ADVISORY COMMITTEE FOR THE AIDS CENTER, 10/85-1/86

Advisory Committee for the AIDS Center
Meeting of Tuesday, October 29, 1985
3:00 - 5:00 pm, UCMC S-222
AGENDA

3:00	Review of minutes from last time and today's agenda	Dr Hulley
3:10	Discussion of plans for responding to the State of California RFP* • Scientific plan • Organization chart • Operations flow chart • Other	Dr Ziegler
3:55	Impediments to vaccine research	Dr Conant
4:10	Strategies for changing the gay education program message	Dr Conant
4:25	Tissue bank followup: responses to NCI request	Dr Greenspan
4:30	Brainstorming: future meeting agenda **(Everyone present, beginning with committee members, will have the opportunity to offer advice on future directions)**	Dr Gold Dr Newman Dr Ockner Dr Root Dr Hulley et al
5:00	Date of next meeting and adjournment	

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*A draft of the RFP response will be delivered to the committee for review prior to the meeting

Advisory Committee for the AIDS Center Meeting
September 26, l985
3:00-5:00 pm
UCSF, S-222

Members in attendance:

Dr. Stephen B. Hulley (Chair)
Dr. Warren Gold
Dr. Thomas Newman
Dr. Robert Ockner
Dr. Richard Root

Others:

Dr. Marcus Conant
Mr. Frank Cook
Dr. John Greenspan
Dr. Harry Hollander
Ms. Christine Ireland
Mr. Dick Pabich
Dr. Merle Sande
Dr. Paul Volberding
Dr. John Ziegler

l. Dr. Hulley reviewed the charge to the committee, emphasizing the importance of the task and the unprecedented public health threat that AIDS poses. The committee agreed on the following goals: to improve the scientific quality of AIDS related research projects on campus; to increase the quantity of AIDS related research; and to favorably influence research directions, the nature of the specific research questions and the designs for answering these questions.

2. Dr. Ziegler presented the history and overview of the AIDS Clinical Research Center. The center evolved from a meeting of concerned investigators in l98l. NCI funding for the center began in Spring l983. Dr. Ziegler replaced Dr. Conant as PI and Director of the Center in June l985 (at the same time, stepping down from his position as Chairman of the AIDS Advisory Committee).

3. The investigators in charge of each of the six components of the AIDS center discussed current problems and future plans.

a. Computer Center - Dr. Volberding: The computer center was born in response to the demand from investigators for clinical specimens and information. Dr. David Feigal was recruited 6 months ago to assist the computer operations; since then the registry form was completed and data from 300 patients from the 3 hospitals have been entered in the system. A problem is how complete and systematic these data are.

b. Tissue Bank - Dr. Greenspan: The specimen bank includes sera, mononuclear cells, Kaposi's sarcoma skin and lymph nodes, and autopsy tissue from AIDS and ARC patients, as well as sera from matched healthy controls. The bank includes over 2000 serum specimens and 500 tissue specimens. A Tissue Committee reviews and approves all requests for sera or tissues. The completeness and systematic collection of specimens is a problem of the bank. Dr. Greenspan requested guidance from the committee regarding extending the use of the bank to investigators outside the UCSF community.

c. Adult Immunodeficiencies Clinic - Dr. Hollander: The clinic has been in operation just over one year; it currently sees l00-l20 patients per month, and is following about 80 patients with diagnosed AIDS and l60-l70 with ARC. The clinic has contributed about 200 serum specimens to the specimen bank, and is the sole contributor of

cerebrospinal fluid. The most significant research has been the isolation of the AIDS associated retrovirus from CSF (in collaboration with Dr. Levy). The clinic has been unable to realize its goal of organizing clinical trials due to the limitations of staffing.

d. Education Center and Longitudinal Study - Dr. Conant: The education center sponsors biweekly KS clinics (and has since l98l); this effort is now funded for the first time, although the amount awarded is not sufficient for the task at hand. A consensus conference in l982 yielded guidelines on safe sexual practices. The major problem facing the education center are too few resources (money and staff). Major issues that could be dealt with given adequate resources, include AIDS in the workplace and AIDS in the schools. Such educational efforts could even produce revenue.

The longitudinal study consists of 50 KS subjects and 50 contacts. The funding this year includes money to collect specimens from other defined control groups (20 in each group). The study needs $70,000 to replace the NCI grant that ends this year.

e. VAMC AIDS Research Center - Dr. Ziegler: There are 60 patients with AIDS and l80 with ARC at the VAMC. The major challenge facing the center is to establish intervention and prevention clinical trials, either alone, or collaboratively.

4. The committee members reacted to the information given them by the investigators and outlined issues for review in the future.

Action: Drs. Greenspan and Conant will write to the NCI for information on how many responses they (NCI) received from the recent notice about new uses for AIDS specimens published in Science. The committee felt that if the response was great, and if NCI felt there was a need, perhaps UCSF could help meet the demand for specimens.

The committe discussed the way in which data (both clinical information and specimens) are collected. Currently all consecutive new AIDS patients are entered; this approach presumes that acquisition of routine clinical information will lead to new insights about the disease. Dr. Rosenberg suggested that more information on fewer patients needs to be collected. Dr. Newman suggested detailed information could be collected on a subset of patients, and the specimens from this subset could be saved for the few investigators that require such detail.

Dr. Root raised the issue of resources going toward patient care, at the possible expense of research. The academic (research) component is the key to UCSF' s involvement in AIDS. Dr. Sande reported that the current limitation is 20 inpatient beds. One of the controls on outpatient growth may be to refer AIDS patients back to their own physicians; the private MDs and hospitals are increasingly willing and able to care for AIDS patients.

Dr. Hulley noted the need to integrate epidemiology into the clinical center studies. Many important questions that will be important for designing strategies to contain this epidemic remain unanswered: the risk factors for sero-conversion, and for developing AIDS; the causes of spread beyond original populations. The AIDS center needs a more ambitious and coordinated plan to attract the major resources required to approach a solution to AIDS.

Dr. Gold suggested that some of the focus in AIDS research be shifted to Moffitt, especially in the area of clinical trials. An example of logistical problems facing clinical medicine is how to handle AIDs patients in the pulmonary lab.

Dr. Ockner noted the need to regulate access to the precious specimens in the data bank. All studies need to be reviewed carefully for scientific merit. The center should develop mechanisms to meet the increasing demand for specimens from healthy

control groups .

Dr. Root asked about the unique roles of the three hospitals (VA, Moffitt, SFGH) ; to what extent should they be separate? What subgroups should be defined for future study? What educational programs should be of high priority, and how can we best design and promote these?

Dr. Newman felt that investigators should identify more specifically the important research questions to be addressed, and plan their designs accordingly.

The committee agreed with Dr. Conant's suggestion that the center should function in a way that encourages the quantum leap in prevention and treatment that are needed.

5. Current research directions and funding opportunities - Drs. Sande and Ziegler

Dr. Sande reported that the AIDS Task Force has $2.3 million dollars to fund clinical trials. The Task Force will issue an RFP in the next month for an organization that has the expertise to conduct clinical trials; the specific topic of the trials to be conducted will be left open-ended. Several organizations will each receive approximately $800,000 and will be evaluated after l l/2 years. The deadline for responding to the RFP is December l and the project will begin January l, l986.

Action: Dr. Ziegler will organize and coordinate a response to the RFP. A draft will be ready for this committee to review at its October meeting. At the same time, a program project grant to the NCI will be prepared.

6. The next meeting will be held 3:00-5:00 pm, Tuesday, October 29.

The meeting adjourned at 5:00 pm.

Respectfully submitted,

Chris Ireland

AIDS CLINICAL RESEARCH CENTER

Overview September 1985

GOALS

1. Create a network of clinical resources (inpatient and outpatient) in the UCSF hospitals to collect patient speciments and data.

2. Provide a central Tissue Bank for collaborative research in AIDS, linking specimens and patient information by computer.

3. Provide an organizational framework to facilitate: education programs, collaborative studies, clinical trials, and scientific interchange among investigators.

ORGANIZATION - COST

1. Computer Center - SFGH Drs. Volberding and Feigal	$ 66,214
2. Tissue Bank - Moffitt Dr. Greenspan	121,621
3. Adult Immunodeficiency Clinic - Moffitt Dr. Hollander	40,000
4. Education Center - Moffitt Dr. Conant	20,000
5. Longitudinal Study - Moffitt Dr. Conant	55,174
6. VA AIDS Research Center - VAMC Dr. Ziegler	13,458
	$316,467

OPERATION

Tissue Committee - Dr. Greenspan (monthly)

Executive Committee - Dr. Ziegler (monthly)

Operations - Dr. Ziegler (weekly)

Clinical Trials Working Group - (biweekly)

OVERVIEW OF THE ADULT IMMUNODEFICIENCIES CLINIC

The A.I.C. has been operational since August 1984. Drawing upon a combination of UCSF, community and self referrals, the clinic now sees an average of 100-120 patients per month. Approximately 80 patients with diagnosed AIDS are being followed as well as twice that number with a variety of AIDS-related conditions. One of the major charges of the clinic was to collect longitudinal information on the spectrum of AIDS-related conditions. Since the summer of 1984 about 200 serum specimens were collected for the AIDS specimen bank, with approximately 70 patients to date having had serial serum banked. The clinic has also been the sole contributor of cerebrospinal fluid to the specimen bank. Since early 1985 we have been using the standardized AIDS registry form for all of our patients with AIDS or ARC and are now in the process of beginning to use follow-up clinical data forms.

Clinical research using our cohort of patients has been started with the help of several other collaborative groups. Most significantly we have described isolation of the AIDS-associated retrovirus from cerebrospinal fluid, working with Dr. Jay Levy's lab. We hope to do more detailed studies in this vein in the future. Unfortunately, the goal of organizing clinical trials has not been met because of the limitations of personnel. We hope that the clinic staff will grow enough to allow participation in these studies in the future.

Finally, the educational efforts of the clinic staff are notable. Each of the three professional members of the staff has been involved in both community based and campus-wide efforts. We have spoken for audiences as diverse as the lay public, medical and dental students, nurse practitioners and practicing social workers and physicians.

AIDS SERUM AND TISSUE BANK UPDATE REPORT 09/20/85

YEAR	Serum	Tissue	Cells	Saliva	CSF
DEPOSITS					
1982	0	25	0	0	0
1983	221	72	0	0	0
1984	1194	16	0	0	0
1985					
January	113	17	0	0	0
February	134	12	0	0	0
March	143	19	0	0	0
April	106	13	12*	3*	0
May	147	26	8	0	0
June	155	16	13	0	3*
July	132	12	8	0	2
August	212	15	15	0	2
September(to 9/20)	126	18	12	0	3
Total	1268	148	68	3	10
Total	2683	261	68	3	10
WITHDRAWALS					
1982	0	0	0	0	0
1983	141	70	0	0	0
1984	2337	184	0	0	0
1985					
January	63	14	0	0	0
February	351	4	0	0	0
March	149	2	0	0	0
April	371	8	0	3	0
May	287	10	5	0	0
June	361	23	8	0	0
July	68	1	0	0	0
August	566	0	0	0	0
September(to 9/20)	70	0	0	0	0
Total	2286	62	13	3	0
Total	4764	316	13	3	0

* New categories of specimens

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AIDS CLINICAL RESEARCH CENTER

SAN FRANCISCO, CALIFORNIA 94143

John L. Ziegler, M.D., Director
VAMC 141

MEMO

TO: UCSF AIDS investigators

FROM: Dr. John L. Ziegler
Director, AIDS Clinical Research Center

DATE: August 5, 1985

RE: Availability of Specimens

The AIDS Clinical Research Center is funded to facilitate the collection of clinical specimens and accompanying clinical data and their distribution to AIDS investigators. The specimens include sera, mononuclear cells, Kaposi's sarcoma skin and lymph nodes, and autopsy tissue from AIDS and ARC patients. Sera from a variety of controls are also available. The current inventory includes 2000 sera specimens and 500 tissue specimens. The AIDS Specimen Bank is directed by Dr. John Greenspan at HSW 604, 666-2220.

A network of clinics supplies the Specimen Bank regularly. These clinics include: San Francisco General Hospital, under the direction of Dr. Paul Volberding; UCSF Adult Immunodeficiencies Clinic, under the direction of Dr. Harry Hollander; AIDS Longitudinal Study, under the direction of Dr. Marcus Conant; and the Veteran's Administration Hematology/Oncology Clinic. Clinical data are entered into a computer database, with all specimens coded to ensure confidentiality. The full integration of data and specimens will be accomplished by the end of September.

A Tissue Committee reviews and approves all requests for sera or tissues. Investigators are asked to send a brief description of their project and serum/tissue requirements to Dr. Greenspan. Requests for fresh material will be directed to the appropriate clinics. Special requests (lymphocytes, CSF, serial samples, etc.) can be accomodated on an ad hoc basis.

It is our hope to facilitate the collaboration of AIDS researchers at UCSF. Enclosed for your information is a compendium of AIDS research projects at this campus.

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AIDS CLINICAL RESEARCH CENTER SAN FRANCISCO, CALIFORNIA 94143

John L. Ziegler, M.D., Director
VAMC 141

AIDS RESEARCH AT UCSF
1985

Principal Investigator
Title
Address, Phone

Jay H. Beckstead
Characteristics and Pathogenesis of the Persistent Diffuse Lymphadenopathy Syndrome (PDLS) and Kaposi's Sarcoma (KS)
HSW 501, UCSF, 666-5443

Edward G. Biglieri
Significance of Reduced Adrenocortical Function in the Acquired Immune Deficiency Syndrome
SFGH B100, R321, 285-2900

Richard E. Chaisson
A Prospective, Controlled Study of Cytomegalovirus Seroconversion in Health Care Workers with AIDS Exposure
5H22, SFGH, 821-8317

Thomas J. Coates
A Prospective Psychosocial Study in Men at Risk for AIDS
The Impact of AIDS on Sexual Behavior of Gay Men
Perceptions of and Reactions to Having the ELISA Test for HTLV-III Antibodies
A 405, UCSF, 666-4362

Marcus A. Conant
A Study of Topical Acyclovir in Treatment of "Hairy" Leukoplakia
350 Parnassus Avenue #808, San Francisco 94117, 661-2613

John E. Conte, Jr.
Pentamidine Isethionate: First Dose and Multiple Dose Pharmacokinetics
Moffitt 181, UCSF, 666-5793

Laurence Corash
Pathogenesis of Platelet Antibodies in Homosexual Men: Possible Mechanism for Autoimmunity in AIDS-Related Conditions
Moffitt 523, UCSF, 666-5750

Morton J. Cowan
Adenosine Deaminase Activity and Immune Function in Persons at High Risk of Developing AIDS
Moffitt 679, UCSF, 666-1736

Robert J. Debs
Liposome Mediated Targeting of Drugs and Immunomodulators for the Treatment of AIDS Related Opportunistic Infections
Moffitt 1282, UCSF, 666-4828

Lawrence Drew
The Role of CMV in the Etiology and/or Complications of AIDS and Prevention of CMV Infection by Vaccination
Mount Zion Hospital, 1600 Divisadero, SF 94115, 567-6600

Nejat A. Duzgunes
Mycobacterium Avium Intracellulare Infection of Macrophages
Moffitt 1282, UCSF, 666-3957

Caroll L. Estes
The AIDS Epidemic: A Public Policy Analysis
Nursing 631Y, UCSF, 666-3236

Julie L. Gerberding
A Cross-Sectional Prospective Cohort Study of Health Care Workers with Occupational Health Exposure
5H22, SFGH, 821-8317

John S. Greenspan
Oral Viral Leukoplakia: A New Lesion in Association with the Acquired Immune Deficiency Syndrome
HSW 604, UCSF, 666-2220

William Keith Hadley
Alveolar Macrophages from Patients with Acquired Immune Deficiency Syndrome: Phagocytic Function and Response to Mycobacteria Infection
Bldg 10, Rm 119, SFGH, 821-8578

Harry Hollander
The Relationship Between AIDS-Associated Retrovirus (ARV) Infection and Unexplained Neuropathology in AIDS
A 555, UCSF, 666-3226

Philip Hopewell
Dapsone vs. TMO/SMX for Pneumocystis
5K1, SFGH, 821-8313

Philip R. Lee
A Prospective Study of the Direct Costs of Hospital and Community Treatment of AIDS Patients
1326 Third Avenue, UCSF, 666-4921

Jay A. Levy
Biologic and Immunologic Features of Infection by the AIDS Associated Retroviruses
S 1280, UCSF, 666-4071

Dan Littman
The Molecular Basis of Virus-Receptor Interaction in AIDS
S 412, UCSF, 666-1211

Bernard Lo
Teaching Patients with AIDS about Decisions Regarding Life-Sustaining Treatments
A 405, UCSF, 666-4362

Francina I. Lozada-Nur
Delayed Hypersensitivity Skin Test in AIDS and AIDS Contacts: Its Clinical Significance
S 647, UCSF, 666-2686

John Mills
Pathogenesis of Herpes Simplex Virus Infection in a Mouse Model of AIDS
5H7, SFGH, 821-8666

William J.W. Morrow
Derivation of an Animal Model for AIDS
HSE 1235, UCSF, 666-4071

Andrew R. Moss
A Followup Study of Men at High Risk of AIDS
HSW 1699, UCSF, 666-1374

John F. Murray
Pulmonary Structure-Function Relationships in Patients with Pneumocystis Pneumonia and AIDS
NH Rm. 5K1, SFGH, 666-2916

Michael S. McGrath
AIDS Virus Interactions with Normal and Neoplastic Lymphoctes
Ward 86, SFGH, 821-8830

James H. McKerrow
Investigation of the Role of a Purified Secreted Enzyme of Entamoeba Histolytica in the Pathogenesis and Diagnosis of Amebiasis
HSW 501, UCSF, 666-2940

Nicholas L. Petrakis
Followup Study of AIDS and AIDS Risk Factors in Parenteral Substance Abusers
HSW 1699, UCSF, 666-1374

William E. Seaman
Use of Monoclonal Antibodies Against T-Helper Cells to Develop Therapies for AIDS
111R, VAMC, 750-2104

Richard A. Sollitto
Ga-67 Citrate Labelling of Lymph Nodes in Acquired Immune Deficiency Syndrome
C 309, UCSF, 666-2666

Daniel P. Stites and Conrad H. Casavant
Protective Immunity to AIDS Virus
M 523, UCSF, 666-1186

Lydia Temoshok
A Longitudinal Psychosocial Study of AIDS Patients
LPPI 306, UCSF, 666-1445

Paul A. Volberding
Studies of Acquired Immune Deficiency Syndrome
Phase II Trial of Alpha 2 Interferon on Kaposi's Sarcoma
Research with the Lymphomas of AIDS
Ward 86, SFGH, 821-8830

Constance B. Wofsy
Point Prevalence Study of Antibody to AIDS Retrovirus (ARV) in Sexually Active Heterosexual Women Not in Known Risk Groups: A Study of Risk of Acquisition of ARV as a Result of Sexual Activity in San Francisco
Pilot Study of the Administration of Suramin to Patients with Early Kaposi's Sarcoma or Lymphadenopathy Syndrome
Ward 86, SFGH, 821-8830

John L. Ziegler
UCSF AIDS Clinical Research Center
Rm 141, VAMC, 750-2048

Jane S. Zones
Personal and Social Consequences of AIDS Antibody Testing and Notification
Nursing 631Y, UCSF, 666-5204

Draft 11/7/85

Advisory Committee for the AIDS Center Meeting
October 29, l985
3:00-5:00 pm
UCSF, Dean's Conference Room

Members in attendance:

Dr. Stephen B. Hulley, Chairman
Dr. Warren Gold
Dr. Thomas Newman
Dr. Robert Ockner
Dr. Richard Root

Others:

Dr. Marcus Conant
Dr. John Greenspan
Ms. Chris Ireland
Mr. Dick Pabich
Dr. Rudi Schmid
Dr. Paul Volberding
Dr. John Ziegler

l. Dr. Schmid expressed his views on the importance of the committee, and his appreciation to its members for undertaking this task. In response to Dr. Hulley's question about the role of the Commitee, he recommended that the Aids Advisory Committee advise on all AIDS research projects at UCSF, not just the AIDS Center. However, investigators outside the Center would seek the advice of the committee on a voluntary basis.

2. Dr. Hulley reviewed the minutes from the meeting of September 26. A motion to accept was unanimously approved.

3. Dr. Ziegler discussed the AIDS Center's response to the State RFP for conducting clinical trials. A draft of the application was distributed in advance to committee members.

a. The scientific plan is organized into three main components, providing the basis for specific trials in three areas: 1) risk of AIDS--viral acquisition/exposure, 2) progression of AIDS to clinical manifestations, 3) treatment of the clinical manifestations (KS, PCP, etc).

b. Dr. Ziegler presented the proposed organization and administration of the Center. The grant would support a core set of activities including the Director's office, a greatly expanded data center, and resources for laboratories and for clinical research at the three hospitals. The core in turn would provide money and other resources for specific clinical trials.

One of the organizational challenges is to bring together the loose federation of AIDS activities at UCMC. Dr. Hulley encouraged the Director of the AIDS Center (Dr. Ziegler) to spearhead the needed administrative direction. Dr. Volberding noted that AIDS activities at SFGH are closely aligned with the Department of Medicine, and that having such a relationship seemed to encourage a sense of unity among the various investigators. Dr. Greenspan suggested that this might be achieved at UCMC via joint appointments (without salary) in the Department of Medicine.

Dr. Ziegler asked the committee to advise him on the priorities of various proposed

clinical trials. The committee responded by recommending that all meritorious projects be included in the budget proposal. Dr. Hulley emphasized the importance of specifying the review mechanism for proposals, and for the subsequent progress reports. Dr. Ockner suggested that an outside peer review group be established (analagous to the NIH study sections) and that this committee give final approval (as NIH Council does). Dr. Root proposed that the AIDS working groups provide the initial evaluation and that our committee review that process and provide final approval (and, in the case of limited funds, set the priority) of projects. Dr. Hulley agreed, noting that adding review layers would delay the projects unnecessarily and that our committee could function effectively as the review mechanism.

4. Dr. Conant discussed strategies for altering the public education message on AIDS. There is evidence that telling people to have "safe" sex doesn't work. The appropriate educational message is: that if you contract the AIDS virus you are at high risk of developing AIDS; if you develop AIDS you will die; if you don't want AIDS you should abstain from sex; if you do have sex it should be limited to those with the same immunological state. The committee suggested that the best strategy for disseminating the message is for the investigators with seroconversion data to publish the scientific facts and their interpretation and policy implications in a well respected journal (e.g. a NEJM Special Report).

5. Dr. Greenspan has arranged a meeting with Dr. Gottlieb of UCLA to discuss the role and value of specimen banks in AIDS research. He has requested information from those who have withdrawn specimens from the bank regarding abstracts, articles, and grant proposals that have evolved from their investigations.

6. The committee members offered suggestions for future directions.

- Dr. Newman requested that the committee continue to fine tune the details of the organization and administration of the AIDS center even after the RFP is submitted.

- Dr. Ockner suggested that ad hoc reviewers of clinical trials proposals be added as appropriate if this committee is to provide the review, but Dr. Gold felt that adding outside reviewers would tend to delay projects. Drs. Hulley and Ziegler will work together on designing the review mechanism for proposals.

- Dr. Hulley suggested that the AIDS center consider behavioral trials to evaluate population interventions to encourage sexual practices that will prevent seroconversion.

- Dr. Hulley proposed the following priorities for clinical trials:

  1) those that test strategies for limiting the spread of the disease (i.e., preventing sero-conversion),

  2) those that test interventions for preventing development of ARC and AIDS in those who are sero-positive,

  3) those that test approaches to treating ARC and AIDS.

- Dr. Hulley suggested that the committee address the issue of space at one of its next meetings. Preliminary investigations have suggested that space limitations may be a more important barrier to conducting AIDS research on this campus than the lack of money, ideas or expertise.

7. Dr. Hulley proposed that at each future meeting, a major portion of the agenda be devoted to one area of science, (eg. epidemiology, virology, immunology), and that key people in each of these areas be invited to address the committee. The committee agreed to invite Dr. Jay Levy and others to its **next meeting to focus of the issues of vaccine development and antiviral treatment.**

The next meeting will be Tuesday, November 26, 3:00-5:00, in a room to be announced.

Respectfully submitted,

Chris Ireland

DRAFT 12/4/85

ADVISORY COMMITTEE FOR THE AIDS CENTER MEETING
November 26, 1985
3:00-5:00 PM
UCSF, 989-M

In attendance:

Dr. Stephen B. Hulley, Chairman
Dr. Thomas Newman
Dr. Robert Ockner
Dr. Diane Wara
Dr. Marcus Conant
Dr. John Greenspan
Ms. Chris Ireland
Dr. Jay Levy
Dr. Dan Stites
Dr. Paul Volberding
Dr. John Ziegler

1. Dr. Hulley reviewed the minutes from the October 29th meeting. A motion to accept was unanimously approved.

2. Old Business: **Dr. Conant** reported that the SF Medical Society's Ethics Committee is developing **guidelines for education efforts to stop the spread of AIDS.** If the Medical Society adopts the committee's recommendations (expected to be along the "no sex" line) the message will reach practicing MDs. Dr. Conant will meet with Dr. Phil Lee to discuss the Health Commission's role in AIDS educational efforts.

3. **Dr. Ziegler reported that the AIDS Center proposal was submitted** on November 25, 1985. A budget of $7.282 million for three years was requested, with approximately 50% allocated for core activities and the rest for about 20 specific projects. Three proposals were submitted (from UCSF, UCLA and USC/Irvine) and will be reviewed December 9. Dr. Ziegler will meet with the loose federation of UCSF researchers in pneumocystis pneumonia (PCP) to coordinate efforts in this area.
Dr. Ziegler passed out a UCLA newsletter entitled "AIDS Medical Update" and said he would distribute it monthly to a large list of interested investigators at UCSF.

4. **Dr. Conant discussed the impediments to AIDS vaccine development,** citing the twin disincentives of low profits and risk of lawsuits to the manufacturers of vaccine (attachment #1). Dr. Levy noted that UC has the expertise to develop a vaccine, but that it would require a major institutional commitment.

5. **Dr. Levy discussed the biological aspects of vaccine development.** He noted that unique research in this area is being conducted at UCSF and Chiron Corporation. Dr. Levy presented his laboratory's major accomplishments in AIDS research and discussed future plans (attachment #2). The most critical constraint facing Dr. Levy is lack of space. He estimated that he would require 4000 sq. ft. of laboratory space to conduct the necessary research for developing an AIDS vaccine. He currently has 300 sq. ft. for tissue culture and 500 sq. ft. for biochemistry.
Dr. Newman emphasized that getting the **optimal space** required as soon as possible should be of the **highest priority** to this committee.
Dr. Wara suggested that a short-term solution might be to obtain 2000 sq. ft.

immediately (perhaps at SFGH or CED) and a long term solution would be to develop some land and build an institute of virology and immunology.

Dr. Ziegler suggested that a successful strategy might be to first identify appropriate existing space and then offer something in return for the space.

Dr. Hulley will meet with Drs. Root and Schmid regarding options for space for vaccine development.

6. **Dr. Stites reported on his work on development of subunit vaccine** for the AIDS virus (attachment #3). Dr. Stites and his colleagues are studying cellular immune response. His problems differ from Dr. Levy's in that he has adequate space to conduct research but no ongoing monetary support for his studies. His immediate needs are: to provide additional biohazard space to protect personnel from proliferating virus (est. $50,000 for renovation) and ongoing support for fellows and technicians, supplies and equipment (approx. $l50,000 per year). Possible sources for the necessary funds include: the AIDS Center grant (just submitted), new RO-l grant applications, and Dr. Volberding's NCI program project grant application.

7. **Dr. Volberding** discussed the **program project grant application** he and Dr. Ziegler are preparing for submission to the **NCI**. Current NCI support for AIDS ends May l986 and is not renewable. NCI invited a response from Dr. Volberding in the form of a program project grant. The grant will be submitted to the NCI's division of cancer treatment, and will request funds for core support for data management, and facilities for virology and immunology (approx. $3 million/year for 5 years). NCI promised an expedited review of the grant application and uninterrupted funding if it received a favorable score.

One of the major problems facing UC researchers is working out the roles and **relationship between UC and private industry**. The legal issues surrounding patents and proprietary interests (which are not confined to AIDS research) appear to be an important logistic barrier to conducting AIDS research. Dr. Wara agreed to distribute the recommendations from a committee chaired by Dr. Larry Martin regarding the relationship (on another topic) between UC and private industry.

8. The next meeting will address the **epidemiologic issues** in AIDS and will be held 3:00-5:00 PM, January 7, l986 in 989-M. Committee members were also asked to **set this time aside for the first Tuesday of every month in l986.**

Respectfully submitted,

Chris Ireland

#1

AIDS ADVISORY COMMITTEE
Tuesday, November 26, 1985

"Impediments to Vaccine Development"

I. Problems

1. Escalating product liability suits which make vaccine development and testing financially unattractive.

2. Incorrect perception by venture capital that the market for an AIDS vaccine would be limited to a small segment of the population.

3. Limited number of companies in this country and abroad with the technical expertise to develop a safe and effective sub-unit vaccine.

4. Sub-type variations of the virus which may mandate innovative approaches to recombinant sub-unit vaccine design.

5. The only animal model for testing the vaccine is the chimpanzee, which is an expensive and dangerous animal to use in biological investigations.

6. The same venture capital that could be used to develop this vaccine can be used to develop vaccines for animal infections and veterinary hormones.

II. Solutions

1. Federal purchase order for 1 million doses of vaccine at $100 per dose as incentive.

2. Federal or state statute to limit liability and/or indemnify vaccine manufacturers.

3. Federal or state venture capital invested in the vaccine industry.

4. Endorsement by the Dean's Advisory Committee for AIDS for solicitation of research proposals at UCSF which will lead directly to vaccine development

III. Background

1. Science, April 1985, 308-309.

2. The Medical Forum, September 1985, 3-5.

3. Science, March 1985, editorial (Dan E. Koshland, Jr).

Major Accomplishments in AIDS Research

A. Biology

1. Identification of the AIDS-associated Retroviruses (ARV)

   This achievement represented the first independent confirmation of the initial French finding that a new type of retrovirus was associated with AIDS.

2. Isolation of over 300 independent isolates of ARV in our laboratory from patients with AIDS or healthy individuals from all the risk categories known to develop AIDS. We have the largest number of individual isolates of any laboratory in the world.

3. First to demonstrate that the biologic features of different ARV may vary, particularly in terms of their replicating and cytopathic properties.

4. First to isolate infectious ARV from brain and cerebrospinal fluid of individuals who presented with neurologic findings. These results linked the virus to "neurologic AIDS", particularly to conditions such as vacuolar myelopathy.

5. Selected ARV recovered from the brain have been examined biologically and have been found to grow in limited titer in peripheral mononuclear cells (PMC) compared to isolates responsible for frank AIDS. Some of these isolates have been passed and grown in human glial cells (studies performed in collaboration with Dr. Mark Rosenblum).

6. First group to report the recovery of infectious ARV from autopsy tissues, particularly the brain. These studies have indicated a high titer of virus in brain tissue at death.

7. Demonstrated for the first time that a lymphocyte infected with one ARV cannot be superinfected by another (viral interference).

8. Isolation of ARV from urine, saliva, semen, tears, serum, and plasma and most likely colostrum. Our laboratory has confirmed and, in some cases, was the first to identify infectious viruses in body fluids. Most importantly, however, we presented definitive data on the relative frequency and quantity of viruses in these fluids.

9. Demonstrated that certain individuals may lack antibodies to ARV but have infectious virus in their PMC.

10. Defined the wide host range of the AIDS virus. It is not only lymphotropic, but can infect macrophages and promyelocytes as well as brain cells.

11. The inoculation of ARV into primates (rhesus monkeys, baboons and chimpanzees) has led to important observations on the immunologic changes and frequency of recovery of virus.

12. We have demonstrated, as well as others, that the leu-3 (OKT4) epitope is closely associated with infection with ARV, perhaps as the receptor. We have also shown that once cells are infected with the virus the expres sion of this antigen markedly decreases.

13. We demonstrated for the first time that ARV infection of normal T lymphocytes can permit them to grow and remain viable for up to four months - a period during which the only sign of the viral infection is a reduction in expression of the leu-3 antigen.

B. Serology

1. This laboratory was one of the first two groups to show that the AIDS retrovirus could infect an established human T cell line (HUT 78). The chronically infected human cell line permitted the successful research in the serology and molecular biology of ARV. The IFA studies performed early in 1984 were extremely helpful in evaluating individuals in San Francisco with AIDS and detecting exposure to the virus. This assay has been adopted by many research laboratories throughout the world. It is an excellent confirmatory test for anti-ARV antibodies tested by more automated systems.

2. Demonstrated that healthy individuals with antibodies to ARV have a 50-75% chance of having infectious retroviruses in their PMC. (In collaboration with Dr. W. Winkelstein).

3. We have shown that antibodies to P25 (gag protein) decrease as the patient's condition worsens. Our studies have also indicated that certain proteins not easily represented in western blot techniques can be detected by IFA.

4. In collaboration with Dr. Warren Winklestein, our laboratory is performing not only the virology (cited above) but also the serology on long-term studies of a cohort of San Francisco men who are at risk for developing AIDS. Our research has indicated that nearly 50% of all homosexual men living in San Francisco have been exposed to the AIDS virus.

5. Neutralizing Antibody

Tests done in our laboratory have indicated the presence of some neutralizing antibodies to the virus, but not at high level.

6. Have demonstrated the presence of immune complexes in AIDS patients, some of which contain ARV antigens.

7. Hemophiliacs

In collaboration with Drs. Koerper and Ragni (Pittsburg), we have demonstrated a high rate of seroconversion in hemophiliacs exposed to ARV through Factor VIII and Factor IX concentrates. These long-term studies have also indicated for the first time that hemophiliacs have about the same chance of developing AIDS and AIDS-related condition (ARC) as virus-infected homosexual men.

8. Oriental Cases

In examining why there are so few cases of AIDS in Oriental homosexuals, we have begun a study of a cohort of Oriental homosexual men in San Francisco. Our results have indicated that they have a similar frequency of antibodies to ARV (50%); however, virus is rarely recovered from their PMC.

9. Dominicans and Haitians

In studies conducted with Professor E. Koenig (Santo Domingo), we have demonstrated that individuals on the same island of Hispanola, but living in the Dominican Republic, have a much lower prevalence of antibodies to ARV than those living in Haiti.

10. Hairy Leukoplakia

Demonstrated that individuals with this disease have a very high prevalence of infectious ARV in their PMC (In collaboration with Drs. J. and D. Greenspan).

C. Molecular Biology

1. In collaboration with researchers at Chiron Corporation, we were one of the first three groups to molecularly clone the AIDS retrovirus and show by restriction enzyme maps that the genome of each isolate can differ in sensitivity to restriction enzymes.

2. With Chiron Corporation, we have completely sequenced ARV-2 and have begun to examine differences between it and the other sequenced AIDS viruses.

3. In collaboration with Dr. Dino Dina (Chiron), we have analyzed the envelope region differences between ARV and HTLV-III/LAV. We are also studying regions of the outside envelope protein (external portion) which are conserved (constant region) and that which varies (variable region). Thus far the studies have indicated, for the first time, that certain AIDS retroviruses will share the same variable region while others will have an entirely different one. These results suggest that eventually the AIDS retroviruses can eventually be subgrouped according to shared envelope antigenic dterminants.

4. Demonstrated that a molecular DNA clone of ARV is infectious when transfected into human lymphocytes. We were the first to show transfection can occur using conventional techniques, and can lead to production of infectious virus, not only in human lymphocytes and monocytes, but also in mouse 3T3 cells, mink lung and monkey cells (cos). These results indicated that the block to ARV infection of many cells is primarily at the membrane and not the intracellular level.

5. Demonstrated for the first time that virus cytopathology induced by the virus correlates with accumulation of unintegrated proviral forms in the cytoplasm.

6. Developed a very sensitive method for detection of ARV through improvements in the reverse transcriptase assay.

D. Epidemiology

1. We were the first group to indicate that infectious retroviruses could survive the treatment used for the concentration of Factor VIII and Factor IX. The data placed further emphasis on a retrovirus, such as ARV, in the transmission of AIDS in hemophiliacs.

2. Studies conducted with individuals in Central Africa and Zimbabwe have indicated that Central Africans have a much higher prevalence of antibodies to ARV than do populations elsewhere in the world except for Haiti. Studies conducted in Kigali, Rwanda with Dr. Susan Allen (who will be setting up a laboratory there in collaboration with our group), have yielded viruses from Rwandan cases of AIDS that are similar to those found in the United States.

3. Seroepidemilogic studies in the Dominican Republic (with Professor E. Koenig) have shown differences in prevalence of exposure to ARV between Dominicans (1%) and Haitians (15%)

E. Antiviral Therapy

1. We are involved in collaborative work with Chiron Corporation towards the ultimate development of a vaccine. Our studies have led to the production of selected viral proteins in bacteria and yeast.

2. In collaboration with Drs. Volberding and Abrams, we have been studying the effect of Suramin on infectious virus recovery from individuals who have viremia or PMC producing the virus.

3. We have attempted to prevent ARV replication in cells in vitro using N-methyl isatin semicarbisone which is a useful drug against other retroviruses, as well as BHT (a drug used against herpes). Neither of these therapies have been helpful in the arrest of ARV replication.

II. Present Work and Future Plans in AIDS Research

A. Biology of the AIDS-Associated Retrovirus

1. Determine the mechanism by which ARV infects a cell and causes cell death (e.g. receptor interaction, reverse transcription and integration).

2. Determine the mechanism by which ARV remain latent in the cell. Study the approaches by which one can induce the virus from the cell (e.g. chemicals, viruses, GVHR). Study the selective production of certain viral antigens by infected cells. Determine how expression of the Leu 3a antigen is reduced in ARV infection (with Dr. D. Littman).

3. Determine biologic differences (particularly replication and cytopathology) among various ARV isolates. Do certain properties correlate with clinical disease?

4. Define further the host range of ARV. Do certain isolates readily infect glial cells, or glioblastoma cells? (in collaboration with Dr. Mark Rosenblum). Are viral antigens expressed in certain cells of the brain? (Studies conducted with Dr. Richard Davis). Do macrophages serve as reservoir for ARV? What subset(s) of T cells is susceptible to ARV (studies on T cell clones with Drs. J. Krowka and D. Stites).

5. Co-factors: Does the virus act in concert with CMV or other herpes viruses in infecting lymphocytes. (In collaboration with Drs. L. Drew and J. Mills).

B. Serologic Studies

1. Is the antibody to specific viral proteins or titers of certain antiviral antibodies prognostic for eventual course of the disease?

2. Further characterize neutralizing antibodies in certain patients' sera. Do they cross-react with all ARV isolates?

3. Shall develop mouse and human monoclonal antibodies to specific ARV proteins.

4. In continued collabortion with Dr. Warren Winklestein (San Francisco Men's Health Study), examine the percentage of individuals who seroconvert from a virus antibody-negative to a virus antibody-positive state. Assay for infectious virus in lymphocytes and serum collected prior to the seroconversion. Shall also examine both the humoral and cellular responses to the viruses in a small cohort of these men. These and other parameters are being used to determine what factors are important

in the development of AIDS or ARC.

5. Antigenemia assay - Develop immunochemical techniques for detection of low levels of ARV in serum.

C. Cellular Immune Studies:

Is there a specific cellular immune response to ARV by virus infected individuals with less severe or no disease. Do cytotoxic T cells kill virus infected cells? (In collaboration with Drs. J. Krowka and D. Stites).

D. Animal Models - To be used for vaccine and antiviral therapy trials.

1. Can multiple injections of different types of ARV cause the development of AIDS or ARC in primates, such as rhesus monkeys, baboons or chimpanzees?

2. Can we manipulate the immune system of the ARV-infected chimpanzee to induce the disease? (use antithymocyte globulins, anti Leu 2b and anti Leu 11 antibodies, CMV infection, or approaches at reduction of antigag antibody response).

3. Can small animals be infected by ARV? These studies involve the passage of ARV isolates through mice and rabbits in attempts to adapt the virus to these animals. Even if disease does not develop, the efficacy of a vaccine made with selective proteins can be evaluated by its ability to block a host response to all viral proteins present on an infectious virion.

4. Do we have neurotropic viruses that can cause central nervous system disease disorders in the chimpanzee?

5. Infection of mouse cells containing the human CD4(Leu 3a) antigen. Studies with Dr. D. Littman will attempt to infect, with ARV, mouse lymphocytes that have been transfected with the CD4 receptor gene. Subsequently transplantation of these cells in appropriately irradiated recipient mice would be attempted.

6. Phenotypic Mixing

Infect animals with the mouse xenotropic virus pseudotype of ARV. These viruses readily infect cells of heterologous species including duck.

E. Molecular Studies: towards development of antiviral drugs and a vaccine.

1. Cytopathology Does an accumulation of unintegrated proviral forms in the cytoplasm give rise to cell death? Study

molecularly manipulated mutants (with P. Luciw) and chronically infected normal and established lines of T cells. Can certain drugs prevent or reverse this process?

4. Transfection experiments with various molecular clones of ARV will examine what changes in the ARV genome affect its cytopathology and its replicating ability (conducted with P. Luciw).

3. Do the variable regions in the envelope portion of different ARV all differ among themselves or are there certain env subgroups that can be used to classify the agents.

4. Sequence other ARV isolates to determine differences particularly in the env gene (collaboration with Dr. J. Stubbs, San Francisco State and scientists at Chiron Corp.)

5. With heat-shock promotor genes in mammalian cells, can we produce sufficient amounts of envelope proteins that can be used for a vaccine? This approach employs studies on mammalian cells that will glycosylate the envelope proteins; bacteria and yeast do not yield a true viral product.

E. Virus Transmission

1. Complete studies examining the presence of ARV in body fluids including sweat and feces as well as vaginal secretions and milk.

2. Examine whether any body fluids are toxic to ARV. We suspect that saliva and seminal fluid will reduce the titer of virus.

3. Immunoglobulin preparations: - In collaboration with Cutter Laboratories, we are examining the recovery of infectious ARV during purification of immunoglobulins.

5. Autopsy - In continued studies of autopsied tissues from individuals with AIDS, we are examining whether the virus can be recovered from cells of other organs, such as adrenal, pituitary, and pancreas.

F. Epidemiology

1. Continue studies on evaluating why Oriental homosexuals infected with ARV do not usually develop AIDS. Shall examine the effect of HLA (in collaboration with Dr. Marvin Garavoy) and other potential co-factors (e.g. CMV, hepatitis B). Their cellular immune response to ARV antigens will also be evaluated (with Drs. J. Krowka and D. Stites).

2. Continue studies on the sero-epidemiology of ARV in the

Dominican Republic and Haiti. (Performed in collaboration with Professor E. Koenig, Santo Domingo).

3. Continue sero-epidemiology in Africa to determine whether ARV or antibodies to the virus are present at higher prevalence in the non-symptomatic individuals (Studies with Dr. Susan Allen, UCSF, in Kigali, Ruwanda).

G. Hemophiliacs

Continue studies with Dr. Marion Koerper investigating the prevalence of infectious ARV and antiviral antibodies in hemophiliacs that have received clotting factor preparations.

H. Antiviral Therapy

1. Continue to test the ability of certain antiviral drugs to reduce virus present in peripheral mononuclear cells and body fluids.

2. Continue work on development of a vaccine through the above stated biologic and molecular studies including those with animal models. Moreover, shall develop human and mouse monoclonal antibodies to virus-specific proteins. If some are neutralizing, they will be used for immunotherapy. Others will be used for diagnostic purposes including detection of ARV and antiviral antibodies in body fluids.

3. Develop anti-ID antibiotics which could be used for immunotherapy.

AIDS Publications

Jay A. Levy, M.D.

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LABORATORY PERSONNEL

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Jacques Homsy, M.D., M.P.H., Postdoctoral Fellow
Chris Walker, Ph.D., Postdoctoral Fellow
Louise Evans, Ph.D., Postdoctoral Fellow (arriving December 1985)

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STUDENT

William Young, Graduate Student

III. Factors that Could Enhance Future Accomplishments in AIDS Research

A. Immediate need: 2,000 sq. ft. of contiguous space.

Divided between tissue culture and molecular/serologic studies of the AIDS virus. A cold room should be available; the cold room presently used must be vacated in two months.

B. Long term requirement: 4,000 sq. ft. of contiguous space.

This space would enlarge the tissue culture, molecular, and serological facilities so that many more AIDS virus studies can be done with researchers in the University of California system.

C. Present Facilities

The tissue culture work needed for the isolation and studies of ARV is performed in two small laboratories that have been approved as P2* facilities (S-1273, 80 sq. ft.; S-1265, approximately 200 sq. ft.).

The molecular and serologic studies are conducted in a space (HSE-1266A, 300 sq. ft.) that has been borrowed, and will be returned to the Cancer Research Institute in July 1986. The cold room (borrowed) is located across from S-1265.

Our research unit also has rooms for funded research on mouse xenotropic viruses, embryonal carcinoma cells, and nutrition and the immune system. No AIDS virus research is permitted in these facilities. These laboratories are Room S-1280 (400 sq. ft. lab space; 300 sq. ft. of office and equipment space), and a room in HSE-1217 of approximately 400 sq. ft.

#3

DEVELOPMENT OF SUBUNIT VACCINE FOR AIDS VIRUS

Daniel Stites, M.D.

Goal: Ultimate goal is to develop protective vaccine or other immunologic intervention to prevent or treat ARV* infections.

Aims:

1. Synthesis of several immunodominant peptides of envelope (env) glycoprotein common to ARV, HTLV-III and LAV.

2. Demonstrate antibody and T cell mediated responses in animals immunized with these peptides coupled to an immunogenic carrier.

3. Attempt to directly demonstrate protection against ARV infection in an experimental animal model.

4. Gather indirect evidence for protection by peptides by examining sera and cells from infected individuals for immune responses to the peptide and attempt to block in vitro infections with virus.

Background and Preliminary Evidence:

The complete nucleotide sequence of ARV, HTLV-III and LAV env glycoproteins has been published. Env was chosen because of its surface location and evidence in cats that immune response to env is partially protective. Employing translated peptide sequence derived from genetic code, we have predicted immunodominant regions of env which are common to these major isolates. The method employs computer prediction of the hydrophilicity and three dimensional structure of env and has already worked for predictions of epitopes antigenic within transplantation antigens. We feel this approach is superior to whole env proteins as immunogens because: (1) we can focus the immune response to determinants common to all isolates, (2) harmful or irrelevant competing immune responses against larger molecules can be evaded and (3) env-gp are notoriously insoluble and difficult to work with.

We have already identified 4 immunodominant regions of env gp and have synthesized one of approximately 17 amino acids. We plan to synthesize the remainder in the UCSF Biotechnology Facility under the direction of Dan Santi.

Testing these peptides for protection against ARV infection must take into account both humoral and cellular responses. Continuing to focus on the issue of neutralizing antibodies alone is likely to be an inferior strategy when one considers the relevance of T cells to elimination of virual infections. In another project in our laboratory, we are studying T cell responses to AIDS viruses using cloned T cells and a variety of viral antigens. Therefore, we will be able to specifically evaluate responses in animals and humans to these peptides for both B and T systems.

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* The acronym ARV is used synonomously with HTLV-III and LAV.

In the absence of an animal model for AIDS, we plan a series of experiments examining the role of synthetic peptides in interfering with ARV in vitro. Competitive inhibition of binding of ARV and peptide to T4 will be studied. Monoclonal or polyclonal antibodies and T cells sensitized to peptides will be studied for their potential effects on viral infection in vitro. Thereby, a new therapeutic as well as prophylactic approach may be forthcoming.

Needs to Accomplish These Goals:

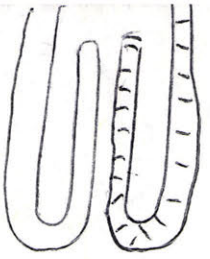
1. We have no support for these studies. Funds are currently being borrowed from Departmental Account. NCI-Program project grant applied for with start date of July 1, 1986.

We Could Use Immediately:

1. Some renovation of laboratory in HSE 593 in order to accommodate additional biohazard space.

2. Salary support for fellows and technicians.

3. Ongoing supplies and equipment.



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Advisory Committee for the AIDS Center
Meeting of Tuesday, January 7, 1986
3:00 - 5:00 pm, Moffitt Hospital 989-M

AGENDA

3:00 - 3:45	**EXECUTIVE SESSION (Committee members, including ex-officio)**	
3:00	Review of minutes from last time and followup on action items Review of today's agenda	Dr Hulley
3:15	AIDS Center budgetary decisions	Dr Ziegler
	Allocation of Core Budget Plans for reviewing projects and allocating moneys	
3:45-5:00	**GENERAL SESSION**	
3:45	<u>Special review of epidemiologic studies</u>	
	Cohort study of probability sample of selected SF census tracts SFGH studies Other studies; commentary	Dr Winkelstein Dr Moss Drs Taeger et al
4:30	Plans for building two new floors at SFGH for molecular research on AIDS	Dr Sande
4:50	Other topics; plans for future meetings	Dr Hulley

NB CONFIDENTIAL ATTACHMENT

ATTACHMENT 1

UCSF AIDS CLINICAL RESEARCH CENTER

Core Budget for 1/1/86 - 6/30/86

	REQUESTED AND APPROVED		REVISED		(+) EXCESS	
Position	%	Salary plus Fringe	%	Salary		
Dr. Volberding	25	$ 11,377	25	$ 11,377		
Dr. Abrams	15	5,850	15	5,850		
Dr. Mills	15	7,822	15	7,822		
Dr. Hopewell	15	7,882	15	7,882		
Dr. Feigal	50	17,704	35	12,393	(+)	$ 5,311
Assoc. Prof. (TBH)	100	46,066	defer to 7/1/86		(+)	46,066
Dr. Newman	25	10,312	20	8,250	(+)	2,062
Dr. Hearst	25	10,036	20	8,028	(+)	2,008
G. Gee	15	3,893	5	1,298	(+)	2,595
G. Carr	100	22,130	100	22,130		
K. Zender	100	20,573	100	20,573		
SAA (Hedberg)	100	21,168	100	21,168		
Secretary II (TBH)	100	11,416	100	11,416		
SRA (Hahn)	100	18,383	100	18,383		
Z. Weingart	100	13,954	100	13,954		
Data Manager (TBH)	100	13,290	67	8,904	(+)	4,386
Data Manager (TBH)	100	13,290	67	8,904	(+)	4,386
K. Molvig	50	12,728	0	0	(+)	12,728
K. Vranizan	40	9,515	40	9,515		
V. Reuther	50	7,407	0	0	(+)	7,407
Key Data (TBH)	100	11,053	85	9,395	(+)	1,658
G. Skellenger	15	2,291	15	2,291		
G. Stouffer	50	6,792	50	6,792		
TOTAL		$304,872		$216,265		$88,607

JUSTIFICATION FOR REVISION

All junior TBH employees will be recruited and hired by March 1, 1986. Therefore 67-85% of salaries (rather than 100%) are needed. Other salary reductions reflect carry-over funds from 1985 or temporary reductions in time commitments due to startup delays. Recruitment for Associate Professor is underway but the position will not be filled until July 1, 1986 at the earliest.

Core Budget for 1/1/86 - 6/30/86 (continued)

ADDITIONAL POSITIONS AND FUNDS REQUESTED

Position	%	Salary plus Fringe
D. Seigal (Epidem.)	20	$ 8,028
D. Stites (Immunol.)	15	10,095
C. Casavant (Immunol.)	10	4,610
J. Wary (Immunol.)	100	16,710
S. Richards (Immunol.)	100	15,255
L. Bakehorn (Immunol.)	100	13,351
H. Hollander, M.D.	25	9,748
S. Charles	50	10,810
TOTAL		$88,607

JUSTIFICATION FOR ADDITIONAL POSITIONS

Dr. Seigal is an epidemiologist who will work with principal investigators on selected trials.

Drs. Stites and Casavant, along with technical staff Wary, Richards and Bakehorn, are collaborating actively with researchers to provide immunophenotypes and immune function tests on patients in clinical trials. This group has pending applications to NIH but requires interim support to maintain the current workload.

Dr. Hollander runs the Adult Immunodeficiency Clinic at Moffitt Hospital. His patients are also a core resource for campuswide clinical trials, and salary support is requested for his time commitment (25%) to clinical research and trials.

Sandy Charles will increase her 10% commitment to half-time to assist Dr. Ziegler in entering VA patients into collaborative trials.

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AIDS CLINICAL RESEARCH CENTER
John L. Ziegler, M.D., Director
VAMC 141

SAN FRANCISCO, CALIFORNIA 94143

December 31, 1985

TO : Chairman, Dean's AIDS Advisory Committee

FROM: Director, UCSF AIDS Clinical Research Center

SUBJ: Core Budget Decisions for Clinical Trials Grant

1. As you know, the Center was awarded $525,372 by the State Task Force. $304,872 of this was allocated to Core Support.

2. Because of the rapid start-up, need to hire new personnel, and shifts of time commitments, a surplus of core funds of $88,607 has been identified (Attachment 1).

3. I propose reallocation of these funds to support additional personnel essential to the core function. The bulk of these should go to the immunology laboratory for interim support until alternative funding is secured. In addition, funds are requested for Dr. Seigal (epidemiologist - 20%), Dr. Hollander (Adult Immunodeficiency Clinic - 25%), and Sandy Charles (VA Research Nurse - 50%). These amounts and further justification are found in Attachment 2.

4. The Committee should consider a mechanism to allocate the remaining $200,000 for projects (January 1 - June 30, 1986). I recommend a mini-REAC scheme, and attach a brief proposal format which can be resubmitted to the Committee for its February meeting. I will ask the principal investigators to submit those projects that can begin at once for priority consideration.

JOHN L. ZIEGLER, M.D.

Extra

DRAFT 12/30/85

ADVISORY COMMITTEE FOR THE AIDS CENTER MEETING
November 26, 1985
3:00-5:00 PM
UCSF, 989-M

In attendance:

Dr. Stephen B. Hulley, Chairman
Dr. Thomas Newman
Dr. Robert Ockner
Dr. Diane Wara
Dr. Marcus Conant
Dr. John Greenspan
Ms. Chris Ireland
Dr. Jay Levy
Dr. Dan Stites
Dr. Paul Volberding
Dr. John Ziegler

1. Dr. Hulley reviewed the minutes from the October 29th meeting. A motion to accept was unanimously approved.

2. Old Business: **Dr. Conant** reported that the SF Medical Society's Ethics Committee is developing **guidelines for education efforts to stop the spread of AIDS**. If the Medical Society adopts the committee's recommendations (expected to be along the "no sex" line) the message will reach practicing MDs. Dr. Conant will meet with Dr. Phil Lee to discuss the Health Commission's role in AIDS educational efforts.

3. **Dr. Ziegler reported that the AIDS Center proposal was submitted** on November 25, 1985. A budget of $7.282 million for three years was requested, with approximately 50% allocated for core activities and the rest for about 20 specific projects. Three proposals were submitted (from UCSF, UCLA and USC/Irvine) and will be reviewed December 9. Dr. Ziegler will meet with the loose federation of UCSF researchers in pneumocystis pneumonia (PCP) to coordinate efforts in this area.
Dr. Ziegler passed out a UCLA newsletter entitled "AIDS Medical Update" and said he would distribute it monthly to a large list of interested investigators at UCSF.

4. **Dr. Conant discussed the impediments to AIDS vaccine development,** citing the twin disincentives of low profits and risk of lawsuits to the manufacturers of vaccine (attachment #1). Dr. Levy noted that UC has the expertise to develop a vaccine, but that it would require a major institutional commitment.

5. **Dr. Levy discussed the biological aspects of vaccine development.** He noted that unique research in this area is being conducted at UCSF and Chiron Corporation. Dr. Levy presented his laboratory's major accomplishments in AIDS research and discussed future plans (attachment #2). The most critical constraint facing Dr. Levy is lack of space. He estimated that he would require 4000 sq. ft. of laboratory space to conduct the necessary research for developing an AIDS vaccine. He currently has 300 sq. ft. for tissue culture and 500 sq. ft. for biochemistry.
Dr. Newman emphasized that getting the **optimal space** required as soon as possible should be of the **highest priority** to this committee.
Dr. Wara suggested that a short-term solution might be to obtain 2000 sq. ft.

immediately (perhaps at SFGH or CED) and a long term solution would be to develop some land and build an institute of virology and immunology.

Dr. Ziegler suggested that a successful strategy might be to first identify appropriate existing space and then offer something in return for the space.

Dr. Hulley will meet with Drs. Root and Schmid regarding options for space for vaccine development.

6. **Dr. Stites reported on his work on development of subunit vaccine** for the AIDS virus (attachment #3). Dr. Stites and his colleagues are studying cellular immune response. His problems differ from Dr. Levy's in that he has adequate space to conduct research but no ongoing monetary support for his studies. His immediate needs are: to provide additional biohazard space to protect personnel from proliferating virus and ongoing support for fellows and technicians, supplies and equipment. Possible sources for the necessary funds include: the AIDS Center grant (just submitted), new RO-I grant applications, and Dr. Volberding's NCI program project grant application.

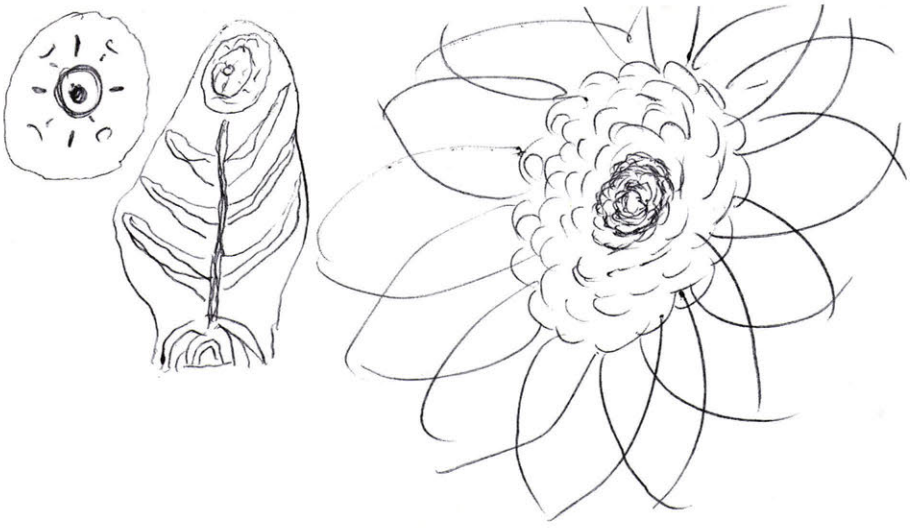
7. **Dr. Volberding** discussed the **program project grant application** he and Dr. Ziegler are preparing for submission to the **NCI**. Current NCI support for AIDS ends May I986 and is not renewable. NCI invited a response from Dr. Volberding in the form of a program project grant. The grant will be submitted to the NCI's division of cancer treatment, and will request funds for core support for data management, and facilities for virology and immunology (approx. $3 million/year for 5 years). NCI promised an expedited review of the grant application and uninterrupted funding if it received a favorable score.

One of the major problems facing UC researchers is working out the roles and **relationship between UC and private industry**. The legal issues surrounding patents and proprietary interests (which are not confined to AIDS research) appear to be an important logistic barrier to conducting AIDS research. Dr. Wara agreed to distribute the recommendations from a committee chaired by Dr. Larry Martin regarding the relationship (on another topic) between UC and private industry.

8. The next meeting will address the **epidemiologic issues** in AIDS and will be held 3:00-5:00 PM, January 7, I986 in 989-M. Committee members were also asked to **set this time aside for the first Tuesday of every month in I986.**

Respectfully submitted,

Chris Ireland



AIDS EPIDEMIOLOGY GROUP

A. R. Moss, Ph.D.

The AIDS epidemiology group of the Department of Epidemiology and International Health at UCSF was established in late 1982 to respond to the first National Cancer Institute request for proposals on AIDS. The group moved into the AIDS clinic at San Francisco General Hospital in July 1983, at the invitation of Paul Volberding MD, and was first funded by the Universitywide Task Force on AIDS in November 1983. The group's activity has passed through three phases. We began with AIDS incidence and mortality studies in 1982-83, and have since moved on first to analytic studies of AIDS risk factors in homosexual men, and then more recently to prospective studies of persons with AIDS retrovirus antibody.

I. INCIDENCE AND MORTALITY STUDIES

In 1982-83 we established a case-finding method for AIDS studies based on the AIDS registry at the San Francisco Department of Public Health. Incidence and mortality studies using this process have been supported by the National Cancer Institute under CA 349080. With Dr. S. Dritz and others, we have carried out a series of incidence and mortality analyses based on this process(4-6,8). Our mortality data is also being used in therapeutic studies of opportunistic infections (13).

II. ANALYTIC STUDIES OF OF AIDS RISK FACTORS IN HOMOSEXUAL MEN

With Universitywide Task Force on AIDS funding, beginning in November 1983, we have carried out a case-control study of risk factors for AIDS in homosexual men. Serology for this study was done by Dr J.-C. Chermann at the Pasteur Institute. In a comparison of AIDS cases and seronegative controls we found strong association with numbers of partners and rectal receptive sexual activities, but no evidence for other modes of sexual transmission. In an examination of cofactors for AIDS we found evidence that use of butyl nitrites ("poppers") was associated with Kaposi's Sarcoma but not other AIDS manifestations. This study was presented at the First International AIDS meeting in 1985 and has been submitted for publication (11,17).

In a second study we recruited a cohort of men who were sexual partners of diagnosed AIDS cases for comparison with men not at risk in this way. Preliminary data from this "partner" study was reported at the first International AIDS meeting in April 1985 (12), and a detailed analysis of seronegativity in this cohort is in progress.

III. PROSPECTIVE STUDIES

A) Homosexual men

With our second year of funding from the Universitywide Task Force on AIDS, beginning November 1984, we established a prospective cohort of 479 homosexual men in which we proposed to examine the natural history of AIDS. 55 percent of the cohort were antibody positive for the AIDS retrovirus at initial study. The first year of followup is currently nearing completion and

preliminary studies show a progression rate to clinical AIDS among seropositives of about five percent (13/260). The seroconversion rate among those seronegative at first study was about 10 percent. Preliminary data from the cohort were presented at the First International AIDS meeting (12), and immunological studies have been reported by our collaborators at UCSF and elsewhere (2,14,15,19).

In 1985 we established a second serological collaboration with the recently-funded State center for AIDS serology and culture in Dr Murray Gardner's group at UC Davis. Serology for our epidemiological studies is currently being done in both places, but is increasingly moving to Davis.

B) Health workers

At the request of the UCSF AIDS Clinical Research Center, we carried out a pilot study of AIDS-exposed health workers at San Francisco General Hospital and collaborating labs at UCSF during the 1984-85 funding year. The study has found no heterosexual health workers positive either by immunofluorescence for antibodies to ARV (J.Levy), or by ELISA for antibodies to HTLV-III (J. Carlson, UC Davis). The project was separately funded as a prospective study beginning in March 1985 and is being continued by J. Gerberding MD (16). This study is collaborative with the group at UC Davis.

C) Intravenous drug users

Beginning in March 1985 we also initiated a series of studies of AIDS exposure in intravenous drug users in San Francisco. A pilot study was carried out by R. Onishi MD, a Robert Wood Johnson Clinical Scholar attached to the group, and found a prevalence of about ten percent antibody positivity in users

in San Francisco treatment programs in 1985. During the current program year we will carry out a case-control study of risk factors for seropositivity in IV drug users. We will also establish a prospective study of seropositives to compare the natural history of the virus in IV drug users with that in homosexual men. Assisting us in this project is R. Chaisson MD, a Mellon Clinical Epidemiology Fellow. This study is also collaborative with the group at UC Davis.

IV. FUTURE ACTIVITIES

The prospective phase of our studies of homosexual men and others has thus been launched successfully with Task Force support. During the current program year we will shift our primary serology collaboration to UC Davis, and will develop exploratory studies of retroviral cultures and viral antigen detection in selected members of our prospective cohorts, in collaboration with Drs. J. Carlson, M. Jennings and N. Pedersen at Davis. The long-term goal of these studies is to explore the issue of transmission in AIDS, including the existence of a carrier state. We will begin with a study of viral culture in antibody-negative partners of diagnosed AIDS cases.

We have also been asked to collaborate with the San Francisco Department of Public Health in developing the evaluation strategy for its AIDS prevention program.

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SCHOOL OF PUBLIC HEALTH
DEPARTMENT OF BIOMEDICAL AND
ENVIRONMENTAL HEALTH SCIENCES

EARL WARREN HALL
BERKELEY, CALIFORNIA 94720

January 6, 1986

MEMORANDUM TO: Dr. Hulley

FROM: Warren Winkelstein, Jr., MD, MPH

SUBJECT: Summary of A.I.D.S. research

In response to your request of December 26, 1985, I am pleased to provide you with the following information regarding A.I.D.S. research in which I am involved:

1. San Francisco Men's Health Study: This is a prospective study of a probability sample of single men, 25-54 years of age, recruited from the 19 census tracts in San Francisco in which most of the A.I.D.S. cases have occurred. The cohort comprises approximately 1,000 men who have now been examined three times at six month intervals. Seroconvertors and other special subgroups are examined at three month intervals. The originally planned duration of the study was for six biannual examinations. Funding from the NIAID under a contract will be sufficient for only four examinations and unless supplementary support can be obtained, the fourth wave of examinations will be the last. The study is designed to provide information on both the epidemiology and natural history of A.I.D.S. Three major papers on baseline findings are in advanced stages of preparation. Several substudies are being carried out or planned for this project:

   a) Study of Psychosocial factors and A.I.D.S., funded by the National Institute of Mental Health, is an add on to the S.F.M.H.S. Data analysis for the wave 2 data is underway.

   b) A study of nutritional factors was proposed to the N.I.H. under an R-01 grant application. The proposal was approved for scientific merit but not funded because of low priority.

   Plans for the S.F.M.H.S. include negotiations with the N.I.A.I.D. for supplementary funds for completion of the 6 waves of examination and for additional funding to provide for another three years of follow-up.

   The project would, of course, benefit from more funds and from additional professional staff particularly biostatistical consultation and another epidemiologist to facilitate the analysis and interpretation of results.

2. The Partner Study: This is a study funded by the University Task Force to investigate transmission of A.I.D.S. virus infection from seropositive men to their female sexual partners. The study utilizes subjects from the San Francisco Health Department Cohort and involves field investigations of named female sexual contacts. The study is being implemented by a graduate student who will use the results for her doctoral thesis. The

project is well funded and is proceeding in a satisfactory fashion. A substudy has also been added: In collaboration with the U.C.S.F. group studying A.I.D.S. in women, an investigation of artificially inseminated lesbian women is being undertaken.

3. Attitude Survey: In collaboration with the Survey Research Center, we are proposing to undertake several surveys of random samples of San Francisco men to ascertain attitudes to participation in vaccine field trials and field trials of chemotheraputic agents designed to prevent the progression of infection to disease. This project is a part of the proposed clinical trial project which is being considered by the University Task Force for funding. As yet, no decisions have been made and the status of funding for this project is not clear.

4. A sero-epidemiological study of ARV infection in a random sample of San Francisco women living in the same high incidence census tracts as our male sample in the SFMHS has been proposed to the Centers for Disease Control in response to an RFP issued by that agency. The project was approved for scientific merit but remains unfunded.

   Clearly, we feel that this project is of the utmost importance and would like to see it funded by some agency, perhaps the University Task Force or the State Health Department. The issue of transmission into the heterosexual population remains unresolved and the continued surveillance of high risk populations has been given high priority by WHO workgroups as well as by the California Department of Health Services.

Thank you very much.

WW:sg

A Seroepidemiologic Study of the Female Partners of Bisexual Men

Almost one year ago, we received Task Force funding to study the heterosexual tranmsission of AIDS through examination of the female sexual partners of bisexual men from the City Clinic Hepatitis B Cohort. This study is unique in its ability to monitor this transmission because we have medical data from both men and women. Since the inception of the study, we have expanded our recruitment efforts to include referrals from clinics and medical professionals, as well as referrals through advertisement. To date we have interviewed 60 women, 53% of whom were the sexual partners of men from the City Clinic Cohort. We now have approval from the State Department of Public Health to act on their behalf in contact tracing of seropositive men from alternative test sites, and we are currently in the process of training test site staff throughout the state to actively recruit participants for us. In addition, although we do not actively solicit partners of men from other risk groups, we occasionally receive such referrals. Thus far, two of our participants have been the partners of hemophiliacs, and one was the partner of an intravenous drug user.

After limiting the sample to include only the partners of bisexual men who were seropositive, and for whom serological data now exists, 11% (with a 95% confidence interval of 3.21% - 26.75%) of our female participants are seropositive. If we further limit the sample to include only those women who had sexual contact with the men within a year before the date of her partner's serologic test, then 14% (4.04% - 32.69%) of the women were seropositive. One of the hemophiliac partners was also seropositive.

All of the seropositive women had repeated exposures to infected men. One had numerous encounters with a large number of gay and bisexual men, and the rest had long term sexual relations with the index case (as defined by sexual relations which lasted more than a month and included more than five sexual contacts). However, close to 90% of the remaining group of women who had also been exposed to infected men also had such long-term relations. Only one of the seropositive women practiced anal intercourse with her bisexual partner, as compared to greater than 35% of the other exposed women who did so.

We are funded to collect data through June of 1986. By that time we hope to have a large enough sample: (1) to narrow the confidence intervals surrounding the infectivity rate, (2) to be able to examine whether infectivity varies at certain points during the natural history of AIDS, and (3) to study the association between infection and other risk factors such as concomitant medical infections (either in men or women), the protective role of contraception, and other behavioral factors. We will soon begin to examine lymphocytes stored from the men to assess which of the seropositive men were shedding virus at the time of their serological test, and whether this has any bearing on infection in their partners. We are also collaborating with Dr. Wofsy in a case-control study in which we follow seropositive women, seronegative women who are still in a high risk sexual relationship, and a group of controls. This study includes viral cultures and a more extensive physical examination of participants, and should add to our knowledge of the natural history of AIDS in women. Finally, we are encouraging seropositive women to refer other male sexual partners to the study, and have recruited two such men so far; both are seronegative.

The results from this study indicate that a significant amount of disease is transmitted from men to women and that it is biologically feasible for men to infect women through vaginal intercourse. Whether the proportions of women who ultimately become infected will approach the numbers of men, as it has in central Africa, still remains a mystery. Such questions will have to be answered through more broad-based surveillance of infection in women.

Please address questions to Nancy Padian, Project Director, at (415)-642-5512.

Prepared: 5 January 1986 (N.S.P.)

AIDS CLINICAL RESEARCH CENTER (ACRC)

Format for AIDS Clinical Trial Proposal

Principal Investigator: _____
Campus Address: _____
Telephone Number: _____
Other Investigators: _____
_____
_____

PROJECT SUMMARY

Title (Question(s) to be asked): _____
_____

Nature of Trial: Pilot ___ Phase I ___ Phase II ___ Phase III ___
Study Design: uncontrolled ___ random controls ___ blinded ___
Location of Patients: SFGH ___ Moffitt ____ VA ____
Number and type of patients: AIDS (OI) _____ AIDS (KS) _____
ARC _____ Other _____
Starting Date (assuming ACRC funding): _____

PROJECT ABSTRACT (Brief summary of trial including objective, design, duration of study, statistical analysis of data. Append protocol draft if available).

PROJECT SIGNIFICANCE (Brief statement of background data, justification, and anticipated result relative to prevention, morbidity, and mortality).

BUDGET AND JUSTIFICATION (List expenses by year of project and justify below)

	Year 1 (1/1/86-6/30/86)	Year 2 (7/1/86-6/30/87)	Year 3 (7/1/87-6/30/88)
Personnel			
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
Laboratory Costs			
_____	_____	_____	_____
_____	_____	_____	_____
Clinic Costs	_____	_____	_____
Supplies	_____	_____	_____
Travel	_____	_____	_____
Other	_____	_____	_____
TOTAL	_____	_____	_____

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UNIVERSITYWIDE TASK FORCE ON AIDS
OFFICE OF HEALTH AFFAIRS
785 UNIVERSITY HALL
UNIVERSITY OF CALIFORNIA
BERKELEY, CA 94720

December 16, 1985

John L. Ziegler, M.D., Director
AIDS Clinical Research Center
Veterans Administration Medical Center
4150 Clement Street (141)
San Francisco, CA 94121

Dear Dr. Ziegler:

The Universitywide Task Force on Acquired Immune Deficiency Syndrome (AIDS) has completed its review of applications for the establishment of Clinical Trials Consortia and has made award recommendations to me.

I am pleased to inform you that your project, entitled "Clinical Trials in AIDS", was approved for a total of $525,372 for the period January 1, 1986 - June 30, 1986. A breakdown of your award is attached. Support for the core totals $325,372; an additional $200,000 shown as start-up funds under supplies and expenses in the budget, are provided to initiate clinical trial protocols.

As specific treatment protocols are developed by your group, these are to be submitted for evaluation to a Coordinating Council made up of investigators active in clinical trials and representatives from the AIDS Virus Laboratory and the AIDS Task Force. The responsibilities of this group will be to ensure that all members of the consortia are working together, that no overlap exists, and that all treatment protocols meet criteria of merit and have appropriate budgets. Approximately $800,000 are available for allocation to meritorious protocols before June 30, 1986.

Your core support for the period July 1, 1986 - June 30, 1987 will be prorated so as to remain at essentially the same level as the initial award. Funds for treatment protocols will be allocated as recommended by the Coordinating Council.

UNIVERSITYWIDE TASK FORCE ON AIDS APPROVED BUDGET

FOR CLINICAL TRIALS IN AIDS, U.C. SAN FRANCISCO

PERSONNEL	PERCENT	SALARY
Principal Investigator	25%	$11,377
Assist. Clin. Prof.	15%	$5,850
Assoc. Professor	15%	$7,822
Assoc. Professor	15%	$7,822
Assist. Ad. Prof.	50%	$17,704
Assoc. Professor	100%	$46,066
Epidemiologist	25%	$10,312
Epidemiologist	25%	$10,036
Admin. Nurse IV	15%	$3,893
Nurse Pract. II	100%	$22,130
Nurse Pract. II	100%	$20,573
Sr. Admin. Analyst	100%	$21,168
Secretary II	100%	$11,416
SRA III	100%	$18,383
Data Manager	100%	$13,954
Data Manager	100%	$13,290
Data Manager	100%	$13,290
Systems Analyst	50%	$12,728
Statistician	40%	$9,515
Assist. Programmer	50%	$7,407
Key Data Entry	100%	$11,053
AA III	15%	$2,291
Word Processing	50%	$6,792
SUBTOTAL		$304,872

SUPPLIES AND EXPENSES	
Consultant Costs	$2,000
Start-up Funds	$200,000
Mainframe Computer Time	$10,000
Office Supplies	$8,500
SUBTOTAL	$220,500

GRAND TOTAL	$525,372

If you have any questions please direct them to Dr. Lottie Kornfeld in my office. I wish you success in this important undertaking.

Sincerely,

C. L. Hopper

C. L. Hopper, M.D.
Vice President

Attachment

cc: Chancellor Krevans
Contracts and Grants Office

Recommended Format for AIDS Center Proposal

Title

1/2 page ← Abstract

Table of Contents (we recommend using the outline below)

Specific Objectives, including research questions

Methods

- Overview of design, including classification (RCT, case-control, etc.)
- Study subjects
  - selection criteria that define the target and accessible populations
  - design for sampling from the accessible population
  - sample size estimates
- Measurements
  - target predictor variables (intervention, if an experiment)
  - confounding predictor variables
  - outcome variables
- Pretest strategies
- Quality control and data management plans
- Statistical issues
  - stratistical hypotheses
  - plans for analysis
  - Sample size estimate
- Potential problems and solutions
- Timetable and organization chart

Ethical Considerations

Resources

- Resources, equipment and physical facilities
- Consultants and arrangements between institutions

Do not exceed 3 pages, single spaced, ordinary size font.

Budget

Background of investigators, including two page bio-sketches

References

Appendices