Progress

# AIDS VACCINE EVALUATION GROUP (AVEG)

## PROTOCOL ACTIVITY OVERVIEW CHART

| STUDY # | PROTOCOL DESCRIPTION AND **SPONSOR**<br>*STUDY CHAIR; VEU PARTICIPANTS* | ACCRUAL COMPLETED |
|---|---|---|
| 002 | Safety/immunogenicity of HIVAC-1e vaccinia-env **Bristol/Oncogen** in vaccinia naive subjects; Amended to add booster dose of 640 µg of rgp160 IIIB [VaxSyn] **MicroGeneSys**<br>*Chair: Graham; Sites: Hopkins, Saint Louis, Rochester, Washington, Vanderbilt* | 1/92 |
| 002A | Safety/immunogenicity of combination: 640 µg of VaxSyn and HIVAC-1e in prior vaccinia recipients<br>*Chair: Corey; Sites: Saint Louis, Washington, Vanderbilt* | 9/91 |
| 002B | Continued study of safety/immunogenicity of HIVAC-1e plus VaxSyn (160 µg); volunteers originally entered U. Washington<br>*Chair: Corey; Sites: Washington* | 7/91 |
| 003 | Safety/immunogenicity of VaxSyn 40 and 80 µg doses VaxSyn **MicroGeneSys**<br>*Chair: Dolin; Sites: Baylor, Hopkins, Saint Louis, U. Maryland, Rochester, Vanderbilt* | 5/88 |
| 003A | Safety/immunogenicity of VaxSyn 160 µg dose<br>*Chair: Dolin; Sites: Hopkins, Saint Louis, Rochester, Washington, Vanderbilt* | 10/90 |
| 003B | Safety/immunogenicity of VaxSyn 640 µg dose<br>*Chair: Dolin; Sites: Hopkins, Saint Louis, Rochester, Washington, Vanderbilt* | 3/91 |
| 004 | Safety/immunogenicity of **IMMUNO-AG** mammalian cell expressed rgp160 IIIB<br>*Chair: Belshe; Sites: Hopkins, Saint Louis, Rochester, Washington, Vanderbilt* | 7/91 |
| 004A | Safety/immunogenicity of **IMMUNO-AG** 200 µg dose of rgp160 IIIB<br>*Chair: Belshe; Sites: Hopkins, Saint Louis, Rochester, Vanderbilt, Washington* | 10/92 |
| 004B | Safety/immunogenicity of accelerated schedules of **IMMUNO-AG** rgp160 IIIB<br>*Chair: Belshe; Sites: Hopkins, Saint Louis, Vanderbilt* | 3/92 |
| | 005: Two-part evaluation of **Biocine** Product: | |
| 005A | Safety of the MTP-PE/MF59 adjuvant emulsion<br>*Chair: Dolin; Sites: Rochester* | 2/91 |
| 005B | Safety/immunogenicity of 30 µg yeast-derived ENV 2-3 in combination with MTP-PE/MF59<br>*Chair: Dolin; Sites: Rochester, Washington, Vanderbilt* | 10/91 |
| 005C | Safety/immunogenicity of 100 µg ENV 2-3 in combination with MF59<br>*Chair: Dolin; Sites: Rochester, Washington, Vanderbilt* | 11/91 |

| STUDY # | PROTOCOL DESCRIPTION AND **SPONSOR**<br>*STUDY CHAIR; VEU PARTICIPANTS* | ACCRUAL COMPLETED |
|---|---|---|
| 006 | Safety/immunogenicity of **Genentech** rgp120 IIIB vaccine<br>*Chair: Clements; Sites: Hopkins, Saint Louis* | 6/91 |
| | 007: **Three part evaluation of Biocine Product:** | |
| 007A | Safety/immunogenicity of mammalian cell expressed rgp120 SF-2 with/without MTP-PE adjuvant in MF59 emulsion<br>*Chair: Graham; Sites: Rochester, Washington, Vanderbilt* | 3/92 |
| 007B | Safety/immunogenicity of five monthly doses rgp120 protein<br>*Chair: Graham; Sites: Hopkins, Saint Louis* | 3/92 |
| 007C | Safety/immunogenicity of 200 µg of rgp120 with MF59 Emulsion<br>*Chair: Graham; Sites: Rochester, Washington, Vanderbilt* | 12/92 |
| 008 | Safety/immunogenicity of HIVAC-1e **Bristol/Oncogen** in combination with a panel of recombinant HIV envelope vaccines in non-vaccinia naive subjects<br>*Chair: Corey; Sites: Hopkins, Saint Louis, Rochester, Vanderbilt, Washington* | 1/93 |
| 009 | Safety/immunogenicity of **Genentech** MN rgp120 vaccine alone or in combination with rgp120 IIIB **Genentech**<br>*Chair: Belshe; Sites: Rochester, Saint Louis, Vanderbilt* | 7/92 |
| 010 | Safety/immunogenicity of HIVAC-1e **Bristol/Oncogen** in combination with a panel of subunit recombinant vaccines in vaccinia-negative subjects<br>*Chair: McElrath; Sites: Hopkins, Saint Louis, Rochester, Vanderbilt, Washington* | 6/93 |
| 011 | Safety/immunogenicity of **United Biomedical, Inc.** SynVac HIV-1 octameric V3 peptide vaccine<br>*Chair: Gorse; Sites: Saint Louis, Rochester* | 6/93 |
| 012A | Safety/immunogenicity of **Connaught/Pasteur Merieux** live recombinant CanaryPox-gp160 MN (ALVAC vCP125, HIV-1 gp160 MN)<br>*Chair: Clements; Sites: Hopkins, Rochester, Saint Louis, Vanderbilt, Washington* | 8/93 |
| 013A | Safety/immunogenicity of **IMMUNO-AG** mammalian cell expressed rgp160 MN vaccine<br>*Chair: Gorse; Sites: Saint Louis, Washington* | 6/93 |
| 015 | Safety/immunogenicity of **Biocine** mammalian cell expressed rgp120 SF-2 individually combined with seven adjuvants<br>*Chair: McElrath; Sites: Rochester, Saint Louis, Vanderbilt, Washington* | In progress |

| STUDY # | PROTOCOL DESCRIPTION AND **SPONSOR**<br>*STUDY CHAIR; VEU PARTICIPANTS* | ACCRUAL COMPLETED |
|---|---|---|
| 016 | Safety/immunogenicity of **Genentech** mammalian cell expressed rgp120 MN in combination with QS21 adjuvant and/or alum<br>*Chair: McElrath; Sites: Hopkins, Rochester, Saint Louis, Vanderbilt, Washington* | In Progress |
| 101 | Safety/immunogenicity of **IMMUNO-AG** mammalian cell expressed rgp160 IIIB in asymptomatic HIV seropositive subjects<br>*Chair: Schwartz; Sites: Hopkins, Saint Louis, Vanderbilt* | 2/93 |
| 102 | Safety/immunogenicity of **MicroGeneSys** VaxSyn in HIV-1 infected pregnant women<br>*Chairs: Graham, Lambert, Wright; Site: Yale (ACTG site)*<br>*AVEG Clinical Coordination: Vanderbilt* | In Progress |
| | 103: Three-part evaluation of **Biocine** Product: Safety/immunogenicity of yeast-derived ENV 2-3 in combination with MF59/MTP-PE in asymptomatic HIV seropositive individuals | |
| 103 | Pilot Study: ENV 2-3 30 µg + MTP-PE adjuvant with/without MF59 emulsion<br>*Chair: Corey; Sites: Rochester, Washington* | 1/92 |
| 103A | ENV 2-3 0 and 30 µg + MTP-PE adjuvant 0 and 100 µg with/without MF59 emulsion<br>*Chair: Corey; Sites: Rochester, Washington* | 9/92 |
| 103B | ENV 2-3 0 and 30 µg + MTP-PE adjuvant 100 µg with MF59 emulsion<br>*Chair: Corey; Sites: Rochester, Washington* | 7/92 |
| 104 | Safety/immunogenicity of **Genentech** mammalian cell expressed rgp120 MN in HIV-1 infected pregnant women<br>*Chairs: Graham, Lambert, Wright; Sites: Hopkins, Rochester, Saint Louis, Vanderbilt, Washington, UCSF (ACTG site)* | In Progress |
| 201 | Phase II - Immunogenicity/reactogenicity of recombinant subunit HIV-1 envelope vaccines; **Biocine** mammalian cell expressed rgp120 SF-2 in MF59 adjuvant and **Genentech** mammalian cell expressed rgp120 MN in alum adjuvant<br>*Chairs: Corey/McElrath; Sites: Hopkins, Saint Louis, Rochester, Vanderbilt, Washington* | In Progress |