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GRANT NO: DAMD17-88-Z-8007

TITLE: HUMAN IMMUNODEFICIENCY VIRUS (HIV) RESEARCH (AIDS)

PRINCIPAL INVESTIGATOR: Bryce Redington, Ph.D.
John W. Lowe

CONTRACTING ORGANIZATION: Henry M. Jackson Foundation
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1401 Rockville Pike, Suite 600
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REPORT DATE: July 15, 1993

TYPE OF REPORT: Final Report

PREPARED FOR: U.S. Army Medical Research and
Development Command, Fort Detrick
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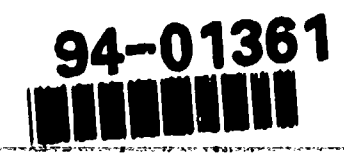

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	15 July 1993	Final Report (2/25/88-3/31/93)

4. TITLE AND SUBTITLE
Human Immunodeficiency Virus (HIV) Research (AIDS)

5. FUNDING NUMBERS
Grant No.
DAMD17-88-Z-8007

63105A
3M2631050H29
AD.041
WUDA314851

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research & Development Command
Fort Detrick
Frederick, Maryland 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

A comprehensive HIV Research Program conducted studies in the areas of Vaccines and Immunotherapy/Immunoprophylaxis, Epidemiology/Natural History, Behavioral Medicine, Chemotherapy/Chemoprophylaxis, Retroviral Biology, Animal Models, Diagnostics and Opportunistic Infections. Research was directed towards ameliorating the effects of HIV infections within the US Armed Forces. Program priorities were early stage disease over late stage disease; interventions over descriptive studies; and primary anti-retroviral therapy over treatment/prophylaxis of opportunistic infection or symptomatic therapy of late stage disease. Research involved clinical trials, natural history studies, and laboratory and animal model studies. Significant outcomes of this research included (but not limited) to:

14. SUBJECT TERMS	15. NUMBER OF PAGES
Volunteers; EA I; Therapeutic Trials; HIV; Retroviruses; Clinical Facility; WRAMC; Biotechnology	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

13. Abstract (continued)

Initiation and continuation of the world's largest Phase II Vaccine Therapy Trial.

Completion of the Army-wide HIV/AIDS survey (over 18,000 surveyed).

Genetic analysis of more than 250 international field isolates of HIV-1 from 21 countries on 5 continents - one of the largest international collections of isolates to date.

Collection of Natural History data from over 5,000 HIV patient visits providing invaluable information about disease progression.

Conduct of over 35,000 protocol patient visits with 31 currently active protocols and 9 completed protocols.

Development of animal models to further the development of preventive vaccines and drugs against HIV.

Development and evaluation of enhanced sensitivity diagnostic techniques for HIV, and techniques to quantitate viral genes in blood and tissue.

Initiation and continuation of the only U.S. study of AZT that allowed continued follow-up of matched cohorts of patients (DoD-VA) receiving early versus late AZT therapy..

Initiation of outside collaborations with the National Institutes of Health (NIH) and pharmaceutical firms to offer new drug therapies.

Foundation authorship and co-authorship of 135 manuscripts, 150 abstracts and 197 presentations.

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the management of the Henry M. Jackson Foundation for the Advancement of Military Medicine and are not necessarily endorsed by the U.S. Army.

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For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 45CFR46.

In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

John W. Lowe
HIV Research Program Director
President
Henry M. Jackson Foundation
for the Advancement of Military Medicine

July 15, 1993

Table of Contents

TITLE:
HUMAN IMMUNODEFICIENCY VIRUS (HIV) RESEARCH PROJECT

GRANT #DAMD 17-88-Z-8007

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BRADLEY WILLIAM P
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CARROLL RICHARD G
CARROLLWILLIAMS CECILIA
CASTRO BEATRIZ A
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CHOCK CHRISTIAN P
CLAIBORNE ELSIE B
CLAIRMONT VIRGINIA J
CLASBY SUSAN
COATES JERRY A
COGAR EDWARD T
COHEN HENNA G
COLLINS LYNDA S
COOLEY JOHN D
CORNFELD DANIEL M
CORPREW MARY-MARGRET
CORTESE LINDA M
CORTS KAREN J
COUCHENOUR DEBRA A
COVELL WILLIAM
COYLE CAROL M
CRABILL KARIN L
CROMBRUGGHE INES
CROSS CONNIE B
CURRIER DEBORAH L
CURRY ELLEN E
D'ARCY LISA A
DAHLBERG JOHN E
DAIGNEAULT DIANE
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DANK BONNIE
DAVIS KIM E
DAYAL LAXMI P
DAYHOFF DEBORA E

NAME

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DEAN JANE A
DENT HOWARD C
DEPONTE JOE P
DEVINE FRANK E
DIAMOND MOLLY G
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DREW CHRISTINA M
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DUNDON MARTHA M
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EDDY GERALD A
EHRENBERG PHILIP K
EICHENLAUB BRIAN E
ERIKSON JOHN C
ESCOBAR MATILDE S
ESPOSITO MATTHEW
EVANS LILLIE M
EVANS NANCY S
FEELY BRIAN R
FELDMAN JOY T
FELTHAM MARY A
FERGUSON FREDERICK C
FERGUSON III HILTON J
FLETCHER CHRISTINE S
FLOOD BARBARA J
FOSTER JANET S
FRANKEL JANA L
FRAZIER RENA M
FREDERICK WANDA S
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GUZMAN CONCEPCION
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HADICK SUSAN P
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HALL ERIC R
HALL MARY K
HALL REGINALD C
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HUMPHRIES MARY J
HUNTER EDWARD A
HUNTER VICTORIA D

NAME

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JACKSON BARBARA G
JACKSON JANIE
JAMES LINDA E
JARBOE LORRAINE K
JARVIS-WALKER LINDA A
JENKINS PAMELA R
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JESSE MARGARET W
JEWETT ERIC S
JEWETT KATHRYN J
JOHNSON ANGELIA B
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JOHNSON KEITH W
JONES DEBBIE F
JONES SANDRA C
JONES SANDRA E
JONES TONY M
JONES VICLA
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KALTER DEBRA C
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KAUSHAL INDERJIT K
KAVANAGH CAROL ANNE
KECK LOIS T
KENDALL SARAH N
KERNOZEK PAUL A
KERSEY KATHRYN S
KIRKLAND-DEMPSEY VONJA M
KISH BARBARA M
KOCH JANE M
KOLESSER CAROL J
KONCHAN CAROL L
KONZELMAN JOSEPH L
KOOPMAN TAMMY L
KOZJAK JOHN A
KRASNICKA BARBARA
KUBRAK CORINNE A
KUCHERA MARY J
KUHNEY FRANCIS
KUTTLER RUTH L
LAI CHUN-YEH
LAMBERT MARY BETH
LASALVIA SUSAN M
LASHLEY JESSIE S
LAW WENDY A

NAME

LAWSON APRILEONA Y
LEADER WILLIAM
LEDSKY REBECCA A
LEE DIANNE M
LEON CECILIA F
LEON ENRIQUE C
LESCALLETT MOLLY D
LEWIS BARBARA
LEWIS CHARLENE S
LEWIS MARK G
LIN JEN-TSUN J
LIU YILING
LONG PAUL E
LOOMIS LAWRENCE D
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LORTON LEWIS
LOUDER MARK E
LOUWAGIE JOOST J
LOVELAND JOHN E
LYNCH ANN A
MAGUIRE ROBERT F
MAKINOONI ROBERT E
MANN FELECIA
MARKFIELD JAY L
MAPOU ROBERT L
MARAKOVITZ MARETTE M
MARKS CHRISTOPHER A
MARKS KAREN M
MARSH NICHOLAS A
MARSH SHARON J
MARTIN JENNIFER A
MARTIN LAURA J
MCCARTHY WILLIAM F
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MCDONALD MARGARET J
MCDONALD RICHARD A
MCGRADY GEORGE T
MCGUIRE CATHERINE M
MCHUGH SUZANNE C
MCKINNON KATHERINE M
MCLAIN CAROLYN
MCLUCEN ROBERT J
MCNEAL JILL T
MCNEIL CARLTON B
MCNEIL WILLIAM S
MCPHERSON GERALD R
MCQUADE ANNE M
MEDINA LEAH C
MEGNA SCOTT J

NAME

MENN DAVID R
MERRITT DONNA
MERRITT SCOTT E
MERZ NAOMI J
MIAO JING
MICKLEY JACQUELINE R
MILAWSKI CHRISTOPHER K
MILLER PAULINE M
MISENCIK SHERRY
MITCHELL MARGARET M
MOORE GEORGE H
MOORE MATTHEW D
MORGAN CHARLENE E
MORGAN PATRICIA A
MORISI-BOOTH STACY M
MORROW PAUL J
MOSCA JOSEPH D
MUELLER DE ANN S
MUELLER JUDITH L
MULLIGAN MAURITA M
NANNIS ELLEN D
NAU MARTIN E
NEAL RICHARD K
NEMAZIE ANN
NEWBY JOHN H
NG TIE-HUA
NGUYEN GEORGE T
NICKLAS MARTIN A
NIELSEN ROBIN K
NIZHNIKOV GALINA
NOLAN-POLITE EILEEN E
NUNLEY-BAILEY MARSHA K
O'BRIEN KAREN L
O'NEILL DEBORAH S
OFFE BEVERLY L
OGUNDEPO ADEWOLE A
OGUNDEPO RUTH A
OK KETTYA
OKOTO FELICIA E
OLDROYD MICHELLE C
OLIGNY CHRISTOPHER J
OLSEN CHRIS C
ORGANIC MIRIAM S
OSLEY NEEDA H
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REYES MENINA
RICE MELANIE A
RILEY DEBRA
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ROBINSON ALLEN L
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ST LOUIS DANIEL C
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STEVENS-JONES LYNETTE G
STEWART LOUIS S
STINNETT BILLY D
STOCKER CRYSTAL M
STODIVANT ADDREY W
SUBANEY GAYLE
SULLIVAN MARY A
SUMMAN SONJA R
SWAYSON MERCY P
SWINGLER RALPH S
TAKISHI DEIDRE C
TAVERNA BARBARA J
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TEMESGEN LYDIA
TENCER KATHLEEN L
TERRY ADRIENE L
THEUNS KIMBERLY M
THOMPSON EVELENE F
THOMPSON S. RENEE
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WESTERLUND ASHLEY L
WESTERLUND L. ERIC
WHITE BRIAN D
WHITE ELLA J
WHITE SHERRY D
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WILBURN DAIJON D
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WILLIAMS DEBORAH A
WILLIAMS KENNETH W
WILLIAMS LORI M
WILLIAMS MELINDA A
WILLIAMS PATIENCE A
WILSON PATRICIA A
WISE NEAL A
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WOODFORK SHARLES L
WYMAN ELIZABETH T
XU JIN
YALLEY-OGUNRO JACOB E
YOUNG LORETHA F
YOUNG PAULINE S
YOUNG-HUMPHREY MELENDA D
YU ZHIPENG
ZACHARY ROBERT A
ZHAO FU

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I. INTRODUCTION

Nature of the Problem

In the mid-1970s a silent epidemic began. Infections spread rapidly and unnoticed until 1981, when clusters of young men presented symptoms of an unusual type of immune-system failure. In 1982 this new disease, which also had been found in hemophiliacs, was termed AIDS - Acquired Immunodeficiency Syndrome. These first clinically apparent cases were merely the "tip of the iceberg" of a deadly epidemic; the true extent of the disease still remained a mystery. In 1984, the virus which caused this immune deficiency syndrome was successfully isolated and named the Human Immunodeficiency Virus (HIV). Discovery of this virus led to the rapid development, in 1985, of blood tests which detected antibodies for HIV. Wide-scale screening was conducted that year, and it was determined that 1 million to 1.5 million Americans, mostly young adult males, were infected.

The immediate implications to the military became clear with the realizations that HIV is a sexually transmittable disease, HIV infects blood, and HIV is a fatal disease. In 1985, realizing the urgency of this threat to the Armed Forces, the Department of Defense (DoD) began screening all active-duty military personnel and all applicants for HIV. A total of 1,752,191 persons who remained on active duty from January of 1986 to April 1988 were screened. HIV-1 antibody was confirmed by Western Blot (termed seroprevalence) in 2,232 of these persons (1.3 per 1,000). Seroprevalence was highest in men, unmarried persons and enlisted personnel. One in every 600 applicants for United States military service was found to be infected with the virus, and in some urban screening centers, the infection rate was as high as one infected applicant in every 50. Additionally, over 5,000 HIV-infected military health care beneficiaries were receiving medical care at U.S. Military Hospitals. Projections made in 1988 postulated that 1 out of every 1,500 active duty personnel would become infected with HIV. Extrapolation of this data to the entire active military force suggested that between 1,000 to 1,500 military personnel were becoming infected each year with this transmissible and ultimately fatal disease. Projections such as this quickly mobilized the military to address this threat to readiness. The military also realized, that with the implementation of routine screening of military personnel for HIV, it was in a very unique position to study the incidence and prevalence of the disease in a large population. Additionally, such early diagnosis afforded the military valuable opportunities for studies of treatment and prevention, opportunities which were not readily available in civilian populations. With immediate access to a well disciplined population, and appropriate resources, the military was ready to

assume a leadership role in the fight against HIV and AIDS.

Background of Previous Work

Congress, in the 1982 DoD Appropriations Bill, designated the Army as the lead agency for infectious disease research within the Department of Defense (DoD). In 1985, realizing the impact of HIV on the military, Congress, through the Senate Defense Appropriations Committee, held meetings with DoD medical experts to discuss the global threat the Human Immunodeficiency Virus (HIV) epidemic posed to force readiness. The incidence of HIV infection in the military population was identified as a serious health hazard and a threat to operational readiness. In response to this threat, the DoD designed a research program to study the natural history of AIDS infection, virus and immune response, chemoprophylaxis, and vaccine prevention.

In August, 1986, Congress directed the Army to initiate a military relevant, non-duplicative and state of the art research and development program on the Human Immunodefiency Virus (HIV), under the direction of the United States Army Medical Research and Development Command (USAMRDC). Research was to be conducted in the areas of vaccine development, chemoprophylaxis, diagnostics, natural history, and epidemiology. Since there was no established intramural military retrovirus research expertise at that time, 1986 and 1987, research funds were spent as grant and contract awards to extramural research teams in both academia and private industry. Proposals submitted under Broad Agency Announcements to the USAMRDC garnered over 40 exceptionally qualified research teams. These scientists provided expert assistance which furthered the development of the military research program. A major impediment still remained, however. Even though sufficient funding was appropriated, no new personnel authorizations had been released. Lack of these authorizations hindered the growth of the military HIV research program.

The Purpose of the Current Work Under the Grant

In December 1987 the Foundation submitted a proposal in response to the USAMRDC Broad Agency Announcement with the primary objective to "conduct and support clinical trials of therapeutic regimens which show promise of ameliorating or preventing the effects of HIV infection". On February 25, 1988, the DoD, through USAMRDC, awarded a five year grant to the Foundation for the conduct of HIV research. The initial purpose of the grant was to conduct a research program on Human Immunodeficiency Virus (HIV) Disease to determine the natural history of HIV and to conduct basic and applied research in the areas of chemo/immunotherapy and chemo/immuno-prophylaxis. The work statement stipulated that "The

Foundation shall furnish the necessary personnel, materials, services, facilities, and otherwise do all things necessary for or incident to the performance of work in accordance with the Foundation's proposal dated December 31, 1987, entitled "Human Immunodeficiency Virus (HIV) Research". Research could be conducted in Military Medical Care Facilities to benefit military readiness and military health care beneficiaries. Research was to be executed through Foundation and Government submitted protocols. Independent but supporting laboratory research plans were to be established. These protocols and plans were to be integrated into one research strategy to provide a solid foundation on which to begin a comprehensive HIV research program.

In November of 1988, a team of physicians and scientists from the Walter Reed Army Institute of Research (WRAIR), the Walter Reed Army Medical Center (WRAMC), and the Foundation met in Hagerstown, Maryland to develop a strategy for and to prioritize the HIV research effort for 1988-1993 (Appendix 1). Ambitious goals were set for the military:

- Reduce the incidence of new HIV infections to zero
- Reduce the rate of progression from asymptomatic to symptomatic disease to zero
- Reduce the HIV attributable death rate to zero

Also during this plenary session, the Army developed a hierarchy of research priorities defined by category to study, from highest to lowest priority: Viral immunology, Epidemiology, Chemotherapy, Natural History and Diagnostics. Each area had a planning document known as the "Mission Area Protocol" or "MAP". These MAPs were subsequently expanded in number to eight; and the clinical research and laboratory efforts within each MAP constituted the overall HIV research effort for Grant Years 1-5. The eight MAPs were: Vaccines and Immunotherapy/Prophylaxis, Epidemiology/Natural History, Behavioral Medicine, Chemotherapy/Chemoprophylaxis, Retroviral Biology, Animal Models, Diagnostics, and Opportunistic Infections. Each of the eight mission areas delineated highly specific research approaches to combatting HIV; yet each mission area also maintained the common goal of investigating new strategies to control the HIV epidemic. The scope of the grant was subsequently expanded to include US Navy and US Air Force personnel, to incorporate related National Institutes of Health (NIH) research initiatives with military relevance, and to conduct a specialized survey within the Department of the Army to establish a baseline of information of service members' knowledge, attitudes, beliefs and practices concerning HIV infection (Army Wide AIDS Survey - AWAS). In 1990, the Military Medical Consortium for Applied Retroviral Research (MMCARR) was established to insure coordination of this multi-disciplinary Tri-Service endeavor. MMCARR membership was composed of Foundation, Military and Government scientific and professional

personnel with the common mission of conducting HIV research in a military setting.

The growth and successes of the research resulting from the Grant have been notable. During the past five years over 2,800 research patients (all military medical beneficiaries) were recruited into 31 active protocols and 9 completed protocols at three primary sites and six smaller sites. These research patients represented over 8,000 protocol enrollments and completed over 35,000 research protocol visits during Grant Years 1 - 5. At each of the primary clinical research sites, Walter Reed Army Medical Center (WRAMC), National Naval Medical Center (NNMC), and Wilford Hall Medical Center (WHMC), the Foundation provided the groundwork, personnel, and coordination of the critical technical support network needed for the overall execution of clinical HIV research trials. In addition to staffing the clinical research sites, the Foundation provided the staff (scientific, technical and administrative) to execute and facilitate the laboratory components of the HIV research effort. As a direct result of the research and findings resulting from this Grant, Foundation Scientists and research staff authored or co-authored over 134 manuscripts, 150 abstracts and 197 presentations.

This final report describes this research effort in the technical approach (Section II). The technical approach outlines and summarizes the goals, objectives and results of the work directly arising from this Grant and the HIV Research Program. Conclusions are submitted and future recommendations to address the issues are also provided; references are noted where applicable. Additionally, protocol summaries of all active, completed and terminated protocols are provided for further reference in Appendix A. The research infrastructure is detailed in the organizational approach (Section III and IV). The organizational approach also describes the assurances and management mechanisms that the Foundation initiated and/or followed to guarantee the highest caliber of research and to insure proper and efficient use of resources. Concluding remarks follow the organizational approach in Section V. A complete bibliography is provided in Appendix B for all publications that Foundation personnel either authored or co-authored as a direct result of the Grant.

II. TECHNICAL APPROACH

INTRODUCTION

Notable progress and scientific achievements were made over the past five years in the HIV Research Program. This section of the Final report provides an overview and a summary of the work accomplished within the eight mission areas: Vaccines and Immunotherapy/Prophylaxis, Epidemiology/Natural History, Behavioral Medicine, Chemotherapy/Chemoprophylaxis, Retroviral Biology, Animal Models, Diagnostics and Opportunistic Infections. An individual "MAP" fact sheet prefaces each Mission Area summary, delineating the active or completed protocols and Principal Investigators. The fact sheet is followed by an in-depth review of the goals, objectives and accomplishments within each Mission Area. Conclusions are made for each mission area, and future plans to further address the science are also included.

A. VACCINES AND IMMUNOTHERAPY/PROPHYLAXIS MISSION AREA

LTC ROBERT R. REDFIELD, M.D., MC, U.S. ARMY, DIRECTOR

MAP SUMMARY: The overall mission of the Vaccines and Immunotherapy MAP was to develop an effective vaccine(s) for the treatment and prevention of HIV infection.

Protocol #	Protocol Title (Abbreviated)	Principal Investigator
RV15	Skin Testing	Birx
RV21A	Recombinant gp160 Phase I	Redfield
RV21B	Recombinant gp160 Phase II	Redfield
RV21C	Civilian Expansion gp160 Phase II	Redfield
RV51	rgp120	Redfield
RV57	gp160/AZT	Redfield

VACCINE AND IMMUNOPROPHYLAXIS MISSION AREA

Overview

Over the past five years the Vaccines and Immunoprophylaxis Mission Area made a number of sentinel scientific observations in the area of HIV immunoregulation and vaccine development.

Dr. Myron Essex, Director of the Harvard AIDS Institute, reviewed the first four years of this mission area (Nov 1988-1991). He concluded that no other single site in the world has the breadth of immunological, virological and molecular biologic expertise represented in the Walter Reed Army Institute of Research (WRAIR) Department of Retroviral Research and this mission area and that this Department and mission area has emerged as a unique national effort that would be difficult or impossible to duplicate elsewhere.

This mission area successfully blended the unique and diverse talents of scientists and clinicians into a cohesive unit with the goal to evaluate and comprehend HIV immunoregulation, which will ultimately lead to innovative approaches in HIV therapy. During the past five years, as outlined below, this area grew from two full time scientists and two technicians to eleven full time researchers and 41 research associates, research assistants, and support personnel; three clinical fellows also trained in basic research techniques in this mission area. The productivity within this area resulted in numerous presentations and manuscripts. Additionally, Dr. Redfield and his colleagues collaborated with scientists around the world and attracted three international visiting scientists to spend time working in this area.

Research Goals and Objectives

The overall goal of this mission area protocol was the development, evaluation and demonstration of efficacy of HIV specific vaccines for both treatment and prevention of HIV infection and disease. The primary concentration of this mission area was to:

a) define HIV immunoregulation mechanisms in the setting of chronic HIV infection.

b) characterize each in terms of their impact of viral host interaction.

Therapeutic interventions with products designed to modify the

adaptive humoral and cellular immune responses either by active vaccination or designed to alter *in vivo* viral specific expression via active vaccination/infection with retroviral vector vaccine products were to be exploited to define and validate in mechanisms responsible for effective *in vivo* HIV control.

To accomplish this goal the following objectives were pursued:

1). Develop and apply new technology to measure and characterize HIV specific immune responses.

2). Develop and apply new technology to measure and characterize HIV load and expression *in vivo*.

3). Define mechanisms responsible for effective post-infection HIV immunoregulation.

4). Develop the required technology and scientific infrastructure to define the protective immune response and successfully execute preventive vaccine trial.

5). Develop and evaluate candidate HIV vaccine for efficacy in the treatment and prevention of HIV infection.

Objective 1: Develop and apply new technology to measure and characterize HIV specific immune responses

--During this period, significant progress was accomplished. Under the direction of LTC Birx, a comprehensive HIV Immunology Laboratory was created. Foundation staff comprised a major portion of this laboratory effort.

--The technology was developed to characterize the human HIV epitope-specific humoral and cellular immune responses and these techniques were applied to the evaluation of volunteers with HIV infection. New technology to characterize HIV envelop antibody was successfully developed. These included quantitative peptide ELISA, fusion protein western blotting quantitated by phosphoimaging techniques, linear epitope mapping by geysin pin peptide analysis, real time biospecific analysis techniques capable of assessing antibody binding kinetics (association and dissociation constants) and the impact of distinct molecular conformation on binding, and antibody spectrotyping to characterize conformational antibodies

--A functional assay to characterize neutralization capacity was developed to include a PBMC autologous neutralization assay.

--Technology to characterize cellular immune responses was successfully developed. These included T-cell proliferative response to HIV proteins, and the fine mapping of T cell anti envelop responses and cytotoxic T cell assays. Specific human T-cell lines and subcloning of epitope specific T-cells were developed to explore their specific function and potential HIV immunoregulatory properties.

--In addition, *in vitro* assays required to characterize and assess the immunological status of patients were applied. These included T cell proliferative assays to mitogen and recall antigens (such as candida and tetanus), assays to quantitate antibodies to control antigen (tetanus), assays to measure cytokine production (sIL-2r, TNF, IL-6), and assays to measure natural killer cell activity. This comprehensive approach to the evaluation of HIV-infected immune system allowed this research area to extensively describe and categorize the extent of immunologic dysfunction associated with early stage, asymptomatic HIV infection.

--Early and mid stage patients were previously postulated to have significant immunological dysfunction, based on *in vitro* analysis of immunological function. However, *in vivo* functional integrity of early and mid stage HIV infected patients was demonstrated. HIV infected volunteers demonstrated the capacity to mount a new primary response to administered control [illegible]ccines (rabies vaccine) and demonstrated a norma[illegible] booster response to recall antigen (tetanus toxoid va[illegible]). This observation documented the immunological resi[illegible]nce of early stage HIV patients and failed to confirm previous suggestion of significant irreversible immunological end organ damage in early stage disease.

--The use of delayed hypersensitivity skin test in the evaluation of HIV infection was standardized, and the independent prognostic value was demonstrated. The standardization of this test and the demonstration of prognostic value of delayed hypersensitivity skin tests has important implications both in the medical management of HIV infection and clinical evaluation of potential therapeutic agents as a validated surrogate marker of disease progression.

--The development of a comprehensive HIV immunology laboratory to conduct the laboratory components for the vaccine research was an enormous achievement and was a prerequisite to the successful accomplishment of the primary objective of this mission area, the development and demonstration of safe and efficacious HIV vaccine for

treatment and prevention of HIV infection and disease. Under the guidance of the MAP Director, LTC Deborah Birx spearheaded the development of the laboratory which successfully resulted in a premier human HIV immunology laboratory. Foundation participation was an integral component of this effort.

Objective 2: Develop and apply new technology to measure and characterize HIV load and expression *in vivo*

--Substantial progress was made in the development of technology to measure HIV replication and expression *in vivo*. Quantitative PCR based assays measuring HIV proviral copy number, RNA copy number, and RNA transcript analysis were developed and applied. Techniques to sequence and analyze proviral LTR function were developed. These techniques provided critical tools for further dissection of HIV immunoregulation when combined with the comprehensive immunologic evaluation.

Objective 3: Define mechanisms responsible for effective post-infection HIV immunoregulation

--Adaptive (memory) immunity directed against HIV in the setting of chronic infection was partially characterized. An important accomplishment was the discovery that, in natural infection, the anti-envelope humoral and cellular immune responses are restricted. This observation has important implications for vaccine development. Subsequent evidence that post infection vaccine could induce broad anti-envelop recognition confirmed that the restricted response was not predominantly caused by a genetic restriction but rather a consequence of antigen processing and presentation.

--The characterization of antibody directed against the V3 loop structure (type specific versus broad reactivity) in all stages of HIV infection was defined. Early stage patients (WR1) demonstrated a type specific reactivity, whereas HIV mid-stage, (WR 2-5) demonstrated broader recognition of V3. Late stage patients again had a restricted type specific V3 reactivity. These results have important implications in terms of understanding HIV pathogenesis, immunity and potential vaccine development.

--Evaluation of HIV expression *in vivo* demonstrated the absence of viral latency in patients with HIV infection. This observation confirmed that host directed immune responses which occur as a consequence of natural infection do not result in viral clearance.

--Studies of HIV transcription revealed a novel and potentially extremely important observation: HIV transcription was not restricted to the production of positive stranded mRNA, both in cell lines as well as *in vivo*. Negative stranded transcription occurred. Sequence analysis confirmed the presence of multiple open reading frames, thereby potentially increasing the coding capacity of the HIV genome. Additional studies demonstrated a unique promoter for negative strained transcription which can be down regulated by tat. These observations could have important diagnostic and therapeutic implications.

Objective 4: To develop the required technology and scientific infrastructure to define the protective immune response and successfully execute preventive vaccine trials

--While the pace of vaccine development for treatment was accelerating, measurable progress in primary vaccine development for prevention was limited. This limitation was primarily due to the lack of scientific delineation of candidate protective immune responses and the lack of scientifically agreed selection criteria for product development and selection for efficacy trials. This mission area was instrumental in the development of two planned Thailand based Vaccine trials. Progress was made in the identification to field trial site. A cooperative relationship towards the goal of preventive vaccine development with the Thai military research unit was established. The incidence of HIV infection was defined in the candidate volunteer populations, technology transfer initiated to include training and personnel exchanges, and prototype seronegative and seropositive Phase 1 preventive and therapeutic protocols were prepared and approved. Local infrastructure development was in progress. To insure the success of these trials, MMCARR scientists from all mission areas worked to build a strong base for this long-term scientific collaboration between the United States and Thai military. Working towards this major effort, this mission area, specifically, accomplished the following:

--A scientist from this research area performed on site consultation in Thailand (Sept 1991). In addition, training was provided by scientists and nurses from this area to Thai investigators, nurses, and a technician. Clinical vaccine research procedures and the laboratory techniques required to execute "in country" prophylactic and therapeutic vaccine

trials were topics covered in November 1991 and August-September 1992.

--Specific assays were developed to facilitate trial execution in Thailand. A battery of unique DTH antigens were selected, a series of recall antigens for *in vitro* T cell assays were selected and utilized to screen Thai reactivity.

--The entire HIV Research Immunology Laboratory was replicated in the Thai portion of Armed Forces Research Institute of Medical Sciences (AFRIMS). All of the equipment needs, source, and consumable supplies were organized by this mission area.

--A series of humoral and cellular assays were developed to immunotype the viruses present in Thailand to allow dissection of type vs. group anti-HIV responses and to define their role in HIV treatment and vaccine development for prevention.

--Specific assays were developed to separate vaccinated volunteers from HIV-infected individuals in preparation for preventive vaccine trials.

Objective 5: Develop and evaluate candidate HIV vaccine for safety immunogenicity and efficacy in the treatment and prevention of HIV infection

To meet objective 5, clinical evaluations of several candidate HIV recombinant envelop derived vaccines were initiated and in some cases, completed, in patients with early HIV infection. One of the most notable documentations of these trials, to date, was the feasibility of post-infection vaccination to safely broaden the host anti-HIV humoral and cellular immune responses. A brief discussion of each clinical research protocol, conducted during the Grant period, is given and significant findings are noted:

Protocol RV 21A - *"Active immunization of HIV infected patients with recombinant gp160 HIV protein: Phase 1 study of Immunotherapy, immunogenicity and toxicity"*-

This initial protocol was designed to evaluate the feasibility of post HIV infection vaccination with HIV viral products utilizing a recombinant rgp160 vaccine. This Phase I safety and immunogenicity trial began in April 1989, was completed in November 1990 and was published in the New England Journal of Medicine in June

1991. A continuation trial was designed to assess the long term immunogenicity and safety of this product and was implemented in light of the programmatic decision to pursue a five year Phase II/III efficacy trial with rgp160. The continuation trial began in November 1990 and was modified by addendum in May 1992. As of March 31, 1993 each volunteer was receiving 160ug of rgp160 on a monthly schedule.

Significant Outcomes and Findings of RV 21A:

-first to demonstrate the safety and feasibility of concept of vaccine therapy for HIV infection. Subsequently, 5 independent groups have confirmed our published findings.
-refined the schedule for post infection vaccination Data provided by this trial continued to be exploited by multiple companies and investigators currently involved in therapeutic vaccine development which facilitated the optimization of immunization schedule.
-demonstrated immunologic resilience of early and mid stage HIV infection volunteers.
-provided critical information related to long term immunogenicity and duration of vaccine induced immune responses and facilitated optimal execution of ongoing Phase II trial (eg. extension protocol provided critical information related to vaccination booster schedule applied to modify phase 2 trial from every 4 months to every 2 month boosters prior to expansion)
-provided critical information related to long term safety and serves as a sentinel for the possibility of safety issues related to long term hyper-immunization with gp160/alum.
-continued to facilitate the development of novel assays developed to assess the human adaptive anti HIV immune responses and evaluation for application to phase II/III efficacy trial and prophylactic vaccine development program.
-continued to facilitate the development of novel assays designed to assess *in vivo* HIV replication kinetics which can subsequently be applied to drug development, gene therapy and prophylactic vaccine development program areas.
-provided opportunity to assess *in vivo* interrelationship between induction of specific adaptive anti-HIV immune responses and viral variation (currently under development).
-demonstrated unique anti-HIV cellular responses. Combined with the CHO expressed products provided an immunologic profile to all future treatment and prevention employing envelope-based products.

Protocol RV51 - *"A Phase 1 Study of the Safety and Immunogenicity of IIIB rgp120/HIV Vaccine in HIV-1 Seropositive Adult Volunteers"*-

This initial trial was a Phase I open label dose finding trial (100ug, 300ug, 600ug) in 19 volunteers followed by a blinded randomized component (300ug verses placebo) in 25 volunteers. Volunteers were vaccinated 0,1,4,8,16 weeks with follow up evaluations every 2 weeks through 24 weeks. This trial opened in November 1990 following confirmation of immunogenicity of 300ug and 600ug rgp120 dosage (8/92); a subsequently randomized arm enrollment opened September 1992 and closed December 1992. An extension addendum to evaluate variation in boosting schedule in terms of immunogenicity and safety began in April 1992. Forty-one (41) of the original volunteers re-enrolled and continued on this trial.

Significant Outcomes and Findings of RV51:

-first to demonstrate the immunogenicity and safety of a CHO cell expression HIV envelope product in volunteers with early stage HIV infection.
-first to document dosage response of this product. All subsequent investigators took advantage of the results of this trial to optimize trial design using CHO expression Genentech vaccine products in both seronegative and seropositive trials.
-product found to have a unique dose response profile which led to extensive evaluation of the character of the CHO product.

- significant percentage of product found to be denatured.
- primary immune response linked to "denatured" portion of molecule.
- diminished cellular response has lead company to explore adjuvant techniques.
-development of *in vitro* assay techniques required to assess T cell anti HIV responses utilizing CHO cell expressed rgp120. Currently utilized by sponsor in all other prophylactic and therapeutic clinical trials.

- development and application of novel techniques to measure humoral response directed against "conformational intact" rgp120 (sero-spectrotyping and biospecific interaction analysis.
-comparative immunogenicity of CHO cell derived rgp120, and baculoviral derived gp160 demonstrated unique immunologic profile was under intense investigation.
-no evidence of continued expansion of V3 reactivity post 9 injections to "group specificity" as suggested by prior baboon studies.

Protocol RV21B - *" Active immunization of early patients with recombinant gp160 HIV protein: phase 2 study of toxicity, immunogenicity, in vivo immunoregulation and clinical efficacy"-*

This was a phase II, multi-center, double blinded, placebo controlled trial designed to evaluate the clinical efficacy by surrogate markers of post infection vaccination with rgp160 in the treatment of HIV infection and to validate adaptive anti-HIV immune responses in terms of *in vivo* HIV expression and clinical progression. Enrollment began in November, 1990 and was initially limited to 140 volunteers. Following confirmation of safety and immunogenicity within this initial group, complete enrollment was approved Spring 1992 and completed on schedule in the Fall of 1992. Initial efficacy analysis by surrogate markers was scheduled for November 1993, and final analysis was scheduled for November 1995.

Significant Outcomes and Findings of RV21B:

-Ongoing double blinded trial, only limited information available to date. Developed network of DOD, NIH and civilian sites for efficient trial execution. Currently, 601 volunteers are on trial and being evaluated at 2 month intervals. 311 volunteers are beyond 6 months, 134 volunteers beyond 18 months (range of follow up 3 - 27 months). Protocol execution continues with less than 1% missed visits.
-Confirmation of immunologic resilience of patients with early HIV infection in terms of primary response to novel antigen (rabies) and secondary response to recall antigen (Tetanus toxoid).
-Confirmation of natural history of adaptive immune responses
- demonstrated highly restricted T/B cell response directed against envelope
- demonstrated lack of expansion of T/B cell repertoire during natural infection
-Confirmation of immunogenicity of rgp160 in setting of HIV infection (first 140 patients)
-Confirmation of short term safety of rgp160 in setting of HIV infection
-Independent of outcome in terms of clinical efficacy this cohort of patients would provide the opportunity to validate adaptive immune responses directed against HIV in terms of in *vivo* HIV regulation and clinical disease progression in both the treatment and placebo arms. Specifically, cohorts of placebo patients stratified by clinical course in blinded arms will be extensively evaluated.

Protocol RV57 - *"Active Immunization of AZT- Treated HIV- Infected Patients With Recombinant gp160 HIV Protein: Phase 1/2 Study of Immunogenicity, Toxicity, and Effect on In Vivo Immunoregulation"-*

This protocol was a Phase II/III multi-center, open label feasibility trial of rgp160 in patients with HIV infection Walter Reed stage 1-5 and who were receiving AZT. Specific objectives included: a) assess the immunogenicity and safety of rgp160 in patients with more advanced HIV disease and in patients with early disease receiving AZT; b) determine parameters predictive of post infection immune responsiveness. Patients were stratified by T cell interval. Each volunteer received 160ug of rgp160 on days 0,7 and at months 1,2,4,6,10 for a trial duration of 12 months (not inclusive of preevaluation).

Significant Findings and Outcomes of RV57:

-This trial opened for enrollment Nov. 92 enrollment will be completed within 6 months. Patient accrual was on schedule, as of March 31, 1993, currently 64 volunteers were on trial and 53 post initial vaccination. Duration of follow up ranged up to Day 90.
-Data obtained from this trial will provide important information related to effect of AZT on the immunogenicity and safety profile of rgp160.
-In addition, this trial will provide systematic information related to immunogenicity and safety in HIV infected populations with more advanced disease.
-Provided platform for additional human adjuvant studies. To date, 8 adjuvants have been studied extensively in small animals in collaboration with Dr. Britta Wahren.
-Verified unique relationship between adjuvant and antigen combinations, requiring verification of each combination.
-The sponsors agreed to utilize this population to study these adjuvants which can then be exploited in future therapeutic and prophylactic strategies, addendum currently in preparation.

Conclusion

This mission area has been an international leader in furthering the scientific understanding of HIV immunoregulation and provided novel approaches to therapeutic and prophylactic product development. Numerous research "firsts" have been attributed to this research area. Specifically, they include, chronologically:

••first to document and publish restriction of anti HIV envelope adaptive immunity as a consequence of natural infection (1989).

••first to demonstrate and publish the scientific feasibility to augment HIV specific adaptive immunity by vaccination (vaccine therapy) in the setting of chronic HIV infection (1989).

••first to demonstrate the independent prognostic ability of delayed hypersensitivity skin testing(1989-90).

••first to demonstrate and publish the safety and immunogenicity of rgp160 in seropositive adults(1989-1990).

••first to demonstrate the superiority of hyper immunization for optimal immunogenicity of therapeutic vaccines (1990).

••first to begin double blinded placebo controlled clinical efficacy vaccine therapy trial(1990).

••first to demonstrate the safety and immunogenicity of rgp120 in seropositive adults (accomplished 1990-91).

••first to demonstrate the ability of IIIB based rpg160 to induce broadly cross reactive humoral and cellular immunity to divergent HIV strains (1991-92).

••first to apply and publish use of real time biospecific analysis to the characterization of HIV immunity (1991-92).

••first to develop cellular based RNA PCR based assay to assess *in vivo* viral expression(1991-92).

••first to demonstrate and publish the absence of HIV latency in patients with HIV infection demonstrating active HIV transcription in circulating cells in all HIV infected patients at all stages of disease (1991).

••first to discover negative strained RNA transcripts (physiological antisense)*in vitro* and *in vivo* (1991-92).

••first to develop serological assay to serotype antibodies directed against northern Thai HIV strain (1992).

••first to demonstrate the ability to superinfect chronically infected cells lines with a second distinct HIV isolate (1992).

As a result of the research and accomplishments during this period, the Mission Area Director and the scientists in this area effectively established themselves as leaders in the field HIV immunoregulation and vaccine development. Over 60 manuscripts were published or were under scientific review and over 100 abstracts describing the progress of this department were presented throughout the world.

Additionally, several scientists from the Vaccine area were invited speakers at National and International meetings, specifically:

International

•••International Conference on AIDS (1988,1989,1990,1991,1992,1993) including the honor of being selected as a plenary speaker at 4th international AIDS conference (1988)
•••Colloque des Cent Gardes meetings (1991,1992)
•••International congress of Biological Modifiers (1992)
•••The International Congress of Chemotherapy (1993)

National

•••Keystone HIV conferences (1988, 1990, 1992)
•••Cold Spring Harbor Vaccine and Gene Therapy Meetings (1992)
•••National Cooperative Vaccine Development Group for AIDS (1990,1991,1992)
•••National Forum on AIDS and Hepatitis (1992)
•••Clinical Immunology Society (1992)
•••Federation of Experimental Biology Meeting (1991, 1992)
•••American Academy of Allergy and Immunology (1990-1993)
•••ICAAC (1990,1991,1992) and IDSA (1992).

Additionally, investigators contributed articles and editorials for such prestigious medical publications as Scientific American, the New England Journal of Medicine, Annals of Internal Medicine and Current Opinion in Immunology and served on the scientific advisory board of the World AIDS Foundation. Investigators in this area were invited to write two chapters on Vaccine Therapy.

In summary, despite these advancements over the past five years, the immunoregulation mechanism responsible for effective control of *in vivo* replication post-infection and the immunological mechanism for a protective HIV immunity remain unknown. Major scientific obstacles to the successful completion of our ultimate mission of the development of a preventive vaccine still linger:

1. the limitations of current animal models
2. the potential role of viral heterogeneity, and
3. the lack of *in vitro* assays of *in vivo* relevance with regard to effective immunoregulation and protection.

However, the continued scientific evaluation of innate and adaptive immune responses induced by candidate HIV vaccines in seropositives combined with the comprehensive evaluation of candidate surrogate markers of disease progression, and clinical outcomes in volunteers enrolled the cooperative DOD/ NIH rgp160 Phase II trial will provide important progress in the definition effective post infection immunity and will give potential insight into the definition of protective immunity. The fact that RV21B has been in progress for almost two years and has only a one percent occurrence of missed visits is absolute testimony to the cohesiveness and expert talents of the scientific, technical and administrative Foundation and military personnel who work in this mission area.

Future Studies Planned

To continue the evaluations of the aforementioned, this research area has proposed several clinical research trials to address these scientific questions. Each "pending" protocol is noted with a brief summary and an outline of anticipated outcomes.

Protocol RV54 - *"Active Immunization of Early HIV-infected pregnant women with recombinant gp160 HIV protein: Phase 1 study of toxicity, dosing and immunogenicity"*-

This will be a Phase I trial of rgp160 in pregnant volunteers with early HIV infection designed to determine the immunogenicity and toxicity of this product in pregnant HIV females and their offspring and to determine the parameters predictive of immunoresponsiveness in this population. Although this protocol was approved by the Tri-service Human Subjects Research Review Board (HSRRB) in the fall of 1991, the FDA requested further preclinical testing prior to approval to proceed. This was completed in the winter of 1992/93 and is currently under review. It is anticipated that FDA approval to proceed will be obtained as a consequence of data provided.

Anticipated Outcomes:

If feasible, future studies could be designed which would allow the validation of vaccine induced adaptive anti-HIV immune responses in terms of adult and infant clinical disease progression as well as direct assessment in terms of human protection and human transmission. In addition, therapeutic use of vaccine could be evaluated as a direct strategy for the prevention of perinatal HIV infection. Such studies could be anticipated to facilitate the characterization of the human protective anti-HIV response in addition to providing an alternative strategy for prophylactic vaccine product development.

RV71 - *"A phase 1 comparative immunogenicity study of vaccines composed of denatured recombinant gp120 (env 2-3) or intact glycosylated gp120 (gp120) combined with MF59 emulsion of MF59/MTP-PE adjuvant emulsion in volunteers with early HIV infection"*-

This will be a Phase I open label safety and immunogenicity trial to evaluate and compare two candidate HIV recombinant SF2 envelope-based vaccines produced in different expression systems, CHO cell expressed native glycosylated recombinant gp120 and yeast expressed denatured env2-3, in patients with early HIV infection. These products provide the opportunity to assess the impact of post-translational modification of envelope proteins on immunogenicity and safety. Although the CHO cell expressed product is similar to the Genentech product evaluated in RV51, these vaccines have been formulated with novel adjuvants (MF59 and MF59/MTP-PE). Comparison of results from this trial and those from RV51 will provide an additional opportunity to assess the impact of these adjuvants on the safety and immunogenicity of envelope-based vaccine therapy in early stage HIV infected volunteers. Trial design includes an escalating dose of MTP-PE with fixed dose of envelope immunogen with vaccinations at months 0, 1, 2, 3, 4 and 6.

Anticipated outcomes of RV71:

The Sponsor for this product withdrew support in May, 1992; it was suspected that this withdrawal was influenced by corporate data obtained from a herpes vaccine product formulated with MF59 MTP-PE; the toxicity profile caused company to rethink product formulation. However, the investigators remain extremely interested in this Phase 1 evaluation of the env2-3 yeast expressed product in MF59 (n=20). This Phase I would provide source of further comparative data to help assess the impact of expression

system, post translational modification of protein and adjuvant on immunogenicity and safety profiles of therapeutic vaccines and provide information for future prophylactic vaccine development. Discussion with the sponsor for product availability continue.

RV75 - *"A phase 1 study of the safety and immunogenicity of MN rgp120/HIV vaccine in HIV-1 seropositive subjects previously immunized with IIIB rgp120/HIV-1 vaccine on protocol VO200g and HIV-1 seropositive subjects who have not previously received HIV-1 vaccine"-*

This Phase I, open label trial will include 20 volunteers from the IIIB gp120 phase I trial and 10 "naive" patients. All individuals will receive 300ug of MNgp120 on months 0, 1, 2, 4, 6, 8 and 10 and patients will be followed monthly through 12 months of study. Scientifically, this trial will provide a direct comparison of the clinical safety and immunogenicity of MN rgp120 in naive volunteers as compared to volunteers who had previously been immunized and extensively studied. In addition, it will provide the immunologic background for future utilization of this vaccine in both seronegative and seropositive trials.

Anticipated outcomes:

Access to the MN vaccine and reagents has facilitated the exploration of the protein composition of the Genentech vaccine products. The Principal Investigators have found the product to contain both "native" and "denatured" components, although not in the same proportions as the IIIB product which should have significant immunologic ramifications. Important scientific questions relative to the native and denatured components and the effect on immunologic responses will be addressed with this protocol. In addition, this trial will provide an important comparison between vaccines which are developed in the same manner from different viral strains, and to discern what impact this has on immunogenicity. It is believed that this information is critical for the development of a vaccine program for treatment as well as prevention, and future vaccine development.

B. EPIDEMIOLOGY/NATURAL HISTORY MISSION AREA

LTC JOHN [illegible], M.D., MC, U.S. ARMY, DIRECTOR

MAP SUMMARY: The objectives of the Epidemiology/Natural History MAP centered on describing the manifestations of HIV with special emphasis on the impact of the disease on military readiness. Focal points included describing the disease with regard to the incidence, prevalence, distribution, progression and risk behaviors for HIV infection in the military and military associated populations.

Protocol #	Protocol Title (Abbreviated)	Principal Investigator
RV1	Natural History	Wagner*
RV3	Dental Natural History**	Konzelman*
RV 13	Pediatric Natural History**	Fisher
RV 41	Perinatal Tissue Bank	Fisher
RV18	Dermatology Natural History**	Smith
RV35	Dermatology Microflora**(completed)	Smith
RV22	Retrospective Review	Oster
RV44	HIV/Syphilis	Johnson
RV46	Propylthiouracil	LaCivita
RV48	Changes-Blood/Skin Test(completed)	Freedman
RV64	Evaluation of Cardiac Function	Doering
RV66	Evaluation/Education/Prevention	Ray
RV56	STD Patterns/Ft Bragg	McKee
RV70	Prevalence/Incidence-Thailand	McNeil

*Foundation Principal Investigator (PI)
**Funded by NIH

EPIDEMIOLOGY/NATURAL HISTORY MISSION AREA

Overview

Scientific management and oversight for this MAP was provided by the Walter Reed Army Institute of Research (WRAIR) through LTC John F. Brundage, M.D., MC. The Epidemiology/Natural History Mission Area Protocol was broad in scope and ultimately served all research MAP areas. Findings derived from the science of this MAP were expected to impact on, at a minimum, personnel policies, deployment scenarios, medical treatment and prevention modalities, and would provide research strategies and trends for future interventions involving the military force structure and military medical beneficiaries.

Research Goals and Objectives

The primary goal of this mission area was to describe the natural history of HIV infection in detail, focusing particularly on events in the early stages of infection. The military services possess a unique opportunity and an urgent need to continue to collect and analyze data to quantify rates of disease progression, to describe manifestations of HIV disease (particularly in the early stages) in the immune and other systems (e.g., neurologic, psychiatric) and to use data from these studies as historical control data on which to base assessments of effects of future therapeutic interventions. Those individuals identified as HIV infected were routinely and periodically evaluated to assess clinical status and medical fitness for continuation of active military service. Results of periodic clinical evaluations (including assessment of the Walter Reed Clinical stage T4 lymphocyte count) have been recorded to databases maintained by the military services. Realizing the wealth of information that such periodic evaluations offer, this mission area developed a number of initiatives studying the natural history of HIV disease. The two primary objectives for this mission area were:

1. Describe, as much as possible, all manifestations of the disease including (with attendant rates and factors) its incidence, prevalence, distribution, progression and risk behaviors in the military and military associated populations.

2. Assess the impact of the disease on military readiness.

To meet Objectives one and two, this research area conducted numerous Natural History Protocols which gathered the data necessary to describe the demography of HIV in the military. This systematically collected data was entered and stored into a single

database which allowed timely, accurate and summarized data for multiple research, clinical and policy decisions. The cornerstone protocol of this MAP was RV 1:

RV-1 - *"Natural History of HIV infection in military infected medical beneficiaries"* -

This protocol focussed on fully characterizing the natural history of HIV infection; identifying significant determinants of HIV disease in its different stages; quantifying rates of progression, particularly in the early asymptomatic stages, using markers of immune status such as CD4+, T-lymphocytes and Walter Reed clinical stage; validating and refining clinical staging; and establishing a historical control experience on which to base assessments of response to early stage therapeutic interventions.

Significant Findings:

This Tri-service protocol gathered data from over 5000 HIV patient visits at three primary medical centers, WRAMC, NNMC, and WHMC. Several analyses were done using this study, including studies on the natural history of HIV infection in women, progression of disease based on the slope of the CD4 cell declines, demographic factors associated with compliance in taking AZT and the effects of AZT on the progression of HIV disease by WR stage. There were ongoing analyses examining the effect of the new CDC criteria on the incidence of AIDS in the military population and examining the variability of CD4 counts obtained less than 30 days apart. This protocol served many other HIV Research protocols in that the RV1 patients formed a study cohort who were then eligible for participation in treatment protocols and for other studies related to specific aspects of the descriptive elements of HIV. This protocol also served as a historical control for intervention studies and provided a historic cohort to validate proposed surrogate markers of disease progression.

Other Natural History protocols conducted within this mission area that described and documented the HIV disease process included:

RV 5 - *"The Natural History of the Oral Manifestations of HIV Infection in a U.S. Military Population"* -

The purpose of this protocol was to determine the prevalence, incidence and risk factors for oral manifestations of HIV infection in relation to the degree of immunodeficiency. This study was unique in that the patients represented a wide range of early to late stage infection. Research patients at

the Walter Reed Army Medical Center received a comprehensive oral and dental examination at study entry and every six months thereafter. The evaluation included clinical examinations for dental caries, periodontal diseases and oral mucosa conditions. Samples of saliva and subgingival dental plaque were collected at each visit for microbial and biochemical assays, and a questionnaire on oral health related behavior was administered.

Significant Findings:

Data was analyzed in relation to the subjects' medical condition and immune status. Over 1000 patients were followed for this protocol and a preliminary analysis determined that the prevalence of HIV-related oral mucosal lesions was 32 percent at baseline and 44 percent after 6 months of follow-up. About 30 percent of those who were initially free of mucosal pathologies developed lesions within six months. Oral candidiasis was the condition that developed most frequently, with 70 percent of incident cases being of the erythematous form. Prevalence of mucosal diseases was clearly associated with depleted CD4 counts. This protocol met its enrollment goal of 1,000 patients in the Spring of 1993, but continued patient follow-up at six month intervals.

RV#13/16 - *"Epidemiology of HIV in Pediatric and Perinatal Patients: A Natural History"* -

The purpose of this study was to utilize existing epidemiological tools (USAHDS, DEERS) and an education program in the military medical community to identify all DoD dependents at risk for HIV. In addition, the protocol sought to identify HIV infection through a limited diagnostic HIV testing program and to collect epidemiological data and natural history data in the identified cohort. A systematic program of interval evaluations with a core of clinical and laboratory data was developed. Attempts were made to note all clinically indicated visits to a care provider as a part of defining the natural history of pediatric HIV and to contrasts these observations with exposed uninfected members of the cohort.

The importance of this and related studies to the overall MMCARR effort were threefold. First, the rapid progression of HIV disease in perinatally infected children and the high incidence of transmission in the perinatally exposed cohort suggested that studies of interventions to interdict transmission or modify disease course can be performed more efficiently in this cohort. A means of identifying and maintaining a study population for the purpose of small phase

1 trials of such interventions can only be achieved with a natural history program as the network device. Second, the relatively rapid progression to symptomatic disease in pediatric HIV permitted a more efficient clinical validation of immunologic and virologic parameters/predictors of transmission or progression. Analysis of safety concerns arising from the use of interventions used in this cohort could only be preliminary addressed in a phase 1 study due to the absence of a control group. The availability of a well and comprehensively characterized natural history population served an important role in assessing safety and planning studies with interventions.

Significant Findings:

Note: RV13/16 are an integrated study which have functionally overlapped extensively with RV 41. As a consequence the findings summary reflects contributions from each protocol.

-Preliminary data reflected a transmission rate and disease progression which was different from published data , i.e. less frequent and slower presentation.
-Defined the diagnostic utility of p24, PCR and culture in the pediatric setting and showed that the latter two are roughly equivalent in sensitivity and specificity (approx. 95-97%).
- Evaluated several measures of viral burden in the pediatric population but have failed to develop a method sufficiently robust to contribute to patient management. Whole culture titrations, plasma cultures and quantitative PCR for the assessment of viren as a corollary of clinical disease progression were evaluated. Of these, the PCR approach showed the greatest promise
-Characterized viral burden and sequence diversity in the plasma, peripheral blood and lymph node as well as longitudinal data from the PBL to identify potential limitations of the PBL compartment in assessing viral diversity or burden. These studies were vital to determining the design of any studies seeking to reliably correlate immunological responses to disease progression or transmission
-Contributed important data characterizing the use and interpretation of T cell phenotype data in the pediatric population. Age related normal values must be applied in interpreting CD4 data, and CD4% is a substantially more reliable measure of the CD4 compartment in young children.
-Careful language skill assessment adds to the recognized spectrum of neurodevelopmental symptoms as many patients have a restricted expressive language delay.

RV# 41 - *"Perinatal HIV Infection: Epidemiology and Natural History"*-

The perinatally HIV-exposed infant is at the highest risk for transmission of HIV among all risk categories prevalent today. Since transmission in this setting occurs in a well circumscribed period of time with a well defined outcome, it could serve as the best model to evaluate viral and immunological factors influencing transmission. The purpose of this study was to characterize those potential factors in terms of the rate of perinatal transmission, the disease course in the infected infant and the natural history of HIV disease in pregnancy. The specific trial goals were as follows:

1) To identify all HIV positive or HIV exposed pregnant women as early in gestation as possible and obtain blood samples in each trimester of pregnancy and at delivery. Specimens were collected in the infant through 24 months of age.
2) To characterize the natural history of pregnancy in these women both in terms of fetal complication as well as maternal outcome and contrast these findings to those being characterized in endemic areas where behavioral and environmental factors effect both outcomes.
3) To define the rate of perinatal transmission in military dependents and characterize any cofactors or features of HIV disease in the mother associated with increased frequency of transmission, fetal loss, poor maternal outcome or rapidly progressive disease in mother or infant.

Significant Findings:

31 mother/infant pairs were evaluated on 63 occasions (20 pairs in 1992) through pregnancy/delivery or early postpartum with maternal blood samples (plasma 108 vials, serum 71 vials, cells 258 vials) in the tissue repository. 5 of these infants acquired HIV. The total number of HIV positive women with children likely or known to have been exposed to HIV evaluated under these protocols (RV2, 41, 13, 16) was 97 with a total of 304 separate evaluations contributing an additional 165 vials of serum to the repository (many of these were not collected during or immediately following pregnancy). This represented a valuable collection of specimens for careful study of immune and viral characteristics contributing to perinatal transmission. Other findings included:

-Preliminary data reflected a transmission rate and disease

progression which were different from published data , i.e. less frequent and slower presentation.
-The diagnostic utility of p24, PCR and culture was defined in the pediatric setting and showed that the latter two are roughly equivalent in sensitivity and specificity (approx. 95-97%).
-Several measures of viral burden were evaluated in the pediatric population but failed to develop a method sufficiently robust to contribute to patient management.
-Important data was contributed which characterized the use and interpretation of T cell phenotype data in the pediatric population. Age related normal values should be applied in interpreting CD4 data and CD4% was a substantially more reliable measure of the CD4 compartment in young children.
-It was likely that relatively few women are identified with our current approach to HIV screening since the majority of HIV infected pregnant women have HIV negative AD spouses and routine screening at Tripler Army Medical Center failed to identify the 7 pregnant women delivered in 1991 (prevalence of 1/500 deliveries: national prevalence =1/1000 deliveries).
-It was possible concluded that the peripartum period is a particularly high risk period for acquiring HIV in view of the researcher's experience with 2 seroconversion among 8 HIV negative peripartum, exposed women.

RV 18 - *"Cutaneous Natural History of HIV-1 Disease"*-

The military population represents a unique study population in that the majority of patients are in early stages of disease due to the mandatory testing required on a bi-yearly basis. Additionally, the patients are followed with regularly scheduled visits. This dermatologic natural history protocol represented an effort to identify cutaneous findings associated with HIV-1 disease and with disease progression as measured by Walter Reed Stage. Additionally, this protocol evaluated the data derived to determine if cutaneous findings could be identified which were predictive of disease progression. For 38 months 832 HIV-1 patients in all Walter Reed stages were followed. All patients had an extensive past and present medical history taken and were given a complete physical examination; periodic follow-up visits were made and appropriate diagnostic procedures performed when necessitated.

Significant Findings:

Increasing dryness of the skin and seborrheic dermatitis were early findings. In a large percentage of patients in WR stage 1, both conditions increased in incidence and severity with disease progression. Tinea infections, condyloma, and verruca were seen early. However, with disease progression, there

was no clear increased prevalence; although these infections become more diffuse and resistant to treatment. Flares in acne vulgaris and folliculitis showed a peak in early and mid stage disease with a decreased occurrence in late stage disease. Herpes simplex infections, oral candidiasis, molluscum contagiosum, S.aureus infections, and oral hairy leukoplakia show a marked increase occurrence with advanced disease. The Investigators concluded that the presence of increasing dryness of skin and seborrheic dermatitis early in disease may be related not only to very early immune deficits, but also to metabolic dysregulation (i.e.lipid metabolism) related to upregulation of certain cytokines. The patterns of cutaneous infections might be related to the mechanisms necessary to control and/or eliminate these infections and the immune deficits present in HIV-1 disease.

RV 35 - *"The Investigation of the Cutaneous Microflora Found in HIV Infected Patients as it relates to the Onset, Severity, and Progression of Disease"* -

The purpose of this second dermatologic protocol was to document skin changes associated with HIV disease, both clinical and histopathologic, and to follow these changes with progression of disease, with emphasis on histopathologic studies to identify both clinical and subclinical infections. The study was completed with 200 HIV-1 positive patients and 200 HIV-1 negative control patients.

Significant Findings:

Results from this protocol included the identification of changes in microflora of HIV-1 positive patients, the identification of increase in Staph Aureus carriage diffusely over the skin surface in all stages of HIV disease and the increase localized cutaneous infections with increase in progression and soft tissue, and Staph Aureus sepsis in late stage disease. Findings from this study led to the development of treatment protocol for cutaneous Staph Aureus carriage and a protocol to determine possible enterotoxin production resulting from Staph Aureus carriage in HIV-1 infected patients and it's relation to disease process.

RV 22 - *"The Clinical Presentation of HIV Infected Patients at Walter Reed Army Medical Center"* -

This protocol entailed a chart review of 127 patients to evaluate clinical and laboratory data on HIV infected patients.

Significant Findings:

CD4 counts decreased with time, in an exponential fashion and that life is prolonged with Zidovudine and/or pneumocystic prophylaxis. With these therapies, CD4 cell counts do not correlate with prognosis. This protocol made the recommendation that other prognostic markers were needed in these patients.

RV 44 - *"The Effect of HIV Infection on the Clinical Manifestations and Response to Treatment of Syphilis"*-

This protocol had the purpose of defining the risk factors and demographics regarding syphilis in the United States. 14 military patients enrolled and there were no findings as of March 31, 1993.

RV46 - *"Evaluation of Propylthiouracil in the Prevention of Cachexia in AIDS patients"*-

This protocol was designed to determine if propylthiouracil (PTU) therapy could decrease weight loss in AIDS patients by decreasing serum levels of triiodothyronin, which is a catabolic thyroid hormone. This protocol was closed early to enrollment due to the stable character of the military population, i.e., decreased development of cachexia. No results were available as of March 31, 1993.

RV 48 - *"Changes in Peripheral Blood Lymphocytes Counts, Subsets, and Activation by Delayed Hypersensitivity Skin Testing in HIV Seropositive and Seronegative Individuals"* -

This study was designed to examine the effects of delayed hypersensitivity skin testing on the peripheral blood lymphocytes, in order to gain greater knowledge about the effects of DTH skin testing on the values of lymphocyte surface markers in HIV positive individual compared to HIV negative individuals. Data from this protocol was in the final stages of data analysis.

RV 64 - *"Evaluation of Cardiac Function in Patients with HIV-1 Infection"* -

This protocol had the objective of identifying the incidence of myocarditis associated with HIV, the typical Walter Reed stage associated with it and any association with common Opportunistic Infections of HIV. It was hoped that by determining the natural history of HIV-1 associated cardiac dysfunction, the prognostic significance of a given cardiac abnormality could be determined. This information will aid the health care provider in making medical management and

military administrative decisions.

Significant Findings:

Over 250 patients participated in this study, data to date suggested that echocardiographic abnormality of left atrial dilation, pericardial effusion, LVH and mitral regurgitation occurred more frequently in the HIV infected.

RV 66 - *"Evaluation of the Efficacy of U.S. Army HIV Education/Prevention Strategies"* -

This protocol was a process evaluation of the Army HIV education program at 41 installations.

Significant Findings:

Thirteen installations were identified as having promising programs, and of these thirteen, three installations were identified as having potentially successful HIV prevention programs through the use of surveys, interviews with program staff, and observation of the intervention. Findings from this Phase I evaluation were utilized in planning a Phase II study. The Phase II study will utilize a pre/post test experimental design to measure the HIV risk reduction impact of interventions identified in Phase I.

An important element of Objective One of this mission area was to develop and apply methods to measure behaviors associated with the current risk of HIV infection in military and military associated populations. This element focused on developing study methods that could elicit accurate information regarding behaviors associated with infection risk; applying methods in field studies of risk associated with acquisition of HIV infection among applicants for military service, military members, and other care beneficiaries; analyzing, summarizing, and reporting data to document significant behaviors associated with current infection risk (overall and in defined subgroups) and monitoring trends of behavior associated risk over time. This element of Objective One was important for several reasons. As the epidemic evolves in the general U.S. population, it is likely that increasing numbers and proportions of HIV infections among males will result from sexual contact with females and vice versa. This trend could be detected and documented in a timely fashion by this research objective. In addition, trends of incident infection risk in age, racial/ethnic, and geographically defined subgroups could be used to assess the effects of intervention efforts and to define needs for modified or new

intervention approaches.

Knowledge of trends of sexually transmitted diseases and pregnancies among service members will allow more precise assessments of trends of sexual behaviors among active service members, by demographic subgroups and by geographic area of assignment. One response to this element has been the implementation of a protocol focused on patterns of Sexually Transmitted Diseases:

RV56 - *"An analysis of Sexually Transmitted Diseases (STD) patterns at Ft. Bragg, NC "-*

This protocol was originally conceived to utilize the Fort Bragg Preventive Medicine Service STD data collection system and its historical files for other Behavioral Intervention studies. To date, this protocol has provided data on STD rates at Ft. Bragg for use as background information for other protocols.

Significant Findings

Data collected from reviews of 50,060 visits, since 1984, represented the most comprehensive current information on STDs in the United States Army. 5,000 to 8,000 patients per year have been entered into this database. The utility of this database for providing outcome measures was apparent, and use of this was incorporated into the design of future behavioral interventions protocols at Fort Bragg.

This research area also looked at the incidence, distribution, and natural history of HIV infection among the military in other countries. Data collected from a study of the military population in Thailand proved quite valuable in making the determination that this Nation was well-suited for two proposed Vaccine trials for the prevention of HIV.

RV 70 - *"Prevalence and Incidence of HIV-1 Infection among Young Men in the Royal Thai Army (Tahan Gan)" -*

The purpose of this protocol was to assess temporal, geographic and demographic correlates of HIV-1 infection among young men entering the Royal Thai Army (RTA), to directly measure the rate of incident HIV-1 infection among young Thai men in the RTA during their two year service obligation, to explore the feasibility of geographically-circumscribed cohorts as possible future participants in field efficacy trials of HIV-1 prophylactic vaccines in Thailand, and to identify a population of recently HIV-1

infected Thais for recruitment into other protocols. This protocol accrued prevalence data on 102,000 recruits and incidence data on 16,800 recruits.

Significant Findings:

Sustained levels of HIV-1 incidence of 3-8% per annum were common in Northern Provinces of Thailand

Several specific sites/cohorts in Thailand were attractive for intensive development for future participation in field efficacy trials

Conclusion

The military population provided a unique and unparalleled opportunity to understand risk factors (both biological and behavioral) for HIV transmission, disease progression, health care costs and intervention methods for preventing HIV infection, HIV related illness, and HIV disease progression. This mission area took advantage of this unique opportunity and addressed important questions that could lead to interventions in this population. This MAP also was successful in the development of a well organized and well maintained epidemiologic and clinical data base and developed extensive information on risk factors for HIV infection. With its broad scope but programmatically defined objectives, this MAP served as a valuable resource databank for both present and future human use protocols.

Future Studies Planned

Surveillance databases will be maintained in support of screening programs conducted among populations representing all geographic areas of the country and a broad range of demographic subgroups. These include civilian applicants for military service, members of the active and reserve components of the military services, and family members who are beneficiaries of care in military systems. Data from seroprevalence screening among applicants for military service will be analyzed to assess seroprevalence and demographic and geographic correlates of infection risk. Indirect estimates of incidence and acceleration rates will be made using "age effect" and birth-year specific temporal trend effects. Determinants of infection risk that may have different effects over time will be controlled in analyses of incidence and acceleration rates by using stratified and multivariate modeling analytical methods. For populations that are routinely serially screened over time (e.g., members of the active Military Forces), incidence and acceleration rates will be

directly estimated based on the number of seroconversions per total person years of time from an initial screening test (as a military applicant or on active duty) to the most recent follow-up test. The method has been used in the past by Dr. John McNeil and Garland, *et al*, to estimate infection incidence rates in the active Army and Navy respectively. Similar methods will be used to estimate incidence rates in the Reserve components and to estimate changes in incidence rates over time in the active components of the Army and the other services. Methods to track the geographic spread of the infection epidemic will be further developed by Gardner to assess the geographic distribution of the infection epidemic and to estimate the rate and determinants of geographic spread over time.

A survey of the outpatient medical records of a sample of active service members will document recent trends of STDs and pregnancies as well as their demographic and geographic correlates. Results of this survey will be correlated with similar data regarding HIV infection risk to make assessments regarding effects of current intervention programs and needs for modified or new intervention methods.

Longitudinal clinical follow-up studies of natural history of disease will continue. Clinical evaluation data that are available in the operational databases of the Services and the Foundation will be used to assess rates and characteristics of disease progression. When feasible, data from all databases will be analyzed together to increase precision of parameter estimates and to validate findings from analyses of data from individual databases. Data regarding hospital discharges with discharge diagnoses (e.g., IPDS (individualized patient discharge system) in the Army) will be used to compare morbidity and mortality experiences of individuals who are HIV infected versus uninfected controls. Mortality experience of HIV infected individuals, including applicants for military service and members of the active and reserve components of the Services, will be assessed using resources such as the National Death Index and the Defense Manpower Data Center. A study is planned for systematic follow-up of all individuals diagnosed with HIV infection while on active duty and currently considered "lost to follow-up."

Several modeling approaches will be applied to military data. For example, an empirical modeling approach has been developed by Miller, *et al*, and has been used to project the short and long term course of the HIV infection epidemic (and associated costs) in the Army, the DoD, and in family members (Pettet, et al). These models will be more fully developed and will be applied to monitor trends, and to conduct sensitivity analyses (that is, to estimate effects over the short and long term of changes in values

of critical factors, conditional on values of other critical factors remaining constant). In addition, models will be developed to assist planners and policy makers to refine and update screening policies (e.g., intervals) and to efficiently plan for and allocate resources. Modeling techniques will also be used to quantify rates of decline of T4 cells (to model a T4 lymphocyte decline function), to revise overall projections based on response to therapy data derived from other sources, and to adjust indirect estimates of incidence rates in military applicant populations.

C. BEHAVIORAL MEDICINE MISSION AREA

LYDIA TEMOSHOK, Ph.D., DIRECTOR*

MAP SUMMARY: The primary goal of the Behavioral Medicine Mission Area was to conduct scientific behavioral research for the prevention of exposure, transmission and progression of HIV infection and disease.

Protocols for Human Studies

Protocol #	Protocol Title (Abbreviated)	Principal Investigator
**	Army Wide HIV/AIDS Survey	Temoshok*
RV26	Tri-service HIV Biopsychosocial Study	Temoshok*
RV4	Neurobehavioral Consequences of HTLV-III Brain Infection	Salazar

* Foundation Principal Scientist
**Funded under the basic Grant by the Office of the Surgeon General, Dept. of the Army

BEHAVIORAL MEDICINE MISSION AREA

Overview

Over the past five years,the Department of Defense (DoD) utilized a multi-faceted approach to the goal of reducing the incidence of new HIV infections. One important facet of the approach was to address behavior modification of infected individuals. Because it is many times more cost-effective to prevent HIV than to treat it, this further reinforced the necessity for researching methods which could modify the behavior of uninfected individuals. This Mission Area incorporated the DoD charge to address these behavioral issues, effectively concentrating on the prevention of HIV exposure, transmission, and neuropsychiatric consequences. Additionally, scientists within this Mission Area worked closely with other HIV research program scientists in the capacity of advisors and collaborators on Behavioral Medicine related protocol issues which impacted on Chemotherapy, Vaccine and Epidemiology trials.

Research Goals and Objectives

In order to achieve the mission, comprehensive research goals were set forth to identify the targets of and outcome measures for biopsychosocial interventions that would:

(1) Reduce the rate of exposures to HIV among uninfected military.

(2) Reduce the rate of HIV transmission by infected military.

(3) Minimize the neuropsychiatric and psychosocial consequences of disease progression among infected military.

(4) Maximize the occupational longevity and productivity among infected military

(5) Maximize compliance with medical treatments and experimental protocols among infected military and other populations as specified by the MMCARR.

The primary efforts initiated to establish the necessary prevalence estimates and databases to meet these objectives consisted of two large research studies, one for seronegative Army personnel; the U.S. Army-Wide HIV/AIDS Survey (AWAS) and one for HIV-infected military medical beneficiaries in all military services, the Tri-Service HIV Biopsychosocial Study (RV26).

Briefly, the U.S. Army-Wide HIV/AIDS Survey (AWAS) was administered anonymously to over 18,000 active duty Army personnel at 30 installations in the U.S. and Europe. The purpose of the survey was to assess knowledge, attitudes, and behaviors that would be important in predicting the future behavioral potential for HIV exposure.

The Tri-Service HIV Biopsychosocial Study was a comprehensive, multi-method study designed to assess behavior related to the risk of HIV-infected (HIV+) individuals transmitting the virus to uninfected individuals. The study had as its centerpiece a survey of transmission risk behaviors administered anonymously to HIV-infected individuals seen at five military medical facilities (Walter Reed Army Medical Center, (WRAMC), National Naval Medical Center, Bethesda (NNMC), Wilford Hall Medical Center, (WHMC), Balboa Naval Hospital, San Diego, and Womack Army Medical Center, Ft. Bragg, N.C. (WAMC). Other components of the study included: psychosocial questionnaires that assessed multidimensional psychosocial factors, administered at WRAMC, NNMC, WHMC, Balboa Naval Hospital; a comprehensive neuropsychological assessment, administered at WRAMC, NNMC, and WHMC; and a psychiatric interview, originally administered at WRAMC, NNMC, and WHMC; and currently administered only at WHMC. In addition, a neurobehavioral addendum to the larger study was conducted with a small subsample of HIV+ individuals. Finally, as a recent addition to the psychosocial questionnaires, data was collected concerning expectations of and perceptions about treatment and therapeutic protocols as these psychosocial factors relate to adherence to clinical trials. Other efforts of the Program included:

1) the development of four intervention protocols that are based on the results of the AWAS and the Biopsychosocial Study;
2) the maintenance and oversight of a centralized STD database at Ft. Bragg, N.C.;
3) a study of neuropsychological functioning and job performance in military aviation personnel; and
4) a survey of military obstetricians-gynecologists' affective reactions to clinical uncertainty and discussing HIV/AIDS during routine gynecologic care.

The intervention studies were designed to evaluate the safety, behavioral responsiveness, and efficacy of several behavioral intervention strategies developed for the purpose of reducing the risk of exposure to HIV or transmission of HIV by military medical beneficiaries. These studies are well into the development phase and are planned for implementation by Fall, 1993.

Most of the results discussed below have been reported at scientific meetings and/or journal publications and book chapters. A complete listing of published papers, abstracts, chapters, and scientific and military reports in which these data were presented can be found in the Final Report Bibliography.

The AWAS, RV 26 and RV4, a neurological protocol, were three major components of the research conducted in this mission area and are described in detail below:

Army-Wide HIV/AIDS Survey

The Army-Wide HIV/AIDS Survey (AWAS) was designed as an anonymously administered self report survey with the goals of estimating the prevalence of HIV exposure risk-relevant behaviors; identifying knowledge, attitudinal, sociocultural, behavioral, and situational factors associated with HIV exposure potential; and, identifying factors associated with the occurrence of STDs in an ethnically and geographically diverse, sexually active population. The survey was pilot tested on a sample of 546 soldiers assigned to randomly selected military units on one U.S. Army installation. Results of the pilot testing were used to finalize the content and format of the AWAS.

a. Methods:

The survey sample size was calculated to provide reliable estimates of attitudes, knowledge, and behaviors of U.S. Army personnel world-wide. It also was designed to be large enough to increase precision of statistical estimates from demographic subgroups within the Army. In addition, the sample was required to be large enough to accommodate an expected 75% response rate. The sampling plan comprised a multistage stratified probability cluster design. The sample has statistical validity for, and is representative of the Army in 1991 after the Operation Desert Storm deactivation and return of units to their home bases.

The survey's primary sampling unit, or PSU, was defined as a base with $\geq$ 1,000 assigned personnel or a cluster of geographically proximate bases with fewer than 1,000 personnel. PSUs were stratified according to location (CONUS or OCONUS) and by primary base mission (combat, combat support, or combat service support).

In order to assure that individual soldiers from these PSUs had similar odds of being selected to complete the survey, the sample design was conducted so that PSUs were selected from each stratum with probability proportionate to PSU size. At the end of the first sampling stage, a total of 17 PSUs were selected, comprised of 30 individual bases.

After Primary Sampling Units for the survey were randomly selected, individual military units within those PSUs were classified as combat units, combat support units, or service support units. These Secondary Sampling Units (SSUs) for the survey were then randomly selected with probability proportionate to unit size within each stratum. A total of 127 SSUs were randomly selected within the 17 PSUs.

A total of 18,072 usable surveys were obtained. This represents 95% of those soldiers present for duty, and 74% of those originally assigned to sample units at the time of the study. Survey results were weighted based on an individual soldier's probability of selection as a result of the two stage random probability design, on the individual's unit response rate, and on the proportion of the unit deployed away from the assigned primary sampling unit. Beliefs of survey respondents regarding the survey's anonymity were encouraging. Fewer than 8% had strong concerns about the anonymity of the survey; approximately 90% said they answered questions about sexual behaviors and drug use honestly.

The weighted sample ethnic demographic composition was representative of the U.S. Army. The sample was 58% white, 26% African-American, 7% white Latino-American, 3% black Latino-American, 2% Asian-Pacific Islander, and 2% Native American. Fewer than 1% of surveys had missing respondent ethnicity data. The weighted sample gender breakdown (88% men and 11% women) is also representative of the entire U.S. Army.

The content of the survey contained information about demographic and descriptive characteristics of the respondents, HIV-related knowledge, attitudes and perceptions of HIV exposure risk, social-environmental influences related to HIV exposure risk potential, additional health behaviors such as drug and alcohol use and general risk taking, and descriptive information about sexual partners and sexual practices.

B. Selected Findings:

1. Based on findings from the Army's epidemiological seroconversion risk factor study, eight behavioral risk factors were identified as increasing a soldier's likelihood of exposure to HIV. Forty-two percent of the study population had at least one of these behavioral risk factors. The behavioral risk factors for HIV exposure potential included:

a. One or more "one-night stands"
b. Five or more sexual partners
c. One or more male sexual partners known/suspected of having sex with other men
d. One or more "anonymous" sexual partners

e. One or more prostitutes as sexual partners
f. One or more intravenous drug users as sexual partners in the past two years
g. One or more sexual partners who had HIV/AIDS
h. One or more occasions of sharing needles in the past two years

These behavioral risks were amplified, theoretically, by two factors. The first was not always wearing a condom with partners who were "one-night stands," prostitutes, or "anonymous." The second amplifier was whether these "riskier" kinds of partners were from U.S. cities or countries with the highest HIV/AIDS prevalence, according to 1991 figures from the Centers for Disease Control.

2. In addition to behavioral risk, biological markers for HIV exposure potential were identified. Having had a sexually transmitted disease (STD) indicated that a person had engaged in unprotected sex with someone who had a STD. Thus, a STD was considered a "marker" of that behavior. Similarly, if either partner bled during sex (and this was not the result of a woman menstruating), this was considered a possible indicator of a lesion associated with a STD. The third biological marker was whether the sexual partner had genital or anal sores, which are also suggestive of having a STD. All three markers were demonstrated in the Army's seroconversion risk factor study and/or in civilian studies to increase susceptibility for HIV infection.

3. Combining behavioral risk factors and biological markers, it was found that approximately 50% of the study population was determined to be at "some" level of risk for exposure for HIV, with almost 16% of the study population at "high risk" for HIV exposure by virtue of having four or more risk factors or markers.

4. Using the weighted data, three multivariate, logistical regression models were developed separately in order to predict association with having a behavioral risk factor, having a STD, or having one or both of the other two biological markers for HIV exposure. Within each model, ratios were calculated to determine those factors that would be significantly "protective", and those factors that would increase a soldier's likelihood of having a behavioral risk factor, having a STD, or having one or both of the other biological markers for HIV exposure potential.

5. Being older was protective for all three models. Being more educated was protective for having a behavioral risk factor only. Interestingly, being female was protective for having a behavioral risk factor, but females were twice as likely to have a STD than were males. Not living with one's partner or spouse increased the likelihood of having a behavioral risk factor, having a STD, or having one or both biological markers. Ethnicity

was significantly associated with higher relative risk for having a STD for African-Americans and Black Latino-Americans. Having had more than one STD within the last 2 years and having sought HIV testing outside the military were both associated with having the biological markers of bleeding during sexual intercourse and/or having partners with genital/anal sores.

6. Never refusing the opportunity to engage in sex increased the odds of having a behavioral risk factor. Perceiving one's chances of HIV infection as somewhat or very likely, and believing that it was difficult to ask one's sexual partner to get tested for HIV before having sex, increased the odds of having both a behavioral risk factor and a STD. Increased knowledge about condoms, strongly negative attitudes about condom use,greater knowledge of preventive behavior, and somewhat agreeing with the statement that soldiers should not have sex to protect themselves, increased the likelihood of having a STD. Having irresponsible prevention attitudes above the median for the survey--for example, believing that using condoms is up to one's partner, or that "sex without condoms is worth the risk of getting HIV"-- was associated with greater likelihood of having one or both of the other biological markers, as was being distrustful of the military to provide accurate HIV/STD information.

7. Always carrying a condom (or having one available) was predictive of having a behavioral risk factor. Having more multiple, simultaneous sexual partners was significantly associated with increased risk of having a behavioral risk factor and having one or both of the other biological markers. Having one or more periods of sexual "binging" within the last 12 months was associated with increased risk in all 3 models. Having used any alcohol in the last 12 months, looking for sexual partners in high risk places (e.g., public bathrooms), and acknowledging one or more incidents of non-menstrual bleeding during sex were all predictive of having a STD. Using condoms less than always with casual partners was also associated with having one or both of the other biological markers. Engaging in manual sex only with >50% of one's partners was protective against having a behavioral risk factor and having one or more of the other biological markers. Always asking new sexual partners to get tested for HIV was highly protective against having a behavioral risk factor.

8. Having used any kind of drugs in the last 12 months, having drunk alcohol during the last time one had sex, and having gone out to seek new sexual partners increased one's likelihood of having a behavioral risk factor. Those who strongly agreed that their behavior and decisions were influenced by friends and who viewed their friends as having multiple sex partners or having paid for sex also were at increased odds for having a behavioral risk factor than other respondents. Having a strong military career orientation was associated with decreased odds of having a

STD.

9. Those individuals with more than 11 sexual partners during their lifetime, who had sexual partners in geographic areas with high HIV prevalence, had (non-spousal) sex partners either when deployed or when on TDY, or had other sex partners within the military were all at increased odds of having a behavioral risk factor. Having more than 11 lifetime sexual partners, having partners living in high HIV prevalence areas, having non-spousal sexual partners while deployed or sexual partners within the military, having had sex partners with genital sores and sex partners suspected of having sex with other men or of being an intravenous drug user were all significantly associated with having one or both of the other biological markers.

C. Implications

These (and other) data were used as the basis for identifying foci for behavioral interventions designed for individuals at high risk for exposure to HIV. The research intervention protocol: "Prevention of Exposure to HIV and Other Sexually Transmitted Disease (STDs) in a Seronegative Military Population: A Comparative Study of the Safety and Efficacy of Intensive STD/HIV Prevention Interventions" (RV81) is currently under development. It will serve as the major vehicle for transforming these research findings into planned future behavioral interventions, and then assessing the safety, behavioral responsiveness to and efficacy of the interventions in reducing behavioral risk for exposure to HIV.

RV-26 Tri-Service HIV Biopsychosocial Study

The Tri-Service HIV Biopsychosocial Study contained four distinct components: the anonymously administered Seropositive Behavior Survey (SBS), the Psychosocial Questionnaires (PSQ), the Structured Clinical Interview for DSM-IIIR (SCID), and the Neuropsychological Assessment.

A. Seropositive Behavior Survey (SBS):

The SBS was a self-report survey of HIV transmission-relevant behaviors, knowledge, and attitudes which was administered anonymously to 1104 HIV infected U.S. military medical beneficiaries. The objective was to estimate the prevalence of transmission-relevant behaviors in HIV infected individuals, in order to understand the factors underlying these transmission risk behaviors, so that effective prevention programs might be developed.

1. Methods:

All HIV seropositive military medical beneficiaries (>18 years) who were available to be contacted were invited to participate. Exclusionary criteria were unwillingness to participate, or being too sick to participate. Because of some differences among the sites regarding to recruitment procedures, the Principal Investigators chose to examine representativeness of the sample collected by comparing the demographics from our sample of those completing the SBS to all HIV infected (HIV+) military medical beneficiaries enrolled in MMCARR's most encompassing research protocol, the medical natural history study (RV1). The representative profile of the SBS participant was an active duty, enlisted, never married, Caucasian male with a mean age of 31. This profile paralleled that of the HIV seropositive military sample. The actual demographics of SBS respondents generally paralleled most demographic data from the comparison group of HIV+ military medical beneficiaries enrolled in RV1. The sole exception was "rank", for which the SBS had fewer respondents from lower enlisted ranks (E1-E4) and more respondents from the higher enlisted ranks (E5-E9).

The questionnaire was designed so that it progressed from the least to the most sensitive items in an attempt to reduce response bias. Measures in the main section assessed the following areas: standard demographics, including military relevant information such as number of days on deployment, leave or TDY during the previous 6 months; general health information including the date of HIV notification, most recent Walter Reed staging, and a history of STDs during the previous 12 months. Questions about associated risk behaviors including drugs and alcohol usage were asked in terms of the past 30 days, the past 12 months, as well as lifetime usage. Another section inquired about HIV knowledge, attitudes and situational beliefs, including: social influences, such as peer norms for condom use;HIV/AIDS knowledge and educational exposures; attitudes towards HIV/AIDS and prevention, such as attitudes toward condom use and safer sex negotiation.

The section measuring sexual transmission risk activities and practices inquired about the respondent's five most recent sexual partners during the last 6 months. Participants completed questions that described specific types of partner, and recorded specific risk-relevant sexual behaviors during the previous 6 months. Transmission related questions inquired about condom

use, as well as the partner's behavior (STD history, drug use, and HIV testing history). Finally, questions were asked about non-penetrative sexual activities, and bleeding during intercourse that was not due to menstruation. All sexual activity items were stated in conventional language for types of sexual practices and partners.

2. Selected Findings:

Preliminary data analyses on a sample of the first 767 respondents were performed to identify factors associated with HIV transmission potential. Respondents were assigned according to their highest transmission-risk potential relationship to five separate transmission potential categories based on their potential risk (no risk to high risk) of infecting HIV seronegative sexual partners. In order of transmission potential risk, the categories were: a) no sex or only manual sex (11%); b) penetrative vaginal, oral or anal sex only with HIV seropositive partners (15%); c) only oral sex with HIV seronegative partners (7%);d) always used condoms with HIV seronegative partners (25%); and e) inconsistent condom use with HIV seronegative partners (29%).

Results from analyses comparing these five groups suggested that HIV infected respondents who had unprotected penetrative sex with HIV seronegative partners differed significantly from most other HIV infected individuals in the following ways: they were more likely to have had friends who engaged in unsafe vaginal or anal sexual practices, had no close friends or family members who were also HIV infected, and had fewer people with whom they could talk about concerns related to HIV infection and AIDS. Further, they were more influenced than most other groups (except those reporting only HIV infected partners) by their sexual partners, perceived their sexual partners to be more negative about preventive measures, had a general disregard for personal health, and had higher scores on general risk-taking than all other groups. These respondents tended to drink alcohol more often and with greater intensity than other HIV infected individuals. They were not only at increased risk for transmission to uninfected partners, they were also less likely to inform sexual partners, and know their partners' HIV serostatus. Finally, these respondents had greater difficulty with safer sex negotiations, expressed more negative attitudes towards condoms, reported irregular use of condoms, had poor sexual impulse control, and

were more likely to report periods of increased sexual activity.

Similarly, elevated transmission risk potential was found with respondents who had only oral sex with HIV seronegative partners in the previous 6 months. This group was similar to those who used condoms inconsistently for vaginal and anal sex with HIV seronegative partners, but differed significantly from most other HIV infected individuals, in that respondents who had only oral sex with HIV seronegative partners had both more non-steady partners and more sexual partners overall. They also were less likely to inform sexual partners of their serostatus. Finally, this group was less likely to recommend safer sex practices for sexual partners.

3. Implications:

Preliminary data analyses strongly suggested that despite current HIV transmission reduction education programs currently implemented in the military, HIV infected individuals were continuing to engage in clinically significant levels of transmission risk-relevant behaviors. In response to these findings, (and utilizing other data from the HIV Biopsychosocial Study), the Program is in the process of developing and piloting a tri-service research intervention study, the goals of which are to develop and evaluate the safety and efficacy of four intervention technologies to reduce transmission risk-relevant behavior in military medical beneficiaries. This protocol, RV 82, is entitled "Phase I/II Study of Safety, Behavioral Responsiveness, and Efficacy of Behavioral Interventions in HIV Seropositive Military Medical Beneficiaries".

B. Psychosocial Questionnaires (PSQs) and Structured Clinical Interview for DSM III-R (SCID):

1. Methods:

Psychosocial and psychiatric data were collected from military medical beneficiaries (MMBs) for the purposes of documenting levels and manifestations of psychological dysfunction that would occur with HIV-seropositive individuals and interfere with their social/occupational functioning. Two major data collection methods were utilized: (1) the use of self-report, standardized questionnaires,and (2) a standardized psychiatric interview (Structured Clinical

Interview for DSM-IIIR [SCID]; Williams, Gibbon, First, Spitzer, Davies, Borus, Howes,Kane, Pope, Rounsaville, & Wittchen). Questionnaires and SCIDs have been administered at participants' consecutive staging evaluation visits at the major medical centers. The range of time between visits was approximately 5-24 months. However, in general, those participants still on active duty were seen at 6-8 month intervals and those on temporary or permanent retirement lists were seen at 12-18 month intervals.

The core questionnaire measures which were administered throughout RV-26 encompassed a number of domains. These included: depression (Beck Depression Inventory; Beck & Steer, 1987), anxiety (Spielberger State Anxiety Inventory; Spielberger, 1983), transient mood states (Profile of Mood States; McNair, Lorr, Droppleman, 1981), coping styles (Cortauld Emotional Control scale [Watson & Greer, 1982]; Multidimensional Health Locus of Control scale [Wallston, Wallston,& DeVellis, 1978]; Temoshok Coping Vignettes), and social functioning (short-form version of the UCLA Loneliness scale; Hays & DiMatteo, 1987). These standardized questionnaires have well-established reliability and validity. Most of these measures were used in civilian studies of HIV-infected individuals, providing comparability with the Multicenter AIDS Cohort Study (MACS) and other important cohort studies. They also were used widely with other populations, including those with medical illnesses, or conditions, lending comparability to other disorders and life circumstances.

A total of 1043 HIV-seropositive military medical beneficiaries (MMBs) completed the questionnaires at Time 1 in RV-26. Those completing Time 2 questionnaires number 597; Time 3 = 223 respondents; Time 4 = 71 respondents; Time 5 = 12 respondents. Several questionnaires were originally included in this battery of instruments but were discontinued because they were empirically redundant with other measures (e.g., Symptom Checklist-90 Revised [Derogatis, 1979]; Schaefer, Coyne, & Lazarus (1981) Social Support Inventory; Zich & Temoshok Social Support scale [Zich & Temoshok, 1987] and Spielberger Trait Anxiety Inventory [Spielberger, 1983]; or unrelated to important psychosocial outcomes (Kobasa Hardiness Scale [Kobasa, Maddi, & Kahn, 1982]). Each of these measures used in the early phases of the study was completed by 400-700 individuals, depending on the measure, and typically completed only at Time 1. Several questionnaires were added to the study to assess specific issues that appeared important to our

population. These included the Perceptions of AZT questionnaire (Pivar & Temoshok, 1989) and a religious coping questionnaire(Pargament, Grevengoed, Hathaway, Kennel, Newman, & Jones, 1988). These later measures were completed by 850 individuals at Time 1, 324 at Time 2, 77 at Time 3, and 8 at Time 4. Most recently, a questionnaire was added to investigate attitudes and beliefs relevant to participation in vaccine trials. This measure was adapted from the AZT questionnaire and was completed by 67 participants in the gp160 trials.

SCIDs were completed at least one time by 870 individuals at the WRAMC and WHMC (the SCID was never initiated at NNMC). Longitudinal data from the SCID were available at Time 2 for 551 individuals, 217 at Time 3, 65 at Time 4, and 4 at Time 5. The SCID incorporated the Hamilton ratings of depression (Hamilton, 1960) and anxiety Hamilton, 1959).

2. Selected Findings:

Psychosocial distress appeared greatest at time of notification and when infected military personnel progress to Walter Reed Stage 3, a time when they typically are placed on Temporary Disability Retirement and become eligible for treatment with AZT, both very concrete signs of disease progression. This was also a time when our data indicated that religion became more important in coping with HIV-related problems. Depression was associated with concurrent alcohol use problems, social isolation, and poorer occupational functioning. Depressive behaviors also were more common in divorced and unemployed MMBs. As in studies with other populations, suicidality (i.e., suicidal thoughts, gestures, and in rare cases, attempts) appeared related to factors such as substance abuse, chronic problematic patterns of adjustment, and past, as well as present evidence of serious depressive symptomatology. Psychiatric disorders tended to be chronic over time, with participants' current diagnoses tending to correspond to problems they experienced before becoming HIV infected. Depression, anxiety and the use of dysfunctional coping (i.e., helpless/hopeless style) were associated with gender, such that men showed more negative affect, as well as more dysfunctional coping.

MMBs with more social support tended to be more open in expressing negative feelings, more likely to be married than single; and less depressed or anxious. On the contrary, socially isolated MMBs reported low levels of support, more depression and anxiety, less open

expression of negative feelings, and more identification with dysfunctional coping styles such as stoicism and helplessness/hopelessness.

From a methodological perspective, interview measures of depression and anxiety from the SCID were highly correlated with self-administered questionnaires, suggesting the utility of relying on the less expensive questionnaire technique for future study with this population. Persons taking AZT tended to see its psychological benefits as the most clear and obvious. Specifically, they saw AZT as a source of hope and some sense of control over their situation. AZT-related side effects such as nausea, vomiting and headaches appeared more severe in the presence of higher levels of anger, anxiety, and depression.

Adherence to physician-prescribed AZT appeared to be influenced by a number of factors. Those who discontinued AZT reported more feelings of hostility, feeling they had been pressured more by their physicians to take the drug, and reported more side effects. They also were identified with a more stoic coping style. Those who altered their dose without discussing it with their physicians reported more depression, more AZT side effects, more negativity regarding the drug, and a more assertive (adaptive) coping style. They also were more likely to be later stage patients.

Positive perceptions of the therapeutic vaccine trials were shown to be related to feeling better informed and expecting fewer side effects. Concerns about side effects were greatest in those patients who identified most with a stoic/detached coping style.

C. Neuropsychological Assessment:

1. Methods:

A total of 766 HIV-infected and 124 seronegative control participants were assessed for this study. Of those HIV positive individuals, 501 were assessed twice, 214, three times, 54 four times, and 2 five times. Twenty-three seronegative individuals received second assessments and 2 received a third assessment.

Two neuropsychological batteries, described below, were administered on alternating visits. For HIV positive participants, Battery A was administered at baseline and at odd-numbered visits. Battery B was administered at

even-numbered visits. Half of the HIV negative participants began with Battery A, and half began with Battery B. On follow-up evaluations, administration alternated between batteries, for a total of three visits (i.e., HIV negative subjects received either A-B-A or B-A-B).

a. Neuropsychological Measures:

A combination of standard and experimental neuropsychological measures were selected, based upon prior research at WRAMC and WHMC, to:

1) provide assessment of all realms of cognitive and motor function;
2) assess in depth those areas most likely to be affected at the early stages of HIV disease.

Two alternating batteries were used, maximizing the number of measures administered, while not increasing evaluation time further. These two components will be described in greater detail below.

Battery A, requiring 3 hours, included measures of estimated intellectual level (American version of the National Adult Reading Test [Grober & Sliwinski, 1991]; Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale-Revised [WAIS-R, Wechsler, 1981]); attention and speed of information processing (Digit Span and Digit Symbol subtests of the WAIS-R [Wechsler, 1981]; Visual Memory Span subtest of the Wechsler Memory Scale-Revised [Wechsler, 1987]; Trail Making Test[Reitan & Wolfson, 1985]; Digit Vigilance [Heaton, Grant, & Matthews,1991]; Paced Auditory Serial Addition Test [PASAT; Gronwall, 1977]; Simple and Choice Reaction Time tasks [Martin, et al., 1992]); motor functions (Strength of Grip [Reitan & Wolfson, 1985]; Grooved Pegboard Test [Klove, 1963]); language skills (Boston Naming Test [Kaplan, Goodglass, & Weintraub, 1983]; Controlled Oral Word Association Test [Lezak, 1983]; Vocabulary subtest of the WAIS-R [Wechsler, 1981]); visuospatial skills (Block Design subtest of the WAIS-R [Wechsler, 1981];Standardized Road Map Test of Direction Sense [Money, 1976]); learning and memory (Digit and Visual Memory Supraspan procedures [Benton, Hamsher, Varney, & Spreen, 1983]; Story Memory Test [Heaton, Grant, & Matthews, 1991]; Figure Memory Test [Heaton, Grant,

& Matthews,1991]; Rotary Pursuit [Heindel, Butters, & Salmon, 1988]); and problem-solving (Category Test [Reitan & Wolfson, 1985]).

Battery B, requiring 2.5 hours, included measures of attention and speed of information processing (Arithmetic subtest of the WAIS-R [Wechsler, 1981]; PASAT [Gronwall, 1977]; Simple and Choice Reaction Time tasks[Martin, et al., 1992]; Posner Spatial Cuing Task [Posner, Cohen, & Rafal, 1982]; Sternberg Memory Search Task [Sternberg, 1966]); motor functions(Finger Tapping Test [Reitan & Wolfson, 1985]; Grooved Pegboard Test[Klove, 1963]); learning and memory (California Verbal Learning Test [Delis, Kramer, Kaplan, & Ober, 1987]; Rey-Osterrieth Complex Figure Test [Lezak, 1983]).

b. Computerized Cognitive Tasks:

(1) A subset of tasks from COGSCREEN (Kay, in press), a group of computerized cognitive tasks which evaluate accuracy and reaction time in several different cognitive realms, were subsequently added to Battery B in November, 1991, at the Washington, DC sites. The tasks were added because they offered potential utility as an early screening tool and assessed areas particularly relevant to issues of job performance.They included measures of attention (Visual Sequence Comparison Divided Attention Task); spatial awareness (Mannikin Task); and short term learning and memory (Delayed Matching to Sample Task).

c. Self-Report Performance Measures:

Standardized questionnaire measures of self-reported cognitive and motor functioning (Awareness of Functioning, Downer et al., 1991); job performance (Employment Questionnaire, Downer et al., 1991), and job satisfaction (Job Descriptive Index, Balzer & Smith, 1990), also added to Battery B at Washington, DC sites, in November, 1991. A subset of items from the Awareness of Functioning questionnaire was administered to subjects at WHMC, beginning in November, 1991.

d. Neurodiagnostic Measures:

Participants in the neurobehavioral addendum to RV-26 also received a brief neurological examination

and a magnetic resonance imaging scan. In addition, 20 of these participants agreed to undergo a lumbar puncture. Analyses of cerebrospinal fluid (CSF) included cell count, protein and glucose, oligoclonal bands (paired serum and CSF), IgG, cryptococcal antigen, HIV culture (paired serum and CSF), and quinolinic acid. These neurodiagnostic measures were included to determine whether non-specific neurological abnormalities due to HIV might have had any bearing on behavioral measures of performance.

2. Selected Findings:

One set of analyses examined the impact of potential confounding variables on neuropsychological performance. With regard to pre-HIV infection history, analyses revealed that neuropsychiatric history factors did not influence neuropsychological performance, and that individuals with such factors were not more vulnerable to deficits at the later disease stages. It was concluded that those individuals with premorbid psychiatric histories did not have to be excluded from our sample when examining the effects of HIV on neuropsychological performance on methodological grounds. This decision rendered the findings more generalizable to the types of patients seen in HIV clinics. With regard to age, analyses showed that participants in the oldest age group (40 and older) performed more poorly than younger participants on measures of attention, response speed, motor skills, and learning/memory, consistent with expected age-related differences. Older subjects at later stages, however, were not more vulnerable to the effects of HIV than were younger subjects at later stages. Thus, age did not appear to exacerbate HIV-associated neuropsychological difficulties. Finally, the effect of mood state was examined, by correlating results from neuropsychological measures with those from self-reported mood state measures. The magnitudes of the statistically significant correlations found were small, indicating that, across the continuum of mood state, mood had little impact on performance. When analyses were limited to subjects at the extremes of mood state (very few symptoms vs. many symptoms), however, both disease stage and mood state impacted on attention, response speed, and motor skills. Participants at later stages or with many mood symptoms performed most poorly. Thus, findings suggested that clinically-significant, self-reported mood disorder might produce neuropsychological decrement, but these effects were independent of the effects of HIV disease stage.

Another set of analyses examined the types of neuropsychological difficulties observed. Factor analysis revealed six domains of functioning: encoding/executive function, visuomotor/focussed attention, psychomotor speed, language/dominant hemisphere skills, visual memory, and verbal memory. As compared to HIV- study participants, HIV+ subjects were poorer only on the encoding/executive function and psychomotor speed factors demonstrating impairment specificity at the early disease stages. Dual task performance was used to explore the effects of HIV on complex attention and learning. In contrast to findings for individuals with other dementing disorders, the HIV+ and HIV- groups showed a small, but equivalent decrement during dual task performance, as compared to single task performance. Further, this finding was independent of slowed processing, observed in the HIV+ group only. These results confirmed prior reports of slowed response speed in early HIV disease and demonstrated the specificity of slowing by showing that it was not associated with a dual task performance deficit. Finally, reaction time performance was examined in more detail, to understand underlying impairment. Again, HIV+ participants were slower than HIV- participants on all measures. In addition, although HIV- participants improved their performance when given extra warning before having to respond, HIV+ participants showed no such improvement. Findings suggested that response slowing in HIV+ participants might be due to difficulty in: 1) mobilizing attention initially and/or 2) initiating a response.

One analysis examined data from the neurobehavioral addendum. It was found that HIV+ subjects with positive HIV CSF cultures had: 1) higher (but not statistically significant) levels of quinolinic acid, a neurotoxin, in CSF; and 2) poorer performance on measures of attention, response speed, and motor skills, compared to HIV+ participants with negative HIV CSF cultures. These preliminary findings suggested a possible biological marker of neuropsychological difficulties.

A final set of analyses explored self-reported occupational functioning. Questionnaire data revealed that, compared to HIV- controls, HIV+ participants reported a) more cognitive difficulties, b) lower work productivity, c) less job satisfaction, and d) more mood disturbance. Relations among difficulties, however, were complex and differed between HIV+ and HIV- control groups. Findings were interpreted as indicating the potential for reduced job satisfaction and perceived reduction in job performance in HIV+ individuals.

Results from the neuropsychological assessment portion of RV 26 can be summarized as follows: First, age and pre-existing

neuropsychiatric history did not appear to affect neuropsychological performance unduly in HIV+ individuals. Second, although commonly-experienced symptoms of depression and anxiety did not appear to substantially affect performance, clinically significant levels of mood disturbance might affect performance. The impact of mood on neuropsychological functioning, however, appeared to be independent of the effects of disease stage. Third, at early disease stages, HIV+ individuals manifested particular types of cognitive difficulties, characterized by slowed response speed and deficits in aspects of attention, initiation, and encoding skills; these might be related to specific biological markers of CNS infection. Deficits were not universal,however. Finally, there were indications that, by their own reports, some HIV-infected individuals experienced early changes in job performance and satisfaction. Further analyses will examine the prevalence of deficits and the relation to self-reported job satisfaction and job performance difficulties.

RV4 - "Neurobehavioral consequences of HIV-III Brain Infection and Acquired Immune Deficiency Syndrome (AIDS) Encephalopathy: A Prospective Study" -

In addition to the Tri-Service Biopsychosocial Study and the AWAS HIV/AIDS Survey, another protocol which investigated the neurobehavioral consequences of HTLV-III Brain infection was implemented and completed at one site, WRAMC. The objectives, methods and findings for this protocol are outlined below:

A. Objectives

1. Prospectively characterize the neurological and cognitive manifestations of early HIV infection in military medical beneficiaries
2. Develop a screening instrument to detect the early onset of neurobehavioral changes in HIV infection in military medical beneficiaries.
3. Investigate host response to virus infections and epidemiologic factors affecting these manifestations and their progression.
4. Establish a structure for the systematic neurobehavioral testing and evaluation of patients in anti-retroviral, anti-opportunistic infection, psychoactive, and immunotherapeutic drug trials.

B. Methods:

These objectives were addressed by building a cohort of HIV-

infected subjects who were followed prospectively with detailed multi-disciplinary evaluations every six months for up to 30 months. Each evaluation included comprehensive neurological examination, neuropsychological testing, psychiatric examination, lumbar puncture, magnetic resonance imaging, EEG, evoked potentials (EP), and Brain Electrical Activity Mapping (BEAM). Specialized laboratory studies included blood and cerebrospinal fluid (CSF) HIV cultures, CSF quinolinate and kynurinate, and assay for a GP-120-like neurotoxin. A frozen serum, CSF, and cell bank was maintained for future studies.

A neurology/neuropsychology physical, logistical, and personnel core was established to conduct these studies. This included compiling standardized data entry forms and standardized procedures for patient scheduling, evaluation, data collection, and data verification and analysis. A methodology was developed for objective quantification of cerebral atrophy and white matter plaque load on MRI using a light pen.

157 individuals were enrolled in the study. This included 94 HIV seropositive (HIV+) individuals, 29 HIV-seronegative (HIV-) normal controls, 23 (HIV-) controls with adjustment disorder or depression, and 26 (HIV-) controls with other neurologic disease. Of the HIV+ participants, 60 were evaluated twice (baseline, six months), 44 were evaluated three times (baseline, six, and 12 months), and 33 were seen four times (baseline, 6, 12, and 18 months). On study entry, 65% of (HIV+) participants were asymptomatic by CDC criteria, 57% were in WR Stages 1 and 2, 21% in WR 3 and 4, and 21% in WR 5 and 6. About 15% of the original HIV+ participants dropped out of the study. Although HIV+ participants completed the entire evaluation, HIV- participants completed only neuropsychological testing. Since the original analyses, additional subjects were enrolled and tested; analyses of more recent data are still in progress. With regard to neurologic findings, the most consistently found abnormalities were in the CSF. Up to 98% of the HIV+ participants had at least one abnormal CSF parameter. The most common finding in the CSF was the presence of oligoclonal bands. CSF cultures were positive in 25% of HIV+ subjects and virus was cultured as early as WR 1. A negative blood culture did not preclude a positive CSF culture. Positive CSF cultures correlated with elevated CSF cell count, and positive blood cultures correlated with Walter Reed stage. EEGs were usually normal, except in HIV+ participants with advanced disease (WR 5 or 6, T4 cells less than 80). In all cases, auditory and visual EPs were normal. In 16% of the cases, somatosensory EPs were abnormal. The majority of abnormal EPs were due to defects in central

conduction. Abnormalities were found as early as WR 2 and in individuals with T4 cells greater than 760.

At the time of the initial evaluation, 39 % of the HIV+ participants were found to have abnormalities on cranial MRI scan, Focal white matter lesions accounted for 26% of the abnormalities, and 15% were found to have cortical atrophy. Over the course of one year, an additional 11% developed cortical atrophy and an additional 20% developed focal white matter lesions, resulting in a total of 60% of HIV+ subjects having abnormalities. Both cortical atrophy and focal lesions were noted as early as WR 1.

The standard neurological examination remained essentially normal in the majority of HIV+ participants. Seven participants developed sensory complaints and two developed cranial neuropathies (Bell's Palsy). An additional two participants in latter stages developed myopathies. The mean score on the Mini Mental Status Examination remained normal (29/30 total).

The results of neuropsychological assessment were equally revealing in establishing cognitive changes and CNS involvement in early HIV infection. Fifty-two HIV+ participants were originally evaluated and compared to 15 HIV- psychiatric subjects with diagnosis of Adjustment Disorder (ADJ DIS) and 18 HIV- normal controls (NORM). The HIV+ participants performed significantly more slowly on measures of speeded information processing and attention, and exhibited difficulty with spatial abilities, verbal learning, and verbal memory, relative to both HIV- groups (See Appendix A). The HIV+ and ADJ DIS participants did not differ in self-reported symptoms of depression (Beck Depression Inventory, Means: HIV+ 14.9, ADJ DIS 14.4). In contrast, 48% of the HIV+ participants were impaired on more than 10 of the 51 neuropsychological measures examined, while only 7% of the ADJ DIS group showed similar deficits.

Although HIV+ and ADJ DIS participants did not report differences in depression for either the total number of symptoms or the types of symptoms endorsed, a specific subgroup of symptoms, associated with feelings of sadness and complaints consistent with psychomotor slowing, were correlated with speeded information processing in the HIV+ group ($r=.44$, $p<.001$), but not in the ADJ DIS group ($r=.16$, $p>.05$), whose diagnosis was, by definition, the result of a psychiatric reactive response. Thus, it was concluded that psychiatric complaints in early stages of HIV infection might reflect early HIV-related CNS involvement (See Appendix A)

In addition to the results obtained at baseline assessment,

repeat evaluations of the HIV+ participants at six month intervals revealed progressive slowing of cognitive and motor performance. In contrast, no significant change was found in the NORM group re-evaluated over the first six month period (See Appendix A). Progressive changes in the HIV+ participants over the first six month period were not correlated with changes in mood state, measures of immunological functioning (i.e., T4 count, T4/T8 ratio), or presence of constitutional symptoms. However, at the initial evaluation, 66% of the HIV+ subjects were found to have abnormally elevated levels of quinolinic acid (QUIN), an endogenous neurotoxin, with a two to three fold increase relative to reported normal values. In addition, the progressive motor and cognitive slowing noted in the HIV+ participants over time was correlated with initial levels of QUIN ($r=.41$, $p<.05$), as well as with increasing levels of QUIN obtained on repeat evaluation ($r=.85$, $p<.01$).

C. Selected Findings

With regard to the objectives of RV-4, the following may be stated. Objective 1 was accomplished for those in the early stages of HIV infection. Because many subjects were in the early stages of infection, it was not clear how early neurobehavioral changes might progress over the later stages of HIV disease. It was also unclear how neurobehavioral changes might relate to military performance. Objective 2 has been partially accomplished. Findings to date indicate that it would not be possible to develop a "screening instrument" to detect early neurobehavioral changes. Rather, a multi-measure assessment was still required. Objective 3 was partially accomplished, but much remained to be learned about the mechanisms which produce neurobehavioral changes and how such changes may be slowed or stopped. Finally, Objective 4 was partially accomplished, in that it is now possible to employ a subset of the original neurobehavioral measures in drug trials, where practice effects must be minimized.

Conclusion

The Behavioral Medicine MAP made considerable inroads into understanding behavioral issues as they related to possible behavioral interventions, utilizing a conceptually logical and progressive step-wise research plan to reduce the rate of HIV exposure and rate of transmission among military personnel. During the 1992 Military Disease Hazards Research Program Review, the American Institute of Biological Sciences (AIBS) made these comments regarding a major component of this mission area, the AWAS: "The recent completion of the Army-wide HIV/AIDS survey is a technological feat. It represents a gold standard of population-based HIV interventions. This survey is a landmark research effort that will serve as the foundation for future behavioral interventions. It is unparalleled in other military and civilian population-based behavioral efforts. Data from this study will serve to focus the direction, scope and breadth of future Army HIV behavioral research and program design." This MAP has perpetuated this tradition of excellence in all its current and future studies.

Future Studies Planned

Two additional protocols were constructed to evaluate the safety and efficacy of interactive videodisc technology in reducing transmission risk relevant behaviors in HIV infected individuals and HIV exposure risk behaviors in seronegative individuals. The videodiscs were produced jointly by the Center for Interactive Media in Medicine/the Center for Medical Educational Technology.

One of these research protocols was designed for HIV infected military medical beneficiaries, RV 72, and is entitled "Using interactive media to promote responsible sexual behavior in HIV infected individuals." Using data from a self-report survey of HIV transmission-relevant behaviors, tri-service patient focus group discussions, consultations from inside and outside MMCARR, and Behavioral Medicine MAP Scientific Development/Review Committee meetings, an interactive videodisc (IAVD) was developed in collaboration with the Center for Interactive Media in Medicine (CIMM) and the DoD HIV/IAVD Oversight Committee. The IAVD content areas include:

1. Knowledge: Focus on transmission prevention (not exposure prevention); military policy on partner notification and safer sex behaviors.

2. Disclosure of serostatus: Focus on ways to tell spouse, parents, new/potential sexual partners, health care

professionals, co-workers, and supervisors of one's HIV status; this will include content on whether, when, and how to inform others.

3. Responsible sexual behavior: Focus on how responsible sexual behavior can still be enjoyable; safe sex alternatives with seropositive and seronegative partners; deepening relationships in dimensions other than the sexual.

The video is planned to be shown to 250 military medical beneficiaries at one of three military medical centers: WRAMC, NNMC, and WAMC. An evaluation of changes in knowledge, attitudes and behavioral intentions with regard to transmission risk relevant behaviors will be assessed.

A second approved protocol, entitled "Use of Interactive Media to reduce the risk of HIV exposure in the United States Air Force Basic Trainees", RV 76, proposes to assess the effectiveness of already existing interactive videodiscs in reducing the risk of exposure to HIV and other STDs in a large, seronegative group of new recruits in the U.S. Air Force. A portion of two interactive videodiscs that focus on issues of condom use, negotiation for safer sex, and knowledge and attitudes concerning unsafe sexual practices will be shown to Air Force recruits. Pre-post test evaluations of knowledge, attitudes and behavioral intentions will be assessed immediately after viewing and at 6 month follow-up.

Additional efforts of the Behavioral Medicine mission area initiated towards the end of the grant period include:

A protocol that maintains the centralized STD database at Ft. Bragg, N.C.only very recently has been under the auspices of the Behavioral Medicine MAP, and is discussed within the Natural History/Epidemiology MAP, RV 56, entitled "An Analysis of Sexually Transmitted Diseases (STD) Patterns at Ft. Bragg, North Carolina". This database allows for the tracking of unit STD incidence rates and individual recidivism rates which will be needed as supporting outcome measures for the safety and efficacy study of behavioral interventions designed to reduce exposure risk behaviors at Ft. Bragg. An addendum to the protocol will facilitate the consolidation of a combined clinic to treat sexually transmitted diseases and provide STD/HIV preventive education. This clinic and the STD database will constitute the Foundation and assessment component of all future behavioral medicine program protocols at Ft. Bragg that aim to prevent HIV/STD exposure and transmission.

RV 89 - *"Obstetrician's and Gynecologists Affective Reactions to Uncertainty and Discussing HIV-1/AIDS During Routine Gynecologist care"* -

This is a protocol assessing military obstetricians' and gynecologists' affective reactions to uncertainty and discussing HIV/AIDS during routine gynecologic care was developed to address two important areas that had not yet been addressed by the behavioral research program: women and primary health care providers. The survey will be conducted during the next year and should provide the research basis for developing interventions that would enhance the delivery of primary and secondary HIV prevention efforts by primary health care providers.

RV 62 - *"Neurobehavioral effects of early Human Immunodeficiency Virus: Foundations for Study of Military Aviator Performance"* -

This is a protocol which will assess neuropsychological functioning and job performance in military aviation personnel over a 3 year period. The protocol will assess the neuropsychological functioning of 30 aviation personnel and 30 demographically matched control subjects. HIV+ aviation personnel also will complete neurologic and neurodiagnostic studies in an effort to determine whether non-specific neurological abnormalities due to HIV have any bearing on behavioral measures of performance. The goals of the study are to:

1) determine the prevalence of neurobehavioral deficits in HIV+ aviation personnel and progression of deficits over time:
2) clarify relations among neuropsychological changes, mood state, job satisfaction, and perceived changes in job performance;
3) establish a core battery of measures sensitive to early changes in performance, which may be applied to clinical screening of aviators; and
4) establish initial targets of intervention to minimize the effects of disease on performance and to maximize occupational longevity.

Data collection was planned to begin in the Summer of 1993. The theoretical and practical impetus for this protocol was a conference concerning HIV and military job performance that was organized by senior scientists in this mission area.

Behavioral Medicine staff have also been involved in providing neuropsychological assessment for several Phase I

clinical trials to assess potential neuropsychological deleterious effects of experimental therapeutic agents for HIV. These include Alpha Interferon (Alferon), for which no adverse neuropsychological side effects were found; and an open-label trial of U87201E, manufactured by Upjohn. Further information on these two chemotherapy trials can be found in the Chemotherapy/ Chemoprophylaxis MAP section.

D. CHEMOTHERAPY/CHEMOPROPHYLAXIS MISSION AREA

CAPT DOUGLAS MAYERS, M.D., MC, U.S. NAVY, DIRECTOR

MAP SUMMARY: The Chemotherapy and Chemoprophylaxis Mission Area Protocol investigated and conducted clinical trials of promising drugs to identify the best agents and regimen for the military HIV-infected population.

Protocol #	Protocol Title (Abbreviated)	Principal Investigator
RV3	Early Rx AZT	Hawkes
RV23A	Soluble CD4	Hawkes
RV27	AZT Pharmacokinetics	Bjornson
RV28	Pharmacology Database	Cortese*
RV49	Dipyridamole (completed)	Hendrix
RV60	Alferon N	Skillman
RV65	Prospective Study of Oral U-87201E	Mayers
RV43	Prospective Emergence/AZT	Mayers

*Foundation Principal Investigator (PI)

CHEMOTHERAPY/CHEMOPROPHYLAXIS MISSION AREA

Overview

Scientific management and oversight for this MAP was provided by the Walter Reed Army Institute of Research (WRAIR) through the directorship of CAPT. Douglas Mayers, MC, Naval Medical Research Institute (NMRI). The HIV chemotherapy/chemoprophylaxis research program was predominantly oriented toward drug susceptibility testing of HIV isolates and clinical efficacy trials of promising agents although there was effort devoted to basic research on antiviral agents. With access to a large population of well characterized early stage HIV-infected patients, it was possible to conduct clinical efficacy trials in the military that could be difficult to accomplish in the civilian population. Through the USAMRDC, this mission area forged collaborative agreements with other government agencies and private industry to gain early access to promising drugs for use in the military HIV-infected population.

Research Goals and Objectives

This MAP pursued the following goals and objectives for Grant Years 1-5:

- Develop chemotherapeutic strategies to prevent progression of early stage HIV disease with an emphasis on combination chemotherapy.

- Develop assay systems to monitor drug agents and determine the clinical significance of *in vitro* drug resistance.

- Evaluate the molecular mechanisms of drug-resistance and develop rapid assays for drug-resistant HIV.

- Target strategies to prevent the emergence of drug-resistant HIV variants or treat patients with drug-resistant strains; and evaluate agents for use in chemoprophylaxis of HIV transmission after high risk exposure.

A major focus in this MAP was to conduct clinical trials of chemotherapeutic agents focused on the prevention of progression of HIV disease in patients with early disease (secondary prevention). This objective closely followed the mission of the military HIV research program, i.e. to prolong the period that the HIV infected service member maintains good health with

preservation of his/her immune defenses. As such, the focus of the chemotherapy research program was to continually evaluate promising drugs that may slow or halt the progression of early HIV infection. Chemotherapeutic trials and database surveys were conducted at multiple sites under the auspices of this Mission Area:

Chemotherapeutic trials

RV 3 - *"Follow-up of Patients with AIDS-Related Complex (ARC) Originally Randomized to Early versus Later Treatment with Zidovudine"*-

The purpose of this protocol was to follow a randomized sample of 24 participants (out of 338 study total) until the study endpoint, 1994 or death. This protocol addressed the evaluation of the clinical effects of early versus late AZT therapy and looked at the differential effects of early vs. late therapy on the development of AZT resistance. This was the only study in the United States that allowed continued follow up of matched cohorts of patient who received AZT early vs. late in their clinical course. Continuation of this study will allow evaluation of the clinical and epidemiologic effects of the FDA decision to approve AZT therapy for all patient with T4 counts less than 500. This protocol was a collaborative effort between the Foundation, the DoD and the Department of Veteran's Affairs (VA).

Significant Findings:

1. Early administration of Zidovudine (CD4 200-500) significantly delayed progression to AIDS.
2. There was no significant difference in survival among those patients started on AZT early versus later.
3. There were no significant differences between early versus later AZT in terms of quality of life, as measured by the Sickness Impact Profile (SIP) and the Time Without Symptoms or Toxicity Profile (TWIST).
4. The apparent lack of response by minorities to early AZT was observed. Preliminary results from the pharmacokinetic studies revealed a shorter half-life by 60-90 minutes with respect to AZT in non-whites.

RV 23A -*"Phase I and II Study of the Use of Soluble CD4 Protein (sCD4: St4 SK&F 106528) in Human Immunodeficiency Virus Infection"*-

This was a Phase 1 open, randomized, but unblinded trial. Subjects,who met the inclusion criteria, were randomly assigned to one of three treatment arms using Soluble CD4 at doses of 0.1, 0.3, or 1.0 mg/kg. There was no placebo group. The study objectives were:

1. To assess the safety and tolerability of a singl intravenous infusion of Soluble CD4 in HIV-infected patients, Stages WR 3-5.
2. To evaluate the pharmacokinetics and bioavailability of Soluble CD4 at the beginning of the study, during the course of the study and at the end of the study.

Significant Findings: A total of nine (9) HIV-infected patients were enrolled in this study in 1989. There were no serious or unexpected adverse reactions. All patients completed the study. There was no observed benefit to any of the patients, but none was expected in this short term infusion. The Principal Investigators drew the following conclusions:

1. No serious toxicity observed following single 2 hour infusion of CD4; study drug was well tolerated.

2. Pharmacokinetics of Soluble CD4 revealed a t1/2 (half-life) of 47.9 ± 10.5 minutes.

3. There was no significant change in HIV viremia during or post infusion.

KV 27 - *"A Pharmacokinetic Study to Develop a Database to Describe the Relationship between Zidovudine (AZT)/Glucoronyl (GAZT) Blood Levels and Drug Toxicity in HIV-Infected Patients"* -

The purpose of this protocol was to define the relationship of zidovudine (ZDV) and glucuronyl zidovudine peak and trough plasma blood levels with drug toxicity. The technical approach to this protocol called for patients who were prescribed zidovudine for the first time have venous blood samples drawn each month for 12 months at prescribed intervals of 0, 15, 30, 45, 60 and 75 minutes. Levels of ZDV and GZDV were analyzed with the ZDV-Trac RIA kit, and concurrent toxicity parameters were followed. Multiple regression analysis was used to analyze data.

Significant Findings:

Interim analysis in December 1990 on 15 patients suggested an association between hemoglobin decline and peak metabolite (GZDV) levels and granulocyte decline and both peak GZDV and ZDV levels. The best predictor in each case was peak GZDV. There was wide intrapatient variations in plasma concentrations from month to month and wide interpatient variations in plasma concentrations even when corrected for body weight. The nineteen patients enrolled in the study

completed the 12 month pharmacokinetic portion of the study with one-year follow up on all patients. There was no known benefit to the patients. Final analysis of the data is pending.

RV 28 - *"Pharmacoepidemiologic study to develop a database to document variations in outcome of illness which may be due to drug effects, both beneficial and adverse and to document patterns of drug use in HIV infected patients"-*

The purpose of this protocol was to collect data on all patients treated with antiretroviral agents. This database was constructed to study the outcome of illness due to drug effect, both beneficial and adverse and to gather information on the drug use patterns of HIV infected patients.

Significant Findings:

The Principal Investigator is currently in the process of determining the rate of zidovudine medication compliance in HIV infected patients and factors associated with patient medication compliance.

RV 49 - *"The Effect of Dipyridamole On Zidovudine Pharmacokinetics"-*

Dipyridamole (DPM) augments the anti-HIV effect of zidovudine (ZDV) *in vitro*. The Principal Investigator sought to establish a well tolerated dose of DPM that could be used in combination with ZDV in clinical studies and to define whether concomitant administration of DPM altered the pharmacokinetics of ZDV. Both objectives were essential for planning efficacy studies of the ZDV-DPM combination. Eleven asymptomatic HIV-infected subjects who were already on 500mg/day of ZDV were admitted to the study. ZDV pharmacokinetics were measured on day 1, DPM was then added and pharmacokinetics measured again on day 5. Each subject served as his or her own control.

Significant Findings: Eleven (11) patients enrolled in this study and eight (8) patients completed the protocol. Zidovudine pharmacokinetics were not altered by concomitant use of DPM. A dose of 450 mg/day was well tolerated in the subjects. Trough plasm concentrations of DPM exceeded the synergistic concentrations identified in cell culture studies. This data was presented to NIH on December 1991 and an abstract was published in the Proceeedings of the VIIIth International AIDS Conference, July, 1992.

RV 60 - *'Phase I Study of Alferon N Injection in Persons with Asymptomatic HIV Infection'* -

This was a Phase 1 study of natural interferon alfa-n3. This agent has shown a 10 to 100 fold increase in anti-HIV activity in human monocytes when compared on a unit per unit basis to recombinant interferon $IFNa2_a$ or $IFNa2_b$. A Phase I study was initiated in anticipation of an efficacy trial since the recombinant interferons have already shown evidence of clinical benefit in HIV infection. Before one could determine if the increased *in vitro* activity translated to a 10 to 100 fold increase in clinical benefit, it was necessary to determine if the toxic effects of recombinant interferon were likewise increased 10 to 100 fold. Twenty patients took the drug subcutaneously Monday-Wednesday-Friday for 12 to 24 weeks at increasing doses:

Five took 1 million IU per dose
Ten took 5 million IU per dose
Five increased the dose to their Individual Maximum Tolerated Dose (MTD).

The MTDs for these five were as follows:

1=12.5 million IU/dose; MTD event was a >10% decline in CD4+ T-Cell Number
1=15 million IU/dose; MTD event was reversible neutropenia (750 neutrophils/mm^3)
1=20 million IU/dose; MTD event was the development of flu-like symptoms
1=10 million IU/dose; MTD event was a >10% decline in CD4+ T-Cell Number
1=15 million IU/dose; MTD event was a >10% decline in CD4+ T-Cell Number

Enrollment was completed and the last patient took his last dose of natural interferon alfa-n3 on May 31, 1993. Unless complications arise, this patient will then have two follow-up evaluations at 30 day intervals, after which the protocol will be completed.

Significant Findings:

Interferon alfa-n3 was extremely well tolerated. It was much superior to published reports of tolerances of recombinant interferons. Only one patient developed the flu-like symptoms usually reported with interferon administration. Significant, reversible laboratory toxicity developed in another patient, at 17.5 million IU. Therapy was interrupted

in five patients due to protocol defined toxicity of a 10-20% decline in CD4+ T-Cells from baseline. This drug continues to slow superior *in vitro* anti-HIV effects in comparison to recombinant interferon alpha, and it was extremely well tolerated in this Phase 1 study.

RV 65 - *"Prospective Open-label Study of the Emergence of Drug Resistance in Patients Infected with HIV-1 taking Oral - 87201 E"-*

This protocol was an open label study of U-87201 E in 6 patients with AZT-resistant virus and was perfcrmed to determine the rate of emergence of U-87201 E resistance and the genomic changes in the HIV reverse transcriptase gene, associated with *in vitro* resistance. The patients received a loading dose of 600mg of U-87201 E orally, three times per day for 2 days, followed by 400mg orally three times a day (tid) for up to 1 year. Objectives of the study were:

1. To determine the time course of development of resistance to U-87201 E in patients with HIV isolates showing *in vitro* resistance to AZT.

2. To determine the genotypic changes in HIV reverse transcriptase associated with phenotypic resistance to U-87201 E.

3. To determine the genotypic and phenotypic effects of treatment with a nondideoxynucleoside agent on the alterations of the HIV-1 virus population associated with *in vitro* AZT resistance.

4. To determine whether serial passage of patient pre-drug HIV isolates in the presence of U-87201 E will generate the resistant mutants that may subsequently emerge in the patients.

Significant Findings:

•Four of six patients (67%) developed a rash at 9 to 14 days of therapy. Skin biopsy suggested that the rash was not allergic in nature and approval was given to rechallenge two patients with U-87201 E.

•Analysis of pharmacokinetic data and *in vitro* drug resistance was in progress.

Studies of Drug Resistance

Studies of drug resistance in military personnel who will need treatment with antiretroviral drugs was highly relevant to the HIV military research effort. Efforts concentrated on monitoring and preventing the emergence of drug-resistant HIV strains and developing alternative treatment regimens for use in patients with clinically significant resistance. One protocol examined AZT resistance:

RV 43 - *"Prospective Study of the Emergence of Zidovudine (AZT) Resistance in Patients infected with the Human Immunodeficiency Virus (HIV) Who are Treated with AZT"*-

A cohort of 100 patients with CD4 counts <400 cells/mm^3 on zidovudine monotherapy was evaluated every three months for a period of 3 years. The patients had a screening history and physical exam along with T cell subsets, p24 antigen and drug level determination. HIV isolates at each time point were evaluated for susceptibility to AZT, ddi and ddC, along with syncytial phenotype. Multiple aliquots of plasma and PBMC were stored from each time point for further studies. The objectives of the protocol were:

1. To determine the time course, frequency and clinical parameters associated with the development of AZT resistance in HIV isolated from patients on AZT.

2. To determine if there existed a level of AZT resistance, measured *in vitro*, which correlated with clinical deterioration in patients who are receiving AZT.

3. To develop a repository of frozen HIV-infected peripheral blood mononuclear cells (PBMC) with resistant virus for future studies into the molecular basis of dideoxynucleotide resistance.

Significant Findings to date:

•CD4 cell counts remained stable in patients with AZT-susceptible virus for periods as long as 4 years.

•CD4 cells declined by 120 cells/mm^3 in the year preceding the emergence of *in vitro* AZT resistance (defined as IC_{50} > 1 I_uM AZT).

•Susceptibilities of clinical HIV isolates to ddi and ddC decrease 2-fold for each log_{10} decreased in AZT susceptibility.

•Multi-drug resistant HIV isolates emerged as patients were switched from AZT to ddi to AZT+ ddC.

•The time course of AZT resistance in patients on ZDV monotherapy was reassessed. At 2+ years of therapy, 40% of patients HIV isolates remained AZT susceptible (compared to earlier estimates of 5 to 15% using plaque assays).

•The relationship between CD4 decline and emergence of phenotypic AZT resistance, codon 215 mutations in plasma virus and proviral DNA in PBMC, syncytial phenotype and viral burden, was being assessed in collaboration with Stanford.

•The relationship between ddI susceptibility at initiation of ddI therapy and subsequent changes in viral burden continued under evaluation.

Chemoprophylaxis of Acute HIV Exposures

Another objective within this MAP was to develop chemotherapeutic strategies (both topical and systemic) to prevent development of HIV infection following acute, potentially infectious exposure to HIV. The prevention of transmission of HIV infection to active duty service members who are sent to areas of the world with a high prevalence of infection and to individuals with an accidental potentially infectious exposure to HIV has been a significant concern of military medicine. While the primary role of education and the use of condoms in preventing the transmission of HIV cannot be overemphasized, prudence dictated that emerging therapies for treatment of HIV disease should be considered for use in a prophylactic manner. Due to the low incidence of infection in the active duty population, any therapy which was seriously considered for human use should be validated in an acute animal challenge model to demonstrate efficacy.

A primate/SIV mucosal challenge model using SIV-infected cells was explored in coordination with the Animal Models Mission Area. This model, when validated, could serve as the screening system for potential chemo- and immunotherapeutic prophylaxis strategies. If an agent or combination of agents is found to be effective using this model, human trials in an appropriate high risk population would be performed.

Conclusion

The Chemotherapy/Chemoprophylaxis mission was successful in addressing the military relevant goals and objectives prescribed, creatively translating outside resources into innovative

chemotherapeutic trials for military individuals. Collaborative efforts with the National Institutes of Allergy and Infectious Diseases (NIAID) and other Pharmaceutical firm sponsors continue to offer new chemotherapy alternatives which have the potential to ultimately preserve or prolong the activity status of the infected service member.

Future Studies Planned

Chemotherapeutic Trials

As noted above, there is an ongoing trial of AZT in patients with 200 to 500 T4 cells. While this trial is in progress, evaluation of single agents or combinations of non-dideoxynucleotide with AZT in Phase I studies at the individual medical centers is planned. A major goal of this mission area will be to obtain a protease inhibitor for Phase I trials as soon as possible, with evaluation as a single agent and in combination with AZT in patients with early HIV disease. *In vitro* testing of any new agent against current patient isolates with appropriate synergy studies and monitoring for development of resistance will be a fundamental part of any protocol developed. Combination therapy trials are planned in both early and late stage patients to prevent emergence of resistance in patients with sensitive isolates and as salvage therapy for patients with resistant isolates. *In vitro* studies of potential genetic therapies using tat-primed interferon are currently being evaluated.

Drug Susceptibility Studies

A 100 patient prospective cohort study of AZT resistance will continue to determine the clinical significance of AZT resistance and to obtain a library of resistant isolates with frozen plasma and PBMC to look at AZT resistance at a cellular and molecular level. A panel of patient HIV isolates was developed for evaluating new chemotherapeutic agents and drug susceptibility test system as they become available. If AZT resistance is found to be clinically relevant, a prospective randomized treatment protocol for patients with resistant HIV isolates may be initiated based on the results of the HIV susceptibility testing program and the available agents.

The DoD/VA (A joint study with the DoD and Department of Veteran's Affairs) Early AZT (RV3 - see above) clinical trial was extended three years to allow evaluation of the clinical effects of early versus late AZT therapy and to look at the differential effects of early versus late therapy on the development of AZT resistance. This is the only known study in the United States that will allow continued follow up of matched cohorts of patients who received AZT early versus late in their clinical course.

Continuation of this study will allow evaluation of the clinical and epidemiologic effects of the FDA decision to approve AZT therapy for all patients with T4 counts less than 500.

Peripheral Blood CD4+ T Cell Population

A Principal Scientist in this mission area has constructed several hybrid retroviral vectors that contain a heterologous packaging signal. The scientist engineered putative HIV packaging cell lines that appeared capable of packaging HIV and murine leukemia virus HIV (MuLV-HIV) hybrid vectors. In this scheme, the MuLV (or SIV) packaging site was postulated to substitute for the HIV packaging site in packaging of a MuLV- HIV vector. An antiviral such as an antisense construct or a ribozyme against the HIV packaging site of HIV could be utilized as payload.

Transfection of HIV infected cells with the HIV-MULV hybrid vector with a payload empowered with the ability to either prevent translation or to potentiate cleavage of the HIV packaging site, should inhibit the packaging of HIV genomic RNA without inhibiting the packaging of the antiviral RNA as the later utilizes the MULV packaging sequence and is not subject to disruption by the payload. Expression of the HIV-MuLV particles should continue, allowing transmission and spread of the antiviral payload until the depletion of the HIV proteins required for virion assembly occurs. This scheme provides for a self limited replication competent retroviral vector.

Stromal Cell CD34+ Population

In collaboration with Dr. Steven Kessler, Naval Medical Research Institute (NMRI), Chemotherapy scientists have obtained highly purified populations of the T lymphocyte progenitor CD34+ cells,and an effort to productively infect such cells with a retrovirus will be initiated soon. The priority of this effort will be to draw on the considerable expertise of Chemotherapy scientists to design a murine based retroviral vector capable of immortalization of a highly purified stromal cell line (CD34+ cells) and efficient transformation of these progenitor cells with an HIV antiviral gene product. Antiviral genes delivered to progenitor cells of the lymphocyte lineage will result in progeny containing antiviral genes capable of preventing or suppressing HIV infection of the mature cell (CD4+ cells) derived from the transduced progenitors.

In addition to the CD34+ cells, Principal Scientists obtained an SV-40 immortalized stromal cell line from bone marrow, Lof-10 cells and are in the process of establishing an efficient MuLv retroviral line in these cells. Experiments are also being designed to assess the degree of productive infection in stroma lines by retroviral vectors, as well as to ascertain the

efficiency of transmission of expressing retroviral gene products to progenitor cells and the degree of resistance such alteration in the stem cells will provide to the mature CD4+ cell in the face of HIV infection.

Genetically Based Immunization

The purpose of this research will be to design and characterize gene therapeutic immunogenic strategies. The goal is to enhance immune function by modification of the immune response or augmentation of the immune response using facilitated antigen or cytokine presentation. There are a number of approaches that might be taken in this context.

In collaboration with Vaccine Research area scientists, Chemotherapy scientists have recently completed the construction of a live, nef deleted HIV-1 similar to the SIV construct developed by Dr. Ron DeRosiers at the New England Primate Center. One of the applications of this construct would be as a partially defective, genetically attenuated or crippled virus, but perhaps capable of generating a productive immune response against the parent backbone of HXB2. Experiments are in progress to demonstrate the attenuation of this defective viral product *in vitro*.

Several potential gene expression systems employing MuLv and HIV constructs have also been assembled. While the characterization of these constructs as potential vehicles for antigen presentation was on hold, investigation of these products could now be prioritized. In addition, preliminary results in monkeys with directly injected nucleic acids as stimulants for an immune response are encouraging.

E. RETROVIRAL BIOLOGY MISSION AREA

FRANCINE McCUTCHAN, Ph.D., FOUNDATION, DIRECTOR*

MAP SUMMARY: Research in this mission area involved viral genetic analysis directed at the outcome of designing and implementing strategies to prevent HIV-1 infection and in delaying disease progression in individuals already infected with HIV. This area utilized an extensive collaborative network and conducted research in accordance with an extensive and integrated research plan rather than individual protocols. The plan was approved by the MMCARR and was subject to the Mission Area Protocol review process.

* Foundation Scientist and Investigator

RETROVIRAL BIOLOGY MISSION AREA

Overview

The Foundation provided the leadership for this Mission Area through its Director and Principal Scientist, Francine McCutchan, Ph.D. Dr. McCutchan provided scientific direction and guidance to a group of researchers with diverse and complementary skills and technical strengths which included genetic engineering of cells, evaluation of virus/host specific interactions, polymerase chain reaction, gene cloning and DNA sequencing. The group's expertise in molecular biology, virology and immunology was directed to the design and implementation of strategies to prevent HIV-1 infection and to delay disease progression in those individuals already infected by the virus.

Research Goals and Objectives

The Retroviral Biology Mission Area set forth, at its inception, the following objectives:

1. To develop clinically useful methods to study the genetic characteristics of HIV and other lentiviruses as they relate to transmission, progression, and therapeutic or vaccine interventions.

2. To refine and adapt current methods for assessment of the serologic response to HIV and other lentiviruses.

3. To develop and test tools for genetic therapy of HIV disease.

Substantial progress was made towards all of these goals. The following text details the progress and significant findings in each of three objectives, under the titles Viral Variation, Serologic Responses in Lentivirus Infections, and HIV Gene Therapy, respectively.

VIRAL VARIATION

OBJECTIVE:

To assist development of globally effective HIV-1 vaccines by determination of the worldwide genetic variability of HIV-1 and by characterization of prevalent strains in major centers of the pandemic.

BACKGROUND:

The HIV-1 virus exhibits considerable genetic variation among isolates from different geographic locales (1-9). Recent contributions to the genetic database have provided evidence for the existence of multiple HIV-1 subtypes, many of which are broadly distributed geographically (10,11). Possible differences among these subtypes with respect to antigenicity of major structural proteins, host immune response, and pathogenic potential need to be considered, particularly in conjunction with anticipated field trials of vaccines or therapeutic agents.

The genetic diversity of HIV-1 was appreciated soon after the first virus sequences were derived. Initial efforts were focused on isolates from a geographic sphere essentially limited to North America, Europe, and Zaire. From this work, the concept of two geographically separated groups of variants arose, one group prevalent in North American and Europe and another, more diverse group, in Africa(9). The need to select vaccine prototype strains relevant to multiple, geographically dispersed locales has revitalized efforts to capture the regional prevalence of HIV-1 variants (6-8,10,11). Technical advances that facilitated and accelerated the acquisition of genetic data permitted a more comprehensive evaluation of worldwide HIV-1 variation.

PRESENT/FUTURE STUDIES

Evaluation of the relationship of genetic variation to antigenicity, immunogenicity, and vaccine cross protection will require a coordinated effort by many laboratories. In particular, adequate sampling of HIV-1 virus variants in populations where vaccine field trials are anticipated is essential and requires careful planning. Specimens should be representative of the local population, which may harbor a mixture of diverse subtypes of HIV-1. Both coagulated and anticoagulated blood, drawn concurrently and each in sufficient quantity, must be included. Arrangements for sample identification, transport, and prompt processing need to be in place, which could pose logistic problems in some parts of the world. Separation of whole blood into peripheral blood mononuclear cells (PBMC) and plasma by Ficoll-hypaque gradient centrifugation was required, which imposed a need for experienced laboratory personnel cognizant of P2/P3 practices and biosafety considerations. All aspects of the evaluation procedure, which includes genotyping, serotyping, neutralization assays, evaluation of biological phenotype, and other assays, needs to be co-ordinated in advance, so that sufficient materials are available. Finally, the data needs to be collated, analyzed, and reported promptly to the scientific community. In the face of a rapidly expanding global pandemic, these required activities, which take place early in the vaccine development effort and influence many subsequent steps, are ever more pressing.

16. Naidu YM, Kestler HW, Li Y, Butler CV, Silva DP, Schmidt DK, Troup CD, Sehgal PK, Sonigo P, Daniel M, and Desrosiers RC. Characterization of infectious molecular clones of simian immunodeficiency virus (SIV_{MAC}) and human immuno-deficiency virus type-2: persistent infection of rhesus monkeys with molecularly cloned SIV_{MAC}. J. Virol. 62:4691-4696 (1988).

EXPERIMENTAL APPROACH

1. To gain an accurate and comprehensive understanding of the genetic variability of HIV-1 worldwide.

2. To develop a genetic typing system for HIV-1 so that broad epidemiologic surveys of incident and prevalent subtypes can be conducted.

3. To conduct an in-depth evaluation of genetic variants prevalent in locales selected as candidate vaccine evaluation sites.

4. To conduct an *in vitro* immunologic evaluation of strains selected with reference to pending vaccine field trails for possible vaccine cross protection.

METHODS

Design of PCR Primers

PCR amplification of specific segments of the HIV-1 genome required the use of two oligonucleotide primers located on opposite strands of the DNA and flanking the region to be amplified. Ideally, a set of "universal" primers would be used for all HIV-1 isolates. However, the considerable genetic variability of HIV-1 limited the experimental attainment of this goal. Currently, it is thought that HIV-1 viruses exhibit a number of genetically equidistant subtypes. The goal of universally conserved HIV-1 primers might be logically re-stated as a set of primers containing reagents matched to each of the known genetic subtypes of the virus. Nonetheless, even subtype-specific primers might be incompletely conserved and additional undiscovered subtypes could emerge. Mispairing of primer/ template due to genetic diversity could be minimized but probably not eliminated.

PCR amplification could accommodate some primer/template mispairing before the efficiency of amplification began to decline. Certain mispaired nucleotide combinations dramatically reduced product while others seemed to have little influence. Our current understanding of the effects of primer/template mispairing can be incorporated into primer design. For example, the most conserved nucleotide positions could be placed at the 3'ends of primers where effects of mispairing seemed most significant. Also,

genetically variable positions that involved nucleotide alternatives having relatively little influence on PCR could be selected when variation could not be avoided. A frequent interplay between newly accumulated sequence data and the design of PCR primers should be anticipated. Strategies for universal recovery of PCR amplified segments should include alternative plans when initial success is not attained.

The researchers' ability to design primers that consistently recover PCR products was greatly enhanced by previous experience. In 1990, they initiated development of a genetic typing system for HIV-1 using PCR. These scientists sought HIV-1 specific primer combinations that consistently amplified field isolates and other primers that exploited genetic differences among isolates. Primer sequences were initially selected from the 1989 HIV-1 sequence database and tested for reactivity with multiple HIV-1 isolates. An anchored PCR scheme was employed in which DNA segments to be amplified shared a common "anchor" primer but varied with respect to the distal primer used. The amplified segments overlapped a common probe region that was used for PCR product detection. Radiolabeled probes were used and products were quantitated directly from Southern blots using a Betagen blot analyzer. Because of this design, the quantity of PCR product attained was influenced primarily by the homology of one primer with the template DNA; this permitted an objective comparison of primer performance. Suitable primer combinations that performed well with both domestic and international HIV-1 isolates were established in the laboratory and were to be used in this project. A description of these with respect to segment amplified and primer sequence appears in Table 3. Additional primers would be synthesized based on new sequence information collected during the project and in consultation with Los Alamos National Laboratory, which maintained a comprehensive genetic database for HIV-1 and other lentiviruses.

PCR amplification often employs primers containing added restriction sites to facilitate cloning into the desired vector. In the experience of these researchers, the addition of "extra" nucleotides to the 5'ends of primers decreased the efficiency of PCR amplification. Recently, it was established that the termini of PCR products bore a single-nucleotide, 3' A extension, which made it possible to clone them directly into vectors bearing a single-nucleotide 5' T extension. This discovery abrogated the need for addition of restriction sites, provided a universal cloning vector and strategy, and eliminated some of the cloning steps for PCR products.

An Applied Biosystems 380B DNA synthesizer was employed for oligonucleotide synthesis with a capacity of 15 oligo-nucleotides per week. This synthesizer was carefully maintained by trained personnel and only quality reagents were used. These steps ensured consistent high coupling efficiency and product yield. The

researchers were able to routinely generate primers from 18-35 nt in length that were largely if not entirely full length by the assay used. After deprotection, oligo-nucleotides were purified by organic extraction and ethanol precipitation, evaluated using polyacrylamide gel electrophoresis, and quantitated by optical density at 260nm. Primers were aliquoted and stored at -20°C. Primer combinations were prepared as 20 uM stocks of each primer in sterile water and 5 ul was added to each 100 ul PCR reaction.

PCR Amplification of Specific Gene Fragments

Recovery of HIV-1 proviral DNA from patient or cell culture materials required selective amplification of the viral genes from a large background of cellular DNA sequences. The quantity of the HIV-1 proviral DNA could not be predicted in advance, but in general, patient PBMC and other materials had a much lower HIV-1 DNA content than cells from virus cultures. The requirements for PCR amplification of HIV-1 gene segments were adjusted depending on the materials provided. From patient PBMC, where, typically, from 1/100 to less than 1/100,000 cells contain proviral DNA, two successive PCR amplifications were typically used. The initial amplification used primers outside the desired region. Products from the first amplification were re-amplified with internal "nested" primers, which generated sufficient material for analysis. When cells from virus cultures were provided, a single step, 30-cycle PCR amplification was usually sufficient to provide the needed material, but nested PCR could also be employed in the event of low HIV-1 DNA content.

PCR amplification became less efficient as the amplified segment increased in length. The additive effects of primer/template mispairing and the length of the amplified segment made recovery of gp160 genes (2.5 KB) from diverse isolates particularly challenging. One of the strengths of this mission area was the consistent recovery of full length, structural genes of HIV-1 from a highly heterogeneous collection of field isolates. Amplification of shorter env segments, including gp120 (1.5 KB), gp41 (1.0 KB), the v2-v5 region of gp120 (1.0 KB) and the V3 region (0.3 KB) was also accomplished.

Starting from patient PBMC, which were often provided in limited quantities, one strategy was to prepare a crude lysate of the cells for use in PCR. The advantages were that recovery of small amounts of DNA template was more certain and that multiple samples could be rapidly processed. The disadvantages were that substances not removed (ex. heme) could interfere with PCR and that the template could not be quantitated. When sufficient cells were provided, be they from patients or from virus cultures, bulk DNA isolation and purification could be used. The main advantage was to provide optimal template of known quantity.

Another consideration with recovery of longer gene segments was the specificity of the PCR amplification. Since the amplified segments were to be cloned, which depended directly on the number of ligatable fragment ends generated, samples containing multiple, short undesired amplification products might contain a paucity of desired "ends" and a plethora of non-specific "ends". With incomplete template/primer matches, and for other, technical reasons, non-specific products might represent the majority of the amplified material.

Many of the technical problems described above were largely overcome. Strategies included, but were not limited to: use of optimal primers, including subtype-specific primers, adjustment of primer annealing temperature, "hot start" PCR, use of purified, quantitated DNA template, use of nested PCR to improve specificity, gel purification of full length products, high efficiency cloning, and colony screening to locate desired clones. Lastly, the researchers devised a standard procedure for dealing with failed PCR reactions, which was a major factor limiting full recovery of genetic segments from field isolates.

Before PCR amplification could begin, cells were processed and template DNA was prepared. This work was done in P2 containment with P3 practices. PCR reactions were assembled in space free of contamination with previously amplified DNA and molecular clones containing HIV-1 DNA sequences. PCR reactions (100 ul) included 10 mM Tris/HCl, pH 8.3, 1.5 mM $MgCl_2$, 0.01% gelatin, 200 uM dATP,dCTP,dGTP, and dTTP, 100 pmol of each primer, 1 ug purified DNA template or crude lysate equivalent,and 2.5 U *Taq* polymerase (Perkin-Elmer Cetus). The thermocycling conditions varied but typically, they were: rapid heating to 95oC, hold on 95oC for 30 s, cooling to 55oC over 1 min, hold on 55oC for 30 s, heat to 72 oC over 30 s, hold on 72oC for 5 min. Amplification was for 30-35 cycles.

After thermocycling, an aliquot of the PCR reaction was analyzed by agarose gel electrophoresis and EtBr staining. Each gel included a lane loaded with DNA restriction fragments of known length, so that the size of the amplified segment could be discerned. Gels were blotted onto nylon membrane (Genescreen Plus, Dupont) by the procedure of Southern and hybridized to a ^{32}P-labeled oligonucleotide probe whose sequence lies internal to the amplified segment. Hybridized radioactivity was quantitated with a Betagen blot analyzer. DNA samples that yielded PCR product of the expected length and in an amount greater than 3 x background were considered positive and carried forward to the cloning stage.

Prevention of PCR Contamination

The PCR technique provided an unparalleled level of sensitivity for detection of specific DNA sequences. It was demonstrated

that, using nested PCR, a single HIV-1 genome among many millions of cells can be amplified. With this added sensitivity came added vulnerability to contamination of PCR reactions with unwanted molecules. Laboratory levels of HIV-1 DNA contamination within reagents, supplies, and equipment that were formerly considered negligible became a significant problem in recent years. Among the steps that could be taken to guard against contamination, perhaps the most significant was physical separation of activities with amplified DNA and molecular clones from the site where DNA template was isolated and PCR reactions were set up. Strict quality control of reagents was also essential. A reliable, consistently applied method for sample identification could help avoid procedural problems with contamination. Lastly, a plan should be in place to deal with instances of sample contamination, should they occur.

Reagents were the most frequent source of PCR contamination. None of the reagents used for PCR were made up using laboratory glassware and none were autoclaved. Only disposables were used and filter sterilization accomplished where necessary. The researchers planned to purchase ready-made reagent concentrates rather than make them up in our laboratory. This included dNTPs, reaction buffer, primers, Taq polymerase. Laminar flow hoods were used for reagent preparation. Reagents at the working concentration were made up in large batches and stored in small aliquots, each of which was used once and the unused portion discarded. Tubes, pipet tips, pipet devices, and other supplies were reserved for PCR set-up and were kept separated form all other uses.

Detection of contamination required adequate controls. DNA isolated from uninfected PBMC was used and a "no template" or buffer blank in every set of PCR reactions was used. All reagents going into the reactions except the DNA template were assembled as a master mix, aliquoted tc tubes. Thus, contaminated reagents are readily detected. The second requirement was accurate product quantitation, so that low levels of contamination could be distinguished from samples with low HIV-1 DNA content. Ethidium bromide staining of agarose gels provided a first evaluation but did not allow detection of low levels of PCR product. The researchers used hybridization of Southern blots containing PCR products with ^{32}P labeled probes, followed by quantitation of hybridized radioactivity with a Betagen blot analyzer. The Betagen provided extraordinary sensitivity plus a very wide linear response range for ^{32}P. With this instrument, detection of any level of radioactivity above background could be completed in eight hours, as compared to two weeks with conventional X-ray film detection. Thus projects moved forward without delay because validation of negative controls was prompt. Controls must have exhibited radioactivity no greater than two-fold background to be considered negative.

Automated DNA Sequencing

Automated DNA sequencing was used in support of this project. The advantages of automated sequencing, as compared to manual methods, were considerable. Radioactive labelling of products was replaced with fluorescent dyes, which avoided numerous safety and waste disposal issues. The labeling of sequencing products was stable, permitting the storage of samples for long periods before sequencing gels were run. The strategy for discrimination of the four bases was different. Manual methods used a single radioactive label (^{32}P or ^{35}S), and four reactions with different dideoxy terminators that must have been kept separate throughout the procedure. To obtain 300-400 bases of sequence required twelve lanes and multiple loadings (typically, four lanes were loaded three times over a period of 6-7 hours). With automated sequencing, four different labels were used (fluorescent dyes that can be discriminated with filters) so that the sequencing products with different terminators could be combined in one lane. Continuous detection was used with dye-labeled products electrophoresed past a laser and detector; one loading of the gel replaced three loadings over 6-7 hours. The yield of sequence per reaction using dye labels was typically 400-500 bases. Thus, a single 36 lane manual gel would provide about 1000 bases of information and would require monitoring for most of a working day. A single automated gel, under optimal conditions, would provide up 16,000 bases of sequence and requiredapproximately one hour to set up and load.

Another advantage of automated sequencing was accuracy. Two aspects of the procedure contributed to this. The use of thermostable *Taq* polymerase permits cycle sequencing, which increased product yield, minimized template DNA requirements, and suppressed noise because non-specifically terminated products were extended during subsequent cycles. Second, data was collected directly on the computer's hard disk. With manual methods, radioactivity in sequencing gels was detected by X-ray film autoradiography and files were read and entered into the computer. The investigator made decisions about sequence ambiguities and was responsible for correct sample identification and for the accuracy of the data input. With automated methods, fluorescence intensity was collected in real time on the computer disc and placed in the appropriate file automatically. Sequence ambiguities were impartially and consistently identified by the analysis software. The net result was a greatly decreased potential for sample misidentification and for bias in data interpretation, plus far less investigator time required. The storage of waveform data using computer discs replaced cataloging and filing of innumerable X-ray films.

The net result of these advances would be diminished, however, unless supporting technologies were also developed in parallel.

High yield automated sequencing required more efficient PCR amplification, more reliable cloning techniques, faster and cleaner template preparation, and a well constructed plan for the management of sequence information. This laboratory converted to automated sequencing more than three years ago and has been able to refine and improve virtually every step leading up to the automated sequencing and activities after data is collected. Current projects are supported by Applied Biosystems 373A sequencer and by completely revamped supporting technologies.

Cloning

Cloning procedures were developed that provided an efficient, rapid, and widely applicable cloning strategy for HIV genes. It could be completed within days of the PCR amplification. Products were taken directly from the PCR reactions and ligated with the vector. While the ligation efficiency was low, this could be overcome by use of maximum cloning efficiency *E. coli* competent cells. Over a background of <1% white colonies, ligated PCR products typically generated 10-70% white colonies. Of these, up to 50% contained the desired insert. Thus it was often unnecessary to screen colonies by hybridization, but the researchers were prepared to perform colony screening rapidly and efficiently. The researchers largely replaced a screening step with plasmid minipreps, which allowed evaluation of clones and provide template for sequencing in one step. Further, plasmid minipreps allowed discrimination of full length from partial clones, which could be a significant problem in HIV-1 envelope cloning. For the miniprep procedure, the researchers replaced conventional methods with Quiagen columns, which provide high yield of purified DNA. Recently, a multisample manifold that permits simultaneous processing of up to 96 samples had further streamlined the researchers' miniprep procedure.

Sequencing Strategies

The accuracy of DNA sequences was a function of the strategy used to assemble projects. Each individual sequencing reaction yielded information that was highly but incompletely accurate. To achieve fully accurate sequences, a comparison of data from several reactions and from both strands of the DNA was required. Our Sequencing strategies for these researchers provided complete coverage of both strands of the DNA and built-in redundancy. On average, the researchers compiled 4.3 KB of raw data to compile each 1 KB segment of completed sequence.

Obtaining completed gp160 sequences was the most challenging aspect of the work. An initial panel of 40 sequencing primers was used. These primer sequences were relatively conserved among diverse HIV-1 isolates, including those from different subtypes as

shown in the Figure. Data collected from this initial effort was assembled and analyzed. About 75% of the data was usually obtained at this point, with some gaps and incompletely covered regions remaining. A library of more than fifty additional envelope primers was then considered. This was done by computer-assisted shotgun assembly of primers with the incomplete assembled sequence, noting those primers with sufficient homology and in locations that would fill in gaps. These were then applied to complete the sequence. Finally, custom primers were synthesized as needed to gain access to any remaining difficult regions. The researchers accumulated a library of more than 90 envelope sequencing primers.

Sequencing Reactions and Gels

Several decisions concerning sequencing reactions influenced the success and efficiency of automated DNA sequencing. This had been an area marked by frequent technical refinements and some early approaches had proved unworkable or been supplanted by more efficient methods. The researchers' experience in these aspects significantly enhanced the project performance.

One important decision concerned the method for fluorescent labelling of sequencing reaction products. Fluorescent dyes could be attached to the 5'ends of sequencing primers. In this approach, four separate reactions were performed with each template, which were combined for loading on gels. Primers homologous to commonly used plasmid vector sequences were commercially available but only provide access to one strand of the 400 nt segment adjacent to the vector at either end of the inserted segment. Double strand sequencing and sequencing of inserted segments larger than 400 nt either required additional primers or recloning to bring every 400 bp segment adjacent to plasmid vector sequences. While in theory any primer could be labeled with dyes, and while the aminolink chemistry provided a simple procedure for dye labeling, the generation of custom dye-labeled primers had not proved practical in this setting. The limitation was with the software that interprets automated sequence data. The mobility of sequencing products was influenced by the dye, and this influence was a function of the local sequence context. Mobility correction files had been perfected for the "universal" dye labeled primers that anneal to vector sequences but these were insufficient to analyze reactions with custom dye labeled primers. Applied Biosystems was initially encouraging about custom labeled primers but failed to provide software support for mobility corrections. Commercially available dye labeled primers were used but only to sequence ends (one strand) of clones where needed. Re-cloning strategies such as erase-a-base were found to be time consuming and were seldom universally applicable or satisfactory. The convenience of multiple sequencing reactions from a single cloned template was

replaced by a requirement for one sequencing reaction from each of a multiplicity of cloned templates, which slowed down projects significantly.

A more powerful approach was the use of dye-labeled terminators. Here the mobility of the sequencing products was more uniform due to the chemistry of dye linkage; the same analysis software could be used for any primer. Because the dyes were linked to the dideoxy terminators, a one-tube reaction was performed instead of four separate reactions, with considerable savings in time and manipulations. At the time of the initial introduction of dye-labeled terminators by Applied Biosystems, this attractive strategy was plagued with numerous problems, not the least of which was the low yield of sequence information per reaction. Recently, these problems had been largely overcome, and the yield of sequence information per reaction was now equivalent to dye primer reactions. Our laboratory performed more than 95% of each project using dye terminators. The main advances that contributed to this were the use of Quiagen columns for template DNA preparation, accurate quantitation of the template DNA input, development of a library of envelope primers, and other changes in protocol developed by Applied Biosystems.

Automated sequencing required the generation of more reaction products than manual methods. This was accomplished through thermocycle sequencing, where multiple denaturation, annealing, and extension steps are performed. Fluorescent dye-labeled products were then separated from unincorporated dyes using spin columns. Finally, reaction products were concentrated by ethanol precipitation and dried.

Sequencing gels were prepared from fresh solutions of acrylamide and urea and were cast by standard procedures using a comb blank. Wells were created with a 36-lane, sharkstooth comb prior to sample loading. Samples were redissolved in <5 ul of formamide, heat denatured, and loaded using specialized, disposable pipet tips with flat tips. Electrophoresis was continued for 12-14 hours.

Compilation and Analysis of Sequence Data

Efficient collection, storage, and analysis of automated sequence data was required for this project. The Foundation laboratory maintained a network of Macintosh computers and peripherals in support of DNA sequencing projects and other laboratory activities. The main components were a file server, two external hard drives, a read/write optical CD drive, many Macintosh computers, and two laser printers, all connected through ethernet cable.

Data collection began with a 373A DNA sequencer. This was operated

by a dedicated Macintosh computer, connected to the network. Data collection was driven by software supplied by Applied Biosystems. At the completion of each sequencing run, the data was stored in two forms: a large, color graphic "gel" file containing a complete record of dyes passing the detector over the entire run, and individual files for each gel lane, which resulted from "tracking" of lanes and recording of the sequence of fluorescent peaks passing the detector. The gel file occupied 18 MB and each segment of the waveform data occupied 140K.

The next step was data analysis using a software module from Applied Biosystems. This software interpreted the dye peaks as a nucleotide sequence and recorded the sequence in a file. We performed this function on a second Macintosh computer so that the sequencer could be set up for another run while analysis was proceeding. The gel file was retained until analysis was completed because, occasionally, lanes were incorrectly tracked and manual re-tracking is needed. After this step, the gel file was discarded. The waveform data and the sequence files (36 lanes per run, total of 5MB) were transferred via the network to an external hard drive (capacity 1 gigabyte) where they were cataloged by date of run and stored while the project is in progress. The contents of this drive was backed up by the network manager and secured. Since every sequencing run generates 5MB of data, it was impractical to envision permanent data storage on conventional hard disks; the researchers used both an optical (read/write CD) drive and an archive tape drive for storage of completed projects.

During the course of this work, the researchers examined virtually every commercially available software program for DNA sequence analysis using personal computers as well as some packages designed for more powerful microcomputers such as Applied Biosystems "Inherit". For some software modules, this mission area served as a beta test site and participated in the actual development process. Out of this experience, the researchers continually improved the speed and ease of data assembly and analysis, and planned to continue participation in this important area because of its significant impact on performance of DNA sequencing tasks.

DNAStar software was used for data assembly and analysis. The advantages of this program were numerous. They included easy importation of sequences for analysis, excellent algorithms for assembly of overlapping sequence segments into a contiguous sequence, capability for protein translation and generation of restriction maps with flexibility in output formats, and alignment of related DNA and protein sequences. Two features, however, made this software an overwhelming first choice. One was the strategy for editing aligned sequences to resolve disparities, and the

other was a provision for multiple sequence alignments called Megalign.

Nucleotide sequence ambiguities arose because individual sequence files were imperfect. Ambiguities could occur within a sequence file because the dye passing the detector was not discriminated, or they could arise when overlapping sequence files were aligned and compared. To resolve ambiguities, the relevant regions of the waveform data were re-examined. DNAStar had recently developed software to locate the regions of the waveform data to be compared and to bring them up on the computer screen. Sequences in the antisense orientation were temporarily converted to their reverse complement for purposes of comparison. This replaced a time-consuming process where paper copies of waveform data were inspected by hand, without the assistance of the computer to locate the relevant regions and to generate inverse complements. This advance had two additional consequences. Paper copies of waveform data were no longer required, which was a considerable advantage for project management. However, each project must keep the waveform data available (140KB per file) until analysis was complete; this increased the space needed to store projects in progress. Another advantage of DNAStar was the capability to generate multiple sequence alignments. Heretofore, this had been possible with only one other software package, Geneworks from Intelligenetics. While both programs could perform this task, each suffered serious hardware limitations even when operated on the most advanced Macintosh computers. The DNAStar algorithm was found to be superior for both the speed and accuracy of multiple sequence alignments, but projects involving several long sequence segments were still painfully slow. Geneworks still suffered from numerous program "bugs" and frequently "crashed" after many hours of computation.

To begin analysis using DNAStar, folders corresponding to each project were set up on an external hard drive. This permitted reorganization of the data from its chronological form into working units. Sequence files were converted to DNAStar format and assembled using the Seqman II module. Our sequencing strategy always encompassed both strands of the DNA and covered each region at least four times.

When the final assembled sequence was obtained, it was saved to a file. This sequence was then translated to protein in all possible reading frames using the MAPDraw module of DNAStar, and the corresponding protein sequence(s) were stored in files. The sequence was also aligned with previously determined HIV-1 gene sequences using Align. The Align module permitted two-by-two sequence comparisons of DNA (Wilbur-Lipmann or Martinez-Needlman-Wunsch algorithm) or protein (Lipmann-Pearson) sequences. User-settable parameters included the Ktuple, gap penalty, gap length penalty, etc., permitting multiple iterations with different

parameters to find the optimal alignment. The output of this program was a similarity index", permitting initial assessment of sequence relationships. These procedures were used to verify the identity and integrity of clones. Occasionally, cloned HIV-1 gene segments exhibited frame shift mutations, in-frame stop codons, or substantial insertions/deletions relative to other HIV-1 sequences.

SUMMARY OF SIGNIFICANT FINDINGS

1. Genetic analysis of more than 250 international field isolates of HIV-1 from twenty-one countries on five continents was completed, constituting one of the largest international collection of HIV-1 isolates analyzed to date.

2. DNA sequences of fifty complete *gag* genes and twenty complete *env* genes of international HIV-1 isolates were added to the genetic database for HIV-1. These data revolutionized concepts of HIV-1 genetic variation and uncovered major flaws in current vaccine development approaches with respect to viral strain selection.

3. By phylogenetic tree analyses, at least five genetically equidistant, geographically dispersed subtypes of HIV-1 have been identified, which served as a guide for rational selection of vaccine prototypes relevant to the worldwide epidemic.

4. Subgroup-specific genetic signature sequences were used to develop a PCR typing system for HIV-1 with >85% accuracy. Field evaluation of HIV-1 genetic variation will employ these and other methods to prepare for vaccine trials.

5. A comprehensive evaluation of two genetic variants prevalent in Thailand, a site which may participate in early field trains of HIV-1 vaccines, was completed and applied to vaccine development/deployment strategies.

6. *In vitro* neutralization tests comparing viruses and sera representing prevalent Thailand and North American variants demonstrated limited cross reactivity, a finding of considerable importance for vaccine selection both in Thailand and elsewhere.

MAJOR COLLABORATORS:

The Military Medical Consortium for Applied Retroviral Research (MMCARR), particularly those investigators at Army and Navy laboratories overseas and clinicians at military hospitals in the U.S. who provide materials for study.

Guido van der Groen and colleagues, Prince Leopold Institute of Tropical Medicine,Antwerp, Belgium

Gerald Myers, HIV Sequence Database, Los Alamos National Laboratory, Los Alamos, New Mexico.

The Technical Working Group for HIV Isolation and Characterization, Vaccine Development Unit, Global Program on AIDS, World Health Organization, Geneva, Switzerland

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SEROLOGIC RESPONSES IN LENTIVIRUS INFECTIONS

OBJECTIVES

1) To find serologic markers for progression of HIV disease and evaluation of therapeutic efficacy
2) To perform serologic evaluation of vaccine efficacy in the simian model for acquired immunodeficiency disease.
3) To determine the mechanism of GP120 retention by virions of certain HIV and SIV strains, and its relationship to infectivity and pathogenesis.
4) To develop a synthetic subunit vaccine.

EXPERIMENTAL APPROACHES

1) Serum antibodies to HIV proteins appear early after infection and persist throughout most of the clinical phase of the disease. Yet some infected individuals become ill within 2 years while others stay asymptomatic for 10 years or more. No definitive pattern of antibody response indicative of immunity had been found.(1) Recent study of Shafferman et al (2) revealed, however, that serum antibodies against selected segments of the HIV envelope protein (gp160) could be correlated with progression of the disease. While antibody titers against certain regions of the molecule remain high in the late stage of infection, that against the NH2-terminal segment of gp 160 declines drastically.

To identify epitopes in gp160 that correlate with disease state in HIV-1 infected individuals, recombinant HIV gp160 were chemically cleaved (with BrCN) at 17 sites with Met residues. The resulting peptides were separated by polyacrylamide gel electrophoresis in the presence of SDS, transferred onto a cellulose nitrate membrane and reacted with serum of a HIV-infected individual. The epitopic peptides would react with respective antibodies which were detected with peroxidase-linked anti-hu-antibodies. Quantitation was achieved by reacting the blot with 125I-labeled protein A and

the radioactivity of the reacted bands cut out and counted. Under the optimum conditions, 1 mg of gp160 would yield 1000 Western-blot strips for serological testing. These were used to test seroreactivities in the sequential samples from patients under gp160 immunotherapy study (of Redfield et al).

The same strategy was employed with the simian model of the immunodeficiency virus infection, except that the envelope glycoprotein was isolated from the disrupted SIV particles. Purification method was developed, but the yield was too low to carry out the experiment. Preliminary study with genetically engineered protein containing 1/2 of gp160 sequence indicated that the BrCN fragments did not separate well on SDS-PAGE for mapping.

2) Monkeys develop immunodeficiency syndrome upon infection by SIV. Similarity of the structure of SIV and HIV and clinical course of infection make it a good animal model for the study of HIV infection in man. Four synthetic peptides with conserved sequences, 88-98, 500-511, 582-602, and 647-667 (Shafferman peptides), were purified and used to develop a reproducible peptide-ELISA. The procedure was used to evaluate antibody responses in monkeys immunized with b-Gal fusion proteins containing the four sequences. These monkeys were challenged with live SIV, and their clinical courses of infection as well as antibody responses were monitored (with peptide ELISA).

3) Mature HIV envelope protein gp160 consists of two proteins, the surface protein gp120 attached non-covalently to the transmembrane protein gp41. It had been known that gp120 of HIV tends to detach from the virion in the course of virus isolation, and the virus infectivity diminishes. The corresponding protein in SIV, however, was thought to stay bound to its transmembrane protein during virus isolation. How the shedding of gp120 affect the viral infectivity *in vitro* or *in vivo* had not been studied in detail.

In the course of preparation of HIV-3B on H-9 cells, the researchers observed that ultracentrifuge supernate contained a large amount of gp120/160 detectable by Western-blot analysis. Study of the phenomenon of gp120 shedding was thus undertaken. Viral culture supernatant was ultracentrifuged, and content of gp120/160 as well as virus infectivity in the supernatant and virus pellet were measured, the former with specific antibodies to gp120, and the latter by infection of H-9 (for HIV) or AA2 cells (for SIV)

4) A synthetic vaccine with a peptide coupled to a macromolecular carrier could have 10-20 fold more antigenic groups on the same weight basis, and was expected to elicit higher immune response with less dose. Four Shafferman peptides were chemically coupled to Carbopol, a biologically inert anionic polymer, and used to

immunize guinea pigs for antibody response. Antibodies to the four peptides were measured using the peptide ELISA developed in the study 2) above.

SIGNIFICANT FINDINGS

1) An optimized condition for the fragmentation, separation and Western-blotting was developed. With this method, a pattern of antibodies to nearly all regions of gp160 could be demonstrated with as little as 0.8 ug of gp160 and 10 ul of the test serum.

The results with clinical samples obtained from the gp160 immunotherapy study (of Redfield) indicated that among responders, antibodies directed against certain regions, 27-95, 105-147 and 435-475*, were much more abundant than those against other area of the molecule. The method thus appeared applicable to the search for serological markers correlating with stage (and possibly with protection) in HIV infection.

2) When monkeys were immunized with a mixture of 4 b-galactosidase fusion proteins containing the conserved sequences in SIV envelop, then challenged with live virus, most of them were protected from the virus infection (Shafferman, A., et al, 6th Int.Confer.on AIDS Abst.#SA. 74, 1990).

The four Shafferman peptides were purchased from UCLA peptide-synthesis facility, and purified by HPLC in the lab. Optimum conditions for peptide coating and ELISA procedures have been defined.

Antibody titers in the sera from monkeys infected with SIV E11s against each peptide were determined. Antibody titer against peptide s88 was the lowest and that against s582 was the highest in general. High antipeptide titers correlated well with protection of the immunized monkeys toward subsequent challenge with live virus.

The monkey sera from the protected monkeys, containing high anti-peptides titers, were found to protect native monkeys from infection with live virus.

3) Using a CD4 binding assay, 90-95% of the total gp120 was found in the virus-free ultracentrifuge supernatant (of HIV3B culture). On the other hand, the pelleted virus fraction was found to contain over 99% of the infectivity of the culture supernatant. The extensive shedding of gp120 was also observed with cultures of HIV-RF and, contrary to the general belief, of SIV culture on AA2.

In order to determine whether shedding of the envelope protein was related to the virus viability, a HIV3V culture supernatant (cell free-virus) was incubated at 37o for various

time, and their relative infectivities measured. The results indicated that as much as 80% of the virus infectivity was lost in 4 hr at 37o. On ultracentrifugation and measurement of gp120 content, over 90% of total gp120 was found in the virus-free supernate at 0 time. It thus appeared loss of gp120 might not be the only reason for the thermal inactivation of the virus.

4) Four Shafferman peptides chemically coupled to Carbopol were found to elicit 5-50 times higher antibody response in Guinea Pigs than did with b-Gal fusion proteins (with complete Freund's adjuvant). The results indicated that Carbopol acted not only as macromolecular carrier for the peptide epitopes, but also as adjuvant. Experiments on dose response and effect of peptide contents were needed to establish its efficacy.

FUTURE DIRECTIONS:

1) It is proposed that the test be extended to sera from patients at various clinical phases of the HIV infection. The analysis will provide information on the epitope(s) which are correlated with rapid progression of the disease. Identification of these peptide sequences will be useful in developing subunit vaccine for therapeutic use.

It will also be interesting and informative, if the test is carried out on the sera of chimpanzees infected with HIV-1. Chimpanzees may be infected with HIV-1, but they do not develop immuno-deficiency syndrome.

2) Participation in the study of the simian model of HIV-infection continues. In order to develop more reliable peptide ELISA, covalent coupling of peptides to the 96-well titer plates through Carbopol have been tested, with very promising results. This will be our immediate research project in the new grant years.

3) The clinical relevance of gp120 shedding by virions will be of interest. It has not been established whether gp120 is shed by cell-free virus *in vivo*. If they are, blocking of CD-4 and prevention of viral infection (by the free-gp120) is conceivable. It would make cell-free transmission of virus rather unlikely.

4) The Carbopol-linked peptides appear to be the more effective vaccine than genetically engineered proteins. Further studies on its safety and efficacy *in vivo* appear warranted.

HIV GENE THERAPY

OBJECTIVES:

Development of an efficient gene delivery system capable of transducing and expressing HIV immunogens and anti-HIV antiviral agents to prevent HIV infection in Military population or to preserve the immune system of HIV infected combat personnel. Specifically, to:

1) Develop efficient gene delivery systems capable of transducing and expressing genes encoding HIV and SIV antigens and anti- HIV/-SIV antivirals.

2) Evaluate efficacy, safety and toxicity of prophylactic and immunotherapeutic vaccine and antiviral strategies using gene delivery systems in mouse, SCID-Hu mouse and Rhesus macaque models.

3) Evaluate clinical efficacy of the gene therapy strategies in both early stage HIV infected and uninfected military populations.

BACKGROUND:

To date, the immune mechanisms that might contribute to the prevention or reduction of the pathological effects of HIV infection in the military population are poorly understood. Early stage military personnel infected with HIV show potent T cell proliferative and cytotoxic T cell responses specific to HIV. Moreover, these individuals have developed high titer anti HIV antibody responses capable of neutralizing cell free viral transmission in culture. Despite the apparent potency of these responses, the immune mechanisms induced in infected individuals are not sufficient to clear the virus and thus prevent disease progression. However, the immune response induced in HIV infected personnel may significantly contribute to controlling early stages of infection before manifestation of AIDS. This research area was designed with two arms of intervention. The first intervention strategy involved the use antigen delivery systems to either boost immune responses in early stage HIV infected military personnel or to prophylactically vaccinate uninfected combat troops. The second intervention strategy required the use of delivery systems capable of expressing anti-HIV antiviral agents such as antisense or ribozymes in CD4+ target cells to thwart HIV dissemination in early stage HIV infected personnel.

EXPERIMENTAL APPROACHES:

Element 1: The Development of Gene Delivery Systems: Production of Recombinant Retroviral Vectors

i) MoMuLV based Retroviral Vectors
ii) MoMuLV Vector Packaging Cell Lines
iii) HIV-IIIb based Retroviral Vectors
iv) HIV-IIIb Vector Packaging Cell Lines

ELEMENT 2: The Development of Prophylactic and Immunotherapeutic Vaccine Strategies.

i) Direct Intramuscular Injection of DNA Encoding HIV and SIV Antigens
ii) The development of Retroviral Vectors as Antigen Delivery Vehicles
iii) Development of other Antigen delivery systems

ELEMENT 3: The Development of Antiviral Intervention Strategies

i) Somatic Cell Therapy - Engineering Mature CD4+ T-cells Resistant to HIV Expression and Replication.
ii) Stem Cell Therapy - Engineering Pluripotent Bone Marrow Derived CD34+ Cells Resistent to HIV Expression and Replication.

METHODS AND SIGNIFICANT FINDINGS

A) Immunization of Rhesus Macaque by Direct DNA Injection

The researchers set out to test whether direct intramuscular DNA injection of an SIV based plasmid expression vector could lead to specific anti-SIV cellular and humoral immune responses in Rhesus macaque. Three Rhesus macaques were injected 4 times at 7 day intervals with 200ug of a purified plasmid expression vector encoding SIV-ENV239. Sera from animals bled at weekly intervals for a two month period developed no detectable SIV-ENV specific antibody responses. Since neither T cells proliferation assays nor cytotoxic T lymphocyte assays were developed at this time neither were performed.

These 3 monkeys were boosted with a fifth intramuscular injection of the DNA expression vector 2 weeks prior to challenge with 10 ID50 of SIV 251. Sera drawn from the animals prior to challenge again showed no detectable antibody response. However, T cell proliferation assays performed in the presence of IL-2 and antigen on the PBMC derived from each animal revealed that each animal did indeed react to the injection protocol. Animals 1710, 0711 and

1306 developed stimulation indices (SI) of 4.3, 12 and 21.3 respectively. Control animals routinely showed SI of approximately 0.7. Upon challenge with SIV 251 monkey 0711 and 1306 developed anamnestic response to the SIV envelope protein. Monkey 1710 responded poorly to challenge and never developed high titer antibodies. Levels of p28 during the acute infection were barely detectable in animal 1306 while p28 levels 6 ng/ml in animals 1710 and 0711. Typically p28 levels drop after the acute phase of infection presumably due to anti-SIV antibody responses. Although none of the animals appeared to experience any toxic effects from the injection of the DNA, their sera were not monitored for anti-DNA activity. Animal 1710 died of SIV associated complications.

The intent of this preliminary experiment was not to assess vaccine efficacy but rather to determine if direct intramuscular injection of a DNA expression vector could lead to a specific immune response and if such an approach would be well tolerated in a non-human primate. Since the data from this experiment was compelling and showed the induction of SIV specific immune responses by direct DNA injection, the researchers plan to pursue the following strategy.

FUTURE PLANS:

1) Construction of CMV/SIV-239GAG/Pol/ENV, whole defective virus expression vector, April 1, 1993

2) Construction of CMV/hu-IL-2 and CMV/hu-GMCSF cytokine expression vectors (for possible use as immune modulating molecules), June 1, 1993.

3) Establish collaboration with Karl June and Kelvin Lee to develop rodent model system for analyzing immune response, May 1, 1993.

4) Direct intramuscular injection of Rhesus macaques with above expression vectors, July 1, 1993.

5) Challenge animals with low dose SIV 239, December 1, 1993

6) Set collaboration with Mary Anne Vahey: To quantify viral burden in challenged monkeys, July 1, 1993.

B) Immunization by Infection with Retroviral Vectors

The researchers previously reported the initial demonstration in mice of the feasibility of using retroviral vector mediated gene transfer as a means of delivering genes encoding HIV antigens to induce HIV specific immune responses. Mice immunized with autologous retrovirus transduced cells developed CD8+ Class I restricted immune responses specific to HIV-ENV capable of killing

specific target cells *in vitro* and *in vivo* despite the low levels of envelope expression in the transduced cells. The specificity of killing appeared to be in part directed against determinants within the variable loop, V3, of HIV-IIIb gp120. Memory CTL specific to envelope were observed in animals immunized 9 months prior to testing. This result suggested that immunization with transduced cells led to at least some memory responses. Moreover, the induction of neutralizing antibody responses specific to gp160 in this study suggested that the transduced gp160 was also presented to B and T helper cells in the context of Class II MHC. The mechanism of Class II presentation in this context or the role of T helper cells in the induction of cytotoxic T lymphocytes was not evaluated.

The researchers constructed several retroviral vectors capable of expressing either the HIV envelope protein or the SIV envelope protein. Each vector construct ranged in titer from 5x104 to 105 CFU and varied in its ability to express gp160, gp120, gp41 and REV in the transduced cells. These vectors were ready to be tested as possible vaccine candidates in Rhesus macaques.

FUTURE PLANS:

1) Evaluate recombinant retroviral titer and expression of envelope gene in transduced autologous primary rhesus skin fibroblasts, July 31, 1993.

2) Construct retroviral vectors capable of expressing hu-IL-2 or hu-GMCSF, July 15, 1993.

3) Set collaboration with Mary Anne Vahey: To quantify the possible presence of replication competent MoMuLV viral vectors in transduced cells and to quantify viral burden in challenged monkeys, July 1, 1993.

4) Immunize Rhesus macaques with transduced autologous skin fibroblasts, September 1, 1993.

5) Analyze immune response in immunized animals, October 15, 1993.

C) MoMuLV based Retroviral Vectors

There are two prototype retroviral vectors developed by our laboratory, N2* and N2*SD/SA. Both vector types can be engineered to transduce a dominant selectable marker in addition to the segments of the HIV or SIV genome or anti-HIV antiviral coding sequences. The dominant selectable marker in the retroviral vector facilitates the identification of transduced cells by conferring resistance to cytotoxic drugs. Since the researchers observed that some promoters used to direct expression of the

dominant selectable marker down regulated the constitutive expression of genes directed by the 5' LTR, the vectors were designed to express the dominant selectable marker either from a spliced mRNA or from a bicistronic mRNA the containing EMCV ribosome binding site upstream from this gene. Finally, to optimize expression of the recombinant provirus in specific cell types, the enhancer sequences located in the LTRs could be replaced with other viral or cellular enhancer elements with known specificity. Alternative retroviral vector designs also constructed by Gilboa included the expression cassette in the U3 region of the LTR. positioning of the gene in this position of the vector results in more consistent expression of the transduced gene.

MoMuLV Based Packaging Cell Lines: In order to prevent the generation of replication competent virus by recombination events, the researchers were currently developing packaging cell lines which are non murine in origin in both African Green Monkey Kidney Vero cells and a Dog cell line, D17. Neither of these cell types harbored any known endogenous retrovirus. Furthermore, Howard Temin had successfully developed a safe packaging cell line for spleen necrosis viral vectors using D17 cells. Both the Vero and the D17 cells had been stably transfected with separate GAG/POL and ENV expression vectors. The researchers were also in the process of setting up a contract with ABI to generate rabbit anti Moloney GAG, GAG/POL and ENV antibodies using either of both purified inactivated amphotropic virus and a recombinant vaccinia vector expressing the amphotropic ENV gene. This sera will used to measure the levels of viral protein expression in the two packaging cell lines. Furthermore, clones derived from the transfection would be assayed for their ability to produce high titer recombinant retrovirus, free from replication competent virus.

FUTURE PLANS:

1) Construction and testing of MoMuLV based Retroviral Vectors: March 15, 1993

2) Construction and preliminary testing of MoMuLV GAG/Pol and ENV expression vectors: May 15, 1993

3) Characterization of anti MoMuLV antisera produced at ABI: June 30, 1993

4) Construction and characterization of 3rd generation MoMuLV packaging cell line: November 15, 1993

D) Molecular and genetic characterization of first generation HIV packaging cell lines

Three putative HIV-1-based packaging cell lines were engineered within the laboratory; a) Vero line, Vero/LTR-Hygro, and a HT1080 cell line, HT1080/LTR-Hygro, were stably transfected with an expression vector containing an HIV-1 provirus derived from HXB2 from which the 3' LTR, the NEF and VPU genes and packaging signal were deleted and a synthetic polyadenylation signal was added, and b) a Vero cell line, Vero/CMV-Hygro, was stably transfected with an expressing vector similar to the one above except that the CMV promoter replaces the 5' HIV LTR. To date only the Vero/LTR-Hygro had been characterized. Two subclones derived from this transfection, D3.2 and B4.7 showed high levels of p24 GAG antigen and reverse transcriptase activity into the culture supernatant. Electron microscopic analysis of both cell lines revealed the presence of both mature and immature virus like particles budding from the cell surface. Both precursor GAG, GAG/POL, and ENV proteins and processed p24 and mature gp120 were detected in these packaging cell lines by radioimmunoprecipitation with antigen specific anti-sera. Preliminary transduction experiments suggested that both cell lines were capable of packaging a recombinant HIV-1 vector (see below) with a titer of approximately 103 CFU/ml.

Construction and characterization of first generation retroviral vector systems: The HIV-1-based retroviral vector pSK-HXMoNe was derived from HXB2 and includes both the 5'and 3' HIV-1 long terminal repeats and gag coding sequences extending to the Apa I site at nt 2005, the splice donor site (S.D.) and packaging signal (Ψ) derived from HIV-1 (all nt coordinates are with respect to the HXB2 genomic map). A frameshift mutation was introduced into the gag coding sequences, resulting in termination of translation 21 codons downstream from the initiation signal. To ensure the stability of the vector RNA, an 853 nt DNA fragment containing the HIV-1 RRE was inserted downstream of the gag coding sequences. The Moloney murine leukemia virus (MoMuLV) promoter directs the expression of the dominant selectable marker, neomycin phosphotransferase gene. The 3' terminus of pSK-HXMoNe contains HIV-1 coding sequences downstream of the Xho I site at nt 8896, as well as the 3' LTR.

To generate transducing particles the packaging cell lines D3.2 and B4.7 were stably transfected with duplicate clones of pSK-HXMoNe. Titration of the recombinant HIV vector by exposing the human T cell line, SupT1, to dilutions of filtered culture supernatant derived from the pooled putative vector producing clones resulted in vector titers approaching 103 CFU/ml.

FUTURE PLANS:

1) Confirmation and characterization of transducing properties of first generation retroviral vector systems: end July, 1993.

2) Molecular and genetic characterization of HIV-1-based packaging cell lines: end November 1993.

3) Optimization of packaging cell line properties and construction of improved HIV-1-based packaging cell lines: begin November 1993.

Conclusion

The Retroviral Biology Mission Area made substantial progress in the three areas of Viral Variation, Serologic Responses in Lentiviruses and HIV Gene Therapy. Foundation and Military scientists and technicians diligently worked to achieve the stated objectives. The results have been a comprehensive and collaborative effort towards the ultimate goal of developing and assessing new vaccine candidates for the prevention of HIV infection. Utilizing a PCR typing procedure developed by the mission area Director, more than 250 international HIV-1 isolates from North America, Europe, South America, Africa and Asia were being characterized. DNA sequencing of isolates identified as divergent by polymerase chain reaction (PCR) typing greatly enriched the genetic database for HIV-1, adding several new "branches" to the phylogenetic tree. Studies from more than 26 worldwide locales have shown that HIV-1 subtypes were often intermixed geographically, including those locations that were under consideration for early vaccine trials. A repository of cloned, sequenced HIV-1 genes relevant to vaccine development was established and is now available to all requestors interested in HIV vaccine development. Additionally, a bank of titrated viruses and patient sera was generated and then assayed to develop data on neutralizing antibodies and cross reactivities to compile matrices of neutralizing antibody serotypes. These data combined will provide a rational framework for the selection of HIV-1 vaccine prototypes and the development of reagents and assays related to planned vaccine evaluations.

Future Studies Planned

Future work in Retroviral Biology will continue as outlined in the aforementioned areas. Summarily, this mission area will serve as a primary laboratory effort supporting the development of a vaccine for the prophylaxis of HIV infection.

F. ANIMAL MODELS MISSION AREA

GERALD A. EDDY, D.V.M., Ph.D., DIRECTOR*

MAP SUMMARY: The Animal Models MAP utilized the concept that the best method for developing therapeutic and prophylactic vaccines for the prevention of HIV related human disease is to compare, select and refine HIV strategies in an animal model system.

Protocol #	Protocol Title (Abbreviated)	Principal Investigator
RV-A1	Mouse Primate Chimeras	Rosenberg*
	(ADD)SCID/HU and SCID/MAC	Rosenberg
RV-A2	SIV-647 Peptide Vaccination	Lewis*
RV-A3	Vaccine for SIV (Peptides)	Lewis
	(ADD)Lymph Node Transfer from RVA3	Lewis
	(ADD HIV-2 Challenge of RVA3	Lewis
	(ADD) Lymph Node Biopsy from RVA3	Lewis
RV-A4	Immunologic Potential (Galactosidase)	Lewis
RV-A5	HIV-2 of Rhesus Monkeys	Gartner*
RV-A6	Immunology with Individual Peptides	Lewis
RV-A7	Immunogenicity of HIV-1 Peptides	Lewis
RV-A8	Protective Effect of Neutralizing Antibody	Lewis
RV-A9	Evaluate Whole virus vaccine SIV	Lewis
RV-A10	Immunogenicity of SIV Transgenes	St. Louis*
	(ADD)Immune Response Against Expressed Antigen	St. Louis
RV-A11	Routine Antibodies Collection	Lewis
RV-A12	Vector Expression of SIV Env Gene	St. Louis
RV-A13	Heterologous Challenge/Developed Immunity	Lewis
RV-A15	HIV-1 Models in Primates	Gartner

***Foundation Principal Investigator (PI)/Scientist**

ANIMAL MODELS MISSION AREA

Overview

The use of animals for HIV research was a major component of the HIV Research program, and the effort included both primate and rodent studies. Animal models were utilized to address safety and toxicity issues of new drugs and vaccines, before human use, and also were used to examine the mechanisms of HIV disease and the nature of the immune response to HIV. Animal studies conducted to meet these objectives were necessarily diverse and ranged from the establishment of a colony of severe combined immunodeficient (SCID) mice and SCID-human (SCID-hu) chimeras to the testing of a vaccine in rhesus monkeys for the purpose establishing and validating a product with potential for use in humans.

The SCID-hu mouse was thoroughly characterized and found to be difficult to establish as a SCID-macaque (SCID-ma) system because of the large number of cells required and because the macaque cells do not persist as well in the SCID mouse. Nevertheless the human chimeras, the SCID -hu mouse, has been found to have utility. It was initially used in the Foundation program to assess the effects of AZT in the system. Mission Area scientists showed by PCR that AZT treated infected mice retained viral genome in the transplanted human cells for an extended period of time as compared to the untreated infected animals which lost their human cells early due to viral activity.

The simian immunodeficiency virus (SIV)-macaque model was thoroughly characterized and it was used to explore the efficacy of the Shafferman peptide vaccine. These studies showed an altered course of disease progression in monkeys immunized with the vaccine even though the monkeys became infected. Another experiment revealed that vaccinated monkeys serum could protect other monkeys against challenge with the E11s strain of SIV. This use of the SIV model provided a foundation for experimental approaches and expertise that could directly strengthen future testing of vaccines for relative efficacy. In addition, the attempt to adapt HIV-1 to macaques achieved preliminary success in that the virus was successfully passaged in pigtailed macaques by Principal Investigators in this mission area.

Summaries of three areas of concentration are discussed in detail below: Model development and characterization, Pathogenesis Studies, and Vaccines and Immunization. In the discussion outlined below, summaries are given of the major research accomplishments in each area. It should be emphasized that the animal studies conducted under this MAP were reviewed for scientific validity by the Animal Studies Steering Committee of

the Foundation and were then reviewed for ethical use of animals by the Foundation's Laboratory Animal Use Review Committee (LAURC).

MODEL DEVELOPMENT AND CHARACTERIZATION

In collaboration with others, scientists within the program characterized different SIV macaque models of infection. This was done to provide options for the conduct of research with a spectrum of viruses and virulence. The viruses were initially evaluated and the disease course characterized either by Foundation mission area scientists or other scientists from outside organizations. Those viruses selected for use were then titrated *in vivo* and the patterns of circulating virus, hematologic changes, immune responses, opportunistic infections and time intervals to disease and death were measured.

In addition to the primate models, other mission area scientists developed and used the SCID mouse for modelling HIV. The SCID permitted the establishment of selected components of the human immune system within a mouse for the purpose of studying those functions in an *in vivo* system. Specific studies conducted under the research area of model development and characterization included:

•SCID Mice as an Animal Model for HIV and SIV Infections.

The SCID mouse model was developed as a means of extending our knowledge regarding the patho-physiology of HIV and SIV *in vivo* and for developing a read-out to assess the efficacy of potential drugs, therapeutics and immune lymphocyte populations derived from protected or partially protected patients or monkeys. An efficient breeding program was established which produced healthy SCID mice and to date >100 were injected with monkey or human PBMC to learn the best method for reconstitution. A staining procedure was developed to separate the few primate cells from the predominately mouse cell suspensions. Tissues from several foetal monkeys were obtained and inserted under the kidney capsule, and sections cut to see how well these tissues developed. Several modifications of the original protocol appeared to result in more successful reconstitution, e.g. the use of young mice (<2 weeks), more than one injection of cells, and increased cell numbers. Transfer of human PBMC was very successful (30% of SCID spleen). To optimize the system, mice given macaque LN cells also received the virulent SIV-PBj-14 and co-culture; PCR assays were also developed to assess viral replication.

•SIV/PBj Studies.

A variant of simian immunodeficiency virus, SIVsmPBj (PBj virus), isolated from a chronically infected *Macaca nemestrina*, in previous studies, produced acutely fatal disease in this species. These studies extended investigation of PBj virus pathogenesis to rhesus and cynomolgus monkeys. Both species were sensitive to infection after intravenous inoculation with PBj virus. Cynomolgus and rhesus macaques were uniformly infectable, but the rhesus were not uniform in their response to infection. Five of six rhesus monkeys that received intravenous inoculation of 100 TCID from either spleen or lymph node homogenates developed acute disease; 4 died acutely (days 8-10), 1 recovered, and one rhesus remained asymptomatic. Three of three cynomolgus macaques and four of four pigtailed macaques receiving the same inoculum died acutely within 9 days. Clinical disease in macaques that died was characterized by diffuse lymphadenopathy within 5 days of inoculation and severe diarrhea beginning 1 to 3 days before death. Anorexia, lymphopenia (<1000 cells/mm), and mild hypoalbuminemia preceded onset of diarrhea by 24 hours. Viral structural protein was detected in circulation by day 6 post infection and all animals dying acutely had detectable gag antigen, p27, in their serum and no detectible humoral response at death. Acute lethality was attributed to severe metabolic acidosis (pH <7.20) which was observed 24-48 hours prior to death in the pigtailed and cynomolgus macaques. Immunohistochemistry revealed numerous SIV antigen positive lymphocytes and macrophages in the lymph nodes, spleen, gut-associated lymphoid tissues and gastrointestinal lamina propria. Histopathologic lesions included marked to severe hyperplasia of the T-cell dependent areas in lymphoid tissues and diffuse non-ulcerative lymphohistiocytic enteritis of the gastrointestinal tract. Surviving rhesus developed strong humoral immune responses to the major SIV proteins.

•Infection of Rhesus and Cynomolgus Macaques with a Rapidly Fatal Isolate (SIVsmm/PBj).

A variant of simian immunodeficiency virus SIV_{PBj}, isolated from a chronically infected pigtailed macaque at the Yerkes Primate Research Center, was shown in previous studies to produce acutely fatal disease in pigtailed macaques. These studies extended the investigation of SIV_{PBj} pathogenesis to rhesus and cynomolgus monkeys. Rhesus monkeys were inoculated intravenously with human peripheral blood lymphocyte or with spleen cell cultures from the original pigtailed macaque SIV_{PBj}. All seroconverted, but only one rhesus died acutely. Homogenized tissues from this rhesus were passaged to 6 additional monkeys in an attempt to increase lethality. Five of six juveniles receiving 100 cell culture doses of spleen or lymph node virus developed acute disease, and four died, one recovered and

subsequently died after 382 days, and 1 remained asymptomatic. All cynomolgus macaques receiving the same inoculum died acutely within 8 days. After three additional *in vivo* passages, virulence increased. Clinical disease was characterized by diffuse lymphadenopathy within five days of inoculation and severe diarrhea beginning one to three days before death. SIV p27 antigen was detectable in the blood of acutely infected animals as early as 4 days after inoculation, and its appearance correlated with the lymphopenia and lymphadenopathy. Surviving animals developed strong antiviral immune responses. Viral burdens, as measured by immunohistochemistry and *in vitro* titration of tissues correlated with disease severity, as did concentrations of cytokines. The role of soluble mediators in pathogenesis of SIV, and the possible beneficial effects of cytokine antagonists in reduction of SIV induced disease warrants investigation.

•SIV Titrations and Infection Studies

Three SIV challenge stocks were titrated in rhesus macaques to determine their respective fifty percent infectious doses (ID50) for future studies. The virus isolates were SIV/MneE11s, SIVmac251 and SIVmac239. The E11s pool is a biological clone derived from *Macaca nemestrina* at the Washington Primate Center and maintained continuously in a human T cell line, HuT 78. The SIVmac isolates were grown in rhesus peripheral blood lymphocytes. The SIVmac251 isolate was obtained directly from the tissue of original rhesus macaque Mm251-79. This virus inoculum was chosen to make a challenge pool in order to eliminate any potential screening of the virus population by passage through a neoplastic or a nonrhesus cell. The mac239 pool was generated by electroporation of cloned proviral DNA into rhesus PBL. For the mne/E11s titration 21 monkeys were used, and were separated into 6 groups. Log10 dilutions of the pool were generated with the first dilution starting at 10-4. The ID50 determination was a dilution of 10-4.66. The SIVmac titrations used 18 monkeys per virus pool. The SIVmac251 was diluted starting at 10-2.5 with log10 dilution to 10-6.5. The ID50 for this pool was calculated to be 10-4.58. The SIVmac239 pool starting dilution was 10-3.5 with log10 dilutions to 10-7.5. The ID50 for the 239 pool was calculated to be 10-5.75. A comparison of the virologic and immunologic reactions during the infection of the macaques with the different pools showed that the 251 and 239 virus developed a detectible viremia within 7 days and developed antigenemia within 14 days. Antibody could be detected within 5 weeks. E11s gave a different pattern with r, detectible antigenimia and detectable viremia by 3-4 weeks. Antibody to E11s was usually observed by 4-6 weeks. In separate studies with SIVsm/PBj it was found that viremia and antigenemia was observed within 2-4 days and antibody was detectible by 2-3 weeks.

•Infection of Pigtailed Macaques with HIV-1

This specific study pursued the goal of developing a macaque model for HIV-1 infection. Initially, animal model scientists systematically evaluated the susceptibility and permissivity of peripheral blood mononuclear cells from three species of macaques to HIV-1 *in vitro*. It was observed that peripheral blood-derived TO lymphocytes and monocyte/ macrophages from pig-tailed macaques were considerably more permissive for HIV-1 than comparable cells from cynomolgus and rhesus macaques. Optimal infectivity was dependent upon the virus strain and multiplicity of infection used, and in the case of the TO lymphocytes, their proliferative status. The kinetics of HIV-1 infection in pig-tailed macaque TO lymphocytes was comparable to that observed for normal human TO cells, but peak expression was only 1/10-1/100th that of human cells. Semi-quantitative PCR analyses indicated that the low virus expression observed was a consequence of limited permissivity rather than limited susceptibility of the cells. Although electron microscopic examination revealed the presence of morphologically normal HIV-1 particles in the cultures, the infectivity of these particles was frequently limited, as determined by infectivity experiments using human and macaque target cells.

Four pig-tailed macaques were inoculated with cultured HIV-1-infected autologous cells harvested at peak virus expression. HIV-1 was isolated from peripheral blood mononuclear cells from 3 of the 4 animals at various times during the first 10 weeks post inoculation (PI), and from biopsied lymph node tissue from one animal at week 6 and another at week 10. Additionally, HIV-1 genome was detected in some uncultured specimens from which infectious virus was not recoverable. During the first 12 weeks after infection, no HIV-1-specific antibody was detected by Western blot, but in some cases, was detected by radioimmunoprecipitation. Later serology revealed strong antibody patterns which developed 25 to 30 weeks following initial infection. *In vivo* passage experiments were ongoing with originally passaged virus and with macrophage passaged derivatives.

PATHOGENESIS STUDIES

Essential to the understanding of how vaccines and therapeutic interventions work, or fail, are studies of pathogenesis which tell much about the mechanisms of disease and immunity. The studies summarized in this section describe much of what is known about HIV/SIV infections and disease:

The Role of CD45RA Low Cells in CD4+ Cell decline

Although circulating CD4%, CD4+ cell counts and CD4/CD8 ratios are most commonly used in evaluating clinical progression to AIDS, it is not known how these values reflect changes in the much larger CD4+ cell pool in lymphoid organs of infected individuals. Studies in 15 monkeys infected with SIV-PBj-14 and 6 immunized monkeys challenged with the E11S isolate both indicated that despite the well characterized loss of CD4+ cells from the circulation during the acute and chronic phases of infection, the CD4+ pool in LN remained within the normal range. However, when blood CD4/CD8 ratios fell below a value of around 0.5, several major changes in Lymph Nodes (LN) were consistently observed :

(i) a dramatic decline in CD4% and CD4/CD8 ratios
(ii) the appearance of SIV antigen staining on follicular dendritic cells within germinal centres by immunohistochemical techniques and
(iii) a marked phenotypic change in the LN CD8+ pool from predominantly CD45RA high to an activated CD45RA low population.

Such a population, which was not seen in nodes from normal monkeys,was observed in mesenteric, inguinal and axillary LN of all infected macaques with decreased nodal CD4 percentages. These CD8+ cells proliferated well *in vitro* when cultured with rIL 2 and appeared to selectively grow out of semi-purified Follicular Dendritic Cell (FDC) cultures from infected LN. They may play a role in the destruction of autologous infected or uninfected LN CD4+ cells as well as the degeneration of follicular dendritic cells, particularly in interdentritic spaces where antibody complexed whole virions and viral proteins are localized. CD8+ cell lines from infected LN were maintained *in vitro* and tested for gd TO cells, NK cells and ab TO cell cytotoxicity. These findings suggested that despite CD4+ cell loss from the circulation throughout HIV infection, it was the immunological collapse of the LN which resulted in the disease susceptibility characteristic of AIDS. Many of the underlying mechanisms leading to such a collapse e.g. the accumulation of virus in LN, loss of FDC function, decline in CD4% and an emerging destructive imbalance between LN CD4+ and CD8+ TO cells appeared to be autoimmune in nature.

The Appearance of SIV Antigen on the Follicular Dendritic Cells of SIV Infected Macaques Is Associated With a Dramatic Decline in the CD4+ TO Cell Pool.

Although circulating CD4%, CD4+ cell counts and CD4/CD8 ratios were most commonly used in evaluating clinical progression to

AIDS, it was not known how these values reflect the CD4+ cell pool as a whole. Studies in 22 monkeys infected with either the SIV_{PBJ} and E11S isolates both indicated that during the acute disease and for most of the long term infection, the marked changes in the circulating CD4+ cell pool occurred without any quantitative loss of CD4+ cells from lymph nodes which remained within the normal range. However in monkeys where the blood 4/8 ratio fell below a value of around 0.5, major changes in LN were consistently observed as described above and the appearance of SIV antigen staining on follicular dendritic cells within germinal centres by immunohistochemical techniques were observed. This did not appear to be produced within these cells. Findings indicated that since only 1-2% of lymphocytes circulate at any one time and LN remained relatively constant despite the changes in blood, the loss from the total CD4+ population was minimal until the final stages of SIV disease and suggested that the onset of AIDS in monkeys and humans might occur as a consequence of this large decrease in CD4+ cells from within the lymph node pool. Thus, the increase in SIV antigen expression on FDC reflected increased viral replication, a corresponding loss of FDC function and decline CD4% and a potentially destructive imbalance between CD4+ and CD8+ T cells might all be interrelated and could lead to the final collapse of the immune system and AIDS.

Differences in T cell Function in Rhesus and Pigtailed Monkeys: Implications Regarding Susceptibility to SIV Infection.

Circulating TO lymphocytes in primates were usually divided into two subsets: CD45RA+, CD29-, CD45RO- antigen naive resting cells and CD45RAlo/-, CD29+ CD45RO+ memory cells which also expressed other activation markers, e.g. CD44, CD11a (LFA-1) and CD54 (ICAM-1). Using the anti-CD45RA MAb ALB11, a third CD45RA high subset was further delineated in the periphery in addition to that described above for memory and naive TO cell pools. This third peak appeared to be partially activated, and contained cells which also expressed high levels of CD29, CD11a, CD44 and CD69. Accordingly, FACS purified CD45RA high cells, unlike purified CD45RAmed cells, were unresponsive *in vitro* to PHA but reacted to IL 2, indicating the presence of high affinity IL 2R+ cells. Thus, the larger the pool of circulating CD45RAhi, the relatively more defective the PHA response was. Although CD45RA staining profiles in humans and monkeys varied depending on the sizes of the three peaks, different monkey species usually exhibited characteristic profiles and functional properties. Following infection with SIV, defects in TO cell function became even more dramatic in that responses to PHA, PMA and IL 2 were all diminished. This altered responsiveness, both prior to SIV infection and especially post infection, was not irreversible and responses could be increased 5-10 fold by two

different but related procedures; first, by the addition of indomethacin to the PHA cultures and secondly by resting the cells *in vitro* prior to the addition of mitogen. The above findings could account for increased susceptibility of pigtailed monkeys to infections with SIV both *in vivo* and *in vitro* and suggested that PHA activation alone might not be sufficient for detection of virus present in CD45RAhi cells.

Follicular Dendritic Cell (FDC) Function In Lymph Nodes of SIV Infected Macaques.

This study demonstrated that FDC served at least two major functions(i) to present unprocessed antigen in the form of iccosomes to B cells and(ii) as a source of costimulatory signals required for B cell (and TO cell) proliferation. In late stage HIV and SIV infections, decline in CD4/CD8 ratios was associated with accumulation of viral antigens on FDC and infiltration of germinal centres by activated CD8+ cells culminating in FDC degeneration and follicular involution. The data in this study examined the ability of such damaged FDC from lymph nodes of SIV-infected macaques to promote cluster formation and B and TO cell proliferation and effector function. The results indicated that surprising FDC-enriched cultures of lymph node cells from infected macaques exhibited more vigorous germinal center reactions than control LN cultures. Proliferation was still evident in some cultures cell growth at 20 days. This enhanced ability to support B and TO cell proliferation suggested that FDC damage did not reduce their capacity to provide costimulatory signals and that when present in germinal centres, CD8+ cells might also benefit from FDC-derived factors.

Phenotypic and Functional Alterations in Primate Lymphoid Organs Following SIV and HIV Infection.

The goals of these studies were to examine the susceptibility of lymphoid organs to infection with HIV and SIV and to compare alterations in the phenotypic and functional properties of those TO cell subsets which may be differentially affected by infection. The anti-CD45RA MAb ALb11, which delineates human and monkey TO cells into three distinct CD45RAlo memory cell, CD45RAmed antigen naive cells and a third CD45RAhi partially activated 'anergic' subsets was used in conjunction with MAb to other activation markers to both define the subsets present in thymus, spleen , lymph nodes and PBL of single individuals and to monitor the extent of TO cell triggering. Studies were performed with tissues either removed from infected monkeys or with normal human or monkey thymuses or spleens cultured as fragments *in vitro*.

(I) Analysis of peripheral lymphoid organs from SIV_{PBj} infected rhesus and pigtailed monkeys indicated that despite the absence of circulating lymphocytes, activation in lymph nodes, in contrast to that seen in spleen, was quite vigorous. Proliferative potential in mesenteric LN however differed from that in the distal axillary nodes.

(II) Examination of the susceptibility to,and efficacy of, infection of lymphoid organs in which lymphocytes were 100 times more concentrated than in PBL, by establishing fragments cultures of monkey and human thymus and spleen which were infected with HIV and SIV. In agreement with previous reports using PBL, these results demonstrated that, depending on the viral isolate, a loss of CD45RAlo, CD45RO+, CD44+, CD4+ memory cells in addition to CD45RAhi, CD45RO- activated cells can occur within 11 days after infection. In contrast, CD45RAmed, CD45RO-, CD44lo naive resting cells remained in the fragments. However, in studies with PBL from rhesus monkeys infected with the less cytopathic E11S virus or those rhesus that survived SIV_{PBj} infection, modulation of CD45RAmed to CD45RAhi expression could be demonstrated. Indeed, this skewing, which led to a change in the ratio of resting/activated CD45RA+ cells appeared in most cases to be an indicator of circulating virus. Alterations in CD45 expression resulting from binding of inactivated virus to cells in these cultures will also be discussed.

Cytokine Studies in Acute SIV Infection.

Interleukin-6 (IL-6) is an important mediator of the acute inflammatory responses associated with tissue damage and B cell activation. It is released by numerous cell types, and one of its roles is induction of acute-phase reactants in the liver. IL-6 and other cytokines have also been implicated as potential activators of lentivirus replication. Animal Model scientists measured the levels of the cytokines IL-6 and tumor necrosis factor (TNF) alpha in serum samples of macaques experimentally infected with PBj virus, an acutely lethal SIV strain that causes death within 10 days of inoculation. Three different species of macaques (rhesus, cynomolgus and nemestrina) were used in this study, and all were susceptible to SIV_{PBj} virus infection and acute death. (See Model Development Section above.) No significant increase in circulating levels of TNF-alpha was observed in serum samples. High levels of circulating IL-6 were observed in all acutely infected macaques. The highest levels of circulating IL-6 were observed in *Macaca*

nemestrina, pigtailed macaques, which died acutely with a 10,000 fold increase over normal. Cynomolgus macaques dying acutely developed between 100 to 10,000 fold increases of IL-6 and rhesus macaques had between 10 to 100 fold increases. Rhesus that survived the acute disease associated with SIV_{PBj} virus had an initial rise of circulating IL-6 which returned to normal or near-normal levels by 10 to 15 days post challenge. *In situ* hybridization for IL-6 message in tissues collected from animals that died acutely showed high levels of IL-6 mRNA in numerous cell types including lymphocytes, monocyte/macrophage and fibroblasts. The amount of IL-6 found in tissues samples collected at death correlated directly with tissue virus load as determined by virus isolation and immunohistochemistry.

VACCINES AND IMMUNIZATION

A primary goal of the HIV research program was the prevention of infection with the emphasis on the development of an immunogenic vaccine that protected exposed recipients against disease and halted transmission. The development of a potential vaccine was initially demonstrated by animal studies. These and other studies are described below. It should also be noted that as a result of the studies described below, the MMCARR has decided to proceed with the production of the human use product for further study in man as a prophylactic vaccine and for possible consideration as a therapeutic product in infected persons.

A Peptide Vaccine Consisting of Conserved Envelope Peptides Protects Rhesus Monkeys Against Lethal Disease Caused by SIV

Principal Investigators evaluated the immunizing efficacy of conserved, hydrophilic virus envelope peptides to vaccinate rhesus macaques against SIV infection and disease. Rhesus macaques were immunized with a mixture of four SIV envelope peptides, 11 to 21 amino acids in length and representing highly conserved, hydrophilic regions of the gp120 and gp41. These were from envelope regions SIV-88, SIV-500, SIV-582 and SIV-647. The peptides were given as recombinant-origin fusion proteins of ß-galactosidase (ß-gal). The selection of the peptides was based on analogous peptides from similar regions of HIV-1. Immunization consisted of four inoculations of 4 µg of each peptide-ß gal protein. Three weeks after the fourth inoculation of peptide vaccine, the immunized and control (ß-gal only) macaques were challenged with about 100 cell culture infectious doses of a biological clone of SIV/Mne.

Before challenge, the vaccinated macaques developed virus neutralizing antibodies and antibodies by ELISA to the individual peptides. Post-challenge (pc) both immunized and control monkeys became infected as determined by coculture of peripheral blood lymphocytes (PBL) and polymerase chain reaction (PCR), but the interval of virus positivity in the immunized monkeys was relatively brief. The immunized macaques developed an anamnestic response to the SIV envelope polypeptides 3 to 4 weeks pc, and then exhibited a gradual, fluctuating decline in anti-SIV titers. In contrast, control monkeys developed gradually increasing antibody titers as measured by ELISA and exhibited extensive immunoblot responses to all major viral proteins. The immunized monkeys remained PBL coculture negative since the last virus isolation at week 17 pc over a period of nearly two years. Controls have been intermittently and increasingly coculture positive since challenge. The suppression of SIV proliferation by immunized macaques correlated with neutralizing antibody titers on the day of challenge and ELISA titers to peptide, SIV-647. At 44 months after challenge, immunized monkeys were healthy and two of three remained virus negative by PBL coculture. Two of three controls died of SIV induced disease and the third was consistently virus positive. The SIV peptide vaccine protects against disease but not initial infection. The similarity between the SIV peptides and the corresponding, equally conserved, HIV peptides suggests their use may broadly protect against disease.

At about 20 months after infection lymph node cells and peripheral whole blood were transferred from each of the immunized macaques to individual susceptible macaques. This was done to determine whether the immunized macaques were infectious. None of the recipient macaques seroconverted after 18 weeks, and they remained virus negative by coculture and PCR negative.

In a similar peptide immunization study with the same peptide vaccine but using the more rapidly virulent SIVmac251, there was no protection against disease or death. However, there was a non-significant increase in mean time to death in the vaccinated animals as compared to controls.

Passive Immunization With Antibodies To Conserved Envelope Peptides Protected Rhesus Macaques From SIV Infection.

Extending the studies described above, the investigators attempted to determine whether macaques immunized with four conserved peptides fused to ß-galactosidase and formulated in complete Freund's adjuvant generated protective antibodies towards conserved regions of the SIV envelope proteins. Antibodies were derived from peptide immunized macaques. These antibodies were able to inhibit SIV_{E11s} induced syncytia

formation *in vitro*. Additional hyperimmune plasma was derived from macaques infected with SIV that had high antibody titers to the whole virus and high neutralizing antibody titers. Three of six animals receiving 5ml/kg anti-peptide hyperimmune plasma 24 hours prior to inoculation with SIV_{E11s} remained virus isolation negative and seronegative for 14 weeks post challenge. Lymph node biopsies were obtained from these three monkeys and two were found to be free of SIV DNA by PCR while the third animal was PCR positive and virus was isolated from LN cells following coculture. The three remaining animals that received anti-peptide plasma and all of the control animals that received ßgal hyperimmune plasma became infected by two weeks p.c. and seroconverted by four weeks p.c. Nine of eleven animals receiving anti-SIV_{E11s} hyperimmune plasma were protected from infection and seroconversion when the plasma was given 24 hours prior to challenge. Summarily, results indicated that antibodies to conserved regions of the SIV envelope could inhibit SIV infection both *in vitro* and *in vivo*.

Monkeys Infected with a Lethal Strain of SIV Can Be Superinfected With a Second, Closely Related SIV.

Rhesus macaques infected with the E11S biological clone of simian immunodeficiency virus (SIV/Mne) were assessed to determine whether they could be superinfected with SIVmac239. The macaques were monkeys which had been originally infected with E11S virus as part of a passive antibody study. From among all of the monkeys in the original study, the fraction selected was that which, following infection, had become virus isolation negative. All were originally virus positive, and they remained antibody positive. Prior experience with such monkeys was that they ultimately reverted to a virus positive status and die with immunodeficiency. This group of monkeys, following their initial viremia, had been virus negative for varying intervals ranging from 4 to 13 months. Four animals were inoculated with 10 infectious doses of SIVmac239 and four with 1000 doses. Seven of eight monkeys became infected as measured by virus isolation and PCR, however, they circulated a much lower level of the second virus compared to controls, and three of four ceased circulating isolatable virus after several weeks, whereas controls continued to circulate virus at high, continuous levels. These data indicated that it is possible to generate a protective immunity which partially protected against viral persistence and the potential for transmissibility, but not against infection.

SUMMARY AND RESULTS OF ANIMAL STUDY PROTOCOLS (RVA)

Summaries of the individual, approved, animal protocols carried out under the auspices of the Animal Models MAP are listed below, by consecutive RVA number. Each summary outlines the purpose and significant findings and result of each protocol.

RVA 1 - *"Development of Mouse-Primate Chimeras for the study of HIV and SIV infections in vivo"*-

Severe combined immunodeficient (SCID) mice lack TO and B lymphocytes due to a defect in their recombinase system that prevents the productive rearrangement of their antigen receptor genes. SCID mice may be reconstituted with human peripheral blood mononuclear leukocytes (hu-PBL-SCID) or with human hematolymphoid organs (SCID-hu) without any apparent graft versus host disease. These mice are susceptible to infection with HIV and may serve as a small animal model to study viral pathogenesis. During the past three years animal model Principal Investigators developed and employed the hu-PBL-SCID model to assess:

1. the efficacy of anti-HIV therapeutics;
2. the immune elements in immunized humans and macaques responsible for partial or total protection against viral challenge;
3. and,to develop gene therapy strategies *in vivo*.

Approximately 600 to 700 SCID mice were analyzed. In addition,the SCID mice were bred and maintained at Bioqual, Inc. (Rockville MD) which provided a continuous supply of approximately 100 to 150 four to six week old mice for new experimental protocols.

RVA 2 - *"Immunogenic potential of genetically engineered SIV-envelope peptides fused to B-galactosidase in rhesus macaques"*-

Three rhesus macaques were used as controls for RVA 3 to determine the immunogenic potential of 4 ug/dose SIV 647 ß-galactosidase fusion peptide. The three monkeys reacted to the 647 peptide in a similar fashion as monkeys receiving the four ß-galactosidase fusion peptides mixture of 88, 500, 582 and 647.

RVA 3 - *"SIV peptide vaccine; 4 peptides in Freund's complete adjuvant"*-

This protocol involved the vaccination of rhesus macaques with peptides selected from regions of the simian immunodeficiency virus (SIV) envelope that are hydrophilic, immunoreactive, and

highly homologous with corresponding conserved envelope sequences of the human immunodeficiency virus (HIV). The peptides, produced as ß-galactosidase fusion proteins, induced virus-neutralizing and peptide-specific antibodies. After challenge with $SIV_{mne/E11s}$, controls became virus positive and developed gradually rising antibody titers to SIV. Immunized macaques developed a postchallenge anamnestic response to SIVenv antigens within 3-6 weeks followed by a gradual, fluctuating decline in SIV antibody titers and partial or total suppression of detectable SIV. Virus suppression correlated with prechallenge neutralizing antibody titers. Although the average CD4+ cell count in the blood of immunized macaques remained constant, the control macaques exhibited a progressive decrease developing about week 55 after challenge. Two of the three controls died from SIV induced AIDS by two years post challenge. All three vaccinates were alive at 4 years post inoculum (PI).

RVA 3 addendum 1 *"Lymph node transfer from monkeys in RVA 3"-* **and addendum 3** *"Lymph node biopsy from monkeys in RVA 3 (Addendum 1) for virus genome isolation"-*

The macaques involved in protocol RVA 3 (3X7, 4GC and 4GP) which were immunized with a mixture of four SIV peptides from conserved hydrophilic envelope regions and challenged with $SIV_{mne/E11s}$ along with one control (4HS) had lymph node biopsies performed and analyzed for virus presence. Data generated demonstrated that lymph node cells from all vaccinated monkeys and peripheral blood lymphocytes from one of the vaccinees were positive for SIV pol DNA by polymerase chain reaction (PCR) amplification analysis. However, by 36 months after infection, all immunized monkeys were healthy while 2 of 3 controls had died and the remaining animal was virus culture positive and had declining CD4+ lymphocytes. Viable lymph node cells and peripheral lymphoid cells in blood were transferred from the three immunized macaques to individual susceptible macaques. As a control for the transfer, one of the vaccine experiment controls was actively producing virus in its peripheral blood. None of the recipients of the vaccinated macaques cells seroconverted and all were virus coculture and PCR negative 25 weeks post transfer (p.to). The recipient from the control infected macaque became positive in these tests by 2-3 weeks p.to. These results suggested that, while peptide vaccinated macaques permitted some level of SIV replication following challenge, the vaccine prevented disease progression and virus transmission.

RVA 3 addendum 2 - *"HIV-2 challenge of monkeys in RVA 3"*

The macaques involved in protocol RVA 3 (3X7, 4GC and 4GP) which were immunized with a mixture of four SIV peptides and

challenged with $SIV_{mne/E11s}$ were challenged with a limitedly titrated stock of HIV-2. Two additional animals were used as challenge virus controls. Following intravenous challenge, no animals showed signs of infection and monkeys 3X7, 4GC and 4GI were removed from the study. The two control animals were rechallenged and one animal became persistently infected.

RVA 4 - *"SIV peptide vaccine in Freund's, Ribi or liposomes"*-

This was a controlled study of the envelope peptide based SIV vaccine in rhesus macaques. The study compared three different adjuvant formulations of the vaccine, Freund's, Ribi, and Liposome-Lipid A, to each other and to unvaccinated controls. The study measured antibody development following immunization, initial viral antigenemia of vaccinates and control monkeys following challenge with SIV_{mac251}, in addition to antibody responses to the whole virus and time to death. All animals developed circulating antibodies to the ßgal carrier protein with titers ranging between 10^3 to 10^4 for the Ribi recipients, 10^4 to 10^5 for the LLA recipients and 10^6 to 10^7 for the CFA recipients following the second booster immunization. Antibodies to SIV derived proteins were only detectible prior to challenge in the CFA immunized group receiving the 4 SIV-ßgal fusion proteins. These antibodies also bound SIV derived envelope proteins as detected immunoblot and SIV gp140 ELISA. Due to the low ßgal antibody levels in the Ribi animals it was decided not to challenge. Following the challenge the remaining 15 animals became infected, and virus was isolated from the PBL on day 7 in every case. A significant anamnestic response was observed in the SIV-ßgal CFA group by day 14 post challenge (pc). Detectible SIV specific antibodies developed in one of the animals receiving SIV-ßgal LLA by day 14 pc and in 4 of 5 animals by day 21 pc as compared to the control group which had 1 animal with detectible antibody on day 21 pc and 3 animals by day 28 pc. To date 4 of the five control animals died of SIV related causes, while 2 of 5 of the SIV-ßgal CFA animals and 3 of 5 of the LLA animals were alive, while remaining virus isolation positive.

RVA 5 - *"HIV-2 infection of rhesus macaques"*-

This study was initiated at another facility, the New Mexico Primate Center, and the monkeys were purchased by the Foundation. There were seven rhesus macaques inoculated with one of two different strains of HIV-2. Currently four of the monkeys were seropositive for HIV-2 and virus could be occasionally isolated from them. The virus positive monkeys remain a source of monkey adapted HIV-2 for use in other studies with this virus.

RVA 6 - *"Immunization of Rhesus macaques with individual peptides"*-

This study involved the immunization of rhesus macaques with individual ß-galactosidase fusion proteins to determine which peptide or peptides are involved with the observed protective response. Following the immunization schedule and challenge with SIV the study was terminated due to insufficient developed immunity and a challenge dose which was unsuccessful at infecting all of the control animals.

RVA 7 - *Immunogenicity of HIV-1 peptides in Rhesus Macaques"*-

Rhesus macaques were immunized with ß-galactosidase fusion proteins which corresponded to HIV-1 sequences in order to develop HIV-1 peptide specific antibodies. The monkeys were immunized with incomplete Freund's adjuvant. This adjuvant was significantly less able to induce both ß-gal and peptide antibodies following the full immunization regime than the complete Freund's adjuvant. Three immunized monkeys developed antibodies to HIV-1 gp160 as detected by ELISA, but all 6 monkeys were immunoblot negative.

RVA 8 - *"Protective effect of passive neutralizing antibodies"*-

Inactivated plasma collected from either SIV infected or peptide vaccinated macaques were transferred into 17 naive rhesus monkeys. Two additional macaques received normal plasma and served as controls. Following transfer all 19 monkeys were inoculated with SIV_{mne}. While the controls became infected and were virus isolation positive, 3 of 6 recipients of SIV peptide vaccine plasma and 9 of 11 recipients of SIV-infected monkey plasma were protected. None of the twelve protected animals became virus isolation positive or seroconverted through 100 days of follow up. One, however was SIV PCR positive. All twelve protected animals were rechallenged 100 days post the initial inoculation, eight became infected and yielded virus as was expected, four remained uninfected. One of the latter was the SIV PCR positive monkey mentioned above, which suggested that cryptic SIV infection may be of significance in immunological protection. The results demonstrated that envelope anti-peptide antibodies had similar protective potential *in vivo* as did antibodies directed to the whole virus. *In vitro* neutralization competition assays performed with sera from vaccinated macaques in presence of the free peptides suggested that of the four conserved envelope peptides of the vaccine, the two originating from gp41 rather than the two from gp110 were responsible for inducing the neutralizing anti-syncytial activity.

RVA 9 -*"Whole virus vaccine for SIV"*-

This was a proposed study for the evaluation of a whole virus SIV vaccine. This study was not initiated during Grant Year 1-5.

RVA 10- *"Immunogenicity of SIV transgene"* - and

Addendum 1 - *"Direct intramuscular injection of high level expression vectors"*-

Three rhesus macaques were immunized with SIV_{mac239} DNA by the intramuscular route. Two of the animals receiving the SIV DNA expression vector produced lymphocyte proliferation response prior to challenge with SIV_{251}. SIV specific antibodies could not be detected in immunized animals prior to challenge, but 2 of 3 animals developed SIV specific antibody 4 to 10 days sooner than control animals. No differences were observed in the levels of virus during the acute disease were observed. The disease course following challenge was not altered when compared to control animals.

RVA 11 - *"Routine immunization for antibody"*-

This was a generic protocol for the preparation of antibodies in rats, mice, guinea pigs and rabbits. Soon after the initiation of this protocol it was decided to utilize antibodies prepared at other facilities in animals owned by those facilities. The Principal Investigator was advised by the Laboratory Animal Use Review Officer, USAMRDC, that as long as the antibody production was done in other facilities in animals not owned by the Foundation, this protocol need not be exercised.

RVA 12 - *"Subcutaneous injection of primary macaque fibroblasts transduced with recombinant murine-based retrovirus vector expressing SIV-239"*-

This protocol was intended to study the possibility that autologous fibroblasts transduced with genes from SIV can induce a protective immune response in monkeys. The protocol was not initiated during Grant Year 1-5.

RVA 13 - *"Immunization with conserved peptides from SIV: Effect of heterologous challenge on developed immunity"*-

This protocol was intended to compare the protective efficacy of peptide vaccines against heterologous versus homologous challenge viruses. The protocol was not initiated during Grant Year 1-5.

RVA 14 - *"Titration of SIV challenge stocks in Rhesus Macaques"*-

This protocol was for the purpose of titrating and characterizing additional SIV strains that would be intermediate in their virulence for macaques. There was a need for SIV strains that were lethal in one to two years but which did not devastate the immune system within the first three weeks of infection. The protocol has not started yet and will be reviewed and updated before initiation.

RVA 15 and addendum 1 - *"Development of an HIV-1 model in primates"*-

The susceptibility and permissivity to HIV-1 infection of peripheral blood mononuclear cells (PBL) from three macaque species *M. nemestrina, M. mulatta,* and *M. fascicularis* were evaluated *in vitro.* Peripheral blood-derived TO lymphocytes and monocytes/ macrophages from pig-tailed macaques *(M. nemestrina)* were significantly more permissive for HIV-1 than cells from *M. fascicularis* or *M. mulatta.* Optimal infectivity was dependent upon viral strain and multiplicity of infection, and the proliferative status of the TO cells used. The kinetics of HIV-1 infection in pigtailed macaque TO cells was comparable to that observed for normal human TO cells, but peak expression was only 1/101/100th that of human cells. Semi-quantitative PCR analyses indicated that the low virus expression observed was a consequence of limited permissivity rather than limited susceptibility of the cells. Although electron microscopy revealed the presence of morphologically normal HIV-1 particles in the cultures, their infectiousness was frequently limited. Four pig-tailed macaques were inoculated with cultured HIV-1 infected autologous cells harvested at peak virus expression. HIV-1 was isolated from PBL from 3/4 animals at various times during the first 10 weeks post-inoculation (PI), and from biopsied lymph node tissue from one animal at week 6 PI and another at week 10 PI. Additionally, HIV-1 genome was detected in some uncultured specimens from which infectious virus was not recoverable. During the first 12 weeks PI, no HIV-1-specific antibody was detected by Western blot, but in some cases, was detected by radioimmunoprecipitation. HIV-1 specific antibodies developed and increased after week 15 PI.

RVA 16 - *"Titration of SIVmac251 challenge stocks in Rhesus Macaques"*-

Nine rhesus macaques that were originally purchased and housed at the Primate Research Laboratories (PRL) in New Mexico were part of a previous titration study with SIV_{mac251}, a virus isolate which is proposed for use in future MMCARR vaccine and pathogenesis studies. The monkeys were followed for the purpose of determining disease outcome. The animals were held at a contracted holding

facility at SRI-FRC in Frederick, MD. The animals will be euthanized for the collection of infected tissues.

RVA 17 - *"Superinfection of Rhesus Macaques with SIV"*-

Eight rhesus macaques that were previously inoculated with SIVmne/E11s and became infected were challenged with SIVmac239 to determine if dual infections of lentiviruses could occur *in vivo*. Prior to challenge with the 239, all eight animals were seropositive, but virus isolation was negative for over 5 months (at least five isolation attempts). Following the 239 challenge 7 of the 8 animals developed viremia within 2 weeks and all 8 animals yielded virus by 5 weeks PI. Anamnestic responses were observed in animals with low to moderate anti-SIV antibody levels but not in animals with high levels. Characterization of the viruses isolated from the monkeys following 239 challenge suggested that the virus is 239 and not E11s.

Conclusion

In HIV research, the utilization of animal models was useful to examine the mechanisms of HIV disease and the nature of the immune response to this infection. This mission area has made considerable progress towards achieving the prescribed programmatic goals and remains a critical component in strategizing and achieving the military research priority of the prevention of HIV infection and prevention of HIV disease progression.

Future Studies Planned

In the broadest sense, animal models will be used in major HIV research efforts for disease prevention through immunotherapeutic vaccination. To accomplish this research effort, the scientists will continue to work with animal model evaluation to provide critical information about vaccine formulation, dose, schedule of administration, homologous and heterologous protection, and other aspects of vaccine efficacy. The MMCARR also plans to assess the results of *in vitro* studies of vaccine efficacy, and of successful HIV vaccine therapy as possible criteria for product selection for vaccine prophylaxis trials. Candidate vaccines with documented ability to prevent infection in animals, to delay disease progression post infection in animals or humans, to reduce or prevent transmission of infection, or to provide protective effects according to criteria yet to be developed, will be incorporated into the overall strategy to develop a protective vaccine against HIV-1 infection.

Among the projects with a high priority for future studies are

the adaptation of HIV-1 to the macaque monkey; the effective use of the chimpanzee model to augment vaccine development, the study of selected simian-human immunodeficiency virus (SHIV) chimeric viruses; the refinement of diagnostic strategies for distinguishing between HIV-1 subtypes both genetically and immunologically. Many of these projects are already underway in various forms under existing Mission Area Protocols.

G. DIAGNOSTICS MISSION AREA

LTC RONALD TURNICKY, M.D., MC, U.S. ARMY, DIRECTOR

MAP SUMMARY: The primary research goal of the Diagnostics MAP was to develop and evaluate new and/or improved laboratory methods to establish the diagnosis of HIV, and to correlate detectable virus, HIV antigen and/or HIV nucleic acid from clinical samples.

Protocol #	Protocol Title (Abbreviated)	Principal Investigator
RV2	Core Diagnostics (Adults)	Turnicky
RV29	Macrophage Studies	Gendelman*
RV25	Autopsy/Pathology	Anderson
**	Cellular Pathology	Turnicky

*Foundation Principal Investigator (PI)
**Research was conducted in accordance with a documented and integrated research plan rather than individual protocols. The plan was approved by the MMCARR and was subject to the Mission Area review process.

DIAGNOSTICS MISSION AREA

Overview

The Walter Reed Army Institute of Research (WRAIR), through LTC Ronald Turnicky, M.D., MC provided the primary scientific direction and oversight for the research conducted in this MAP. The Department of Defense (DoD) has been testing the military population for antibodies to HIV since 1985. This screening process has detected 9,000 infected active duty service personnel. Each year, there are approximately 600 new infections in this population. Since HIV infection is uniformly fatal and will eventually result in the premature death of most and probably all HIV infected individuals, it has been the leading cause of non combat mortality among active duty military personnel.

The Diagnostics mission area research has centered on the following goals and objectives:

- Improve the accuracy, reliability and cost effectiveness of diagnostic tests.

- Develop standardized laboratory tests that are prognostic.

- Develop standardized laboratory tests that evaluate the effectiveness of retroviral therapy, particularly those which measure changes in the total "viral burden" of infectious retroviral virions, antigen and viral nucleic acids.

Critical efforts of the MAP included antibody detection, antigen detection, nucleic acid detection and immunodiagnostics. Additionally, this mission area included efforts within the Cellular Pathology Laboratory, also directed by LTC Turnicky. The CPL demonstrated technologies of in situ hybridization (ISH) in fixed and frozen tissue, double labelling success in immunoperoxidase/ISH staining, and Southern analysis of clonality of viral integration and receptor antigen status.

The Diagnostics MAP has played an integral part of the development and evaluation of new and/or improved laboratory methods for assessing the virus-specific immune response to retroviral infection, and in correlating the detection of virus-specific antibody or cell mediated immune responses with clinical status. The Core Diagnostics Protocol was the primary research protocol for the Diagnostics Mission Area and guided critical efforts in the development and evaluation of new and/or improved laboratory methods to establish the diagnosis of HIV, and to correlate detectable virus, HIV antigen and/or HIV nucleic acid in blood from clinical samples. A description of this primary

protocol and its significant findings follows. In addition, other laboratory efforts have contributed to the stated objectives, these efforts are also summarized:

RV 2 - *"The Core Protocol for HIV Developmental Diagnostics"- (Adults)* -

The purpose of this protocol was to develop and evaluate new and/or improved laboratory methods for establishing the early diagnosis of HIV infection, deciding the stage of illness and determining markers of disease progression. Methods to detect replicating HIV virus, HIV antigens, and HIV nucleic acids were used, including virus culture, antigen capture, immunoassay and polymerase chain reaction amplification of HIV DNA and RNA. This protocol was a foundation for laboratory evaluation of progression of disease for the patients enrolled. Additionally, the protocol provided support in establishing the initial diagnosis of HIV infection. An adjunct to sample testing was the banked repository of frozen cells and sera of each patient. The banking of sequential patient samples could then be utilized for prospective assessment of intervention therapies.

Significant Findings:

HIV detection by culture and PCR were extremely sensitive techniques and could be offered as routine clinical tests. Through these techniques the "window" between infection and detection of that infection was narrowed considerably. Diagnostic assays continued to be evaluated for the best combination of testing panels to enhance sensitivity, specificity while decreasing the period from infection to laboratory detection. Methods to discriminate between HIV vaccine sero-response from natural infection were under development. This protocol processed samples from 1422 patients:

6841 Co-Cultures,
769 PCR HIV, 86 PCR HTLV,
7,590 RIPA HIV, 692 RIPA HTLV,
2455 Serum p24, and 230 Serum antip24.

Total vials of frozen cells = 10,184
Total vials of frozen sera = 7,507
Total vials of frozen plasma = 3,289

Other laboratory and human based projects/protocols were assigned to this MAP; these endeavors were conducted with an emphasis in Cellular Immunology:

RV 25 - *"Pathological Manifestations of HIV Infection at Autopsy"*-

The purpose of this protocol was:

1) To perform complete research autopsies on deceased patients with HIV disease.
2) To document disease processes causing morbidity and mortality in patients enrolled in HIV research.
3) To obtain fresh tissue from major organ systems to be stored in a tissue registry, both unfixed at -70 degrees Celsius and formalin fixed, paraffin-embedded.

Significant Findings:

1. Twenty-two (22) HIV research autopsies at WRAMC and 10 HIV research autopsies at NNMC, Bethesda revealed causes of death as follows (8 cases of 2 causes of death each): 8 PCP; 4 Staph. sepsis; 4 HIV wasting only; 4 dilated cardiomyopathy; 3 Acute pneumonia, 3 KS (one visceral, two pneumonitis); 3 enteric sepsis; 2 ARDS; 2 Pseudomonas sepsis; 2 PML; 2 CMV (Cytomegalovirus) panencephalitis; 1 acute pancreatitis; 1 sudden death; 1 Adenovirus pneumonia.

2. Tissue registries exist for most autopsies and have been used to:

a. validate polymerase chain reaction (PCR) detection systems for HIV proviral DNA in human organ tissues in collaboration with SRA Laboratories as well as M. avium-intracellulare and P. carinii DNA in human organ tissues in collaboration with AFIP;
b. conduct survey of culturable Mycoplasma species from HIV autopsy tissues - NO MYCOPLASMA SPECIES DETECTED.

RV29 - *Macrophage Studies* -

The purpose of this laboratory based protocol was to study biologic, biochemical and molecular properties of HIVs tropic for monocytes. The Principal Investigator proposed to determine the optimal conditions for isolation and propagation of HIV on monocytes, the mode(s) of viral entry and replication cycles, and the proviral DNA sequences involved in selective monocyte tropism(s). The specific objectives were:

1- Determine the optimal conditions for maintaining blood and tissue monocytes *in vitro* for the isolation and propagation of HIV.

2- Determine the utility of monocyte viral isolation techniques for diagnosis and/or confirmation of HIV infection.

3 - Investigate the role of MCSGF (Macrophage Colony Stimulating Growth Factor) in the susceptibility of monocytes to virus infection

4-Define a possible heterogeneity of response of donor monocytes to HIV infection.

5- Study the role of cytokine/lymphokines and DNA and other opportunistic pathogens in affecting virus replication and monocyte function.

6- Determine if the CD4 epitope was the receptor for HIV on monocyte/macrophages and investigate other possible viral receptors.

7- Determine the biochemical and molecular mature of monocyte-HIV tropism(s) and cytopathic effects.

Significant Findings:

Most notable accomplishments of this protocol were the establishment of a central pathogenic mechanism for HIV encephalopathy that the Principal Investigator believed would lead to new therapeutics for brain disorders associated with retroviral disease. The cytokine program also progressed and was demonstrated in the development of new devices for treatment of HIV disorders, and included the use of a therapy which involved immunocytokine pheresis. This will be tried in humans for the first time in the world. The Principal Investigator (departed from the Foundation at the end of Grant Year 5) of this protocol was invited to be visiting professor at the Sorban, and the Pasteur Institute and also was the plenary speaker and Chairman of the molecular brain biology sessions for HIV-induced CNS disorders at the Bougival Conference for Brain Biology for HIV disease.

Other significant laboratory efforts executed under the auspices of this MAP, with an emphasis in Cellular Immunology, include the following, for Grant Years 3, 4, 5 respectively:

Grant Year 3 Laboratory Effort: Inhibition of interferon production in HIV infected monocytes.

Goals and Objectives:

The long range goals of this project were two-fold. First, scientists attempted to understand the mechanisms that regulate interferon (IFN) gene expression in the monocyte and how HIV infection affects this regulation. Second, because exogenously added IFN had such dramatic effects on HIV replication in

monocytes *in vitro*, the scientists attempted to deliver and express an IFN gene into monocytes. This strategy could prove valuable for protection of uninfected monocytes against HIV infection as well as a treatment for cells that are already infected.

To understand the mechanisms that regulate IFN expression in monocytes, a transient assay system would be established in monocytes, and IFN expression analyzed in HIV infected and uninfected cells. For delivery of an IFN gene into monocytes, novel defective herpesvirus vectors would be constructed that are suitable for gene delivery into monocytes. The IFN gene would be expressed using such a vector.

Significant Findings:

Several vectors were constructed for the analysis of IFN gene expression. One plasmid, pIFNa1-CAT, had the promoter sequences of the IFN-a1 gene from -141 to +6, relative to the start of transcription, linked to the marker gene encoding chloramphenicol acetyltransferase (CAT). A second plasmid, pIFNa_{II}-CAT, was made by first isolating the IFNa_{II} promoter from human genomic DNA and then inserting it upstream from the CAT gene. These plasmids, along with one that had the IFNa_{II} promoter upstream from the CAT gene was to be used in transient assays.

A transient assay system was developed using primary human monocytes. The technique utilized monocytes cultured for 6 days as adherent monolayers, removed by gentle scraping, washing and resuspension at a concentration of 4 x 10^7 cells per ml. A control expression plasmid DNA was added to the cells for electroporation at various voltages and capacitances. Cells were replated and assayed for expression 48 hours later.

For the delivery of the IFN gene into monocytes, a defective herpesvirus vector was developed that expressed the marker gene encoding B-galactosidase. When monocytes were infected with this vector, B-galactosidase expression could be detected from 8 hours after infection to 6 days. No infectious virus could be isolated at any time, indicating that the defective virus was not replicating in monocytes. A similar vector that expressed IFN-a was under construction.

Grant Year 4 Laboratory Effort - Understanding the effects of interferons on the replication of HIV in monocytes.

Goals and Objectives:

Efforts during this year were directed towards understanding the effects of interferons on the replication of HIV in monocytes.

It had been shown that Interferon (IFN-1a) had a dramatic effect on the replication of HIV in cultured monocytes. Since HIV infection does not induce IFN-a in these cells, attempts were made to express and deliver an IFN-c- gene into human monocytes. A gene therapy approach such as this had not been exploited, primarily due to the difficulty of delivering foreign genes into monocytes and macrophages. These cells are nondividing, and are not susceptible to traditional methods of gene transfer such as infection with defective retroviruses.

To approach this problem, the investigators developed a defective herpesvirus vector that expressed the E. *coli lacZ* gene. Human monocytes can be infected with this vector and B-galactosidase can be detected for up to 6 days. A similar vector was under construction to express the IFNa gene. IFNa would be expressed in human monocytes with this vector to determine whether protection against HIV infection could be established, an approach that has been termed "intracellular immunization". HIV-infected monocytes were treated with this vector, and the effects on HIV replication determined. Finally,monocytes were used as cellular carriers for gene delivery of IFN-a to HIV-infected monocytes. Since circulating blood monocytes mature and migrate to many, often inaccessible, tissues in the body, such a system might prove to be a valuable means of delivering therapeutically important genes to sites at which they are most needed. Not only does HIV not induce IFN in monocytes, it has been shown that HIV-infected monocytes can not be induced by other means to produce IFN. In order to understand the mechanisms that regulate IFN expression in monocytes and HIV-infected monocytes, the investigators developed a transient assay system in cultured monocytes. In addition, several vectors were constructed for the analysis of IFN gene expression in these cells.

Significant Findings:

This system should allow an understanding at the molecular level how HIV affects IFN expression in monocytes. This transient assay system was a valuable tool that could be used to study HIV gene expression in human monocytes.

Grant Year 5 Laboratory Efforts - Efforts during Grant Year 5 were directed toward developing a gene therapy approach to inhibit HIV-1 replication in human monocytes.

Goals and Objectives:

Human monocytes are non-dividing cells that serve as a major reservoir for HIV-1 at all stages of infection. To investigate viral mediated gene delivery as a means of inhibiting HIV-1

replication in these cells, a replication incompetent herpes simplex virus (HSV) vector was developed that expressed human interferon a(IFNa).

Significant Findings:

Monocytes infected with this vector expressed IFNa and when challenged with HIV-1, showed dramatically reduced cytopathic effects and HIV- 1 replication compared to control vector treated or mock treated monocytes. Similar effects on HIV-1 replication were observed if monocytes were first infected with HIV-1 and then treated with the recombinant vectors. These results demonstrated that replication incompetent HSV gene delivery of IFNa directly to human monocytes could greatly decrease HIV-1 replication, and suggested that such a vector, or possibly vector treated cells, might deliver therapeutically important genes directly to sites of HIV-1 infection.

Conclusion

The search for early, rapid and reliable diagnostic techniques continued to be a strategic area of importance for the military. In response to its assigned diagnostic and prognostic goals, this research area and its core protocol, RV2, successfully accrued thousands of patients samples and performed thousands of tests which served as a solid foundation for the laboratory evaluation of progression of disease. This bank of sequential patient samples has also been utilized for prospective assessment of intervention therapies, making this serum/cell/plasma "database" an invaluable resource for present and future military HIV research endeavors. Additionally, the mission of the Cellular Pathology Laboratory (CPL) successfully augmented the Diagnostic MAP in providing innovative concepts in early diagnosis and evaluation of disease progression.

Future Studies Planned

Specific efforts over the next three to five years will focus on developing assays that will decrease the window between infection and the rise in detectable antibodies and enhance the laboratory's ability to distinguish between different retroviral infection (HIV-1 vs HIV-2, HTLV-1 vs HTLV-II). This will be accomplished through a combination of technology which could include techniques such as Enzyme-Linked Immunosorbent Assay (ELISA) (specifically IgM), Western Blots, Radioimmunoprecipitation (RIPA), Polymerase Chain Reaction (PCR), and Rapid Field Identification and neutralization systems. Emphasis will be placed on developing and testing rapid identification tests suitable for use in the field. Diagnostic developments also include the use of Flow Cytometry.

Fluorescence in situ hybridization by cytometry may provide a highly sensitive assay for very early detection of HIV.

Plans also include further research developments within the Cellular Pathology Laboratory (CPL). Some of the most significant contributions in retroviral research have evolved from the molecular and functional analysis of HIV infected cells in Foundation laboratories. Yet, the ability within the Research Program to characterize these contributions with respect to tissue/cell morphology is absent. The CPL will serve to link morphology to the molecular and functional studies providing the capacity not only to quantitate viral load, but, to provide the additional data as to what population of cells is infected and where in the lymph node architecture they are localized over the evolution of the disease. The ability to study the morphologic features and localization of the virus to the specific molecular and functional assays will provide and is essential to enhanced understanding of the HIV disease.

The CPL will furnish the main diagnostic and investigative pathology support for the Diagnostic and Animal Models Mission Area Protocols. Additionally, two new protocols are planned which involve the assessment of lymphoid tissue in HIV disease:

RV 77 - *"Lymphoid Follicular Tissue Biopsy Protocol: Feasibility Study" and*

RV 78 - *"Feasibility of Pharyngeal Tonsillar Biopsy to Monitor Retroviral Pathology in Early Stage HIV Patients"-*

These protocols will evaluate viral burden in lymphoid tissue and identify surrogate markers of disease progression other than CD4. It is anticipated that these protocols will provide new information which may be used to refine staging parameters in early HIV infection and will provide a template to monitor patient response to therapies to include vaccine or drug effectiveness.

G. OPPORTUNISTIC INFECTIONS MISSION AREA

COL JONATHAN BERMAN, M.D., MC, WRAIR

MAP SUMMARY: The Opportunistic Infections MAP was oriented to conduct clinical efficacy trials of promising agents with the primary objective of preventing and or controlling/slowing the rate of opportunistic infections.

Protocol #	Protocol Title (Abbreviated)	Principal Investigator
RVOI6	WR 6026	Hendrix
RVOI7	RWJ 25213	Hendrix
RVOI3	Azithromycin Doses for M. avium	Hendrix
RVOI8	Prophylaxis of MAC	Berman

OPPORTUNISTIC INFECTIONS MISSION AREA

Overview

COL Jonathan D. Berman, M.D., MC, WRAIR, provided the scientific management and direction for this MAP. The Opportunistic Infection (OI) MAP was oriented toward clinical efficacy trials of promising agents, and participation in these OI protocols has given the late-stage HIV infected patient, who is at significant risk for Opportunistic Infections, and the primary care physician the opportunity to participate in new therapeutic drug trials. Because of the considerable investment in drug discovery being made by private industry and the National Institutes of Health, it was possible to work with outside sources to design therapeutic and prophylaxis protocols. Since the emphasis for this mission area was on later stage patients, a lower priority for the military, funding to support these clinical trials was primarily provided by private industry or the National Institutes of Health (NIH).

The objectives for this mission area were:

- Prevent opportunistic infection.

- If opportunistic infection occurs, control or slow the rate of progression.

In order to offer late stage patients the opportunity to participate in promising chemotherapy trials, this Mission Area initiated an Inter-agency Agreement (IAA) in September, 1991 to conduct collaborative efforts and research between the National Institutes of Health, Division of AIDS (DAIDS), and the DoD HIV Research Program. As a result of this IAA, the DoD HIV Research Program became a member of the AIDS Clinical Trial Group (ACTG) for Opportunistic Infections. An elaborate administrative and data infrastructure was established to allow military medical centers to participate in protocols that interest a site, enroll patients and exchange information with other ACTG sites across the country. This Mission Area had one active ACTG protocol:

RV OI6 *"Escalating Multiple-dose Safety and Tolerance of WR 6026 Hydrochloride in HIV-Infected Patients"-*

This protocol was conducted at Wilford Hall Medical Center in San Antonio, Texas, with MAJ Craig Hendrix, M.D., MC, USAF as the Principal Investigator. WR 6026 is a 8-aminoquinoline compound with promising activity against pneumocystis carinii. The study objectives were:

1) to determine the maximum tolerated dose of WR 6026 in HIV-infected patients;

2) to determine whether any unexpected toxicities were caused by WR 6026 in HIV-infected patients;
3) to determine whether there was additional toxicity when WR 6026 is given for 21 days rather than 14 days;
4) to further investigate the pharmacokinetics and pharmacodynamic of WR 6026

Significant Findings:

To date, 36 patients completed this protocol at the three participating sites. WHMC has contributed 14 patients. Dose limiting methemoglobinemia was identified at the 150 mg level. Therefore, a final cohort of 120 mg (MTP) was opened for enrollment. With the completion of this cohort, the enrollment was closed and the data is currently being analyzed. It is hoped that this compound would be useful as prophylaxis for PCP, as it has been a very active against PCP in preclinical studies and has a long half-life to allow infrequent dosing.

Other protocols that were executed within this mission area were:

RVOI7 - *"A Double-Blind Study to Evaluate the Safety and Pharmacokinetics of RWJ 25213 in Subjects with HIV Infection"* -

This was a randomized, double-blind placebo-controlled, Phase I study which evaluated the safety and pharmacokinetics of a single dose followed by multiple dosing of RWJ 25213 (an antibacterially active isomer of ofloxacin) with concomitant AZT administration. Sixteen patients were enrolled in this protocol over the course of fourteen days. This protocol was 100% outside funded through the Robert Wood Johnson Pharmaceutical Institute (RWJ). All laboratory, personnel, and travel costs were paid for by RWJ.

Significant Findings:

Sixteen (16) HIV seropositive (+) adult male volunteers received drug and placebo. Safety evaluations were made by examination and laboratory tests over a 2-week period. Plasma levels of RWJ 25213 and AZT were collected for evaluation by RWJ Pharmaceutical Institute. No significant adverse events were noted during the actual study period. All samples were sent to the sponsor (RWJ) for assay. To date, no conclusions have been drawn. All patients were discharged in stable condition.

RVOI3 - *"An Open Multicenter, Randomized, Dose-Ranging Study of Azithromycin in the Treatment of Disseminated Mycobacterium Avium-Intracellulare Complex Infection (MAC) in Patients with the Acquired Immune Deficiency Syndrome (AIDS)"-*

This study was done at Wilford Hall Medical Center and Brooke Army Medical Center by the Investigators, MAJ Craig Hendrix and MAJ John Kelly respectively. The DoD's contribution to the total study population of fifty patients was relatively small. This study was funded with a contract between the Foundation and Pfizer Central Research.

This positive controlled study was designed to study the safety and efficacy of 2 doses of azithromycin as treatment for disseminated Mycobacterium avium-intracellulare complex (MAC) infection in AIDS patients. A maximum of 50 patients (10 at WHMC) were to be assigned to receive azithromycin 600 mg/day, or 1200 mg/day for 6 weeks. Patients demonstrating satisfactory clinical response(five-fold or greater reduction in bacteremia (cfu/ml) were offered enrollment in a follow-up study to continue therapy with azithromycin.

Significant Findings:

Two patients have completed the 6-week protocol and continued in follow-up with no adverse drug reactions or misadventures noted. One patient had resolution of fever, night sweats and weight loss, and blood cultures remained negative for MAC once on study. The second patient also had modest symptomatic improvement. Although the initial study was for six weeks, a continuation phase allowed the patients to stay on the study indefinitely. This study has been closed to enrollment, and lab samples are being processed for data analysis. No final results were available at the time of this report.

RVOI8 - *"A Double-Blind, Placebo Controlled, Parallel Group, Multi-center Study for the Prophylaxis of Mycobacterium Avium Complex with Azithromycin in HIV Infected Patients" -*

This protocol was a twenty-four month prophylaxis study using a weekly dose of Azithromycin as possible protection against Mycobacterium Avium Complex (MAC). HIV infected patients with CD4 counts <100 were randomly assigned to placebo or azithromycin (1200 mg weekly) groups. Patients were evaluated monthly for the major endpoints: mycobacteremia, other bacterial infections, signs/symptoms of drug toxicity. This protocol was partially funded by Pfizer (laboratory and clinical site monitoring), and partially funded by the MMCARR.

Significant Findings

Over 60 patients at eight sites have been enrolled and some patients have already reached endpoints in this double blind study. The eight sites are:

- Eisenhower Army Medical Center, Ft. Gordon, Georgia
- Fitzsimons Army Medical Center, Aurora, Colorado
- Walter Reed Army Medical Center, Washington, DC
- Wilford Hall Medical Center, San Antonio, Texas
- National Naval Medical Center, Bethesda, Maryland
- Brooke Army Medical Center, Ft. Sam Houston, Texas
- Naval Hospital at San Diego, California
- Womack Army Medical Center, Ft. Bragg, North Carolina

Conclusion

Although late stage opportunistic infections are not a high priority for the military HIV research effort, this Mission Area has provided appealing protocols to clinicians through outside funding, thereby minimizing the impact of programmatic resources required at any of the participating sites. Additionally, the implementation of the IAA with NIAID provided military researchers the opportunity to participate in innovative Opportunistic Infection therapeutic drug trials on a national scale, again with outside resources.

Future Studies Planned

Other Opportunistic Infection protocols will be added as program relevant clinical research opportunities present themselves. One planned protocol began in the last quarter of Grant Year 5, this protocol is entitled *"A Placebo Controlled Double Blinded Study of the Elimination of Staphylococcus aureus Carriage in HIV Infected Patients with Topical Antimicrobial Agents"*. Contracts between the two companies that market these agents, Smith Kline Beecham and AMSCO, and the Foundation have been signed to obtain the necessary approvals and resources required for this study.

The purpose will be to determine the efficacy of topical antimicrobial agents, mupirocin calcium ointment and chlorhexidine gluconate 4% foam in the eradication of S. aureus Nasal and skin carriage in HIV seropositive patients. S. aureus colonization may predispose to serious S. aureus infections reported in HIV infected patients. It is probably a contributing factor in the increased incidence of skin disease seen throughout HIV disease. Eradication of S.aureus carrier state may decrease subsequent infection as has been demonstrated in other patient populations. Additionally S. aureus has been shown to produce various enterotoxins which have been shown to be superantigens and thought

to be the most potent T cell stimulant recognized. Superantigens may have effects on dysregulation of the immune system. If S. aureus is chronically carried by HIV infected patients there may be significant absorption of these toxins. The Principal Investigators will attempt to show whether S. aureus carriage is a significant factor in disease progression as well as in morbidity and mortality seen in late disease. Four hundred (400) patients will be enrolled in this study located at NNMC only.

Another planned protocol is entitled *Hemophilus Influenza Type B Vaccine in HIV Infected Patients*. The purpose will be to randomize 200 HIV infected patients who have not previously received HIV vaccine to receive one of three FDA approved HIV vaccine preparations. The Principal Investigator will measure before and after antibody titers and will measure toxicity to vaccination by patient self reports.

III. ORGANIZATIONAL APPROACH

A. INTRODUCTION

Grant # DAMD17-88-Z-8007 provided the mechanism to establish a comprehensive HIV research program. Research was conducted through Foundation and Government submitted protocols and independent but supporting laboratory research plans. These protocols and plans were integrated into one research strategy to provide a solid and cohesive HIV research program. Details of the organizational elements of the HIV Research Program follow in this section. Section IV outlines assurances and compliance initiatives which were implemented to ensure the competent and professional conduct of research.

B. OVERVIEW OF THE FOUNDATION

The Henry M. Jackson Foundation is a private, not-for-profit organization chartered by Congress in 1983 to advance military medicine and to provide a vital link between the military medical community and the private sector. Henry Jackson, the late Senator from the state of Washington, originated the legislation for the Foundation so that civilian and military medicine could work together to improve the quality of life The Foundation provides management and scientific expertise to conduct and support medical research and education and embodies a long-standing commitment to military medicine and public health. The linkage of the mission of the Foundation with the objectives of the military HIV research program provided a logical opportunity in which to successfully conduct and execute a state of the art comprehensive HIV research program.

General resources of the Foundation include a hierarchical organization of staff, systems and procedures that provide accounting and financial management, sponsored programs management, legal counsel, human resources management, purchasing and contracting and general administrative support. Subordinate to the Foundation President (HIV Research Program Director) was a separate and well developed infrastructure that managed HIV Research Program activities and functions.

C. HIV RESEARCH PROGRAM DIRECTOR

The HIV Research Program Director was the Foundation's primary servicing representative to USAMRDC's senior management, operating and scientific staff. The Director, as President of the Foundation, had the authority to marshal any and all available Foundation resources that were necessary and reasonable to ensure successful conduct of the HIV Research Program.

The HIV Research Program Director established Foundation HIV Research Program policies and priorities. While scientific

direction and focus was a collaborative effort between the USAMRDC, the Foundation and all involved Principal Investigators, the Foundation HIV Research Program Director retained final authority on all operational issues under the grant and allocated program resources according to MMCARR programmatic priorities.

D. STRATEGIC PLANNING

The Foundation formally met with USAMRDC on a regular basis to provide research and program updates and to give detailed overviews of plans and progress. The Management and Oversight Committee Meetings and the Research Operations Committee meetings provided forums for information exchange and facilitated informed and proactive decisions regarding changing priorities and shifting of resources, when such issues arose. The Foundation's Financial and Resource Management section also implemented decision support software with "what if" parameters for multi-year strategic planning involving HIV Research Program resources and for monitoring program execution vis-a-vis planned requirements.

E. SCIENTIFIC ORGANIZATION

Scientifically the program was structured into the eight major research efforts titled Mission Area Protocols as described in detail in the Technical Approach. The science in each area was directed by a Foundation or Military research scientist or physician. Research was conducted under approved research protocols or plans. All protocols were subjected to extensive scientific, ethical, programmatic "fit" and Institutional Review Board (IRB) evaluation before approval. The approval processes are further detailed in Section IV of this report.

As specified in the Grant, protocols could be and were submitted by Foundation, Military and Government Principal Investigators. While the collective scientific effort under the Grant was collaborative, the Foundation HIV Research Program Director (Foundation President), and, the Director of the Division of Retrovirology (and MMCARR Director) placed special emphasis on maintaining distinct, clear and separate lines of authority and chains of command for their respective organizations and staff.

The research within these mission areas was conducted at the Foundation's Laboratories in Rockville, Maryland and at selected military health care facilities as described in paragraph H of this section.

F. PROGRAM MANAGEMENT

The Foundation established a program management team as one component of the HIV research program infrastructure. The team was divided into functional groups for financial and resource management; research planning and operations, management information systems,travel and graphics. The efforts of the groups were independent yet integrated to insure efficiency and productivity. The groups worked collaboratively to achieve the plans, priorities, objectives and goals established by the President and HIV Program Director and to insure that HIV Research activities were in compliance with the Sponsor's, Federal, State, Local and Foundation regulations and policies. The teams operated independently to support the program's clinical and laboratory research sites, and to provide, within their respective areas, common management and quality assurance practices throughout the program.

Financial and Resource Management

Under the direction of the Deputy Director for HIV Research, the Financial and Resources Management section provided:

- Evaluation of program requirements and determination of eligibility across a number of issues including certification of technical need, conformance with the scope and terms of the award, overall program and cost reasonableness, conformance to stated needs and objectives, appropriate sourcing, availability of funds, potential alternatives, program priority, general business practices and regulatory compliance and legal sufficiency.

- Maintenance of a central multi-year data base of eligible program requirements.

- Maintenance of the program's costing structure within the Foundation's financial accounting system.

- Provision for the central acquisition of HIV Research Program goods and services.

- Manpower management.

- Management analysis.

Research Planning and Operations

Under the direction of the Deputy Director for HIV

Research, the Research Planning and Operations Office provided key management and operational services, and protocol planning/analysis to the HIV Research Program Director, Deputy Program Director and to all principal scientific and management staff within the program. This office also coordinated the initiation of new approved clinical protocols. After protocol implementation, this office served as facilitator and problem-solver between the sites and Foundation Headquarters.

Management Information Systems (MIS)

The Director of the Foundation's Management Information System established a separate MIS Program office to provide management and technical expertise to assess the HIV Research Program MIS needs and establish standards of system and software performance. This office worked with the Program's scientific, management and technical staff to determine the computer and communication technologies needed to meet the program objectives and to then integrate the variety of technologies acquired to support research into a unified system. The office also provided computer programming and operated and maintained systems of data communications and management as an integral part of the HIV research project - both science and management.

Equipment and Application Software

A dedicated Digital Equipment Corporation VAX 6410 super-minicomputer was utilized for the HIV Research Program, with all office and work sites connected through high speed leased lines. File transfers, remote printing, and remote access were facilitated by this wide area network, which made all systems appear local to end users.

The VAX has six gigabytes of mass storage, and all active files were backed up to tape on a daily basis. Tapes of all backup data were maintained on-site and in a fire-proof temperature controlled warehouse off-site. Physical access to the computer was limited to system personnel through a solid door protected by cypher lock.

While the VAX computer provided administrative, management and decision support software access to HIV Research Program staff, its principal effort was devoted to the maintenance and management of the program research data bases. Access to the VAX was controlled through user accounts with system assigned passwords. All user accounts were captive (in a menu driven system) for maximum security with the exception of senior computer systems management personnel. Access to the

HIV databases was further secured through the user identification. Approval from the appropriate Principle Investigator was required before access to data was granted. Additional computer security procedures are discussed in the Data Control Quality Assurance subsection of this section.

The HIV Research Program also provided computing support for researchers using personal computers and Macintosh units. These tools were used where specific software was required, or where data sharing needs were low. The HIV Research Program also used three RISC-based workstations to accommodate statistical analysis needs. All units were networked and had access to the mainframe and modem bank. Translator programs and export utilities to transfer files across the different hardware platforms were used as well as between applications on the same platform. Thus, files were shared between the VAX, the PC's and Macintosh units and the workstations.

Routine administrative tasks were supported by either integrated software packages on the VAX or by a variety of standard office computer software packages.

Research Data Management

The HIV Research Program used a relational database management system to manage clinical research data. Several databases were used to store research data in a logical and efficient manner. A small, very protected database contained confidential and identifying patient information, i.e. protocol registry and demographics. Information was shared across databases at the direction and control of the Principal Investigators.

Data was collected through two methodologies. Clinical and survey data were recorded on forms which were keyed into the system by data entry clerks. Quality assurance mechanisms were implemented at each step in the data entry process; details can be found in Section IV. The second method of data acquisition was through electronic interfaces. Data was acquired directly from participating DoD health care facilities' (clinical sites) information systems wherever possible and inserted directly into the database.

Travel

A Travel Manager maintained program oversight over a research patient travel management system. An on-line Travel Database was implemented to increase efficiency and productivity. This on-line system maintained a secure access patient travel data base linked to the clinical research sites. Approved travel requirements were transmitted daily to a travel agency which arranged for travel at the lowest available cost. Invoices and disbursement requirements for all patient travel, regardless of mode, were received, reviewed, certified and/or reconciled and approved for disbursement at the Foundation Headquarters. This process insured that all charges were appropriate, and reasonable and that refunds due the project were received and properly credited.Travel was also carefully coordinated with all protocols and staff at each site to insure that scheduled research patients participated in all appropriate research protocols.

Graphics and Presentations

A graphics office supported the Foundation's scientific research through the design of graphics and illustrations in slides, posters, manuscripts, and camera-ready art for use in scientific journal publications, posters, medical seminars and other presentations.

Insurance

The Foundation maintained appropriate insurance to protect assets acquired through sponsored awards against major losses. Protection included property and casualty insurance, professional liability insurance and corporate and individual clinician malpractice insurance.

G. BIOSTATISTICS

Comprehensive and expert Biostatistical collaboration was provided to the HIV Research Program. To specifically meet the goals and objectives of the program, the Biostatistical office specialized in two areas: 1) Clinical Trial Applications and 2) Applied Biostatistics and Epidemiology. In particular, the office provided data analysis, statistical design, protocol development, statistical reports for investigators,statistical programming, data base quality assurance [with associated data cleaning, imputation, etc.] Preparation of statistical design and analysis sections for publications, posters, and presentations were generated for the HIV Research Program Principal Investigators.

H. RESEARCH SITES

Clinical Sites

Clinical research within the HIV Research Program was conducted at three primary clinical sites:

Walter Reed Army Medical Center (WRAMC), Washington, D.C. (1989);

Wilford Hall Air Force Medical Center (WHMC), San Antonio, TX (1989);

National Naval Medical Center (NNMC), Bethesda, MD. (1990)

Additional sites were established at:

Naval Hospital at San Diego (NHSD), San Diego, California (1990)

Womack Army Medical Center(WAMC), Ft. Bragg, North Carolina (1991)

Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok, Thailand (1992)

Brooke Army Medical Center (BAMC), Ft. Sam Houston, Texas(1992)

Eisenhower Army Medical Center (EAMC), Ft. Gordon, Georgia (1993)

Fitzsimons Army Medical Center (FAMC), Aurora, Colorado (1993)

Direct data lines maintained by the Foundation linked the primary clinical sites to the HIV central computer and data base. The Ft. Bragg Site and the AFRIMS site achieved the same link via modem. These links subsequently afforded clinical sites with direct lines of communication to all other Foundation sites and the WRAIR.

Each primary site was uniquely tailored to fit the environment of the Host Institution. However, each employed a common management approach. Specifically:

** A Research Program Associate was assigned and on site to manage and coordinate operations and served as the Foundation liaison to the medical center to guarantee coordination of each site's clinical and research efforts.

** Resources were shared across protocols and trials and provided:

- Research protocol execution and management.
- Patient recruiting, scheduling, travel, follow-up and record keeping
- Data collection and input
- Logistical support
- Clerical and administrative support

** Resources were assigned and reassigned among protocols and trials as research demands dictated.

** Scientific and technical efforts were directed and managed by the Principal Investigators in accordance with Mission Area objectives and the approved individual research protocols.

** Strict ethical standards were observed in recruiting patients, and their participation was subject to Institutional Review Board/Human Use Committee approval and signed informed consent.

** Patient scheduling and travel was arranged to coincide with standard of care visits to the maximum extent possible in order to minimize travel costs.

**Centralized recruitment teams facilitated quick protocol starts for approved protocols.

Laboratory Sites

Research was also conducted in two adjacent Laboratories located in Rockville, Maryland which were designed according to strict specifications to accommodate the laboratory based research components for the Vaccine Trials, the Chemotherapy Trials, Animal Model Protocols, Natural History studies and Retroviral Biology Laboratory projects. The Laboratories provided biohazard containment through the BL3 level and both were licensed by the State of Maryland for the use of radioactive materials.

A Foundation Laboratory Director directed and coordinated Foundation research efforts within the laboratories and was responsible directly to the Foundation's HIV Research

Program Director. A nucleus of dedicated staff provided management, logistical, clerical, and administrative support to the Principal Investigators, scientists and research personnel in both Laboratories. Established committees for Radiation Safety, Institutional Biosafety, Institutional and Environmental Safety and Laboratory Animal Use ensured proper oversight and guidance for specific Laboratory research activities(Refer to Section IV for details).

Direct data lines maintained by the Foundation linked the laboratories to each other and to the Foundation's central HIV computer and data base. This link subsequently afforded the laboratories with direct data lines to most other Foundation HIV research sites and the WRAIR.

The Laboratories were further augmented by contractually acquired sites and services. Four contract sites located in Maryland provided housing, husbandry and specific clinical procedures for Foundation owned laboratory research animals. Each site was appropriately credentialed and their practices were monitored by the Foundation's Laboratory Director. Contractually acquired services from the Department of Energy, Los Alamos National Laboratory, provided genetic sequence analysis supporting the Retroviral Biology and Chemotherapy/Chemoprophylaxis Mission Areas.

Additional "Research Management" Site

The Foundation established a site for the Principal Investigators and selected staff of the Behavior Medicine Mission Area and the Natural History Mission Area. This site served as a programmatic direction core for both mission areas, and its proximity to the laboratory and clinical sites allowed for daily networking within and between the mission areas.

Other Sites

Augmenting the Foundation sites were contractually acquired services at the State University of New York, Buffalo, The University of Pennsylvania and the University of California, San Diego. These sites provided clinical diagnostic services and program collaboration for three established protocols in two mission areas.

IV. ASSURANCES AND COMPLIANCES

A. INTRODUCTION

The Foundation integrated into its management practices assurance initiatives designed to ensure that the Foundation HIV Research Program:

a. Science and business practices conformed to strict ethical standards.

b. Executed and/or supported only those research protocols/plans which were approved for scientific design, merit and "fit" within HIV Research Program.

c. Conformed to established ethical standards in the use and treatment of research patients (human and animal) in conduct of its research and in the use and treatment of data derived from that research.

d. Provided for and promoted occupational health and safety.

e. Complied with Federal, State and Local statutes in the conduct of research.

f. Complied with the provisions, terms and conditions of it's sponsors and their awards to the Foundation.

Elements of the Assurance initiatives are outlined in the balance of this section. Many of the elements were specifically tailored to the HIV Research Program and were managed and/or coordinated by the Foundation's HIV Research Program management and scientific infrastructure. The Foundation and its HIV Research Program representatives, including Principal Investigators, participated fully and completely with those elements managed by the MMCARR and the DoD.

B. PROTOCOL APPROVAL PROCESS

All clinical research involving human research was governed by protocols which dictated the course of the Investigators' work. Each protocol was subjected to an evaluation process to ensure that it was scientifically sound, investigators were qualified to conduct the research, the rights of the subjects were carefully guarded and preserved and that the protocol "fit" the overall MMCARR Program goals and objectives.

The USAMRDC Retrovirus Clinical Research Committee (RCRC) reviewed each protocol involving human subjects. The members were appointed by virtue of their office and included the Director,

Division of Retrovirology, WRAIR, the Chiefs of the Departments of Retroviral Research, Diagnostic Retrovirology, and Epidemiology at WRAIR, and the Directors of the Clinical Research Programs for each of the three services. Others were appointed on the basis of their expertise. The purpose of the review was to evaluate each protocol's scientific concept and excellence, importance to the HIV Research Program, and feasibility of conduct. The review resulted in approval, disapproval or deferral of the protocol.

If approved by the RCRC, each protocol was subjected to a rigorous scientific review by a committee of scientifically qualified experts who were selected by the MMCARR Program Director(also the Director of the Division of Retrovirology, WRAIR). This three to five member panel discussed the scientific design and merits of the protocol directly with the Principal Investigator. The designated Chair wrote an evaluation and final recommendations. The protocol was then approved, approved with modification or disapproved.

If approved each protocol was then reviewed by the Tri-Service (Army, Navy, Air Force) augmented Surgeon General's Human Subjects Research Review Board (HSRRB). If approved, the protocol was submitted for local Institutional Review Board (IRB) approval at each DoD Medical facility in which the protocol was proposed for implementation. The IRB and facility commander either approved or disapproved the conduct of the protocol; however, this approval consideration by the IRB and facility commander could not result in any change in any aspect of a protocol approved by the Tri-Service Board. This approval and "no change" process standardized the protocol (science and ethics) and the data that was generated.

After implementation of the protocol, an annual review of the protocol was done by the facility IRB and a final report was required at the completion of each protocol. Procedures ensured that all required annual and final reviews for each protocol were presented to the appropriate oversight office at the individual medical facility and/or the Human Use Office at the USAMRDC.

The Foundation's Clinical Program Coordination facilitated the entire protocol approval process.

C. INFORMED CONSENT

All research patients volunteering to participate in human use protocols provided a signed informed consent as a precondition to participation. Each informed consent was written and specifically tailored to the research protocol being executed and to the medical facility at which it was being conducted. Each prospective volunteer (or parent/legal guardian) was required to read the consent form and had the details of the protocol

explained by a qualified member of the Foundation's research staff. Once signed, the informed consent was filed and maintained at the participating medical facility. The appropriateness of informed consent content was subject to evaluation and approval throughout the protocol approval process, outlined in paragraph B of this section.

D. RESEARCH PATIENT RECORDS

The Foundation developed a system of records in accordance with the Privacy Act of 1974 and Notice No. A0917.01DASG, "Health Care and Medical Treatment Record System". Research records were maintained at the clinical sites for each research protocol patient. Records were accessible only by authorized personnel and all automated records were password protected. Research records were maintained and secured at each site in accordance with Foundation policy and the rules and regulations at each specific site. Records were updated during each protocol visit with the appropriate medical research data (specified by the protocol requirements) by protocol nurses and Principle Investigators. Access to these records was limited to only Principal Investigators and Protocol Nurses/technicians directly involved in the protocols.

E. DATA COLLECTION QUALITY ASSURANCE

Data collection quality assurance was multifaceted and inclusive. The following table summarizes the process:

Step 1 - Double data entry or automatic upload from Medical Center data files
Step 2 - Routine check of administrative records (enrollment forms, etc)
Step 3 - Exactitude of data - data gathered twice at four week interval
Step 4 - Review for data integrity, unlikely results
Step 5 - Review of data by Principal Investigator

The first step in quality assurance was the double entry of all data which could not be uploaded from automated clinical files at the Medical Treatment Facility (MTF) where research was performed. Records were entered into separate files by two different data entry clerks and were then compared by computer. File inconsistencies were researched and corrected. Only files which matched exactly were committed to the final database. Records were dated and time recorded to facilitate any retrieval of data which could be necessary in the future. "Hard" copy files were kept in data rooms, on site indefinitely, as backup to the computer records.

The second effort in quality assurance was based on review of administrative records. Patient enrollments in protocols, signed Informed Consent Forms, basic demographic information, and records from each protocol visit made by every patient were checked routinely for accuracy by the MIS quality assurance team in concert with administrative and clinical staff at each site.

The third quality control step was to ensure the exactitude of data electronically acquired, such as data from participating hospital clinical laboratory computer files. On occasion, a laboratory would find some previously reported value to be in error, and would issue a correction. All data was therefore gathered two times, once four days after a test was performed, and once four weeks following the test. Data retrieved for a second time was compared to the first values retrieved, and corrections

were made as updates to the research database.

The fourth step in the program was a review for data integrity. Values reported in the database were checked for impossible or unlikely results.

Finally, results were returned to the Principal Investigators and protocol coordinators for their review for accuracy and completeness.

F. CLINICAL DATA ACCESS AND SECURITY

After data was checked to the satisfaction of the Investigator, a mechanism was implemented to ensure that results were not changed. All database screens were equipped with a flag that marked records which had been changed after passing the double data entry system or upload verification procedure. Usernames were captured to indicate the person making such changes. Specific security measures were implemented at the operating system level to prevent covert changes and deletions from being made in the database records. All user accounts and privileges were strictly monitored.

User profiles were centrally maintained with hard copy documentation authorizing database access and were kept as backup. User account names were coded derivatives of the actual person's name, so the simple knowledge that John Doe works for the Foundation did not give outsiders access to username information. Additionally, passwords were restricted to prevent the use of dictionary words. Directories and files were protected at the maximum level possible while still maintaining a functional system. User accounts not used within six months were deleted. Operating system generated error logs and event logs of system activities were reviewed periodically by the System's Manager and the Director of Management Information Systems.

G. DATA SAFETY MONITORING BOARD

The Data Safety Monitoring Board was constituted at the direction of the MMCARR Program Director. The Board provided a continuing critical and unbiased evaluation of the progress of selected studies and advised the MMCARR Program Director with regards to operational policy consistent with the best current biomedical research practices. It did not evaluate the scientific merit or methodology of the study nor did it subsequently participate in the study's conduct, as these functions were performed by other committees.

The MMCARR Data Safety Monitoring Board (DSMB) was made up of six to twelve members who were experts in the subject matter of

the study, including an independent biostatistician, and other appropriate technical, scientific, or ethical specialists. The members had to be highly qualified by background, training, expertise and knowledge in relevant disciplines. Every effort was made to avoid potential conflicts of interest. Board members could not have a contractual or a financial relationship with any corporation that was involved in trials under consideration. A person who participated in the planning or the execution of trial under consideration could not participate on the board. Persons from industry could not be nominated for studies involving the evaluations of industrial products of potential commercial value. The MMCARR Program Director was a nonvoting member.

The major guidelines for the Data Safety Monitoring Board are:

A. Efficacy trials only were presented for formal consideration by the DSMB. Background information from related Phase I U.S. military trials and/or other sources were provided to the DSMB as required.

B. The DSMB could advise that a specific study be modified, or stopped. Reasons for modifying or prematurely stopping an ongoing trial could be adverse effects, proof of efficacy or a lack thereof, or, new information from outside sources that alters "standards of care" treatment.

C. The Committee Chairperson prepared a brief report of each meeting and forwarded it to the MMCARR Program Director. The DSMB could make suggestions which were not intended to be binding but were to be considered by the MMCARR Program Director, the Principal Investigator and/or other study representatives.

D. The Board maintained the confidentiality of interim results that were presented at meetings.

Upon receipt of a DSMB report, the MMCARR Program Director, consulted with the Principal Investigator and determined how the recommendations were to be implemented. The MMCARR Program Director concurred or added whatever comments were appropriate and forwarded the report to the Chief, Human Use Review and Regulatory Affairs Office (Army, Office of the Surgeon General). All reports were filed with the protocol in the Human Use Review and Regulatory Affairs Office, U.S. Army, Office of the Surgeon General, and in the MMCARR Program Director's office.

H. PUBLICATIONS/PRESENTATIONS

The Foundation had an established policy regarding all publications for which it was cited as the institution of origin, in whole or part. The term "publications" includes but is not limited to all books, chapters of books, articles, technical reports, abstracts and posters, and subsequent copyrights. All publications and presentations resulting from the research accomplished were subjected to a peer review process to insure scientific merit and as applicable, statistical validity. If approved by this process, all publications were cleared and approved by the Foundation prior to release, printing and/or distribution. The HIV Research Program Director either concurred or provided reasons for nonconcurrence. Scientific or administrative issues were resolved prior to this final step, in the peer review process. The HIV Research Program Director's clearance constituted Foundation authorization to publish.

I. ANIMAL USE REVIEW COMMITTEES

A Foundation Laboratory Animal Use Review Committee (LAURC) provided ethical, regulatory, humane use and care and scientific relevancy oversight to all existing and proposed animal use biomedical research protocols/studies. The committee members were appointed by, and reported directly to, the Foundation's HIV Research Program Director.

This Committee operated under a policy established by the Foundation HIV Research Program Director. The policy incorporated regulations and guidelines of the United States Public Health service (USPHS), the National Institutes of Health (NIH), the United States Department of Agriculture (USDA) and the U.S. Army Medical Research and Development Command (USAMRDC). Specifically, laboratory animal use was to be in conformance with the United States Public Health Service Policy on the Humane Care of and Use of Laboratory Animals, as revised September 1986, and The NIH Guide to the Care and Use of Laboratory Animals. Members of the LAURC were appointed by the HIV Research Program Director according to the policy of the granting agency. Research was not permitted on laboratory animals without written approved research protocols and concurrence by the LAURC.

Animal Use Protocols were also scrutinized to assure protocol compliance and appropriate use of laboratory animals. The Foundation Laboratory Director guaranteed the ethical, and humane use of animals; insured that the MMCARR Animal Studies Steering Committee (ASSC) provided scientific review of all animal research protocols; assured Laboratory Animal Use Review Committee (LAURC) review and approval of all ASSC approved protocols prior to initiation of animal research; warranted that all ASSC and LAURC approved protocols were carried out only in facilities that were

in compliance with existing National Institutes of Health guidelines for research animal care and assured compliance with all parts of the approved animal research study.

J. MISSION AREA PROTOCOL "MAP" REVIEW

Each Mission Area Protocol (MAP) was subjected to scientific scrutiny to ensure that current and planned research efforts were properly directed towards the goals of the overall USAMRDC/MMCARR HIV Research Program, that the science was sound and that each MAP was aligned with and supportive of the other Mission Areas in the program. Each review was conducted by a panel of select members in the research community external to the MMCARR and recognized as experts in the field. This panel was selected by the MMCARR Director in coordination with the MAP Director. While the review initiative and management was that of the USAMRDC, the Foundation fully supported and participated in these reviews.

K. RADIATION SAFETY

The Foundation secured a State of Maryland license authorizing the Foundation HIV Research Laboratory to receive, acquire, possess, and transfer specified radioactive materials. Utilization of any/all radioactive materials in the pursuit of research under the HIV Research Program was governed/sanctioned by the Program's Radiation Safety Committee, whose members were appointed by the Foundation's HIV Research Program Director. The Committee met at least quarterly to evaluate all proposed research protocols involving the use of radioactive materials and to assess the qualifications of personnel proposed to use such materials. Formal records of committee meetings to include approval or disapproval of use and/or specific qualifications were maintained.

Specific guidance as to compliance, materials use and disposition and records management was issued by the Safety Manager to Principal Investigators. Performance oversight was also conducted by the Foundation Safety Manager. Any related issues were presented to the committee and, as applicable, to the HIV Research Program Director for resolution.

L. INSTITUTIONAL/ENVIRONMENTAL BIOSAFETY

The Institutional/Environmental Biosafety Committee (IBC/EBC) of the Foundation provided oversight and guidance on the safe conduct of research at the HIV Research Program facilities and compliance with the NIH Guidelines for Recombinant DNA research. The IBC/EBC reviewed research and safety protocols with the objectives of:

- safeguarding the public health
- addressing occupational health issues

- protecting the environment, and
- maintaining the highest ethical and community standards

The IBC/EBC reviewed ongoing and proposed protocols, conducted site visits and maintained a level of competency that promoted the IBC/EBC objectives. Members were appointed by the Foundation HIV Research Program Director.

M. OCCUPATIONAL HEALTH AND SAFETY

The HIV Research Program offered to all HIV Research employees a comprehensive Occupational Health Program to provide a safe work environment. Designated safety points of contact at each clinical site and the laboratory worked with all employees to safeguard the workplace. On all significant incidents, copies of the investigations with recommendations for corrective action were forwarded to the HIV Research Program Director. A Foundation Safety Manager for the HIV Research Program provided Foundation corporate oversight for safety issues in the research laboratory as well as clinical settings. The Foundation also maintained a database of all untoward events which tracked all incidents and further insured appropriate follow-ups.

N. FINANCIAL COMPLIANCE

The Foundation's financial and compliance audits are conducted annually and are available for inspection by appropriate authority. The audits are submitted to each Federal agency which provided funds during the Foundation's audit fiscal year. The audits are conducted by an independent accounting firm in accordance with generally accepted accounting principals, government auditing standards and the requirements of OMB Circular A-133, "Audits of Institutions of Higher Education and Other Nonprofit Institutions."

The Defense Contract Audit Agency (DCAA) is the Foundation's cognizant audit agency. The DCAA performs audits of the Foundation's activities as required. The DCAA also reviews indirect cost rate proposals and provides recommendations to the Foundation's Administrative Contract Officer (ACO). The U.S. Army Medical Research Acquisition Activity of the U. S. Army Medical Research and Development Command, located at Fort Detrick in Frederick, Maryland, provides the Foundation's ACO.

V. CONCLUSION

As the ninth International AIDS conference in June, 1993, came to closure, it was estimated that there were currently about 14 million people in the world infected with HIV, compared to the 1 and one half million estimated in 1985. Public health experts predicted that, without a major breakthrough or an intensified effort, the 14 million estimate could rise to more than 33 million by the end of this century. Further illustrating the magnitude of the problem to society, a recent Journal of the American Medical Association (JAMA, 269, 93) concluded that HIV infection was the leading cause of death in 1990 among young men and women in many US communities. As the HIV epidemic continues, so does the impact to the military, complicating readiness issues. Reflective of the magnitude of the problem to the military, during the time period of 1985, to December 1992, over 32,000 clinical evaluations related to HIV were conducted in military hospitals.
The message is unfortunately quite clear and the impact is evident. The disease remains a threat to the military.

The HIV Research Program, composed of expert Foundation, Military, and Government scientific, technical and administrative personnel, made considerable progress during the past five years towards better understanding and characterizing the nature of this deadly disease. Details of the five year achievements and accomplishments of research conducted in each mission area are found in the technical approach (Section II). In review, notable contributions of this collaborative Foundation and Tri-service military effort included but were not limited to:

- Initiation and continuation of the world's largest Phase II Vaccine Therapy Trial.

- Completion of the Army-wide HIV/AIDS survey (over 18,000 surveyed) - a landmark research effort.

- Genetic analysis of more than 250 international field isolates of HIV-1 from 21 countries on 5 continents - one of the largest international collections of isolates to date.

- Collection of Natural History data from over 5000 HIV patient visits providing invaluable information about disease progression.

- Development and evaluation of enhanced sensitivity diagnostic techniques for HIV, and techniques to quantitate viral genes in blood and tissue.

- Development of animal models to further the development of preventive vaccines and drugs against HIV.

- Initiation and continuation of the only U.S.study of AZT that allowed continued follow-up of matched cohorts of patients (DoD-VA) receiving early versus late AZT therapy.

- Initiation of outside collaborations with the National Institutes of Health (NIH) and pharmaceutical firms to offer promising new drug therapies for military HIV infected patients

- Development of an effective management and administrative infrastructure which provided an environment conducive to the execution of HIV research.

- Conduct of over 35,000 protocol patient visits with 31 currently active protocols and 9 completed protocols.

- Foundation authorship and co-authorship of 134 manuscripts, 150 abstracts and 197 presentations.

Although, significant strides were made, there is much work still ahead. Manifestations and progress of the disease as well as the biologic properties of the virus remain to be fully charted. Rapid and effective diagnostic methods are only in the conceptual and developmental stages. Effective therapeutic, prophylactic and behavioral interventions have yet to be developed.

A five year Cooperative Agreement was executed between the Foundation and the United States Army Medical and Research Development Command (USAMRDC) to continue the HIV research effort. With appropriate resources, a well-disciplined population, and a cooperative and expert team of Foundation, Military, and Government scientists, the MMCARR will forge ahead with its goal to eradicate AIDS and HIV. Research will be conducted in five program areas: Vaccines for Prevention, Behavioral Prevention, Drug and Gene Therapy, Vaccine Therapy and Intervention Assessment. Drawing upon knowledge and experience gained, efforts will be concentrated in these areas to maximize and intensify objectives and goals most programmatically relevant to the military mission. The goals for the next five years remain the same: reduce the incidence of new HIV infections to zero, arrest and reverse the progression of disease in those already infected, and eliminate fatalities from HIV. At the forefront of HIV research, Foundation, Military, and Government scientists expect to make significant scientific contributions to the national and international HIV/AIDS research effort.

PROTOCOL SUMMARY SHEETS

Protocol summary sheets on all protocols initiated during Grant Years 1-5 are listed in numerical "RV" order. These summaries were originally submitted by each individual Principal Investigator, as of March 31, 1993. Protocols that were completed or terminated have also been included. These summaries represent a scientific snapshot of the protocol, and information included is: brief description, significant findings, the sites at which the protocol was conducted, and enrollment and patient visit numbers, when applicable. The Human Use Protocols are followed by the Animal Model Animal Use Protocols, and then the Army Wide HIV/AIDS Survey (AWAS) follows. A summary sheet is also provided for a pediatric project entitled "Army Pediatric HIV Caregiver Training Project", which was also initiated under the auspices of this grant.

PROTOCOL SUMMARY SHEET

RV # 1

PROTOCOL TITLE: The Natural History of HIV Infection and Disease in U.S. Military Beneficiaries

CLINICAL SITE(S): NNMC, WRAMC, WHMC, BAMC

PRINCIPAL INVESTIGATOR: Kenneth F. Wagner, M.D., Henry M. Jackson Foundation

STATUS: Active

MAP: Natural History/Epidemiology

NUMBER OF PATIENTS ENROLLED THUS FAR: 2,544

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 4,000

NUMBER OF PATIENT VISITS TO DATE: ~5000

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: 56,000 (4000 pts 2x's/yr x 7 more years)

DESCRIPTION/SUMMARY OF PROTOCOL: The purposes of RV-1 were:

1) to systematically document the natural disease progression in individuals With HIV-1 infection in a general military population;

2) to form a study cohort which would be eligible for participation in treatment protocols and for other studies related to specific aspects of the descriptive elements of HIV infection;

3) to avoid duplication of visits and data so that other protocol studies incorporated RV-1 histories, physical, laboratory and medications (RV-18, RV-26, RV-43, and RV-65);

4) for screening purposes. Before any new protocol was undertaken RV-1 was able to provide a list of patients available that met the criteria of the protocol;

5) to serve as a historic control for intervention studies; and

6) to validate proposed surrogate markers of disease progression.

SIGNIFICANT FINDINGS: As of March 31, 1993

Medical Center	#Pt's Signed	#Pt's with at least One Data Submission	Active Pts.
WRAMC	765	378	681
NNMC	1052	854	651
WHAFMC	634	577	601
BAMC	129	129	129
TOTALS:	2580	1938	2062

RV-1 data has been compared to a study of progression and AZT use in Fitzsimons Army Medical Center patients by Dr. Mayers and Lytt Gardner. The data correlated well.

In the data base, 315 patients were diagnosed as having one or more O.I.

82 patients died:

42 from HIV/AIDS related causes
5 for non-HIV/AIDS related reasons
35 unknown causes

There is an ongoing project to retrieve all data from those patients that died and find those patients enrolled that have died.

Of the patients having Opportunistic Infections, the order and date of the occurrences have been defined through utilization of RV -1 data.

Several presentations have resulted from the RV-1 database. RV-1 data has also been used by many other protocols in which presentation/publications have followed (RV-18, RV-26, RV-43, and RV-65).

An aggressive Quality Assurance program for RV-1 data was implemented, initially at NNMC by the Principal Investigator and then extended to the other sites.

PROTOCOL SUMMARY SHEET

RV # 2

PROTOCOL TITLE: The Core Protocol for HIV Developmental Diagnostics (Adults)

CLINICAL SITE: Samples were received from WRAMC, BAMC, NNMC, WHMC.

PRINCIPAL INVESTIGATOR: Ronald Turnicky DO, MC, LTC
Laboratory Section, Intervention Assessment Program, WRAIR.

STATUS: Active

MAP: Diagnostics

NUMBER OF PATIENTS THUS FAR ENROLLED: 2,207 enrolled/1422 active

Contract	Old Contract Totals to 1/92	Curient	Totals
Co-Cultures	3673	3168	6841
PCR HIV	339	430	769
PCR HTLV	25	61	86
RIPA HIV	6129(2 dilutions)	1461 (2 dilutions)	7590
RIPA HTLV	Not available	692 (2 dilutions)	692
Serum p24	1067	1388	2455
Serum antip243	Not done	230	230

Total vials of frozen cells = 10,184
Total vials of frozen sera = 7,507
Total vials of frozen plasma = 3,289

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 2,207 patients signed consent forms for this protocol, 1422 patients participated.

NUMBER OF PATIENT VISITS TO DATE: NA. An RV-2 visit occurred simultaneously with a staging visit or RV-1 visit. An aliquot of the patient's blood was studied for this protocol.

FUTURE NUMBER OF PATIENT VISITS PROJECTED: It was anticipated that all seroconverting patients will be enrolled in the protocol. Currently 150-200 active duty military personnel from each of the services seroconvert yearly.

DESCRIPTION/SUMMARY OF PROTOCOL: The objective of the protocol was to develop and evaluate new and/or improved

laboratory methods for establishing the early diagnosis of HIV infection, deciding the stage of illness and determining markers of disease progression. Methods to detect replicating HIV virus, HIV antigens, and HIV nucleic acids were used, including virus culture, antigen capture, immunoassay and polymerase chain reaction amplification of HIV DNA and RNA. This protocol was a foundation for laboratory evaluation of progression of disease for the patients enrolled. Additionally, the protocol provided diagnostic support in establishing the initial diagnosis of HIV infection. An adjunct to sample testing was the banked repository of frozen cells and sera of each patient. The banking of sequential patient samples could be utilized for prospective assessment of intervention therapies.

SIGNIFICANT FINDINGS: HIV detection by culture and PCR were extremely sensitive techniques and could be offered as routine clinical tests. Through these techniques the "window" between infection and detection of that infection was narrowed considerably. Diagnostic assays continued to be evaluated for the best combination of testing panels to enhance sensitivity, specificity while decreasing the period from infection to laboratory detection. Methods to discriminate between HIV vaccine sero-response from natural infection were under development.

PROTOCOL SUMMARY SHEET

RV # 3

PROTOCOL TITLE: CSP #298 Part II - Follow-up of Patients with AIDS-Related Complex (ARC) Originally Randomized to Early Versus Later Treatment with Zidovudine

CLINICAL SITE(S): WRAMC and VA Cooperative Study Sites (New York, Los Angeles, Houston, Miami, Durham, Washington, D.C.)

PRINCIPAL INVESTIGATOR: Clifton A. Hawkes, MD, MC, LT, US Army

STATUS: Active

MAP: Chemotherapy/Chemoprophylaxis

NUMBER OF PATIENTS THUS FAR ENROLLED: 24 DoD patients in Phase I of a total of 338 patients enrolled in Part I, 10 of those enrolled in Part II with a total of 213.

NUMBER OF PATIENT VISITS TO DATE: 272

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: 60

DESCRIPTION/SUMMARY OF PROTOCOL: As part of the VA Cooperative Study Group, WRAMC contributed 24 participants to the total of 338 symptomatic HIV patients in Part I who were randomized to receive early versus later AZT treatment.

For part II of this study, 10 patients from WRAMC Part I (criterion for inclusion) were enrolled and continued to be followed until the final endpoint, death, is reached, or 1994. Participants on Part II were given the option of remaining on AZT if they were originally randomized to receive it or being started on AZT if they were originally randomized to "Later group". They continued to be followed quarterly according to standard of care with the exception of collection of blood samples for studying AZT resistance. Pharmacokinetic studies were also done on selected patients to assess differences in the handling of AZT among whites and non-whites.

SIGNIFICANT FINDINGS:

Continued follow-up of 213 patients from the original study (Part I) supported findings and conclusions that:

1. Early administration of Zidovudine (CD4 200-500) significantly delays progression to AIDS.

2. There were no significant difference in survival among those patients started on AZT early versus later.

3. No significant difference between early versus later AZT in terms of quality of life, as measured by the Sickness Impact Profile (SIP) and the Time Without Symptoms or Toxicity Profile (TWIST).

4. The apparent lack of response by minorities to early AZT continued to be observed. Preliminary results from the pharmacokinetic studies revealed a shorter half-life by 60-90 min.

PROTOCOL SUMMARY SHEET

RV # 4

PROTOCOL TITLE: Neurobehavioral Consequences of HTLV-III Brain Infection and AIDS Encephalopathy

CLINICAL SITE(S): WRAMC

PRINCIPAL INVESTIGATOR: Andres Salazar, MD, COL, MC, US Army

STATUS: Completed

MAP: Behavioral Medicine

NUMBER OF PATIENTS ENROLLED: 157

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: NA

NUMBER OF PATIENT VISITS TO DATE: 384 visits: 60 patients were evaluated twice, 44 were evaluated three times, and 33 were seen four times.

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: 0

DESCRIPTION/SUMMARY OF PROTOCOL: The purpose of this protocol was to study the natural history of neurologic and behavioral effects on HIV infection. The protocols's technical approach called for an initial and six month follow-up multidisciplinary evaluation of WR Stage I, II, and III patients.

SIGNIFICANT FINDINGS:

The following objectives were obtained:

1. The neurological and cognitive manifestations of early HIV infection were prospectively characterized with multiple examinations on 95 HIV patients and 90 HIV negative controls.

2. A screening instrument to detect the early onset of neurobehavioral changes in HIV infection was developed and successfully tested in 95 HIV patients and 90 controls.

3. Host, virus, infection, and epidemiologic factors affecting these manifestations and their progression were investigated, and two neurotoxins were identified in early HIV CSF, one of these correlated highly with cognitive deficits in information processing.

4. A structure for the systematic testing and evaluation of HIV patients in drug trials was established and successfully tested in one drug trial.

The following conclusions were derived from the work on this protocol:

1. HIV infection in its earliest stages (WR I-III) results in subtle but clearly defined clinical deficits in information processing and procedural learning which correlated strongly with elevations of Quinolinic Acid (an NMDA receptor excitotoxin) in the CSF.

2. These deficits were not seen in HIV negative asymptomatic or depressed control patients.

3. The Quinolinic acid elevations appeared to be related to abnormalities in the interferon systems.

4. Similarly, about 50% of the HIV patients were found to have a GP-120 like neurotoxin in their cerebral spine fluid (CSF).

PROTOCOL SUMMARY SHEET

RV# 5

PROTOCOL TITLE: The Natural History of the Oral Manifestations of HIV Infection in a US Military Population

CLINICAL SITE (S): Ward 11, Building 1, WRAMC

PRINCIPAL INVESTIGATOR: Joseph L. Konzelman DDS, Henry M. Jackson Foundation

STATUS: Active

MAP: Epidemiology/Natural History

NUMBER OF PATIENTS THUS FAR ENROLLED: 1,022

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: No new enrollees, target reached.

NUMBER OF PATIENT VISITS TO DATE: 2,797

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: 850

DESCRIPTION/SUMMARY OF PROTOCOL: The purpose of the study was to determine the prevalence, incidence and risk factors of oral manifestations of HIV infection in relation to the degree of immunodeficiency. Emphasis was given to fungal and viral infections of the oral mucosa, periodontal diseases, and the effect of HIV on salivary constituents.

Volunteers received a comprehensive oral and dental examination at entry and every six months thereafter. The evaluation included clinical examinations for dental caries, periodontal diseases and oral mucosal conditions. Samples of saliva and subgingival dental plaque were collected at each visit for microbial and biochemical assays, and a questionnaire on oral health related behavior and history was administered. Data were analyzed in relation to subjects' medical condition and immune status.

This protocol was unique because the study population spanned the gamut from very early to late stage HIV disease. In addition, no other study of Oral HIV Manifestations employed examiners with comparable diagnostic specialty credentials.

SIGNIFICANT FINDINGS: In a preliminary analysis, prevalence of HIV-related oral mucosal lesions was 32 percent at baseline and 44 percent after 6 months of follow-up. About 30 percent of those who were initially free of mucosal pathologies developed lesions within six months. Oral candidiasis was the condition that developed most frequently, with 70 percent of incident cases being of the erythematous form. Prevalence of mucosal diseases was

clearly associated with depleted CD4 counts.

PROTOCOL SUMMARY SHEET

RV# 6

PROTOCOL TITLE: Evaluation of Renal Function, Protein Excretion and the Urinary Sediment in Patients with Antibody to the Human Immunodeficiency Virus (HIV)

CLINICAL SITE(S): WRAMC

PRINCIPAL INVESTIGATOR: Christine Link, MD, CPT, MC, US Army

STATUS: Completed

MAP: Diagnostics

NUMBER OF PATIENTS THUS FAR ENROLLED: 59

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: NA

NUMBER OF PATIENTS VISITS TO DATE: 59

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: NA

DESCRIPTION/SUMMARY OF PROTOCOL: The objective of this protocol was to describe the renal function, protein excretion, and urinary sediment in patients positive to HIV antibody; and to determine if any abnormalities found were related to the severity of disease. Three urine samples were obtained. These were used to examine the urinary sediment and to determine the ability to acidify and concentrate urine after overnight fasting. A 24 hour collection was used to determine creatinine clearance, total protein, and microalubuminuria.

SIGNIFICANT FINDINGS: There were no adverse reactions and the majority of patients completed all portions of the study. No patients had significant proteinuria or renal insufficiency, although abnormalities on urinalysis were not uncommon. There was no relationship between the severity of HIV disease and frequency of abnormalities. This protocol was completed on May 31, 1991.

PROTOCOL SUMMARY SHEET

RV# 7

PROTOCOL TITLE: A Double-blinded Randomized, Placebo-controlled Trial of Fansidar Prophylaxis in Patients with HTLV-III DIsease (WR Stage 5)

CLINICAL SITE(S): WRAMC

PRINCIPAL INVESTIGATOR: D. Craig Wright, MD, MAJ, MC, US Army

STATUS: Terminated

MAP: Chemotherapy/Chemoprophylaxis

NUMBER OF PATIENTS ENROLLED: 26

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: NA

NUMBER OF PATIENTS VISITS TO DATE: 26 patients were followed on a monthly visits for a maximum time-period of 22 months

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: NA

DESCRIPTION/SUMMARY OF PROTOCOL: The objective of this study was to determine if fansidar prophylaxis (one tablet per week) would prevent patients with advanced HTLV-III Disease (WR Stage 5) from developing Pneumocystis pneumonia. Eighty patients with HTLV-III were to be placed on either fansidar or placebo once a week in a randomized, double blinded fashion. Patients were to be re-evaluated for toxicity every month. This was to be a three year study.

SIGNIFICANT FINDINGS: 26 six patients were entered into this study. Four cases of Pneumocystis carinii pneumonia occurred. The code on this study was broken on 8 November 1988, all cases of PCP occurred in the placebo group. A statistical analysis of this data using Kaplan-Meier survival analysis showed a statistically significant difference between the two groups (p value = 0.035). This information was given to the Medical Monitor who concurred that the study's endpoint had been reached. Patients were notified whether they were receiving Fansidar or placebo and no further patients were entered. In addition, 4 patients, all in the Fansidar group were withdrawn from the study for presumed hematologic toxicity from the study drug.

PROTOCOL SUMMARY SHEET

RV# 8

PROTOCOL TITLE: Human Immune Response to HTLV-III Infection

CLINICAL SITE(S): WRAMC

PRINCIPAL INVESTIGATOR: Joanne Rhoads, MD, MAJ, MC, US Army

STATUS: Terminated

NUMBER OF PATIENTS ENROLLED: 8

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: NA

NUMBER OF PATIENTS VISITS TO DATE: NA

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: NA

DESCRIPTION/SUMMARY OF PROTOCOL: The objective of this protocol was to evaluate HIV specific T memory lymphocyte responses of human peripheral blood lymphocytes of HIV infected patients. The proposed technical approach was to transform donor B cells with EVB and either coated HIV antigen or infected with HIV-vaccinia hybrid to use for targets for HLA restricted cytotoxic T cells from the same patients.

SIGNIFICANT FINDINGS: This protocol was terminated.

PROTOCOL SUMMARY SHEET

RV# 9

PROTOCOL TITLE: Generation of Human Monoclonal Antibodies to HIV

CLINICAL SITE(S): WRAMC, WRAIR

PRINCIPAL INVESTIGATOR: Joseph J. Drabick, MD, MAJ, MC, US Army

STATUS: Active

MAP: Diagnostics

NUMBER OF PATIENTS ENROLLED THUS FAR: 14

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 30

NUMBER OF PATIENT VISITS TO DATE: 14 (one per patient)

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: 16

DESCRIPTION/SUMMARY OF PROTOCOL: HIV-seropositive patients (early Stage) were asked to give 50 cc of whole blood on a single occasion in order to separate the B-cells from which hybridomas secreting monoclonal antibodies are generated. B-cells as part of the mononuclear cell population were separated via Ficoll gradient and were immortalized by EBV-transformation. The immortalized B-cells were fused via polyethylene glycol to a heteromyeloma fusion partner, SHM-D33-0. Clones were screened by ELISA for antibodies to gp120 and p24. The main purpose of the consent form was for the volunteer to waive ownership rights of any hybridoma produced to the federal government.

SIGNIFICANT FINDINGS: The Principal Investigator was successful in producing immortalized B-cells secreting antibodies to gp120 and p24 in culture but had difficulty in maintaining a fused immortal line. The Principal Investigator altered the schema slightly so that B-cells will receive an *in vitro* boost with antigens of interest prior to immortalization and fusion. Also Leu-Leu-OMe will be used along with cytokines in order to force the *in vitro* system along an unopposed humoral route. It is hoped that these changes will improve future success.

PROTOCOL SUMMARY SHEET

RV# 10

PROTOCOL TITLE: Evaluation of Human Immunodeficiency Virus (HIV)-Related Proteins on the Surface of Lymphocytes from Patients with Evidence of HIV Exposure or HIV Illness

CLINICAL SITE (S): WRAMC

PRINCIPAL INVESTIGATOR: James R. Baker MD, MAJ, MC, US Army

STATUS: Terminated

NUMBER OF PATIENTS THUS FAR: 33 as of November 1988.

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: NA

NUMBER OF PATIENT VISITS TO DATE: NA

DESCRIPTION/SUMMARY OF PROTOCOL: The purpose of this protocol was to quantify HIV infection by determining the number of HIV positive lymphocytes. The technical approach to this protocol called for using monoclonal antibodies against viral proteins in conjunction with fluosecein conjugated antibodies to stain the peripheral blood lymphocytes from HIV-infected individuals and to then measure these cells using a flow cytometer.

SIGNIFICANT FINDING: The study was terminated November 1989.

PROTOCOL SUMMARY SHEET

RV# 11

PROTOCOL TITLE: *In situ* Hybridization for Detection of HIV in Langerhans Cells of HIV Infected Patients

CLINICAL SITE(S): WRAMC

PRINCIPAL INVESTIGATOR: Hoover, David, MD, LTC, MC, US Army

STATUS: Terminated

MAP: Diagnostics

NUMBER OF PATIENTS ENROLLED: 33

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: NA, Study terminated 3/25/92

NUMBER OF PATIENTS VISITS TO DATE: 33

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: NA

DESCRIPTION/SUMMARY OF PROTOCOL: The purpose of this protocol was to:

a) determine whether HIV genome was present in Langerhans cells (LC) of the skin and

b) correlate percentage of infected Langerhans cell with degree of immunosuppression related to HIV infection and with infection on blood monocytes.

Skin biopsies, shave excisions and suction blisters were obtained from 28 HIV-positive individuals and 5 controls. LC were identified, studied morphologically and enumerated by stains for HLA-DR and CD1 (#6). Skin was also stained with mA6 to HIV-1, and compared to known positive control cells. In situ hybridization was performed on skin for HIV-1mRNA. DNA-PCR for HIV Ltr/gag was performed on both skin sections and epidermal sheets. Skin samples were cocultured with target HIV-negative monocytes. Electronmicroscopy was also performed on skin samples.

SIGNIFICANT FINDINGS: Langerhans cell number was within normal range in HIV-positive patients, regardless of stage of disease. HIV-1 was readily detected in dermal skin samples, but rarely from epidermal only samples. The Principal Investigator could not support previously published views that LC are an important reservoir of HIV-1. This protocol was concluded and terminated on March 25, 1992.

PROTOCOL SUMMARY SHEET

RV# 12

PROTOCOL TITLE: Identification and Characterization of Human Immunodeficiency Virus in Human Semen

CLINICAL SITE (S): WRAMC

PRINCIPAL INVESTIGATOR: Joanne Rhoads, MD, MAJ, MC, US Army

STATUS: Completed

MAP: Diagnostics

NUMBER OF PATIENTS ENROLLED: 45

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: NA

TOTAL NUMBER OF PATIENT VISITS: 45

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: NA

DESCRIPTION/SUMMARY OF PROTOCOL: The purpose of this protocol was to identify, through culture and antigen detection, HIV in human semen and to characterize the immune response to HIV in the seminal compartment. The technical approach in this protocol included the following:

a) Culture of semen (cell and seminal plasma);

b) Evaluation of seminal plasma for HIV antibodies with comparison to serum HIV antibodies(ELISA and Western Blot);

c) Evaluation of HIV antigens in the seminal plasma (p24 ELISA).

SIGNIFICANT FINDINGS: The data from this protocol supported the concept that the male reproductive tract is an immunologically privileged site, and HIV replication and control in this compartment may differ from the serum. This protocol was completed on March 12, 1991.

PROTOCOL SUMMARY SHEET

RV# 13(16) These protocols were linked and utilized a single consent form but will be presented separately

PROTOCOL TITLE: Epidemiology of HIV in Pediatric and Perinatal Patients: A Natural History Study

STUDY SITES: WRAMC, WBAMC, BAMC, TAMC, NNMC, SDMC, WHMC, MAMC

PRINCIPAL INVESTIGATOR: Merlin Robb, MD, MAJ, MC, US Army

STATUS: Active

MAP: Epidemiology/Natural History

ENROLLED: 175

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 300

PROTOCOL VISITS TO DATE: 902

FUTURE NUMBER OF PROTOCOL VISITS:4-6 per patient per year

DESCRIPTION/SUMMARY OF PROTOCOL: The purpose of this study was to utilize existing epidemiological tools (USAHDS, DEERS) and an educational program in the military medical community to identify all DoD dependents at risk for HIV. In addition, the protocol sought to identify HIV infection through a limited diagnostic HIV testing program and to collect epidemiologic data and natural history data in the identified cohort. A systematic program of interval evaluations with a core of clinical and laboratory data was developed. Attempts were made to note all clinically indicated visits to a care provider as a part of defining the natural history of pediatric HIV and to contrast these observations with exposed uninfected members of the cohort.

The importance of this natural history study to the overall MMCARR effort were threefold. First, the rapid progression of HIV disease in perinatally infected children and the high incidence of transmission in the perinatally exposed cohort suggested that studies of interventions to interdict transmission or modify disease course could be performed more efficiently in this cohort. A means of identifying and maintaining a study population for the purpose of small phase 1 trials of such interventions can only be achieved with a natural history program as the network device. Second, the relatively rapid progression to symptomatic disease in pediatric HIV permits a more efficient clinical validation of immunologic and virologic parameters/predictors of transmission or progression. Analysis of safety concerns arising from the use of interventions used in this cohort can only be preliminarily addressed in a phase 1 study due to the absence of a control group. The availability of a well and comprehensively characterized natural history population served an important role

in assessing safety and planning studies with interventions.

SIGNIFICANT FINDINGS: RV13/16 were integrated studies which functionally overlapped extensively with RV 41, Perinatal Tissue Bank. As a consequence, the findings summary reflect contributions from each protocol.

1). Preliminary data reflected a transmission rate and disease progression which were different from published data, i.e., less frequent and slower presentation.

2). Defined the diagnostic utility of p24, PCR and culture in the pediatric setting and showed that the latter two were roughly equivalent in sensitivity and specificity (approx. 95-97%).

3). Evaluated several measures of viral burden in the pediatric population but failed to develop a method sufficiently robust to contribute to patient management. Whole blood culture titrations, plasma cultures and quantitative PCR for the assessment of viral burden as a corollary of clinical disease progression were evaluated. Of these, the PCR approach showed the greatest promise.

4). Characterized viral burden and sequence diversity in the plasma, peripheral blood and lymph node as well as longitudinal data from the PBL to identify potential limitations of the PBL compartment in assessing viral diversity or burden. These studies are vital to determining the design of any studies seeking to reliably correlate immunological responses to disease progression or transmission.

5). Contributed important data characterizing the use and interpretation of T cell phenotype data in the pediatric population. Age related normal values must be applied in interpreting CD4 data and CD4% is a substantially more reliable measure of the CD4 compartment in young children.

6). Careful language skill assessment adds to the recognized spectrum of neurodevelopmental symptoms as many patients had a restricted expressive language delay.

PROTOCOL SUMMARY SHEET

RV# 16(13) The protocols were linked and utilized a single consent form but were presented separately

PROTOCOL TITLE: Core Project: Evaluation of Diagnostic Assays for HIV in children.

STUDY SITES: WRAMC WBAMC BAMC TAMC
NNMC SDMC WHMC MAMC

PRINCIPAL INVESTIGATOR: Merlin Robb, MD, MAJ, MC, US Army

STATUS: Active

MAP: Epidemiology/Natural History

ENROLLED: 175

PROJECTED ENROLLMENT: 300

PROTOCOL VISITS TO DATE: 902

FUTURE NUMBER OF PROTOCOL VISITS: 46 per patient per year

DESCRIPTION/SUMMARY OF PROTOCOL: The purpose of this study was to extend the laboratory elements of RV 13 and provide a mechanism for the storage of samples for future analysis. In particular the study sought to provide materials for the assessment of both diagnostic assays as well as assays which correlate with the clinical status of the child. The importance of this and its related studies to the overall MMCARR effort were threefold. First, the rapid progression of HIV disease in perinatally infected children and the high incidence of transmission in the perinatally exposed cohort suggested that studies of interventions to interdict transmission or modify disease course can be performed more efficiently in this cohort. A means of identifying and maintaining a study population for the purpose of small phase I trials of such interventions can only be achieved with a natural history program as the network device. Second, the relatively rapid progression to symptomatic disease in pediatric HIV permitted a more efficient clinical validation of immunologic and virologic parameters/predictors of transmission or progression. Analysis of safety concerns arising from the use of interventions used in this cohort can only be preliminarily addressed in a phase I study due to the absence of a control group. The availability of a well and comprehensively characterized natural history population serves an important role in assessing safety and planning studies with interventions.

SIGNIFICANT FINDINGS: As a consequence of this protocol samples and data from 421 visits (47 patients) in 41 patients over a 4 year period were taken and reviewed. Of particular interest was

234 visits in 24 perinatally infected children with a repository catalog of 612 vials of plasma, 170 vials of serum and 674 vials of cells. RV13/16 were an integrated study which functionally overlapped extensively with RV 41 and the findings summary reflect contributions from each protocol. Additional findings included:

1). Preliminary data reflected a transmission rate and disease progression which were different from published data, i.e. less frequent and slower presentation.

2). Defined the diagnostic utility of p24, PCR and culture in the pediatric setting and showed that the latter two are roughly equivalent in sensitivity and specificity (approx. 95-97%).

3). Evaluated several measures of viral burden in the pediatric population but had failed to develop a method sufficiently robust to contribute to patient management. Whole blood culture titrations, plasma cultures and quantitative PCR for the assessment of viral burden as a corollary of clinical disease progression were evaluated. Of these, the PCR approach showed the greatest promise.

4) Characterized viral burden and sequence diversity in the plasma, peripheral blood and lymph node as well as longitudinal data from the PBL to identify potential limitations of the PBL compartment in assessing viral diversity or burden. These studies were vital to determining the design of any studies seeking to reliably correlate immunological responses to disease progression or transmission.

5). Contributed important data characterizing the use and interpretation of T cell phenotype data in the pediatric population. Age related normal values must be applied in interpreting CD4 data and CD4% was a substantially more reliable measure of the CD4 compartment in young children.

PROTOCOL SUMMARY SHEET

RV# 14

PROTOCOL TITLE: Intramuscular Poly-ICLC and Zidovudine in the Management of HIV Infection

CLINICAL SITE (S): WRAMC

PRINCIPAL INVESTIGATOR: Andres Salazar MD, COL, MC, US Army

STATUS: Completed

MAP: Chemotherapy/Chemoprophylaxis

NUMBER OF PATIENTS ENROLLED: 11 patients enrolled, 8 completed the study

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: NA

NUMBER OF PATIENT VISITS TO DATE: 8 patients made multiple protocol visits (1-4 times a month) until the completion of the 18 month study.

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF STUDY PROTOCOL: Study completed.

DESCRIPTION/SUMMARY OF PROTOCOL: The purpose of this protocol was to determine the safety or toxicity of poly-ICLC plus Zidovudine in patients with advanced HIV infection based on historical controls. The protocol also studied the human response to poly-ICLC plus Zidovudine in patients with AIDS. A third objective of this protocol was to explore Zidovudine in the management of HIV infection, based on historical standards. The technical approach of this protocol called for poly ICLC (5,10, 50, or 100 mcgm/kg) to be administered IM one to four times a month. Clinical, laboratory, and immunological parameters were followed.

SIGNIFICANT FINDINGS: Eleven (11) patients were entered into the study, two dropped out, and two were removed for technical reasons. Eight (8) patients remained on study long enough for analysis. Patients generally tolerated their medication well. Poly-ICLC can be safely administered to AIDS patients. There were no unexpected changes in T-Cell subsets or incidence of opportunistic infection, although performance on reaction time tests improved during drug administration. The optimum dose from a clinical tolerance point of view was likely to be in the 10-20 mcgm/kg range two to three times per week. Further studies are required to evaluate efficacy. This study was completed July 17, 1991.

PROTOCOL SUMMARY SHEET

RV# 15

PROTOCOL TITLE: Delayed-type hypersensitivity skin testing: Correlation of intradermal injection vs. epicutaneous antigen placement and CD4 number in normals and HIV seropositive subjects

CLINICAL SITES: WRAMC

PRINCIPAL INVESTIGATOR: Deborah L. Birx MD, LTC, MC, US Army

STATUS: Active

MAP: Vaccines and Immunotherapy/Prophylaxis

NUMBER OF PATIENTS THUS FAR ENROLLED: 42

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 250

NUMBER OF PATIENT VISITS TO DATE: 42

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: 416

DESCRIPTION/SUMMARY OF PROTOCOL: This protocol involved the comparison of subject skin test reactivity to each of the following antigens: tetanus toxoid, candida albicans, and trichophyton when placed by MULTITEST and by a traditional intradermal technique. In addition, this study correlates reactivity with CD4 count. Lastly, this study proposed to correlate anergy, as determined by the both intradermal and epicutaneous method with evidence of HIV disease and disease progression. Protocol participation required only two visits: one to place the two panels and one 48 hours post to read the panels which was done during the routine staging evaluation. This protocol did not recruit patients not already present for staging evaluation. Each visit required only a limited amount of time.

SIGNIFICANT FINDINGS:

- MULTITEST was discordant with the intradermal testing in evaluating reactivity to tetanus and candida.
- In addition, MULTITEST had a significant false positive glycerin control of 5% resulting in an inability to interpret test.
- Despite difficulties in meeting enrollment, this protocol produced significant scientific information. In the setting of HIV infection, delayed type hypersensitivity skin testing can provide another useful prognostic tool. However, many clinicians are reticent to utilize the technique, largely due to a lack of reliability of available skin test panels and epidermal techniques such as MULTITEST. This protocol will

likely highlight the need for use of appropriate skin test panels and techniques and, in addition, underscored the use this technique in clinical immunologic evaluation.

PROTOCOL SUMMARY SHEET

RV# 18

PROTOCOL TITLE: Cutaneous Natural History of HIV-1 Disease

CLINICAL SITE: WRAMC, NNMC

PRINCIPAL INVESTIGATOR: Kathleen J. Smith, MD, COL, MC, US Army

STATUS: Active, Separately funded through NIAMS, funding terminated September, 1992

MAP: Epidemiology/Natural History

NUMBER OF PATIENTS THUS FAR ENROLLED: 1160

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 1600

NUMBER OF PATIENT VISITS TO DATE: 1860

DESCRIPTION/SUMMARY OF PROTOCOL: Over the first three years of the study HIV-1+ patient's skin disease was evaluated. Specific cutaneous diseases were correlated with Walter Reed Stages of disease, and were evaluated in relation to T4 counts. At present there is some preliminary data on cutaneous diseases which may be predictive of disease progression. Patients were also screened for cutaneous neoplasms and trends were found not only in Kaposi's sarcoma, but also epithelial and melanocytic neoplasms in our patient population.

An important part of this protocol was patient education to aid in the prevention of skin disease, including avoidance of environmental conditions which could cause or exacerbate skin disease and predispose the patient to cutaneous neoplasms.

Clinical pathologic correlation of cutaneous disease was also part of the main protocol. The Principal Investigator evaluated inflammatory dermatoses throughout all Walter Reed stages with both routine and special stains and a battery of immunohistochemical markers, and identified determined trends in all these parameters with disease progression. The investigators were in the process of evaluation of another battery of lymphoid markers, adhesion molecules, and activation markers, done on these same biopsies.

SIGNIFICANT FINDINGS: As of March 31, 1993, the Principal Investigator submitted these findings:

1. Patients with HIV disease have a high incidence of skin disease.
2. Skin disease has been shown to be a predictor of disease progression.

3. Over the first 3 years the cutaneous conditions associated with disease and increasing stages of disease were determined.

4. Over the next 24-30 months the investigators will identify cutaneous markers of disease progression, and establish whether control of these conditions may delay disease progression. This study was unique because of the typical early stages of disease seen in the military population.

The skin is readily accessible, and is a T cell organ, and the study of patterns of immune dysregulation in the skin may give clues to patterns present in HIV-1 disease in general. Data from the study suggested patterns of immune dysregulation present in skin disease seen in our patients, and manuscripts were published with this information. That information will be used to develop treatments for these cutaneous conditions. In addition, there are plans to study UV radiation in HIV-I+ patients both for therapy and in terms of disease progression. UV radiation is an immune modulator and is readily accessible and commonly used by patients without medical supervision.

Education decreases the morbidity secondary to skin disease in our patients. The regular screening of the skin showed an increase in cutaneous epithelial and melanocytic malignancies which can be seen early in HIV-1 disease, and a manuscript has been accepted for publication which is the only prospective study on skin neoplasms in HIV-1+ patients. Early removal of these tumors means cure in the majority of immune suppressed patients, while late diagnosis in immune suppressed patients usually means a more aggressive course with increased medical costs.

PROTOCOL SUMMARY SHEET

RV# 19

PROTOCOL TITLE: Evaluation of Human Immunodeficiency Virus Related Proteins on the Surface of Lymphocytes from Children with Evidence of HIV Exposure or HIV Illnesses

CLINICAL SITE (S): WRAMC

PRINCIPAL INVESTIGATOR: Gerald Fisher MD, COL, MC, US Army

STATUS: Terminated

MAP: Diagnostics

NUMBER OF PATIENTS ENROLLED: 46

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: NA

NUMBER OF PATIENT VISITS TO DATE: 46

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: NA

DESCRIPTION/SUMMARY OF PROTOCOL: The purpose of this study was to examine the presence of HIV antigen on different mononuclear cell populations in infants and children to evaluate its use in determining *in vivo* distribution of HIV in various cell lineages. The study's technical approach called for mononuclear cells to be harvested from 1cc to 3cc of heparinized whole blood using standard methods. The mononuclear fraction was diluted to 10^7 cells and paired aliquots were incubated with anti-leu 3a PE, anti -leu 4 PE, and in selected cases anti-leu M3 PE. These paired samples were then incubated with murine monoclonal anti-GP120 or anti-P24 and goat anti-murine IgG FITC. The samples and control specimens were then analyzed using FACS analysis.

SIGNIFICANT FINDINGS: The techniques evaluated in this study based o preliminary data showed a relationship between disease stage and the ability to identify cell associated HIV antigen. However, the technique was labor intensive and might not have any advantage over other techniques currently under development for diagnosis, but could be useful to study HIV infection of specific cell types. Patient enrollment ceased in June, 1991, pending review of the data developed to date and comparison to other techniques used to determine distribution and quantity of HIV in various cell lineages. While the technique was not suitable for use as a diagnostic assay, these studies did identify that in young infants(infected 2^0 maternal HIV infection) the peripheral blood macrophage was the major cell type infected with HIV.

Preliminary data and conclusions were presented at the 5th

International Conference on AIDS, Montreal, Canada in June 1988 and a series of quality control experiments were conducted to verify the specificity of the findings.

PROTOCOL SUMMARY SHEET

RV# 20

PROTOCOL TITLE: The Use of Cimetidine for Immunoaugmentation in HIV Seropositive Patients

CLINICAL SITE (S): WRAMC

PRINCIPAL INVESTIGATOR: Joseph Drabick MD, CPT, MC, US Army

STATUS: Completed

MAP: Chemotherapy/Chemoprophylaxis

NUMBER OF PATIENTS THUS FAR ENROLLED: 5

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: NA

TOTAL NUMBER OF PATIENT VISITS TO DATE: 65

DESCRIPTION/SUMMARY OF PROTOCOL: The purpose of this protocol was to determine if oral cimetidine has the ability to stimulate immune function in already immunodeficient HIV patients and, hence, be useful as an adjunctive therapy in the management of advanced HIV disease. The technical approach of this protocol called for patients in an open label prospective study, to receive cimetidine in a dose known to cause immunoaugmentation. Immunologic parameters such as DHS, *in vitro* blastogenesis to standard mitogens and antigens, as well as HIV antigens, and cell counts were determined before, during and after drug therapy. Virologic parameters such as viral culture and p24 antigen levels were also measured.

SIGNIFICANT FINDINGS: The study was completed and data analysis begun pending receipt of some remaining blastogenesis data. Seven (7) patients were enrolled and two (2)dropped out because of problems not related to the cimetidine, which in all patients was well tolerated and without hematologic effects. There was a significant increase in DHS responses which was dependant on initial CD8 count (p is less than .05). Patients with initial CD8 counts less that 900 did not respond. Only 2 patients were p24 positive and in these there was a decrease in levels, though not significant. All were culture positive without change. No change in CD4,CD8 or ratio was noted. Two (2) responders felt clinically improved.

The Principal Investigator concluded that:

1. Cimetidine is safe and well tolerated in HIV patients.

2. Significant increases in DHS were observed and the presence and magnitude of the response was dependant on the initial CD8 count suggesting the benefit would be limited to only

some HIV patients.

3. No significant effects on virologic parameters were observed though a trend to a decreased antigenemia was observed in responders.

4. Although 2/3 responders felt clinically improved (energy level, appetite), the clinical correlate of improved DHS is certain.

This protocol was completed on March 29, 1991.

PROTOCOL SUMMARY SHEET

RV#: 21A

PROTOCOL TITLE: Active immunization of HIV infected patients with recombinant gp160 HIV protein: Phase 1 study of immunotherapy, immunogenicity and toxicity

CLINICAL SITE(S): WRAMC

PRINCIPAL INVESTIGATOR: Robert R. Redfield, MD, LTC(P) MC, US Army

STATUS: Active

MAP: Vaccines and Immunotherapy/Prophylaxis

NUMBER OF PATIENTS THUS FAR ENROLLED: 30

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 30 (closed)

NUMBER OF PATIENT VISITS TO DATE: 1977

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: Anticipate continuation of this trial as long as this particular product is under advanced development within the program. Current Phase II/III trial is scheduled for completion November 1995. Twenty-eight volunteers followed monthly during this period will comprise 924 total future visits. (336 visits annually).

DESCRIPTION/SUMMARY OF PROTOCOL: The initial protocol was designed to evaluate the feasibility of post HIV infection vaccination with HIV viral products utilizing a recombinant rgp160 vaccine. This phase 1 safety and immunogenicity trial began in April 1989, completed in Nov 1990 and was published in the New England Journal of Medicine in June 1991. A continuation trial was designed to assess the long term immunogenicity and safety of this product was implemented in light of the programmatic decision to pursue a five year phase 2/3 efficacy trial with rgp160. The continuation trial began in November 1990 and was modified by addendum in May 1992. As of March 31, 1993, each volunteer was receiving 160ug of rgp160 monthly.

SIGNIFICANT FINDINGS: As of March 31, 1993, the Principal Investigator submitted these findings:

- first to demonstrate the feasibility of the concept of vaccine therapy of HIV infection. Subsequently, 5 independent groups confirmed our published findings.
- Schedule for post infection vaccination refined. Data provided by this trial continues to be exploited by multiple companies and investigators currently involved in therapeutic vaccine development facilitating the optimization of immunization

schedule.
- immunologic resilience of early and mid stage HIV infection volunteers demonstrated.
- provided critical information related to long term immunogenicity and duration of vaccine induced immune responses and facilitated optimal execution of ongoing Phase II trial (eg. extension protocol provide critical information related to vaccination booster schedule applied to modify Phase II trial from q4 to q2 month boosters prior to expansion.
- provided critical information related to long term safety and served as a sentinel for the possibility of safety issues related to long term hyper-immunization with gp160/alum.
- continued to facilitate the development of novel assays developed to assess the human adaptive anti HIV immune responses and evaluation for application to Phase II/III efficacy trial and prophylactic vaccine development program.
- continued to facilitate the development of novel assays designed to assessed *in vivo* HIV replication kinetics which can subsequently be applied to drug development, gene therapy and prophylactic vaccine development program areas.
- provided opportunity to assess *in vivo* interrelationship between induction of specific adaptive anti-HIV immune responses and viral variation (currently under development).
- unique anti-HIV cellular responses demonstrated. Combined with the CHO expressed products provided an immunologic profile to all future treatment and prevention employing envelope-based products.

PROTOCOL SUMMARY SHEET

RV# 21B (Overall gp160 Phase II trial)

PROTOCOL TITLE: Active immunization of early patients with recombinant gp160 HIV protein; Phase II study of toxicity, immunogenicity, *in vivo* immunoregulation and clinical efficacy

CLINICAL SITES:

DoD sites: BAMC/FT HOOD, NNMC, WBAMC, WHMC, WRAMC

NIH sites: ARCA CPCRA, Chicago CPCRA, Delaware CPCRA, Richmond CPCRA, Washington VA CPCRA

WYETH-AYERST: Georgetown Medica[illegible]er, Graduate Hospital, Infectious Disease Physicians, [illegible]and Biotechnology Center, St. Joseph's Hospital, St. Vincent's [illegible]pital

PRINCIPAL INVESTIGATOR: Robert Redfield, MD, LTC(P), MC, US Army

STATUS: Active

MAP: Vaccines and Immunotherapy/Prophylaxis

NUMBER OF PATIENTS THUS FAR ENROLLED: 608 (closed 11/92)

NUMBER OF PATIENT VISITS TO DATE: 7120

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: This Phase II Trial is scheduled to be completed by Nov 1995. Total future protocol visits within DoD health care system is 6915, total overall future protocol visits, 16,051.

DESCRIPTION/SUMMARY OF PROTOCOL: This is a Phase II, multi-center, double blinded, placebo controlled designed to evaluate the clinical efficacy by surrogate markers of post infection vaccination with rgp 160 in the treatment of HIV infection and to validate adaptive anti-HIV immune responses in terms of *in vivo* HIV expression and clinical progression. Enrollment began in 11/90 and was initially limited to 140 volunteers. Following confirmation of safety and immunogenicity within this initial group, complete enrollment was approved in the spring 1992 and completed on schedule in the fall of 1992. Initial efficacy analysis by surrogate markers was scheduled for 11/93 and final analysis scheduled for 11/95.

SIGNIFICANT FINDINGS: As of 3/31/93, significant findings are as follows:

- Ongoing double blinded trials, only limited information available to date. Developed network of DoD, NIH and civilian

sites for efficient trial execution. Currently, 608 volunteers are on trial and being evaluated at 2 month intervals. 311 volunteers are beyond 6 months, 134 volunteers beyond 18 months (range of follow up 3-27 months). Protocol execution continues with a missed visit rate of less than 1%.

- Confirmation of immunologic resilience of patients with early HIV infection in terms of primary response to novel antigen (rabies) and secondary response to recall antigen (Tetanus toxoid).
- Confirmation of immunologic resilience of patients with early HIV infection in terms of primary response to novel antigen (rabies) and secondary response to recall antigen (Tetanus toxoid).
- Confirmation of natural history of adaptive immune responses
  - -demonstrated highly restricted T/B cell response directed against envelope.
  - -demonstrated lack of expansion of T/B cell repertoire during natural infection.
- Confirmation of immunogenicity of rgp 160 in setting of HIV infection (first 140 patients).
- Confirmation of short term safety of rgp 160 in setting of HIV infection.
- Independent of outcome in terms of clinical efficacy, this cohort of patients will provide the opportunity to validate adaptive immune responses directed against HIV in terms of *in vivo* HIV regulation and clinical disease progression in both the treatment and placebo arms. Specifically, cohorts of placebo patients stratified by clinical course in blinded arms will be extensively evaluated.

PROTOCOL SUMMARY SHEET

RV# 22

PROTOCOL TITLE: The Clinical Presentation of HIV Infected Patients at Walter Reed Army Medical Center

CLINICAL SITE (S): WRAMC

PRINCIPAL INVESTIGATOR: Charles Oster MD, COL, MC, US Army

STATUS: Active

MAP: Epidemiology/Natural History

NUMBER OF PATIENTS THUS FAR ENROLLED: 127 Charts were reviewed as of January, 1993.

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 402

DESCRIPTION/SUMMARY OF PROTOCOL: The purpose of the protocol was to evaluate clinical and laboratory data on the first 402 adults seen in clinic at WRAMC who were infected with HIV-I, by retrospectively reviewing their records.

SIGNIFICANT FINDINGS: CD4 counts decrease with time in an exponential fashion. Life is prolonged with Zidovudine (AZT) and/or pneumocystis prophylaxis. With these therapies, CD4 cell counts do not correlate with prognosis. Other prognostic markers are needed in these patients.

PROTOCOL SUMMARY SHEET

RV#: 23A

PROTOCOL TITLE: Phase I and II Study of the Use of Soluble CD4 Protein (sCD4: St4 SK&F 106528) in Human Immunodeficiency Virus Infection

CLINICAL SITE: WRAMC

PRINCIPAL INVESTIGATOR: Clifton Hawkes MD, MAJ, MC, US Army

STATUS: Completed

MAP: Chemotherapy/Chemoprophylaxis

NUMBER OF PATIENTS ENROLLED: 9

DESCRIPTION/SUMMARY OF PROTOCOL: This was a Phase I open, randomized, but unblinded trial. Subjects who met the inclusion criteria, after screening, were randomly assigned to one of three treatment arms using Soluble CD4 at doses of 0.1, 0.3, or 1.0 mg/kg. There was no placebo group. The study objectives were:

1. To assess the safety and tolerability of a single intravenous infusion of Soluble CD4 in HIV-infected patients, Stages WR 3-5.

2. To evaluate the pharmacokinetics and bioavailability of Soluble CD4 at the beginning of the study, during the course of the study and at the end of the study.

SIGNIFICANT FINDINGS: A total of nine (9) HIV-infected patients were enrolled in this study in 1989. There were no serious or unexpected adverse reactions. All patients completed the study (no withdrawals). There was no observed benefit to any of the patients, but none was expected in this short term infusion. A Phase II study involving a continuous intravenous infusion of soluble CD4 was originally anticipated but progress was slowed by product reformulation and redevelopment at the company level. The Principal Investigators drew the following conclusions:

1. No serious toxicity observed following single 2 hour infusion of CD4; study drug was well tolerated.

2. Pharmacokinetics of Soluble CD4 revealed a t1/2 (half-life) of 47.9 $\pm$ 10.5 minutes.

3. There was no significant change in HIV viremia during or post infusion.

PROTOCOL SUMMARY SHEET

RV# 24

PROTOCOL TITLE: Factors Effecting Heterosexual Transmission of Human Immunodeficiency Virus

CLINICAL SITE (S): WRAMC

PRINCIPAL INVESTIGATOR: Joanne Rhoads MD, MAJ, MC, US Army

STATUS: Terminated

TOTAL NUMBER OF PATIENTS TO BE ENROLLED:

DESCRIPTION/SUMMARY OF PROTOCOL: The purpose of this protocol was to evaluate the factors which determine the heterosexual venereal transmission of human immunodeficiency virus (HIV), in order to develop preventive and interventive therapies. The study was designed in two parts. The first part was to be a case control study of concordant and discordant HIV infected couples. A second part followed with a prospective study of the discordant pairs.

SIGNIFICANT FINDINGS: This protocol was terminated January, 1991.

PROTOCOL SUMMARY SHEET

RV# 25

PROTOCOL TITLE: Pathological Manifestations of HIV Infection at Autopsy

CLINICAL SITE: WRAMC & The Armed Forces Institute of Pathology (AFIP)

PRINCIPAL INVESTIGATOR: David W. Anderson MD, MAJ, MC, US Army

STATUS: Active

MAP: Diagnostics

NUMBER OF PATIENTS THUS FAR ENROLLED: 22

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 34

NUMBER OF PATIENT VISITS TO DATE: 22

ADDITIONAL NUMBER OF PATIENT VISITS PROJECTED TO PROTOCOL COMPLETION: 12

DESCRIPTION/SUMMARY OF PROTOCOL:

1) To perform complete research autopsies on deceased patients with HIV disease.

2) To document disease processes causing morbidity and mortality in patients enrolled in WRAMC HIV research.

3) To obtain fresh tissue from major organ systems to be stored in a tissue registry, both unfixed at -70 degrees C and formalin fixed, paraffin-embedded.

Complete autopsies were performed as soon after death as a valid research autopsy permit was available. Tissues from major organ systems were examined and processed for histochemistry (formalin fixed, paraffin-embedded) or flash frozen for immunohistochemistry. Routine histochemistry and special stains were performed, as well as microbiologic cultures. Results were assembled into a research autopsy protocol report which was returned to the Infectious Disease Service, the deceased patient's chart, and the Jackson Foundation Data Base. Addenda reflecting independent review of the entire autopsy findings by AIDS Division, Armed Forces Institute of Pathology were also distributed as described above.

SIGNIFICANT FINDINGS: As of the 3/31/93 the following findings were given by the Principal Investigator:

1.Twenty-two (22) HIV research autopsies at WRAMC and 10 HIV research autopsies at NNMC, Bethesda revealed causes of death as follows (8 cases of 2 causes of death each): 8 PCP; 4 Staph. sepsis; 4 HIV wasting only; 4 dilated cardiomyopathy; 3 Acute pneumonia, 3 KS (one visceral, two pneumonitis); 3 enteric sepsis; 2 ARDS; 2 Pseudomonas sepsis; 2 PML (); 2 CMV (Cytomegalovirus) panencephalitis; 1 acute pancreatitis; 1 sudden death; 1 Adenovirus pneumonia.

2. Tissue registries exist for most autopsies and were used to:

a. validate polymerase chain reaction (PCR) detection systems for HIV proviral DNA in human organ tissues in collaboration with SRA Laboratories as well as M. avium-intracellulare and P. carinii DNA in human organ tissues in collaboration with AFIP;
b. conduct survey of culturable Mycoplasma species from HIV autopsy tissues - no mycoplasma species detected.

PROTOCOL SUMMARY SHEET

RV# 26

PROTOCOL TITLE: Tri-Service Biopsychosocial HIV Study, Behavioral/ Psychosocial Component

CLINICAL SITES: WRAMC, NNMC, WHMC, WAMC, Balboa Naval Hospital, San Diego

PRINCIPAL INVESTIGATORS: Lydia R. Temoshok, Ph.D., Ellen D. Nannis, Ph.D.

STATUS: Active

MAP: Behavioral Medicine

NUMBER OF PATIENTS THUS FAR ENROLLED: Seropositive Behavior Survey: 1102 HIV+, (145 HIV- controls); Psychosocial Questionnaires: 1042; Adherence/perception questionnaires: 906; Psychiatric interviews: 870.

NUMBER OF PATIENT VISITS TO DATE: (T1 = 1 visit, T2= 2nd visit, etc) SBS: 1102 T1, 384 T2; Psychosocial Questionnaires: 1042 T1, 594 T2, 221 T3; Adherence/ Perception Questionnaires: 836 AZT(T1), 297 AZTC1(2), 64 AZT(T3), 70 vaccine; Psychiatric Interviews: 870 T1, 551 T2, 217 T3.

ADDITIONAL NUMBER OF PATIENT VISITS PROJECTED TO COMPLETE PROTOCOL: Proposed revised SBS: 100 AD or RET women evaluated 3 times, and 50 dependent female Military Medical Beneficiaries evaluated 3 times; Adherence/Perception Questionnaires: 164 AZT, 130 vaccine.

DESCRIPTION/SUMMARY OF PROTOCOL: The overall goal of RV-26 was to provide the necessary data-based foundations for developing mission-congruent interventions to reduce transmission risk-relevant behaviors in infected military medical beneficiaries (MMBs). Sufficient Seropositive Behavior Surveys (SBSs) were collected to answer critical questions about the prevalence of (sexual) transmission risk-relevant behaviors and associated psychosocial factors to provide the data-based foundations for developing transmission preventive interventions for HIV + personnel (RV-82). Therefore, data collection for this component of RV-26 was closed 1 March 93, along with descriptive psychosocial and psychiatric components whose purpose was to identify factors associated with transmission risk. To the extent that certain mission-relevant questions remain unaddressed (i.e., vertical transmission risk behaviors, decisions, and related psychosocial factors in female HIV+ Military Medical Beneficiaries (MMB)), it may be important to adapt the SBS and to continue administering selected psychosocial questionnaires for HIV+ women MMBs only. Finally, because questionnaires to assess perceptions of and adherence to prescribed treatments (AZT) and experimental

protocols (gp160/gp120, gp160 + AZT) were not added to RV-26 until 1992 or 1993, data collection for these instruments was expected to continue to answer critical questions regarding factors associated with adherence. It was hoped that answers to these factors will provide the data foundation for interventions to facilitate and enhance participants' participation in treatment and research protocols. It should be noted that efforts in this latter RV-26 component were directly congruent with and supportive of collaborative investigations with the Vaccine Mission Area and were also aimed at developing the behavioral components of vaccine prophylaxis and therapy initiatives in Thailand.

SIGNIFICANT FINDINGS: Although many MMBs changed their behavior substantially upon learning of their HIV+ status, about 60% reported engaging in behaviors that had the potential to transmit the virus to HIV-partners. Despite explicit military policy, 25% did not inform sexual partners of their serostatus. Factors associated with transmission potential included: alcohol use, limited repertoire of non-sexual stress-reducing behaviors, poor sexual impulse control, and irresponsible prevention attitudes. Adherence with AZT treatment was related to the experience of fewer and less severe side effects, less negative affect, and the reporting of more AZT related benefits. Depressed affect was related to being "less" employed and to being more socially isolated. More solitary patients identified with more dysfunctional coping styles. In early HIV disease, men were at risk for developing major depression and anxiety disorders. Risk factors for suicide attempts included: social isolation, perceived lack of social support, adjustment/personality disorder, alcohol abuse, and HIV-related interpersonal/occupational problems.

PROTOCOL SUMMARY SHEET

RV# 26

PROTOCOL TITLE: Tri-Service Biopsychosocial HIV Study, Neuropsychology/Job Performance Components

CLINICAL SITES: WRAMC, NNMC, WHMC

PRINCIPAL INVESTIGATOR: Lydia R. Temoshok, Ph.D., Ellen D. Nannis, Robert L. Mapou, PhD., Henry M. Jackson Foundation

MAP: Behavioral Medicine

NUMBER OF PATIENTS THUS FAR ENROLLED: HIV+: 766 with neuropsychological data, 100 with job performance data; HIV- Controls: 124 (with all data)

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: No new HIV+; 60/site will be re-evaluated through visit 6 (with job performance information); HIV- controls: 50

NUMBER OF PATIENT VISITS TO DATE: HIV+: Visit 1-766, Visit 2-501, Visit 3-214, Visit 4-53, Visit 5-2; HIV- controls: Visit 1-124, Visit 2-23, Visit 3-2

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: HIV+: 420; HIV- controls: 225

DESCRIPTION/SUMMARY OF PROTOCOL: The focus of the neuropsychology portion of RV26 shifted to examining the relation between neuropsychological functioning and job performance, in order to develop interventions to prevent performance decline. The goals were:

1) develop predictors of job difficulties, through longitudinal assessment of neuropsychological function, job performance, and job satisfaction;

2) test whether specific cognitive profiles can predict specific job difficulties;

3) develop a Phase I/II study to test the safety/feasibility of using cognitive profiles based on neuropsychological assessment to:
   a) predict job difficulties and
   b) define potential areas for interventions to enhance job performance and to prevent decline.

Because job performance data collection began only recently, additional data, collected over time and in combination with neuropsychological data, was necessary. To accomplish these goals, the Principal Investigators proposed to follow 180 current participants, who have returned consistently at 6 month intervals,

through 7 visits. This would provide sufficient data over a duration during which most HIV+ personnel remain in the military, and would allow determination of whether clusters of cognitive deficits relate to specific changes in performance. Longitudinal data would enable the investigators to determine if early deficits could predict current and subsequent job difficulties, because progression of difficulties over time was expected. The researchers must also enroll 50 new HIV- control subjects, and evaluate 100 for two follow-up visits. Data from demographically-matched controls are essential because profiles are based up deficits, defined with respect to a similar control group. Without controls and follow-up, the investigators might under- or over-estimate initial deficit and progression of deficit in the HIV+ group. Approximately 2.5 hours per visit will be needed for neuropsychological evaluation and 30 minutes for job performance data collection.

SIGNIFICANT FINDINGS: Findings of slowed speed of information processing in early stage individuals were replicated using several different instruments; up to 30% may manifest slowing. It was also clear, however, that deficits cluster in several different neuropsychological domains, which may make it possible to distinguish among difficulties of HIV+ individuals on the basis of cognitive profiles. Mood, age, and pre-existing minor neurobehavioral history had minimal impact upon neuropsychological performance at these stages, demonstrating that HIV is having direct effects on cognitive performance. However, in some individuals, high levels of mood disturbance can impact on performance, independently of the effects of HIV. Many HIV+ subjects with neuropsychological deficits could accurately report subtle changes in cognition, but some complained of difficulties due to mood disturbance. HIV+ subjects reported lower levels of job productivity and job satisfaction, and complained of more cognitive and motor difficulties, as compared to HIV- control subjects. However, the relation of job difficulties to neuropsychological performance had not yet been determined.

PROTOCOL SUMMARY SHEET

RV# 27

PROTOCOL TITLE: A Pharmacokinetic Study to Develop a Database to Describe the Relationship Between Zidovudine (AZT)/Glucuronyl (GAZT) Blood Levels and Drug Toxicity in HIV Infected Patients

CLINICAL SITE (S): WRAMC

PRINCIPAL INVESTIGATOR: Darrell Bjornson, Pharm. D., LTC, MS, US Army

STATUS: Completed

MAP: Chemotherapy/Prophylaxis

NUMBER OF PATIENTS THUS FAR ENROLLED: 19

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: NA

TOTAL NUMBER OF PATIENT VISITS: 228

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: NA

DESCRIPTION/SUMMARY OF PROTOCOL: The purpose of this protocol was to define the relationship of zidovudine (ZDV) and glucuronyl zidovudine peak and trough plasma blood levels with drug toxicity. The technical approach to this protocol called for patients who were prescribed zidovudine for the first time to have venous blood samples drawn each month for 12 months: 0, 15, 30, 45 , 60 and 75 minutes. Levels of ZDV and GZDV were analyzed with the ZDV-Trac RIA kit, and concurrent toxicity parameters were followed. Multiple regression analysis was used to analyze data.

SIGNIFICANT FINDINGS: Interim analysis in December 1990 on 15 patients suggested an association between hemoglobin decline and peak metabolite (GZDV) levels and granulocyte decline and both peak GZDV and ZDV levels. The best predictor in each case was peak GZDV. There was wide intrapatient variations in plasma concentrations from month to month and wide interpatient variations in plasma concentrations even when corrected for body weight. The nineteen patients enrolled in the study completed the 12 month pharmacokinetic portion of the study with one-year follow up on all patients. There was no known benefit to the patients. Final analysis of the data is now in process.

PROTOCOL SUMMARY SHEET

RV# 28

PROTOCOL TITLE: Pharmacoepidemiologic study to develop a database to document variations in outcome of illness which may be due to drug effects, both beneficial and adverse and to document patterns of drug use in HIV infected patients

CLINICAL SITE (S): WRAMC

PRINCIPAL INVESTIGATOR: Linda M. Cortese, Pharm. D., Henry M. Jackson Foundation

STATUS: Active

MAP: Chemotherapy/Chemoprophylaxis

NUMBER OF PATIENTS THUS FAR ENROLLED: 658

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: This is an ongoing data collection protocol with long term data collection follow-up. All patients treated with an antiretroviral agent are entered into the database.

NUMBER OF PATIENT VISITS TO DATE: N/A (Data is obtained from chart review)

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: N/A

DESCRIPTION/SUMMARY OF PROTOCOL: To develop a database to study outcome of illness due to drug effects (both beneficial and adverse), and to gather useful information on drug use patterns of HIV infected patients.

SIGNIFICANT FINDINGS: The Principal Investigator is currently in the process of determining the rate of zidovudine medication compliance in HIV infected patients and factors associated with patient medication compliance.

PROTOCOL SUMMARY SHEET

RV# 31

PROTOCOL TITLE: The Effect of Megestrol Acetate on the Cachexia of Human Immunodeficiency Virus HIV disease: A randomized, Placebo Controlled Double Blind Study

CLINICAL SITE (S): NA

PRINCIPAL INVESTIGATOR: Charles Davis, MD, MAJ, MC, US Army

STATUS: Terminated

NUMBER OF PATIENTS THUS FAR ENROLLED: None

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: None, study terminated

NUMBER OF PATIENT VISITS TO DATE: None

DESCRIPTION/SUMMARY OF PROTOCOL: The purpose of this protocol was to determine if megesterol acetate (megace), taken twice a day orally, would stimulate the appetite and result in weight gain and improved nutrition.

SIGNIFICANT FINDINGS: This study was terminated with no patients enrolled.

PROTOCOL SUMMARY SHEET

RV# 35

PROTOCOL TITLE: The Investigation of the Cutaneous Microflora Found in HIV Infected Patients as it Relates to the Onset, Severity, and Progression of Disease

CLINICAL SITE (S): WRAMC

PRINCIPAL INVESTIGATOR: Kathleen Smith, MD, LTC, MC, US ARmy

STATUS: Completed

MAP: Epidemiology/Natural History

NUMBER OF PATIENTS ENROLLED: 225

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: NA

NUMBER OF PATIENT VISITS TO DATE: 225

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF STUDY PROTOCOL: NA, Study Completed

DESCRIPTION/SUMMARY OF PROTOCOL: The purpose of this protocol was to document skin changes associated with HIV disease, both clinical and histopathologic, and to follow these changes with progression of disease, with emphasis on histopathologic studies to identify both clinical and subclinical infections.The technical approach to this protocol called for the following:

1) Cutaneous exam questionnaire and examination at initial visit.

2) Diagnostic biopsy with a battery of special stains to identify both clinical and subclinical infections and primary diagnosis.

3) Immunohistochemical studies of the inflammatory infiltrate.

4) Cultures of cutaneous microflora, in all stages and with progression of disease.

SIGNIFICANT FINDINGS: The study was completed with 200 HIV-1 positive patients and 200 HIV-1 negative control patients. No adverse effects related to the study were noted. Identification of changes in microflora of HIV-1 positive patients was made. Identification of an increase in Staph Aureus carriage diffusely over skin surface in all stages of HIV disease was noted and increase in localized cutaneous infections with increase in progression and soft tissue and Staph Aureus sepsis in late stage disease was also noted. Ongoing studies were being developed to develop topical antimicrobial solutions without the drying effects

of known antimicrobial solutions. The specific study led to the development of a treatment protocol for cutaneous Staph Aureus carriage and a protocol to determine possible enterotoxin production resulting from Staph Aureus carriage in HIV-1 infected patients and it's relation to disease process.

PROTOCOL SUMMARY SHEET

RV# 37

PROTOCOL TITLE: Pneumocystis Carinii Pneumonia in HIV Patients: A Cohort Study to Estimate the Protective Effect of Prophylactic Pentamidine Inhalation on Compliant vs Noncompliant Patients

CLINICAL SITE (S): WRAMC

PRINCIPAL INVESTIGATOR: Darrel Bjornson, Pharm. D., LTC, MS, US Army

STATUS: Completed August 1992

MAP: Chemotherapy/Chemoprophylaxis

NUMBER OF PATIENTS THUS FAR ENROLLED: 146

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: NA

NUMBER OF PATIENT VISITS TO DATE: 146 Patients were studied

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: NA

DESCRIPTION/SUMMARY OF PROTOCOL: The purpose of this protocol was to determine if patients who are compliant with the use of pentamidine inhalation have a decreased risk of developing Pneumocystis carinii pneumonia (PCP) when compared to those who are noncompliant. In addition, this protocol sought to determine if there was a difference between monthly and twice monthly regimens regarding compliance. The technical approach called for a cohort of patients to be selected for the study who had been prescribed prophylactic pentamidine inhalation. Incidence of PCP was collected from the medical records, with compliance data from the pharmacy records. Analysis would determine whether the risk of PCP was greater in patients who are noncompliant with pentamidine therapy versus those who are compliant. In addition, the 300mg monthly dose was compared with the 60mg twice monthly dose regarding compliance.

SIGNIFICANT FINDINGS: 146 patients who were prescribed aerosolized pentamidine 60 mg every 2 weeks were more compliant ($p=0.006$) than those prescribed 300mg every 4 weeks. In addition, those patients who initially received the 60mg regimen and were switched to the 300 mg regimen were more compliant when taking the 60 mg dose ($p=0.027$). There was no association between compliance with either regimen and cases of PCP.

The Principal Investigator submitted the following conclusions:

1. Patients on every 2 weeks regimens of aerosolized pentamidine were more compliant than those on every 4 week regimens.

2. However, regardless of compliance, some patients were not protected by aerosolized pentamidine over the 3.5 year period.

This protocol completed August 1992.

PROTOCOL SUMMARY SHEET

RV# 41

PROTOCOL TITLE: Perinatal HIV Infection: Epidemiology and Natural History

CLINICAL SITES: WRAMC, Naval Hospital, San Diego, NNMC

PRINCIPAL INVESTIGATOR: Gary Pettett, MD, COL, MC, US Army

STATUS: Active

MAP: Epidemiology/Natural History

PATIENTS ENROLLED: 21 (most maternal and all infant specimens collected through RV2 and RV13/16 respectively)

PROJECTED ENROLLMENT: 100-200

PROTOCOL VISITS TO DATE: 63

FUTURE NUMBER OF PROTOCOL VISITS: 10 visits per mother/infant pair

DESCRIPTION/SUMMARY OF PROTOCOL: The perinatally HIV-exposed infant is at the highest risk for transmission of HIV among all risk categories prevalent today. Since transmission in this setting occurs in a well circumscribed period of time with a well defined outcome it may serve as the best model to evaluate viral and immunological factors influencing transmission. The purpose of this study was to characterize those potential factors in terms of the rate of perinatal transmission, the disease course in the infected infant and the natural history of HIV disease in pregnancy. The specific trial goals were as follows:

1) To identify all HIV positive or HIV exposed pregnant women as early in gestation as possible and obtain blood samples in each trimester of pregnancy and at delivery. Specimens were to be collected in the infant through 24 months of age.

2) To characterize the natural history of pregnancy in these women both in terms of fetal complication as well as maternal outcome and contrast these findings to those being characterized in endemic areas where behavioral and environmental factors effect both outcomes.

3) To define the rate of perinatal transmission in military dependents and characterize any cofactors or features of HIV disease in the mother associated with increased frequency of transmission, fetal loss, poor maternal outcome or rapidly progressive disease in mother or infant.

SIGNIFICANT FINDINGS: 31 mother/infant pairs were evaluated on 63 occasions (20 pairs in 1992) through pregnancy/delivery or early post-partum with maternal blood samples (plasma 108 vials, serum 71 vials, cells 258 vials) in the tissue repository. 5 of these infants have acquired HIV. The total number of HIV positive women with children likely or known to have been exposed to HIV evaluated under these protocols (RV2, RV41, RV13,16) was 97 with a total of 304 separate evaluations contributing an additional 165 vials of serum to the repository (many of these were not collected during or immediately following pregnancy). This represented a valuable collection of specimens for careful study of immune and viral characteristics contributing to perinatal transmission. Other findings included:

1. Preliminary data reflected a transmission rate and disease progression which were different from published data, i.e. less frequent and slower presentation.

2. Defined the diagnostic utility of p24, PCR and culture in the pediatric setting and showed that the latter two were roughly equivalent in sensitivity and specificity (approx. 95-97%).

3. Evaluated several measures of viral burden in the pediatric population but have failed to develop a method sufficiently robust to contribute to patient management.

4. Contributed important data characterizing the use and interpretation of T cell phenotype data in the pediatric population. Age related normal values must be applied in interpreting CD4 data and CD4% is a substantially more reliable measure of the CD4 compartment in young children.

5. It is likely that relatively few women are identified with our current approach to HIV screening since the majority of HIV infected pregnant women have HIV negative AD spouses and routine screening at TAMC failed to identify the 7 pregnant women delivered in 1991 (prevalence of 1/500 deliveries: national prevalence =1/1000 deliveries).

6. It is possible that the peripartum period is particularly high risk for acquiring HIV in view of our experience with 2 seroconversion among 8 HIV negative peripartum, exposed women.

PROTOCOL SUMMARY SHEET

RV# 43

PROTOCOL TITLE: Prospective study of the emergence of Zidovudine (AZT) resistance in patients infected with the human immunodeficiency virus (HIV) who are treated with AZT

CLINICAL SITE(S): WRAMC, NNMC

PRINCIPAL INVESTIGATOR: Douglas L. Mayers, MD, CAPT, MC, US Navy

STATUS: Active

MAP: Chemotherapy/Chemoprophylaxis

NUMBER OF PATIENTS THUS FAR ENROLLED: 100

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: NA

NUMBER OF PATIENT VISITS TO DATE: 654

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: 450

DESCRIPTION/SUMMARY OF PROTOCOL: A cohort of 100 patients with CD4 counts <400 cells/mm^3 on zidovudine monotherapy was evaluated every three months for a period of 3 years. The patients had a screening history and physical exam along with T cell subsets, p24 antigen and drug level determination. HIV isolates at each time point were evaluated for susceptibility to AZT, ddI and ddC, along with syncytial phenotype. Multiple aliquots of plasma and PBMC were stored from each time point for further studies. The objectives of the study were:

1. To determine the time course, frequency and clinical parameters associated with the development of AZT resistance in HIV isolated from patients on AZT.

2. To determine if there existed a level of AZT resistance, measured *in vitro*, which correlated with clinical deterioration in patients who are receiving AZT.

3. To develop a repository of frozen HIV-infected peripheral blood mononuclear cells (PBMC) with resistant virus for future studies into the molecular basis of dideoxynucleotide resistance.

SIGNIFICANT FINDINGS: As of March 31, 1993, the Principal Investigator submitted these findings:

- CD4 cell counts remain stable in patients with AZT-susceptible virus for periods as long as 4 years.

- CD4 cells declined by 120 cells/mm^3 in the year preceding the emergence of *in vitro* AZT resistance (defined as IC50 > 1 IuM AZT).

- Susceptibilities of clinical HIV isolates to ddI and ddC decrease 2-fold for each log1 o decrease in AZT susceptibility.

- Multi-drug resistant HIV isolates emerged as patients were switched from AZT to ddI to AZT + ddC.

- The time course of AZT resistance in patients on ZDV monotherapy was reassessed. At 2+ years of therapy, 40% of patients HIV isolates remained AZT susceptible (compared to earlier estimates of 5 to 15% using plaque assays).

- The relationship between CD4 decline and emergence of phenotypic AZT resistance, codon 215 mutations in plasma virus and proviral DNA in PBMC, syncytial phenotype and viral burden, is currently being assessed in collaboration with Stanford University.

- The relationship between ddI susceptibility at initiation of ddI therapy and subsequent changes in viral burden was under evaluation.

PROTOCOL SUMMARY SHEET

RV# 44

PROTOCOL TITLE: The Effect of HIV Infection on the Clinical Manifestations and Response to Treatment of Syphilis

CLINICAL SITE(S): WRAMC, WHMC, NNMC (Also CDC and Multiple Civilian Sites)

PRINCIPAL INVESTIGATOR: Steven Johnson, MD, MAJ, MC, US Army

STATUS: Active

MAP: Epidemiology/Natural History

NUMBER OF PATIENTS THUS FAR ENROLLED: 14 (11 at WRAMC, 3 at NNMC)

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: Unlimited (enrollment ends 31 Dec 93)

NUMBER OF PATIENTS VISITS TO DATE: WRAMC 78, NNMC 24

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: 8 visits plus 8 visits for each additional enrollment

DESCRIPTION/SUMMARY OF PROTOCOL: This was a randomized, double-blind, placebo-controlled trial comparing benzathine penicillin (PCN) 2.4 million units to benzathine (PCN) 2.4 million units plus oral amoxicillin and probenecid in HIV positive and HIV negative patients with early syphilis. The primary Principal Investigator was at the Centers for Disease Control. WRAMC and NNMC were two of the clinical study sites. To date, approximately 450 patients nation-wide were enrolled in this study with a revised goal of 600 by end of enrollment (31 Dec 93). As the study was double-blinded, final results were not yet available. 35 patients were screened at WRAMC and NNMC for the study and 14 were enrolled. Although the military contribution was small in numbers (14), most are HIV positive (11), most underwent Lumbar Puncture (LP) (9), and the follow-up has been excellent (2 missed visits out of 104).

SIGNIFICANT FINDINGS: None at this time. However, this study has the potential to:

1. Define the risk factors and demographics regarding syphilis in the U.S.
2. Alter standard treatment for early syphilis.
3. Refine our understanding of the interaction between HIV-induced immunosuppression and syphilis.

PROTOCOL SUMMARY SHEET

RV: 46

PROTOCOL TITLE: Evaluation of Propylthiouracil in the Prevention of Cachexia in AIDS Patients

CLINICAL SITE (S): WHMC

PRINCIPAL INVESTIGATOR: Craig Hendrix MD, MAJ, MC, US Air Force

STATUS: Completed

MAP: Epidemiology

NUMBER OF PATIENTS THUS FAR ENROLLED: 6

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: NA

NUMBER OF PATIENT VISITS: Approximately 40

DESCRIPTION/SUMMARY OF PROTOCOL: The protocol was designed to determine if propylthiouracil (PTU) therapy could decrease weight loss in AIDS patients by decreasing serum levels of triiodothyronine (T3), which is a catabolic thyroid hormone. The projected number of volunteers was 20. Each patient was to be followed at monthly intervals for five months to determine by way of blood analysis if changes in the thyroid occurred.

SIGNIFICANT FINDINGS: During the period of February 1990 and July 1991, only 8 patients were enrolled due to the stable character of our patient population that decreasingly develop chachexia. This has been especially true since the introduction of AZT use in early stage patients, an option that did not exist at the inception of this protocol. This study has been closed to enrollment. Lab samples are still being processed for data analysis. No final results were available as of 3/31/93.

PROTOCOL SUMMARY SHEET

RV# 48

PROTOCOL TITLE: Changes in Peripheral Blood Lymphocyte Counts, Subsets, and Activation by Delayed Hypersensitivity Skin Testing in HIV Seropositive and Seronegative Individuals

CLINICAL SITE (S): WHMC

PRINCIPAL INVESTIGATOR: Dr. Theodore Freeman, MD, LtCol, MC, US Air Force

STATUS: Completed

MAP: Epidemiology/Natural History

NUMBER OF PATIENTS THUS FAR ENROLLED: 46

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: NA

NUMBER OF PATIENT VISITS TO DATE: 184

DESCRIPTION/SUMMARY OF PROTOCOL: This study was designed to examine the effects of delayed hypersensitivity skin testing on the peripheral blood lymphocytes as measured by Coulter counter, as well as determining the changes in lymphocyte subsets and activation states by fluorescence-activated cell sorting in a population of 16 healthy seronegative adults and 30 healthy seropositive adults (Walter Reed Stage 1 or 2). The study involved 4 blood draws over the course of 7 days and the placement of a 5 antigen anergy panel. From this study the Principal Investigator hoped to gain greater knowledge about the effects of DTH skin testing on the values of lymphocyte surface markers in HIV positive individuals compared to HIV negati[illegible]dividuals

SIGNIFICANT FINDINGS: All 46 volunteers were c[illegible]l and the data analyzed. Dr. Theodore Freeman is in the proc[illegible]of re-analyzing some of the data and plans to submit a manuscript to the Annals of Internal Medicine in the near future.

PROTOCOL SUMMARY SHEET

RV# 49

PROTOCOL TITLE: The Effect of Dipyridamole On Zidovudine Pharmacokinetics

CLINICAL SITE (S): WHMC

PRINCIPAL INVESTIGATOR: Craig Hendrix, MD, MAJ, MC, US Air Force

STATUS: Completed

MAP: Chemotherapy/Chemoprophylaxis

NUMBER OF PATIENTS ENROLLED: 11 patients enrolled and 8 patients completed the protocol.

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: NA

NUMBER OF PATIENT VISITS TO DATE: 22

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: NA

DESCRIPTION/SUMMARY OF PROTOCOL: Dipyridamole (DPM) augments the anti-HIV effect of zidovudine (ZDV) *in vitro*. The Principal Investigator sought to establish a well tolerated dose of DPM that could be used in combination with ZDV in clinical studies and to define whether concomitant administration of DPM altered the pharmacokinetics of ZDV. Both objectives were essential for planning efficacy studies of the ZDV-DPM combination. Eleven asymptomatic HIV-infected subjects who were already on 500mg/day of ZDV were admitted to the study. ZDV pharmacokinetics were measured on day 1, DPM was then added and pharmacokinetics measured again on day 5. Each subject served as his or her own control.

SIGNIFICANT FINDINGS: Zidovudine pharmacokinetics were not altered by concomitant use of DPM. A dose of 450 mg/day was well tolerated in the subjects. Trough plasm concentrations of DPM exceeded the synergistic concentrations identified in cell culture studies. This data was presented to NIH on December 1991 and an abstract was published in the Proceeedings of the VIIIth International AIDS Conference, July, 1992.

PROTOCOL SUMMARY SHEET

RV# 50

PROTOCOL TITLE: Detection and clinicopathologic correlation of HIV-1 nucleic acids and antigens in reticuloendothelial tissues, by immunohistochemistry, *in situ* hybridization, and polymerase chain reaction

CLINICAL SITE: Office of the Chief Medical Examiner, Baltimore, MD

PRINCIPAL INVESTIGATOR: Allen Burke, MD, LtCol, MC, USAF

MAP: Diagnostics

NUMBER OF PATIENTS: 75

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: 24 autopsies, 8 lymph node and pharyngeal biopsies (RV78), 8 lymph node and rectal biopsies (RV 77)

DESCRIPTION/SUMMARY OF PROTOCOL: Lymphoid tissues from autopsy cases of asymptomatic HIV-1 infected drug addicts are subjected to pathologic and molecular analysis. Histologic examination, immunophenotyping, polymerase chain reaction and *in situ* hybridization studies are used to determine if there are clinically relevant stages in asymptomatic HIV-1 infection. Lymph nodes from various sites (supraclavicular, axillary, mediastinal, inguinal, mesenteric, and mediastinal) as well as tonsillar, splenic and ileal lymphoid tissues are sampled. Histologically, lymph nodes are staged as follicular hyperplasia, follicular fragmentation, follicular lysis and lymphoid depletion. In situ hybridization is performed using RNA antisense probes to full length HIV-1 hybridization techniques and standard primers from different areas of the HIV-1 genome. *In situ* polymerase chain reaction is performed using multiplex overlapping primer pairs and nick-translated 35-S labelled DNA probes.

SIGNIFICANT FINDINGS: The majority of lymph nodes in asymptomatic HIV-1 infected individuals demonstrated mild enlargement that histologically contained secondary follicles in different stages of fragmentation and lysis. There was a good concordance in follicular stage from one site to another. The number of CD4 positive cells decreased with increasing stage. HIV-1 RNA was increasingly localized in follicles with advancing histologic stage; in earlier stages, numerous HIV-1 infected interfollicular cells were also present. By *in situ* PCR, there were numerous latently infected T-cells in paracortical areas. These data have been confirmed in lymph nodes from early stage patients and will thus be critical to assess response to early stage treatment protocols. The Principal Investigator has authored or co-authored 4 publications due to this protocol.

PROTOCOL SUMMARY SHEET

RV#: 51

PROTOCOL TITLE: A Phase I Study of the Safety and Immunogenicity of IIIB rgp120/HIV Vaccine in HIV-1 Seropositive Adult Volunteers

CLINICAL SITE(S): WRAMC

PRINCIPAL INVESTIGATOR: Robert R. Redfield, MD, LTC(P), MC, US Army/ Deborah L.Birx, MD, LTC, MC, US Army

STATUS: Active

MAP: Vaccines and Immunotherapy/Prophylaxis

NUMBER OF PATIENTS THUS FAR ENROLLED: 45

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 45 (closed)

NUMBER OF PATIENT VISITS TO DATE: 1309

ADDITION (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: 152 protocol visits will complete the addendum currently being executed. Anticipate submission of addendum in Spring 1993 to maintain enrollment of 20 volunteers on monthly visits (240 protocol visits per year).

DESCRIPTION/SUMMARY OF PROTOCOL: The initial trial was a Phase I open label dose finding trial (100ug, 300ug, 600ug) in 19 volunteers followed by a blinded randomized component (300ug verses placebo) in 25 volunteers. Volunteers were vaccinated at 0,1,4,8,16 weeks with follow up evaluations scheduled for every 2 weeks through 24 weeks. This trial opened in Nov 1990 following confirmation of immunogenicity of 300ug and 600ug rgp120 dosage (8/92); the trial was subsequently randomized and enrollment opened in September, 1992 and closed to enrollment in December of 1992. An extension addendum to evaluate variation in the boosting schedule in terms of immunogenicity and safety began in April,1992. 41 of the original volunteers re-enrolled in the extension addendum and 41 volunteers continued on the trial as of March 31, 1993.

SIGNIFICANT FINDINGS as of March 31, 1993:

- first to demonstrate the immunogenicity and safety of a CHO cell expression HIV envelope product in volunteers with early stage HIV infection.

- first to document dosage response of this product. All subsequent investigators have taken advantage of the results of this trial to optimize trial design using CHO expression Genentech vaccine products in both seronegative and seropositive trials.

- product found to have a unique dose response profile which has lead to extensive evaluation of the character of the CHO product.

- significant percentage of product found to be denatured.

- primary immune response linked to "denatured" portion of molecule.

- diminished cellular response has lead company to explore adjuvant techniques.

- development of *in vitro* assay techniques required to assess T cell anti HIV responses utilizing CHO cell expressed rgp120 (serospectrotyping and biospecific interaction analysis).

- comparative immunogenicity of CHO cell derived rgp120, and behavior derived gp160 demonstrated unique immunologic profile currently under intense investigation.

- no evidence of continued expansion of V3 reactivity post 9 injections to "group specificity" as suggested by prior baboon studies.

PROTOCOL SUMMARY SHEET

RV# 53

PROTOCOL TITLE: Language and Neurodevelopment in Infants With Perinatal Exposure to HIV and Children Without Chronic Illness

CLINICAL SITE (S): WRAMC

PRINCIPAL INVESTIGATOR: William Walker, MD, LTC, MC, MD, US Army

STATUS: Terminated

NUMBER OF PATIENTS THUS FAR: .NA

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: NA

NUMBER OF PATIENT VISITS TO DATE: 0

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF STUDY PROTOCOL: NA

DESCRIPTION/SUMMARY OF PROTOCOL: This study was designed to identify neurodevelopmental deficits which might occur in infants and young children with perinatally acquired HIV infection. This study also proposed to explore the incidence of abnormal neurodevelopment in military dependent infants and children without HIV infection.

SIGNIFICANT FINDING: This protocol was terminated.

PROTOCOL SUMMARY SHEET

RV# 56

PROTOCOL TITLE: Analysis of Sexually Transmitted Disease (STD) patterns at Ft Bragg, NC: Preparation for HIV Behavioral Interventions

CLINICAL SITE: Womack Army Medical Center, Fort Bragg, North Carolina

PRINCIPAL INVESTIGATOR: Kelly McKee, MD, LTC, MC, US Army

STATUS: Active

MAP: Epidemiology/Natural History

NUMBER OF PATIENTS THUS FAR ENROLLED: Patients do not enroll, this is a Surveillance Protocol

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 5,000-8,000 per year

NUMBER OF PATIENT VISITS TO DATE: N/A (50,064 Visits reviewed since 1984)

ADDITIONAL NUMBER OF VISITS PROJECTED TO COMPLETION: 25,000-40,000 (1993-1998)

DESCRIPTION/SUMMARY OF PROTOCOL: This protocol initially was conceived to utilize the Fort Bragg Preventive Medicine Service STD data collection system and its historical files to provide background information around which to design behavioral intervention strategies to prevent transmission of HIV and exposure to HIV. As this database evolved, the utility of this database to provide outcome measures became apparent. This latter function has been subsequently incorporated into the design of future behavioral intervention programs at Fort Bragg. The importance of providing accurate and complete diagnostic information in support of STD intervention protocols is readily apparent. Presently, however, fiscal and program constraints require that etiologic diagnoses be based upon data provided by the hospital clinical laboratory; such information is recognizably deficient in terms of sensitivity and probably specificity. Although diagnosis at this level suffices for general public health purposes, it is not sufficiently accurate for quantitative clinical research measures. To address these concerns, RV56 may be expanded to incorporate a high-level microbiological capability.

SIGNIFICANT FINDINGS: To date, this protocol provided data on STD rates at Ft Bragg for use as background information in other protocols. This data represented the most comprehensive current information on STDs in the US Army.

PROTOCOL SUMMARY SHEET

RV#: 57

PROTOCOL TITLE: Active immunization of AZT Treated HIV-Infected Patients With Recombinant gp160 HIV Protein: Phase I/II Study of Immunogenicity, Toxicity, and Effect on *In Vivo* immunoregulation

CLINICAL SITES: BAMC/FT HOOD, NNMC, WBAMC, WHMC, WRAMC

PRINCIPAL INVESTIGATOR: Robert R. Redfield, MD, LTC(P), MC, US Army

STATUS: Active

MAP: Vaccines and Immunotherapy/Prophylaxis

NUMBER OF PATIENTS THUS FAR ENROLLED: 53 (11 additional in screening)

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 80

NUMBER OF PATIENT VISITS TO DATE: 259

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: 1007 future protocol visits will complete the trial with all 80 volunteer enrolled.

DESCRIPTION/SUMMARY OF PROTOCOL: This is a current Phase I/II multi-center, open label feasibility trial of rgp160 in patients with HIV infection Walter Reed stage 1-5 and currently receiving AZT. Specific protocol objectives included: assess the immunogenicity and safety of rgp160 in patients with more advanced HIV disease and in patients with early disease receiving AZT, and determine parameters predictive of post infection immune responsiveness. Patients were stratified by T cell interval. Each volunteer will receive 160ug of rgp160 on days 0,7 and at month 1,2,4,6,10. Trial duration is 12 months (not inclusive of preevaluation).

SIGNIFICANT FINDINGS AND ANTICIPATED OUTCOMES as of 3/31/93:

- This trial opened for enrollment November 1992 and it is anticipated that enrollment will be completed within 6 months. Patient accrual was on schedule, currently 64 volunteers were on trial and 53 post initial vaccination. Duration of follow up ranged up to Day 90.
- It is anticipated that data obtained from this trial will provide important information related to effect of AZT on immunogenicity and safety profile of rgp160.
- It is also anticipated that this trial will provide systematic information related to immunogenicity and safety in HIV infected populations with more advanced disease.
- This protocol provides a platform for additional human adjuvant

studies. To date, 8 adjuvant have been studied extensively in small animals in collaboration with Dr. Britta Wahren.
- The Principal Investigators have verified unique relationship between adjuvant and antigen combinations, requiring verification of each combination.
-The sponsors are agreed to utilize this population to study these adjuvants which can then be exploited in future therapeutic and prophylactic strategies, an addendum is currently in preparation.

PROTOCOL SUMMARY SHEET

RV# 60

PROTOCOL TITLE: Phase I Study of Alferon N Injection In Persons With Asymptomatic Human Immunodeficiency Virus (HIV) Infection

CLINICAL SITE: NNMC

PRINCIPAL INVESTIGATOR: Donald R. Skillman, MD, MAJ, MC, US Army

STATUS: Active

MAP: Chemotherapy/Chemoprophylaxis

NUMBER OF PATIENTS THUS FAR ENROLLED: 22

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 22

NUMBER OF PATIENT VISITS TO DATE: 325

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: 10 - 1 patient remains

DESCRIPTION/SUMMARY OF PROTOCOL: A Phase 1 study of Alferon N injection was initiated in anticipation of an efficacy trial since the recombinant interferons showed evidence of clinical benefit in HIV infection. This was a Phase 1 study of natural interferon alfa-n3. This agent showed a 10- to 100-fold increase in anti-HIV activity in human monocytes when compared on a unit per unit basis to recombinant interferon $IFNa2_a$ or $IFNa2_b$. Before one can determine if the increased *in vitro* activity translates to a 10- to 100-fold increase in clinical benefit, it was necessary to determine if the toxic effects of recombinant interferon are likewise increased 10- to 100-fold.

Twenty patients took the drug subcutaneously Monday-Wednesday-Friday for 12 to 24 weeks at increasing doses:

Five took 1 million IU per dose
Ten took 5 million IU per dose
Five increased the dose to their Individual Maximum Tolerated Dose (MTD).

The MTDs for these five were as follows:

1=12.5 million IU/dose; MTD event was a >10% decline in CD4+ T-Cell Number
1=15 million IU/dose; MTD event was reversible neutropenia (750 neutrophils/mm^3)
1=20 million IU/dose; MTD event was flu-like symptoms

1=10 million IU/dose; MTD event was a >10% decline in CD4+ T-Cell Number
1=15 million IU/dose; MTD event was a >10% decline in CD4+ T-Cell Number

Enrollment was completed and the last patient will take his last dose of natural interferon alfa-n3 on May 31, 1993 (unless complications arise). This patient will then have two follow-up evaluations at 30 day intervals, after which time this protocol will be completed.

SIGNIFICANT FINDINGS: Interferon alfa-n3 is extremely well tolerated. It is much superior to published reports of tolerances of recombinant interferons. Only one patient developed the flu-like symptoms usually reported with interferon administration. Significant, reversible laboratory toxicity developed in another patient, at 17.5 million IU. Therapy was interrupted in five patients due to protocol defined toxicity of a 10-20% decline in CD4+ T-Cells from baseline.

PROTOCOL SUMMARY SHEET

RV# 64

PROTOCOL TITLE: Evaluation of Cardiac Function in Patients with HIV-1 Infection

CLINICAL SITE: WHMC

PRINCIPAL INVESTIGATORS: Joseph A. Deering, MD, LTC, MC, US Air Force, William L. Schlegel, MD, MAJ, MC, US Air Force

STATUS: Active

MAP: Epidemiology/Natural History

NUMBER OF PATIENTS THUS FAR ENROLLED: 250 patients and 29 control subjects

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 250 patients and 100 control subjects

NUMBER OF PATIENT VISITS TO DATE: 259 patient and 29 control visits.

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: 996 patient and 71 control visits

DESCRIPTION/SUMMARY OF PROTOCOL: This was a single center five year investigation which annually evaluated the cardiac status of 250 adult patients admitted to Wilford Hall Medical Center with a diagnosis of HIV-1 infection. The objectives of this protocol were to identify the incidence of myocarditis associated with HIV, and to identify the typical Walter Reed stage development of the myocarditis. In addition, evidence of any association with the common opportunistic infections of HIV will be sought. The invasive phase of this study attempted to identify the infectious or immune-mediated mechanisms of cardiac patients in this study by utilizing the following techniques: 12-lead electrocardiogram, signal-averaged electrocardiogram, heart variability testing, spectral mapping, Holter monitoring and echocardiogram. An integral part of the study involved the purchase of a state-of-the-art signal-averaging electrocardiography system. Cardiac dysfunction was a common but often unsuspected complication of HIV-1 infection, contributing to morbidity and mortality. This study also can identify the best noninvasive method of detecting cardiac involvement and the optimal time to implement testing. Not only were the effects of HIV-1 on cardiac functioning monitored but data on the effects of opportunistic infections and related medical treatments were evaluated. By determining the natural history of HIV-1 associated cardiac dysfunction, the prognostic significance of a given cardiac abnormality could be determined. This information can aid the health care provider in making medical management and military

administrative decisions, as well as patient counseling and follow-up.

SIGNIFICANT FINDINGS: An initial analysis of data from 127 patients (roughly 9 months of echo data) in this protocol was accomplished. 32 patients evaluated were Walter Reed (WR) stage 1, 47 patients were WR2, 5 patients were WR3, 12 patients were WR4, 23 patients were WR5, and 8 patients were WR6. The age range was 19 to 45 years for this group. Echocardiographic data were available for 127 patients. Two had significant pericardial effusions; one Walter Reed (WR) stage 1 and one WR6. Sixteen had left atrial size between 45 and 56 mm, and one WR5 had left atrial size >56 mm. One WR5 had left ventricular internal dimension in systole (LVID's) >45mm and LVIDd >56mm. LVH was found in 11 of the group; 4 at WR stage 1, 4 at WR 2, 1 at WR 4, and stage 2, 2 at WR 4 and 2 at WR 5. TR(Tricuspid regurgitation) with estimated pulmonary arterial pressure >30 mm Hg was found in 1 WR2. No patients had globally decreased EF (ejection fraction) or segmental wall motion abnormalities. These data suggested that echocardiographic abnormalities of left atrial dilation, pericardial effusions, LVH (left ventricular hypertrophy) and mitral regurgitation may occur more frequently in the HIV infected.

PROTOCOL SUMMARY SHEET

RV# 65

PROTOCOL TITLE: Prospective Open-label Study of the Emergence of Drug Resistance in Patients Infected with HIV-1 Taking Oral U-87201 E

CLINICAL SITE: NNMC

PRINCIPAL INVESTIGATOR: Douglas L. Mayers, MD, CAPT, MC, US Navy

STATUS: Active

MAP: Chemotherapy/Chemoprophylaxis

NUMBER OF PATIENTS THUS FAR ENROLLED: 6

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 6

NUMBER OF PATIENT VISITS TO DATE: 75

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: 20

DESCRIPTION/SUMMARY OF PROTOCOL: An open label study of U-87201 E in 6 patients with AZT-resistant virus was performed to determine the rate of emergence of U-87201 E resistance and the genomic changes in the HIV reverse transcriptase gene, associated with *in vitro* resistance. The patients received a loading dose of 600mg of U-87201 E orally, three times per day for 2 days, followed by 400mg orally TID for up to 1 year. Objectives of the study were:

1. To determine the time course of development of resistance to U-87201 E in patients with HIV isolates showing *in vitro* resistance to AZT.

2. To determine the genotypic changes in HIV reverse transcriptase associated with phenotypic resistance to U-87201 E.

3. To determine the genotypic and phenotypic effects of treatment with a nondideoxynucleoside agent on the alterations of the HIV-1 virus population associated with *in vitro* AZT resistance.

4. To determine whether serial passage of patient pre-drug HIV isolates in the presence of U-87201 E would generate the resistant mutants that may subsequently emerge in the patients.

SIGNIFICANT FINDINGS:

--Four of six patients (67%) developed a rash at 9 to 14 days of therapy. Skin biopsy suggested that the rash was not allergic in nature and approval was given to rechallenge two patients with U-87201 E.

--Analysis of pharmacokinetic data and *in vitro* drug resistance was in progress.

PROTOCOL SUMMARY SHEET

RV# 66

PROTOCOL TITLE: Evaluation of the Efficacy of U.S. Army HIV Education/Prevention Strategies

CLINICAL SITE(S): N/A. Phase I surveyed 63 Army medical treatment facilities throughout CONUS, Europe, and Korea. Forty-one (41) participated. Protected Phase 11 study sites: Ft Campbell, Ft Riley, Ft Lewis

PRINCIPAL INVESTIGATOR: Karen Ray, COL, MS, US Army

MAP: Behavioral Medicine

NUMBER OF PATIENTS THUS FAR ENROLLED: Phase I - N/A; Phase 11 107 soldiers participated in pilot studies of a survey instrument. 423 soldiers participated in piloting Phase 11 interventions.

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: A total enrollment of 2,000 active duty soldiers tn Phase 11.

NUMBER OF PATIENT VISITS TO DATE: N/A

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: Phase II - 2,000 participants will undergo survey testing at 4 intervals (pre/post. 3 months and 6 months) for an optimum total of 8,000 visits.

DESCRIPTION/SUMMARY OF PROTOCOL: This protocol involved a multi-phasic approach designed to evaluate the efficacy of existing Army HIV prevention interventions. To the Principal Investigator's knowledge, it was the only study which attempted to evaluate current Army HIV prevention programs. In this study each phase was ,or will be, based on the results of the one preceding, and the methodology applied increased or increases in complexity with each planned phase.

Phase I: A process evaluation of Army HIV education programs at 41 installations was conducted. This evaluation provided a description of Army HIV program components, staff. and evaluation methods: and identified potentially successful HIV prevention programs through the use of surveys, interviews with program staff, and observation of interventions. Thirteen (13) installations were identified with promising programs as measured by established study criteria. Of the thirteen, three (3) were identified to have interventions which had potential to affect risk behavior change.

SIGNIFICANT FINDINGS:

(Phase 1) The most commonly reported objective for Army HIV prevention programs 85%) is increasing knowledge.

There currently are no specific strategies reported for reducing the incidence of HIV infection in minorities.

There were no specific strategies for uninfected soldiers which used more intensive approaches (i.e, more than "one shot sessions").

Few interventions used strategies which promoted specific risk reduction skills.

STD clinic patients (38%) and HIV+ individuals (15%) were the least frequently reported as target populations for HIV education/prevention.

PROTOCOL SUMMARY SHEET

RV# 67

PROTOCOL TITLE: A placebo controlled double-blinded study of the elimination of Staphylococcus aureus carriage in HIV infected patients with topical antimicrobial agents

CLINICAL SITE (S): NNMC

PRINCIPAL INVESTIGATOR: Catherine F. Decker. MD, Civilian - Contract

STATUS: Active

MAP: Opportunistic Infections

NUMBER OF PATIENTS THUS FAR ENROLLED: 52

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 400 screened, 120 to treatment arm

NUMBER OF PATIENT VISITS TO DATE: 124

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: 1850 - Majority of screening done as part of other clinical visits.

DESCRIPTION/SUMMARY OF PROTOCOL: To determine the efficacy of topical antimicrobial agents, mupirocin calcium ointment and chlorhexidine gluconate 4% foam in the eradication of *Staph aureus* Nasal and skin carriage in HIV seropositive patients. *Staph aureus* colonization may predispose the patient to serious *Staph aureus* infections, reported in HIV infected patients. Staph aureus colonization also may be a contributing factor in the increased incidence of skin disease seen throughout HIV disease. Eradication of *Staph aureus* carrier state may decrease subsequent infection as has been demonstrated in other patient populations. Additionally *Staph aureus* has been shown to produce various enterotoxins which have been shown to be superantigens and thought to be the most potent T cells stimulants recognized. Superantigens may have effects on dysregulation of the immune system. If *Staph aureus* is chronically carried by HIV infected patients there may be signification absorption of these toxins. We will attempt to show whether *Staph aureus* carriage is a significant factor in disease progression as well as in significant morbidity and mortality seen in late disease.

SIGNIFICANT FINDINGS: This is a blinded study, and was in progress as of March 31, 1993.

PROTOCOL SUMMARY SHEET

RV# OI3

PROTOCOL TITLE: An Open Multicenter Randomized, Dose-Ranging Study of Azithromycin in the Treatment of Disseminated Mycobacterium Avium-Intracellulare Complex Infection (MAC) in Patients with the Acquired Immune Deficiency Syndrome (AIDS)

CLINICAL SITE (S): WHMC

PRINCIPAL INVESTIGATOR: Craig W. Hendrix, MD, Maj, MC, US Air Force

STATUS: Active

MAP: Opportunistic Infections

NUMBER OF PATIENTS THUS FAR ENROLLED: 2

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 2

NUMBER OF PATIENT VISITS TO DATE: 24

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: 5 visits per patient in initial phase; 1 visit/month/patient in follow -up (indefinitely).

DESCRIPTION/SUMMARY OF PROTOCOL: This positive controlled study was designed to study the safety and efficacy of 2 doses of azithromycin as treatment for disseminated Mycobacterium avium-intracellulare complex (MAC) infection in AIDS patients. A maximum of 50 patients (10 at WHMC) were assigned to receive azithromycin 600 mg/day, or 1200 mg/day for 6 weeks. Patients demonstrating satisfactory clinical response(five-fold or greater reduction in bacteremia (cfu/ml]) were offered enrollment in a follow-up study to continue therapy with azithromycin.

SIGNIFICANT FINDINGS as of March 31, 1993: Two patients completed the 6-week protocol and continued in follow-up with no adverse drug reactions or misadventures noted. One patient had resolution of fever, night sweats and weight loss, and blood cultures remained negative for MAC once on study. The second patient also had modest symptomatic improvement. Although the initial study was for six weeks, a continuation phase allowed the patients to stay on the study indefinitely. This study has been closed to enrollment, and lab samples are being processed for data analysis. No final results are available at this time.

PROTOCOL SUMMARY SHEET

RV# OI6

PROTOCOL TITLE: Escalating Multiple-Dose Safety and Tolerance of WR6026 Hydrochloride

CLINICAL SITE (S): WHMC in collaboration with Johns Hopkins Hospital, Baltimore MD, and Indiana University, Indiana. (This is a cooperative study with the AIDS Clinical Trials Group (ACTG), National Institute of Allergy and Infectious Diseases (NIAID)

PRINCIPAL INVESTIGATOR: Craig W. Hendrix, MD, Maj, MC, US Air Force

MAP: Opportunistic Infections

NUMBER OF PATIENTS THUS FAR ENROLLED: 14

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 17 (estimated)

NUMBER OF PATIENT VISITS TO DATE: 64 visits

ADDITIONAL (FUTURE) NUMBER OF Patient Visits projected to completion of protocol: 3 (estimate; < or = 6 depending on enrollment other sites)

DESCRIPTION/SUMMARY OF PROTOCOL: This was a randomized, double blind, placebo controlled, escalating, multiple-dose safety and tolerance study to evaluate a new 8-aminoquinoline compound related to the anti-malarial drug primaquine. *In vitro* studies have demonstrated that this drug has inhibitory activity against Pneumocystis carinii (PCP). This study attempted to assess the safety and tolerance of WR 6026 for 21 consecutive days and to identify the maximum tolerated dose. The initial dose was 30 mg/day. This dose will be increased by 30 mg increments until a dose limiting toxicity is identified in 2 or more of the volunteers in each cohort. All subjects were treated as outpatients for the first 21 days of the study and inpatients for the remaining 3 days for pharmacokinetic studies.

It was hoped that this compound will be useful as prophylaxis for PCP, as it is very active against PCP in preclinical studies and has a long half-life to allow infrequent dosing.

SIGNIFICANT FINDINGS: To date, 36 patients completed the protocol at the three participating sites. Dose limiting methemoglobinemia was identified at the 150 mg level. Therefore, the final cohort of 120 mg (MTP) was opened for enrollment. With the completion of this cohort, the enrollment will be closed and the data analyzed. Throughout the study period, all information and clinical data was monitored by the NIAID Medical Officer.

PROTOCOL SUMMARY SHEET

RV# OI7

PROTOCOL TITLE: A Double Blind Study to Evaluate the Safety and Pharmacokinetics of RWJ 25213 in Subjects with HIV Infection

CLINICAL SITE (S): WHMC

PRINCIPAL INVESTIGATOR: Craig W. Hendrix, MD, Maj, MC, US Air Force

STATUS: Completed

MAP: Opportunistic Infections .

NUMBER OF PATIENTS ENROLLED: 16

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 16

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: NA

NUMBER OF PATIENT VISITS TO DATE: 16

DESCRIPTION/SUMMARY OF PROTOCOL: This was a randomized, double-blinded placebo-controlled, phase I study to evaluate the safety and pharmacokinetics of a single dose followed by multiple dosing of RWJ 25213 (an antibacterially active isomer of ofloxacin) with concomitant AZT administration. Sixteen (16) HIV (+) adult male volunteers received drug and placebo. Safety evaluations were made by examination and laboratory tests over a 2-week period. Plasma levels of RWJ 25213 and AZT were collected for evaluation by Robert Wood Johnson (RWJ) Pharmaceutical Institute. (This protocol was 100% outside funded through the Robert Wood Johnson Pharmaceutical Institute. All laboratory, personnel, and travel costs were paid for by RWJ.)

SIGNIFICANT FINDINGS: No significant adverse events were noted during the actual study period. All samples have been sent to the sponsor (RWJ) for assay. To date, no conclusions have been drawn. All patients were discharged in stable condition.

PROTOCOL SUMMARY SHEET

RV# OI8

PROTOCOL TITLE: Double blind, placebo controlled, multicenter trial of weekly azithromycin as prophylaxis vs MAC

CLINICAL SITE	PI	# Patients Screened	#Patients Enrolled	# Patients To be enrolled
WRAMC	Chung	5	0	25
NNMC	Wagner (HJF)	11	10	20
PNMC	Zajdowitz	2	0	7
WHAFMC	Melcher	6.	4	10
BAMC	Kelly	1	1	5
WOMACK	Williams	5	3	7
FAMC	Byrne	10	3	7
EAMC	Craig	>10	8	13
NHSD	Oldfield	40	19	30

STATUS: Active

MAP: Opportunistic Infections

NUMBER OF PATIENT VISITS TO DATE: ~ 300

FUTURE NUMBER OF PATIENT VISITS PROJECTED TO COMPLETE PROTOCOL: ~1400

DESCRIPTION/SUMMARY OF PROTOCOL: HIV infected patients with CD4 counts <100 are randomly assigned to placebo or azithromycin (1200 mg weekly) groups. Patients were evaluated monthly for the major endpoints: mycobacteremia, other bacterial infections, signs/symptoms of drug toxicity. This protocol was appropriate to USAMRDC Science and Technology Objective (STO) 1H (18 Mar 93): "Provide during FY93-97 an evaluation of advanced chemotherapeutic agents effective against both early stage and late stage disease". This protocol continues to be very popular with clinicians at all sites.

SIGNIFICANT FINDINGS: Some patients already reached endpoints in this double blind study.

PROTOCOL SUMMARY SHEET

RV# OI10

PROTOCOL TITLE: Hemophilus Influenza Type B Vaccine in HIV Infected Patients

CLINICAL SITE(S): NNMC

PRINCIPAL INVESTIGATOR: Joseph L. Malone, MD, CDR, MC, US Navy

STATUS: Active

MAP: Opportunistic Infections

NUMBER OF PATIENTS THUS FAR ENROLLED: None

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 200

NUMBER OF PATIENTS VISITS TO DATE: None

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: 200

DESCRIPTION/SUMMARY OF PROTOCOL: Randomize a population of HIV infected volunteers who have not previously received HIV vaccine to receive one of three FDA approved HIV vaccine preparations. Before and after antibody titers will be measured. Toxicity to vaccination will be measured by patient self reports.

SIGNIFICANT FINDINGS: This protocol has not been initiated.

SUMMARY SHEET

PROJECT NUMBER CRV2

RAPID DETECTION OF MYCOBACTERIA IN PATIENTS WITH HIV INFECTION

CLINICAL SITE(S): Armed Forces Institute of Pathology (AFIP)
PROTOCOL NUMBER ZS2R

INVESTIGATORS: David C. Fritzinger, Ph.D.
Ted L. Hadfield, Maj, USAF, BSC

ORIGINAL APPROVAL DATE: 24 July 1991

ESTIMATED COMPLETION DATE: 30 Sept. 1994

NUMBER OF PATIENTS THUS FAR ENROLLED: NA

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: NA

DESCRIPTION/SUMMARY OF PROTOCOL:

The objective of the protocol was to develop a simple and rapid assay employing polymerase chain reaction (PCR) and DNA probes to identify Mycobacteria most commonly seen in clinical specimens from AIDS patients, namely, M. *tuberculosis* and M. avium. The sensitivity and specificity would be determined by (a) detection of the quantity of DNA required to yield a positive reaction and testing primer sets against other Mycobacteria; (b) by testing blinded clinical specimens from WRAMC Mycobacteriology laboratory. After samples are tested, culture results will be compared to PCR results to determine the number of true positives true negatives, false positives and false negatives. The assay sensitivity and specificity will be derived from the latter values.

NUMBER OF PATIENT VISITS TO DATE: NA

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED TO COMPLETION OF PROTOCOL: NA

SIGNIFICANT RESULTS: New primers were tested first for their species (or genus) specificity, then for the limits of their detection of Mycobacterial DNA. Then, the primers were tested for their ability to detect Mycobacterial DNA in previously tested, known positive clinical samples. Finally, the primer sets will be evaluated using unknown clinical samples.

Primer sets used by one Principal Investigator proved to be inefficient and unreliable in detecting Mycobacterial DNA in clinical samples. DNA titration analysis of the primers showed that the genus specific primer set was able to detect 1 pg of Mycobacterial DNA by gel analysis (equivalent to about 200 bacteria), and about 100 fg (20 bacteria) of DNA by hybridization

analysis, while the *M. avium* specific primers were able to detect 10 pg of DNA by the gel assay, and 1 pg by hybridization. The new *M. tuberculosis* primer set was also analyzed by DNA titration, and found to be easily sensitive to less than 1 fg (0.2 bacteria) of *M. tuberculosis* DNA, both by gel analysis, and by hybridization, making this primer set significantly more sensitive than either of the other two. This difference in sensitivity proved to be important in the detection of Mycobacteria in clinical samples.

To evaluate the ability of the first three primer sets to detect Mycobacterial DNA in clinical (sputum) samples, we tested them against 42 different samples containing known Mycobacteria of the 42 samples, 37 were known to contain Mycobacteria by culturing the bacteria from the samples. Of these 37 Mycobacterial positive samples, 29 contained *M. tuberculosis*, 3 contained either *M. avium* or *M. intercullare*, with the remaining 5 containing other Mycobacterial species. The old genus specific primer set was able to detect 20 (54%) of the Mycobacteria containing samples.. The *M. avium* primer set detected *M. intercellulare* in two samples (no samples contained *M. avium*). The *M. tuberculosis* primers proved to be much more sensitive in detecting Mycobacterial DNA in clinical samples, correctly identifying 21 samples (75%). The sensitivity of the *M. tuberculosis* primer set did prove to be a problem at times, in that great care needed to be taken not to contaminate negative samples, either before the PCR reaction, or prior to running the gels.

The results obtained for the *M. tuberculosis* primer set are generally similar to specificities obtained by other workers using PCR to detect Mycobacteria. Variables that may affect the sensitivity of the PCR assay include the method of lysis of the bacteria in the clinical sample, and the age of the sample. The researchers are currently investigating methods of lysis of Mycobacteria in clinical samples since there does not seem to be a standard protocol. In addition, it has been reported that long term storage of samples at 4°C greatly decreases the sensitivity of the PCR assay. One would expect the stability of frozen samples to be significantly greater, though long term frozen storage of clinical samples may result in a notable decrease in the sensitivity of PCR.

The Principal Investigators found a 16S ribosomal RNA sequence that appears to be specific for Mycobacteria DNA titration experiments have shown that it is able to detect as little as 1 fg of Mycobacterial DNA. When tested on clinical samples, it was able to detect Mycobacterial DNA in 9 of 11 (82%) Mycobacterial containing samples (by gel analysis and hybridization). In addition, the researchers found an insertion sequence in *M.* avium that appears specific for that species. Preliminary results with these primers indicate that they are sensitive for the detection of *M.* avium. The researchers are now continuing in the evaluation of this primer set.

The Principal Investigators have 100 blinded samples from the

WRAMC to be assayed . In the course of these assays, they will evaluate different means of isolating Mycobacterial DNA from clinical samples. After performing these experiments, the researchers will be able to evaluate the sensitivity and specificity of the three primer sets on clinical samples. The estimated date of completion for these experiments is 1 September, 1993. At that point, the scientists should be ready to use the three primer sets in a prospective study assaying clinical samples for the presence of Mycobacteria.

Summary of PCR Results

	M.tb.	M.avium	Genus 1	Genus 2
Sensitivity =TP/(TP+FN)	75%	NA	55%	82%
Specificity=TN/(TN+FP)	90%	78%	100%	100%
Positive Predictive Value=TP/(TP+FP)	95%	NA	100%	100%
Negative Predictive Value=TN/(TN+FN)	56%	100%	24%	33%
Efficiency=(TP+TN)/(TP+FP+TN+FN)	79%	78%	60%	83%

SUMMARY SHEET

CRV-7

PROTOCOL TITLE: Prospective collection and banking of Lymphocytes and clinical data on HIV infected individuals taking antiretroviral agents

CLINICAL SITE: Fitzsimons Army Medical Center (FAMC)

PRINCIPAL INVESTIGATOR: Richard Harris, MD, LTC, MC, US Army
Shannon M. Harrison, MD, LTC, MC, US Army

NUMBER OF PATIENTS THUS FAR ENROLLED: 532

TOTAL NUMBER OF PATIENTS TO BE ENROLLED: 0

DESCRIPTION/SUMMARY OF PROTOCOL: This study is an extension of a previous phase II study of AZT therapy in 220 patients followed by investigators at Fitzsimons Army Medical Center and Denver Health and Hospital. Samples of patient sera and cells are collected every 6 months from these patients and stored in a central repository. The systematic collection of clinical data and specimens from patients on prolonged antiretroviral therapy (periods exceeding 5 years) has made the repository at Fitzsimons an invaluable resource for drug resistance studies being conducted at WRAIR.

NUMBER OF PATIENT VISITS TO DATE: N/A

ADDITIONAL (FUTURE) NUMBER OF PATIENT VISITS PROJECTED COMPLETION OF PROTOCOL: N/A

SIGNIFICANT FINDINGS:

A case control study of patients on AZT monotherapy demonstrated the association of AZT resistance with clinical decline.

A natural history study of the entire cohort of patients showed that initiation of AZT therapy delays Walter Reed stage progression by a approximately 1000 days, but subsequent stage progression occurs at similar rates in untreated patients and patients progressing on therapy.

Continuation of the specimen bank at FAMC is critical to ongoing studies of drug resistance.

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA1

PROTOCOL TITLE: Development of Mouse-Primate Chimeras for the study of HIV and SIV infections *in vivo*

PRINCIPAL INVESTIGATOR: Yvonne Rosenberg, Ph.D.

STUDY SITE(s): BioQual, Inc.

STATUS: Ongoing

NUMBER OF ANIMALS USED: 300.

SPECIES: Mice

DESCRIPTION/SUMMARY OF PROTOCOL:

The practical and ethical limitations to studying the pathogenesis and immunology of HIV infections in humans and the expense and unavailability of chimpanzees has highlighted the need for more useful animal models for HIV disease. The goal of this study was to create a reproducible, representative and efficient chimeric primate-mouse model for the study of both HIV and the closely related SIV diseases. Such a model should be easily manipulatable and dissectable so as to enable screening of potential therapies and provide a system for studying natural history, virulence and tropism of the viruses. In addition, these mice should be useful in studies on viral pathogenesis and virus-induced changes in the immune system, particularly those affecting the non-circulating pool of lymphocytes and macrophages within lymphoid organs. This proposal was to be carried out in two phases:

1. To organize the breeding and maintenance of C.B-17Icr (CB-17) SCID (severe combined immune deficient) mice.

2. To reconstitute SCID mice with macaque (SCID-ma) or human (SCID-hu) haemopoietic cells. Selective transfer of either lymphoid and/or myeloid lineages will be done and the resulting chimaeras will be characterized.

SIGNIFICANT FINDINGS:

1. Excellent facilities for breeding and maintenance of SCID mice were established.

2. The protocol for reconstitution of SCID mice with human PBMC was successfully developed. Reconstitution with macaque cells was less successful (30 - 50%) and might be due to foamy virus infection of macaque cells.

3. Line (L1) primate-specific and integrated proviral DNA may be detected from cells of infected ma- and hu-PBL-SCID mice using PCR.

4. Ma and human lymphocytes predominate in the intraperitoneal cavity of reconstituted SCID mice.

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA1(Addendum)

PROTOCOL TITLE: HIV and SIV infection of human-PBL-SCID and macaque-PBL-SCID

PRINCIPAL INVESTIGATOR: Yvonne Rosenberg, Ph.D.

STUDY SITE(s): BioQual, Inc.

STATUS: Ongoing

NUMBER OF ANIMALS USED: 300

SPECIES: Mice

DESCRIPTION/SUMMARY OF PROTOCOL:

1. to establish the conditions required for productive infection of hu-PBL-SCID and ma-PBL-SCID mice with HIV or SIV

2. to compare the various methods for virus detection following infection

3. to analyze the immune elements in immunized humans and macaques responsible for partial or total protection against viral challenge

4. to assess virus susceptibility or resistance to selected drugs or therapeutics *in vivo*

SIGNIFICANT FINDINGS:

1. Hu-PBL-SCID were infected with HIV-IIIB. Ma-PBL-SCID were infected with virulent strains of SIV, including SIVsmmPBj14 and SIVmac251.

2. Viral cocultivation assay detected infectious virus in intraperitoneal cavity and spleen cells of both HIV and SIV blood of infected hu-PBL-SCID and ma-PBL-SCID.

3. AZT extended the life of hu cells and prolonged the latency period of proviral DNA in HIV infected hu-PBL-SCID mice.

4. SCID mice reconstitution appeared more successful with hu cells than with ma cells, which may be due to endogenous foamy virus in the ma cells.

5. Virus infection was evident in ma- and hu-PBL-jSCID mice tissues, in which CD4+ cells were not detected using flow cytometry.

6. Macrophage reconstituted SCID mice were developed and were successfully infected with HIV-BAL.

7. Several HIV stocks were prepared in order to assess neutralizing or enhancing activity of various antisera.

8. Antibody responses in vaccinated ma might be analyzed using ma-PBL-SCID.

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA2

PROTOCOL TITLE: Immunogenic potential of genetically engineered SIV-envelope peptides fused to ß-galactosidase in rhesus macaques

PRINCIPAL INVESTIGATOR: Mark G. Lewis, Ph.D., HJF

STUDY SITE(s): Southern Research Institute

STATUS: Study Terminated

NUMBER OF ANIMALS USED: 3

SPECIES: Rhesus Macaque

DESCRIPTION/SUMMARY OF PROTOCOL:

1. To evaluate the immunologic potential of a genetically engineered SIV envelope peptide fused to ß-galactosidase, as an initial step toward development of a candidate vaccine for SIV and HIV.

2. To characterize the humoral immune response, and possible lymphocyte transformation or other measures of cellular immunity.

3. Determine baseline immunological and clinical parameters for eventual application in a challenge protocol using an appropriate SIV strain.

SIGNIFICANT FINDINGS:

Three rhesus macaques were transferred from USAMRIID in March 1990. These monkeys were used as animals immunized with SIV-647 ß-galactosidase. Their utilization by the Jackson Foundation was totally as sources of normal tissues and plasma.

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA3

PROTOCOL TITLE: SIV peptide vaccine with 4 peptides in Freund's complete adjuvant

PRINCIPAL INVESTIGATOR: Mark G. Lewis, Ph.D.

STUDY SITE(s): Southern Research Institute

STATUS: Ongoing

NUMBER OF ANIMALS USED: 6

SPECIES: Rhesus Macaque

DESCRIPTION/SUMMARY OF PROTOCOL:

Vaccination with conserved regions of the envelope of primate lentiviruses have been shown to induce immune responses in infected individuals. Some of these regions are immunodominant and are associated with both humoral and cellular immune responses. Utilization of these regions as potential vaccine antigens may prove efficacious in preventing lentivirus infection or altering the disease course of infected individuals.

Objectives:

1. To evaluate the immunogenic potential in rhesus macaques of genetically engineered SIV envelope peptides fused to ß-galactosidase.

2. To evaluate the immunogenic potential in rhesus macaques of genetically engineered HIV envelope peptides fused to ß-galactosidase.

3. To characterize the humoral and cellular immune response of the immunized monkeys.

4. To determine the immunologic and virologic responses of immunized animals following challenge with virulent SIV.

SIGNIFICANT FINDINGS:

1. Animals immunized with ß-galactosidase fusion peptides responded with both humoral and cellular immunity.

2. Immunized animals had an altered disease course from controls following SIV_{mne} challenge.

Publications:

Shafferman, A, Jahrling, PB, Benveniste, RE, Lewis, MG, Phipps, T, McCutchan, F, Sadoff, J, Eddy, G, and Burke, DS. A peptide vaccine based on conserved epitopes of SIV inhibits proliferation of SIV challenge in macaques. PNAS 88:7126-7130, 1991.

Rosenberg, YR, Shafferman, A, White, BD, Papermaster, SF, Leon, E, Eddy, GA, Benveniste, R, Burke, DS and Lewis, MG. Variation in the CD4+ and CD8+ population in lymph nodes does not reflect that in the blood during SIVmne/E11s infection of macaques. J. Med Primatol. 21:131-137. 1992

Shafferman, A, Lewis, MG, McCutchan, FE, Benveniste, RE, Jahrling, PB, Burke, DS and Eddy,G. Vaccination of macaques with SIV conserved envelope peptides suppressed infection and prevented disease progression and transmission. AIDS Human Retroviruses 8:1483-1488. 1992

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA3 (Addendum 1)

PROTOCOL TITLE: Lymph node transfer from monkeys in RVA 3

PRINCIPAL INVESTIGATOR: Mark G. Lewis, Ph.D.

STUDY SITE(s): Southern Research Institute

STATUS: Study Terminated

NUMBER OF ANIMALS USED: 4

SPECIES: Rhesus Macaque

DESCRIPTION/SUMMARY OF PROTOCOL:

1. To perform surgical removal of peripheral biopsies from four monkeys from protocol RVA 3 for the purpose of generating tissue for virus detection and tissue transfer to naive monkeys.

2. To determine if peptide vaccinated macaques from RVA 3 are currently carrying SIVmne in their lymphoid tissues and if it can infect naive macaques.

SIGNIFICANT FINDINGS:

Animals immunized with the fusion peptides and challenged with SIV_{mne} did not transmit virus to naive animals by either whole blood or lymph node cells.

Publications:

Shafferman, A, Lewis, MG, McHutchan, PE, Benveniste, RE, Jahrling, PB, Burke, DS and Eddy, GE. Vaccination of macaques with SIV conserved envelope peptides suppressed infection and prevented disease progression and transmission. AIDS Human Retroviruses 8:1483-1488. 1992

Shafferman, A, Lewis, MG, McCutchan, PE, Benveniste, RE, Jahrling, PB, Burke, DS and Eddy, GA. Prevention of transmission of simian immunodeficiency virus from vaccinated macaques that developed transient virus infection following challenge. Vaccine (in press)

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA3 (Addendum 2)

PROTOCOL TITLE: HIV-2 challenge of monkeys in RVA 3

PRINCIPAL INVESTIGATOR: Mark G. Lewis, Ph.D.

STUDY SITE(S): Southern Research Institute

STATUS: Ongoing

NUMBER OF ANIMALS USED: 5

SPECIES: Rhesus Macaque

DESCRIPTION/SUMMARY OF PROTOCOL:

This addendum was proposed to test the degree of protection generated following immunization and subsequent challenge by rechallenging these monkeys with a divergent primate lentivirus, HIV-2. The HIV-2 isolate was previously titrated in rhesus macaques and shown to be infectious. Analysis was performed on the blood and isolated tissues of these animals to determine if an active HIV-2 infection was established following challenge.

SIGNIFICANT FINDINGS:

The three vaccinated animals did not become infected with HIV-2, while one of the two control animals was infected.

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA3 (Addendum 3)

PROTOCOL TITLE: Lymph node biopsy from monkeys in RVA 3 (Addendum 1) for virus genome isolation

PRINCIPAL INVESTIGATOR: Mark G. Lewis, Ph.D.

STUDY SITE(s): Southern Research Institute

STATUS: Study Complete

NUMBER OF ANIMALS USED: 4

SPECIES: Rhesus Macaque

DESCRIPTION/SUMMARY OF PROTOCOL:

To surgically removal of a peripheral lymph node from four existing Rhesus macaques from protocol RVA 3, addendum 1 for the purpose of isolation of DNA for virus genome isolation.

SIGNIFICANT FINDINGS:

Lymph node biopsies were performed and SIV DNA was isolated.

Publications:

Shafferman, A, Lewis, MG, McCutchan, PE, Benveniste, RE, Jahrling, PB, Burke, DS and Eddy, GE. Vaccination of macaques with SIV conserved envelope peptides suppressed infection and prevented disease progression and transmission. AIDS Human Retroviruses 8:1483-1488. 1992

Shafferman, A, Lewis, MG, McCutchan, PE, Benveniste, RE, Jahrling, PB, Burke, DS and Eddy, GA. Prevention of transmission of simian immunodeficiency virus from vaccinated macaques that developed transient virus infection following challenge. Vaccine (in press)

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA4

PROTOCOL TITLE: SIV peptide vaccine in Freund's, Ribi or liposomes

PRINCIPAL INVESTIGATOR: Mark G. Lewis, Ph.D.

STUDY SITE(s): Southern Research Institute

STATUS: Ongoing

NUMBER OF ANIMALS USED: 20

SPECIES: Rhesus Macaque

DESCRIPTION/SUMMARY OF PROTOCOL:

The objective of this protocol is the confirmation and refinement of previous vaccine protocol RVA 3. The results of the previous studies were limited due to the number of animals in each group. This protocol will be used to repeat the protocol with additional animals and to compare alternative adjuvants to Freund's.

Objectives

1. To vaccinate three groups of monkeys with a four-peptide cocktail, using Freund's adjuvant, RIBI and liposome-lipid A.

2. To generate immune sera from the vaccinated macaques.

3. To challenge vaccinated and control macaques with SIVmac251 to determine efficacy of vaccine.

SIGNIFICANT FINDINGS:

Animals immunized with RIBI and liposome lipid A did not develop detectible circulating SIV antibodies. Animals immunized with RIBI also did not respond to ß-galactosidase and were removed from the study. Freund's immunized animals had a lowered virus load and more rapid antibody response following SIV_{mac251} challenge than control challenged monkeys. The course of the disease was not significantly altered.

Publications:

Alving, CR, Detrick, B, Richards, RL, Lewis, MG, Shafferman, A and Eddy, GA. Novel adjuvant strategies for experimental malaria and AIDS vaccines. Annals New York Acad, Sci. (in press)

Shafferman, A, Lewis, MG, McCutchan, FE, Benveniste, RE,

Jahrling, PB, Burke, DS and Eddy, GE. Vaccination of macaques with SIV conserved envelope peptides suppressed infection and prevented disease progression and transmission. AIDS Human Retroviruses 8:1483-1488. 1992

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA5

PROTOCOL TITLE: HIV-2 infection of rhesus macaques

PRINCIPAL INVESTIGATOR: Suzanne Gartner, Ph.D.

STUDY SITE(s): Southern Research Institute

STATUS: Ongoing

NUMBER OF ANIMALS USED: 7

SPECIES: Rhesus Macaque

DESCRIPTION/SUMMARY OF PROTOCOL:

Currently, the only animal other than man known to be susceptible to infection with HIV-1 is the chimpanzee. The lack of sufficient numbers of these animals, the costs associated with their use and care, and the fact that persistently infected chimpanzees do not appear to develop disease, pose major limits to the utility of this animal model. While infection of various monkey species with SIVs can result in the development of an immunodeficiency syndrome quite analogous to the human condition, some scientists and government licensing and regulatory officials have argued that optimal animal models to be used for the endstage evaluation of vaccines and therapies require the use of the human pathogen(s). Experimental infection of macaques with HIV-2 has been documented. Seroconversion and somewhat persistent (several months) virus replication has been observed in these animals in the absence of disease development. The investigator previously isolated a variant of HIV-2 (HIV-$2_{1711H,}$) which exhibited high level replication and cytopathicity in normal human T lymphocytes and macrophages *in vitro*. Additional limited *in vitro* studies suggested that this isolate can also replicate relatively efficiently in normal macaque cells.

Major objectives of this study were:

1) determine if these animals are still infected with the virus (can virus be isolated and/or detected:)

2) determine the nature and extent of any immune responses which may be in effect (humoral and cellular)

SIGNIFICANT FINDINGS: The investigator showed that rhesus macaques could become persistently infected with HIV-2 and that the virus had potential utility for use as a model of human infection.

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA6

PROTOCOL TITLE: Immunization of Rhesus Macaques with individual peptides

PRINCIPAL INVESTIGATOR: Mark G. Lewis, Ph.D.

STUDY SITE(s): Southern Research Institute

STATUS: Ongoing

NUMBER OF ANIMALS USED: 18

SPECIES: Rhesus Macaque

DESCRIPTION/SUMMARY OF PROTOCOL:

The objective of this protocol was to determine the immune response to each of the separate SIV beta-gal linked peptides and to determine if a single peptide will generate a protective immune response. These monkeys will be used for the determination of their immune response to the separated peptides and eventual challenge virus.

Objectives:

A. To vaccinate five groups of monkeys with one of five separate vaccines consisting of either a four peptide cocktail or a single peptide, using Freund's adjuvant.

B. To generate immune sera and cells from vaccinated macaques for the testing of their developed immunity to the single peptides.

SIGNIFICANT FINDINGS:

Animals developed detectible anti-peptide antibodies following immunization with the peptide fusion products. All animals were challenged with SIVmne/E11s. The challenge dose used for this trial was insufficient to cause infection in all of the control animals and the study was ended, except to follow persistently infected animals for disease development.

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA7

PROTOCOL TITLE: Immunogenicity of HIV-1 peptides in Rhesus Macaques

PRINCIPAL INVESTIGATOR: Mark G. Lewis, Ph.D.

STUDY SITE(s): Southern Research Institute

STATUS: Ongoing

NUMBER OF ANIMALS USED: 9

SPECIES: Rhesus Macaque

DESCRIPTION/SUMMARY OF PROTOCOL:

The objective of this protocol was to define the immune response of HIV-1 derived peptides when used as a vaccine in Rhesus macaques. These monkeys will be primarily used for the determination of HIV-1 specific immune response. This will allow for the use of HIV-1 specific reagents. Additional studies currently underway at the Jackson Foundation may allow for the eventual infection of these macaques with a HIV-1 virus.

Objectives:

A. To vaccinate two groups of monkeys with a four peptide cocktail, using Lipid A adjuvant.

B. To generate immune sera and cells from vaccinated macaques for the testing of their developed immunity to HIV-1.

SIGNIFICANT FINDINGS:

Animals were immunized with the HIV-1 peptide fusion proteins mixed in incomplete Freund's adjuvant. Three of the six animals immunized responded limitedly to only the 582 peptide following the final boost.

ANIMAL MODELS ... P
PROTOCOL SUMMARY SHEET

RVA8

PROTOCOL TITLE: Protective effect of passive neutralizing antibodies

PRINCIPAL INVESTIGATOR: Mark G. Lewis, Ph.D.

STUDY SITE(s): Southern Research Institute

STATUS: Ongoing

NUMBER OF ANIMALS USED: 12

SPECIES: Rhesus Macaque

DESCRIPTION/SUMMARY OF PROTOCOL:

One of the basic and still unresolved issues in the development of HIV or SIV vaccines is whether or not protection/enhancement can be mediated by antibodies *in vivo*. Moreover, if such an antibody protection/enhancement mechanism exists *in vivo*, can it be correlated with in vitro assays such as neutralization, and/or antibody dependent compliment mediated cytotolysis (ADCMC) and/or antibody dependent cellular cytotoxicity (ADCC) or antibody dependent enhancement (ADE) activity. Finding answers to some of these questions could have a major impact on the development of a safe and effective HIV vaccine and on other potential treatment modalities. As a first step in this direction the PIs proposed to determine if passively transferred antisera shown to have a varying *in vitro* activity towards SIV can protect *in vivo* naive animals against SIV challenge. This study proposed to use sera from monkeys on two current protocols, RVA 3 and RVA 4. Sera from these monkeys would allow for the inclusion of a diverse range of anti-SIV responses including immunized-protected, immunized-nonprotected, SIV infected and progressing, SIV infected non-progressing and immunized non-challenged. The sera contained a variety of neutralizing antibody levels and a range of antibody to various SIV antigens. These reagent and the results of these studies would provide the necessary tools for future *in vivo* antibody enhancement tests.

SIGNIFICANT FINDINGS:

Passive immunization with both SIV peptide and whole SIV antibodies can protect from $SIV_{mne/elle}$ infection.

Publications:
Lewis, MG, Elkins, WR, McCutchan, FE, Benveniste, RE, Lai, C-Y, Montefiori, DC, Burke, DS, Eddy, GA and Shafferman, A. Passively transferred antibodies directed against conserved regions of SIV envelope protect macaques from SIV infection. Vaccine (in press).

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA8 (Addendum 1)

PROTOCOL TITLE: Protection of macaques from SIV challenge using passive transfer of anti-SIV antibodies

PRINCIPAL INVESTIGATOR: Mark G. Lewis, Ph.D.

STUDY SITE(s): Southern Research Institute

STATUS: Ongoing

NUMBER OF ANIMALS USED: 7

SPECIES: Rhesus Macaque

DESCRIPTION/SUMMARY OF PROTOCOL:

The purpose of this addendum was to increase the numbers of monkeys included in specific groups from the original proposal (RVA 8) and to rechallenge the uninfected animals from the initial study. The additional animals were necessary in order to achieve statistical significance among the groups. Preliminary data indicated that protection from infection was achieved in groups 1, 2, and 3 and partial protection was observed in groups 4 and 5. The Principal Investigators proposed to use eight monkeys to increase the numbers of monkeys in groups 1, 2, 3 and 5 by two monkeys each. Although the Investigators recognized that group #4 should also have an increase number of monkeys, the amount of available immune plasma would not allow for this additional group. The proposed rechallenge of the protected animals was to determine if the animals are infectible following the elimination of the passive antibody.

SIGNIFICANT FINDINGS:

The additional monkeys responded as predicted and were protected from infections by $SIV_{mne/E11s}$. After 100 days of followup at which time not SIV specific antibodies could be detected, the animals were rechallenged with SIV and were found to be infectable.

Publications:

Lewis, MG, Elkins, WR, McCutchan, FE, Benveniste, RE, Lai, C-Y, Montefiori, DC, Burke, DS, Eddy, GA and Shafferman, A. Passively transferred antibodies directed against conserved regions of SIV envelope protect macaques from SIV infection. Vaccine (in press).

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA8 (Addendum 2)

PROTOCOL TITLE: Protection of macaques from SIV challenge using passive transfer of anti-SIV antibodies (Mne/Ells)

PRINCIPAL INVESTIGATOR: Mark G. Lewis, Ph.D.

STUDY SITE(s): Southern Research Institute

STATUS: Ongoing

NUMBER OF ANIMALS USED: 0

SPECIES: Rhesus Macaque

DESCRIPTION/SUMMARY OF PROTOCOL:

The purpose of this addendum was the addition of 8 monkeys to the original RVA 8 proposal for the testing of high titered anti-peptide antisera. Preliminary data indicated that partial protection (50%) from SIVe11s infection was observed in groups 4 and 5, which consisted of animals which received plasma containing only anti-peptide antibodies. The plasma used in group 4 was derived from monkey 3X7 which was in protocol #RVA3. The investigators were currently generating additional high titered antiserum in this monkey. The investigators proposed to use this antibody to expand the RVA 8 study by adding 4 monkeys to group 4 and 4 monkeys as challenge controls.

SIGNIFICANT FINDINGS:

Study not initiated

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA9

PROTOCOL TITLE: Whole virus vaccine for SIV

PRINCIPAL INVESTIGATOR: Mark G. Lewis, Ph.D.

STUDY SITE(s): Southern Research Institute

STATUS: Ongoing

NUMBER OF ANIMALS USED: 0

SPECIES: Rhesus Macaque

DESCRIPTION/SUMMARY OF PROTOCOL:

This protocol proposed to determine the effectiveness of a whole inactivated SIV vaccine in rhesus macaques. The vaccine preparation would consist of psoralin inactivated, formalin fixed simian immunodeficiency virus (mne/E11s) mixed with an adjuvant developed by the Diamond Scientific Corporation. A total of ten monkeys would be used in this study with five receiving four immunizations of virus mixed with adjuvant and five receiving adjuvant alone. The monkeys would receive the vaccines over a 120 day period. They would be followed for specific cellular and humoral immune responses developed towards the virus during the vaccination period and would be evaluated one month after the last boost for challenge with an infectious SIVmne isolate. The monkeys would be challenged with an infectious dose (10-100 ID) of SIVmne/E11s to determine if a protective immunity was generated. All monkeys would be held for up to two years following the challenge to determine the effectiveness of the vaccine.

SIGNIFICANT FINDINGS:

Study not initiated

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA10

PROTOCOL TITLE: Immunogenicity of SIV Transgene

PRINCIPAL INVESTIGATOR: Daniel C. St. Louis, Ph.D.

STUDY SITE(s): Southern Research Institute

STATUS: Ongoing

NUMBER OF ANIMALS USED: 3

SPECIES: Rhesus Macaque

The purpose of this study was to establish whether direct intramuscular injection into rhesus macaques of DNA encoding for the SIV envelope protein can result in class 1 and class 2 MHC restricted immune response specifically directed against Ag expressed transiently in muscle cells. Immunological parameters such as antibody responses and T cells proliferation responses were monitored. The injected animals were challenged with a low dose SIV-239.

SIGNIFICANT FINDINGS:

The Principal Investigators set out to test whether direct intramuscular DNA injection of an SIV based plasmid expression vector could lead to specific anti-SIV cellular and humoral immune responses in Rhesus macaque. Three Rhesus macaques were injected 4 times at 7 day intervals with 200ug of a purified plasmid expression vector encoding SIV-ENV239. Sera from animals bled at weekly intervals for a two month period developed no detectable SIV-ENV specific antibody responses. Since neither T cells proliferation assays nor cytotoxic T lymphocyte assays were developed at this time neither were performed.

These 3 monkeys were boosted with a fifth intramuscular injection of the DNA expression vector 2 weeks prior to challenge with 10 ID50 of SIV 251. Sera drawn from the animals prior to challenge again showed no detectable antibody response. However, T cell proliferation assays performed in the presence of IL-2 and antigen on the PBMC derived from each animal revealed that each animal did indeed react to the injection protocol. Animals 1710, 0711 and 1306 developed stimulation indices (SI) of 4.3, 12 and 21.3 respectively. Control animals routinely show SI of approximately 0.7. Upon challenge with SIV 251 monkey 0711 and 1306 developed anamnestic response to the SIV envelope protein (see attached figure). Monkey 1710 responded poorly to challenge and never developed high titer antibodies. Levels of p28 during the acute infection were barely detectable in animal 1306 while p28 levels 6 ng/ml in animals 1710 and 0711. Typically p28 levels drop after the acute phase of infection presumably due to anti-SIV antibody

responses.

Although none of the animals appeared to experience any toxic effects from the injection of the DNA, their sera were not monitored for anti-DNA activity. Animal 1710 died of SIV associated complications.

The intent of this experiment was to determine if direct intramuscular injection of a DNA expression vector could lead to a specific immune response and if such an approach could be tolerated in a non-human primate. In light of these results from this experiment the Principal Investigators intend to pursue this avenue of immunization.

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA10 (Addendum 1)

PROTOCOL TITLE: Direct Intramuscular Injection of high level expression vectors

PRINCIPAL INVESTIGATOR: Mark G. Lewis, Ph.D.

STUDY SITE(s): Southern Research Institute

STATUS: Ongoing

NUMBER OF ANIMALS USED: 3

SPECIES: Rhesus Macaque

DESCRIPTION/SUMMARY OF PROTOCOL: The purpose of this study was to establish whether direct intramuscular injection into rhesus macaques of DNA encoding for the SIV envelope protein can result in class 1 and class 2 MHC restricted immune response specifically directed against Ag expressed transiently in muscle cells. Immunological parameters such as antibody responses and T cells proliferation responses were monitored. The injected animals were challenged with a low dose SIV-239.

SIGNIFICANT FINDINGS:

The Principal Investigators tested whether direct intramuscular DNA injection of an SIV based plasmid expression vector could lead to specific anti-SIV cellular and humoral immune responses in Rhesus macaque. Three Rhesus macaques were injected 4 times at 7 day intervals with 200ug of a purified plasmid expression vector encoding SIV-ENV239. Sera from animals bled at weekly intervals for a two month period developed no detectable SIV-ENV specific antibody responses. Since neither T cells proliferation assays nor cytotoxic T lymphocyte assays were developed at this time, neither were performed.

These 3 monkeys were boosted with a fifth intramuscular injection of the DNA expression vector 2 weeks prior to challenge with 10 ID50 of SIV 251. Sera drawn from the animals prior to challenge again showed no detectable antibody response. However, T cell proliferation assays performed in the presence of IL-2 and antigen on the PBMC derived from each animal revealed that each animal did indeed react to the injection protocol. Animals 1710, 0711 and 1306 developed stimulation indices (SI) of 4.3, 12 and 21.3 respectively. Control animals routinely show SI of approximately 0.7. Upon challenge with SIV 251 monkey 0711 and 1306 developed anamnestic response to the SIV envelope protein (see attached figure). Monkey 1710 responded poorly to challenge and never developed high titer antibodies. Levels of p28 during the acute infection were barely detectable in animal 1306 while p28 levels 6 ng/ml in animals 1710 and 0711. Typically p28 levels drop after

the acute phase of infection presumably due to anti-SIV antibody responses.

Although none of the animals appeared to experience any toxic effects from the injection of the DNA, their sera were not monitored for anti-DNA activity. Animal 1710 died of SIV associated complications.

The intent of this experiment was to determine if direct intramuscular injection of a DNA expression vector could lead to a specific immune response and if such an approach could be tolerated in a non-human primate. In light of these results from this experiment the Principal Investigators intend to pursue this avenue of immunization.

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA11

PROTOCOL TITLE: Routine Immunization for antibody collection

PRINCIPAL INVESTIGATOR: Mark G. Lewis, Ph.D.

STUDY SITE(s): BioCon, Inc.

STATUS: Ongoing

NUMBER OF ANIMALS USED: 0

SPECIES: Mice, Rabbits, Rats, Guinea Pigs

Description/Summary of Protocol:

The objective of this protocol is the immunization of rabbits, rats, mice or guinea pigs with killed disrupted whole virus preparations or purified viral proteins in order to generate high titered immune sera for future research use. The sera will be collected for use in HIV and SIV research performed at the Jackson Foundation.

Significant Findings:

Study not initiated

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA12

PROTOCOL TITLE: Subcutaneous injection of primary macaque fibroblasts transduced with recombinant murine-based retrovirus vector expressing SIV-239

PRINCIPAL INVESTIGATOR: Daniel C. St. Louis, Ph.D.

STUDY SITE(s): Southern Research Institute

STATUS: Pending

NUMBER OF ANIMALS USED: 0 .

SPECIES: Rhesus Macaque

DESCRIPTION/SUMMARY OF PROTOCOL: This protocol was intended to study the possibility that autologous fibroblasts transduced with genes from SIV could induce a protective immune response in monkeys. This protocol was not initiated during Grant Years 1-5.

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA13

PROTOCOL TITLE: Immunization with conserved peptides from SIV: Effect of heterologous challenge on developed immunity

PRINCIPAL INVESTIGATOR: Mark G. Lewis, Ph.D.

STUDY SITE(s): Southern Research Institute

STATUS: Ongoing

NUMBER OF ANIMALS USED: 0

SPECIES: Rhesus Macaque

DESCRIPTION/SUMMARY OF PROTOCOL:

This study was proposed to test the character of the immunity generated following vaccination with conserved regions of the primate lentivirus envelope. To test this the Principal Investigators proposed to immunize two groups of rhesus macaques (4 monkey/group) with a mixture of 88, 500, 582 and 647 peptides from HIV-2 and SIV_{mac}. A third group would be immunized with ß-gal alone. The monkeys would be challenged with a monkey titrated pool of HIV-2. The SIVmac and ß-galactosidase alone groups would be used as before and would serve as the heterologous and control group, respectively.

SIGNIFICANT FINDINGS:

Study not initiated

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA14

PROTOCOL TITLE: Titration of SIV challenge stocks in Rhesus Macaques

PRINCIPAL INVESTIGATOR: Mark G. Lewis, Ph.D.

STUDY SITE(S): Southern Research Institute

STATUS: Ongoing

NUMBER OF ANIMALS USED: 0

SPECIES: Rhesus Macaque

DESCRIPTION/SUMMARY OF PROTOCOL:

The Principal Investigators had stocks of rhesus passaged $SIV_{mne/E11s}$ virus and virus infected cells which were proposed for use in future MMCARR vaccine and pathogenesis studies. The stocks of cell associated and cell free virus were generated using cells isolated from an $SIV_{mne/E11s}$ chronically infected macaque. Stocks of cell free virus were produced in normal macaque PBL. These stocks will be titrated *in vivo* in rhesus macaques.

Objectives:

A. To determine the monkey infectious dose 50% endpoint for two virus challenge stocks in rhesus macaques.

B. To monitor disease pathogenesis for comparison and control values for use with future vaccine and pathogenesis studies.

C. To observe and characterize inapparent infections in monkeys beyond the MID_{50} endpoint.

SIGNIFICANT FINDINGS: Study not initiated

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA15

PROTOCOL TITLE: Development of an HIV-1 model in primates

PRINCIPAL INVESTIGATOR: Suzanne Gartner, Ph.D.

STUDY SITE(s): Advanced BioScience Laboratories, Inc.

STATUS: Ongoing

NUMBER OF ANIMALS USED: 0

SPECIES: Pigtailed Macaque .

DESCRIPTION/SUMMARY OF PROTOCOL:

This study was proposed to attempt to develop a primate model for HIV-1 infections in humans. Monkeys proposed for this study included pigtailed and rhesus macaques, and African green monkeys. HIV-1 virus isolates proposed for use in this study would be prescreened *in vitro* for their growth characteristics in the proposed monkey species. Depending upon the *in vitro* growth characteristics the isolates would be further passaged *in vitro* in the monkey cells prior to their introduction into the host species. The *in vivo* model development would involve inoculation of the monkey with infected autologous cells and/or free virus. If animals became actively infected they would be followed for disease development and collected virus would be passaged to naive animals in an attempt to increase viral persistence and pathogenicity for the primate model.

SIGNIFICANT FINDINGS: Pigtailed macaques were inoculated with a selected HIV-1 isolate and followed for 6 months. The indications were that the virus was persisting in at least one monkey. The monkeys were seroconverting to an antibody positive status and might yield infectious virus soon.

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA15 (Addendum 1)

PROTOCOL TITLE: Development of an HIV-1 model in primates

PRINCIPAL INVESTIGATOR: Suzanne Gartner, Ph.D., HJF

STUDY SITE(s): Advanced BioScience Laboratories, Inc.

STATUS: Ongoing

NUMBER OF ANIMALS USED: 1

SPECIES: Cynomolgus Macaque .

DESCRIPTION/SUMMARY OF PROTOCOL:

This addendum was proposed as an extension of macaque species used in the initial proposal in an attempt to develop a primate model for HIV-1 infections in humans. The Principal Investigators proposed the addition of 8 Cynomolgus macaques to the proposal due to the finding that HIV-1 virus isolates prescreened *in vitro* for their growth characteristics were found to infect cynomolgus cells. The *in vivo* model development would involve inoculation of the monkey with infected autologous cells and/or free virus. If animals became actively infected they would be followed for disease development and collected virus would be passaged to naive animals in an attempt to increase viral persistence and pathogenicity for the primate model.

SIGNIFICANT FINDINGS:

One cynomolgus was inoculated with HIV-1 and has become PCR positive but had yielded no virus antibody yet.

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA16

PROTOCOL TITLE: Titration of SIVmac251 challenge stocks in Rhesus Macaques

PRINCIPAL INVESTIGATOR: Mark G. Lewis, Ph.D.

STUDY SITE(s): Southern Research Institute

STATUS: Ongoing

NUMBER OF ANIMALS USED: 9

SPECIES: Rhesus Macaque

DESCRIPTION/SUMMARY OF PROTOCOL:

Nine rhesus macaques that were originally purchased and housed at the Primate Research Laboratories (PRL) in New Mexico were part of a previous titration study with SIV_{mac251}, a virus isolate which was proposed for use in future MMCARR vaccine and pathogenesis studies. The monkeys were followed for the purpose of determining disease outcome. The Army contract at PRL was scheduled to end as of the end of June 1992. The Principal Investigators should continue to hold these animals at our contracted holding facility at SRI-FRC in Frederick, MD. Following a short adjustment period at SRI-FRC, these animals were euthanized for the collection of infected tissues.

SIGNIFICANT FINDINGS:

The animals were euthanized for tissue collection and tissue was used to study the disease course of SIV_{251} in rhesus macaques.

Publications:

Rosenberg, YR, Zack, PM, White, BD, Papermaster, SF, Rippy, MK, Eddy, GA, Burke, DS and Lewis, MG. Collapse in the CD4+ population in lymph nodes from SIV-infected macaques is predictive of AIDS progression. AIDS Human Retroviruses (in press).

ANIMAL MODELS MAP
PROTOCOL SUMMARY SHEET

RVA17

PROTOCOL TITLE: Superinfection of Rhesus Macaques with SIV

PRINCIPAL INVESTIGATOR: Mark G. Lewis, Ph.D.

STUDY SITE(s): Southern Research Institute

STATUS: Ongoing

NUMBER OF ANIMALS USED: 10

SPECIES: Rhesus Macaque

DESCRIPTION/SUMMARY OF PROTOCOL: The purpose of this protocol was to test for the possibility of dual infection *in vivo* by a second pathogenic strain of SIV. The Principal Investigators proposed to use a group of rhesus macaques currently infected with $SIV_{mne/E11s}$ and to test the ability of a more virulent and pathogenic molecular clone SIV_{mac239} to superinfect the seropositive macaques. The Principal Investigators planned to observe for more acute disease pathogenesis due to exposure to the more pathogenic and more rapidly fatal SIV isolate.

SIGNIFICANT FINDINGS:

The animals were challenged with SIV_{239} as proposed. All animal were virus isolation negative, but seropositive at the time of the challenge. All of the animals became virus isolation positive following challenge and most developed an anamnestic response. Preliminary analysis showed that some of the animals are dually infected.

SUMMARY SHEET

ARMY-WIDE HIV/AIDS SURVEY

PRINCIPAL INVESTIGATOR: Lydia R. Temoshok, Ph.D., Henry M. Jackson Foundation

MAP: Behavioral Medicine

SURVEY SITES: 30 Army Bases, CONUS and OCONUS

STATUS: Completed

NUMBER OF PARTICIPANTS: 18,072 Active Duty Soldiers

DESCRIPTION/SUMMARY: The survey sample size was calculated to provide reliable estimates of attitudes, knowledge, and behaviors of U.S. Army personnel world-wide. A total of 18,072 usable surveys were obtained. This represents 95% of those soldiers present for duty, and 74% of those originally assigned to sample units at the time of the study.

SELECTED FINDINGS: Based on findings from the Army's epidemiological seroconversion risk factor study, eight behavioral risk factors were identified as increasing a soldier's likelihood of exposure to HIV. Forty-two percent of the study population had at least one of these behavioral risk factors. The behavioral risk factors for HIV exposure potential included:

a. One or more "one-night stands"
b. Five or more sexual partners
c. One or more male sexual partners known/suspected or having sex with other men
d. One or more "anonymous" sexual partners
e. One or more prostitutes as sexual partners
f. One or more intravenous drug users as sexual partners in the past two years
g. One or more sexual partners who had HIV/AIDS
h. One or more occasions of sharing needles in the past two years

Combining behavioral risk factors and biological markers, it was found that approximately 50% of the study population was determined to be at "some" level of risk for exposure for HIV, with almost 16% of the study population at "high risk" for HIV exposure by virtue of having four or more risk factors or markers.

SUMMARY SHEET

ARMY PEDIATRIC HIV CAREGIVER TRAINING PROJECT

SUMMARY: Staff members from the Office of the United States Army Surgeon General secured support for a proposal to create and test a model for comprehensive, family-centered, community-based services for HIV infected children and their families. A major thrust of this proposal was to help military families meet child care needs by implementing a training system that would recruit and train paraprofessionals to care for these children in the providers' homes. In November of 1989, the Department of Defense (DoD) received a one year grant to start work on this project. The grant funds were made available by a Department of Health and Human Services (HHS) interagency agreement between the National Institute of Child Health and Human Development (NICHD) and DoD. The Maternal and Child Health Bureau (MCHB), by interagency agreement with NICHD, also provided funds to support this grant. Project funds are being administered by the Henry M. Jackson Foundation for the Advancement of Military Medicine (Jackson Foundation), in coordination with the Uniformed Services University of the Health Sciences and the U.S. Army Medical Research Acquisition Activity.

SIGNIFICANT FINDINGS: Early in 1990, the Jackson Foundation recruited and hired a Project Coordinator and an Early Childhood Specialist. This staff, in collaboration with the Army Surgeon General Consultant to the Exceptional Family Member Program (EFMP) and the Army Child Development Services (CDS) Office, and with the assistance of a local community college, conducted a thorough HIV child care provider training needs assessment. The assessment used a competency-based approach to identify the knowledge, skills, attitudes, and traits of a child care provider for children with special health care needs. A decision was made to develop a new curriculum to train family members and child care providers, particularly Army family child care providers who were already trained in the Army CDS system. The Project Coordinator and Early Childhood Specialist enlisted the technical services of a number of different experts and organizations to create the multidisciplinary approach required to develop a comprehensive, integrated curriculum. By November, 1990, writers for all the curriculum modules had been identified, and approximately one-third of the work had been completed.

On January 22, 1991, NICHD informed the DoD that funds were no longer available to continue support for this project. In April of 1991, the Jackson Foundation, with the assistance of an additional grant from the Army, arranged for the completion of all the curriculum modules by October 1, 1991.

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