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AIDS CLINICAL RESEARCH CENTER

John L. Ziegler, M.D., Director
VAMC 141
4150 Clement Street
San Francisco, CA 94121
(415) 221-4810 ext. 3676

July 16, 1986

TO: ACRC Advisory and Executive Committees

FR: John L. Ziegler, M.D., Director

RE: 6-Month Progress Report

Because of wide interest in the conduct and progress of clinical trials supported by the UCSF AIDS Clinical Research Center, I have prepared this brief 6-month progress report. The document may be useful for AIDS-research Site Visits to the campus or for inquiries from members of the legislature.

A handwritten signature in cursive script, appearing to read "John", is written over the typed name.

JOHN L. ZIEGLER, M.D.
Director
UCSF AIDS Clinical Research Center

Enclosure

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
AIDS CLINICAL RESEARCH CENTER

CLINICAL TRIALS IN AIDS
SIX MONTH PROGRESS REPORT
JANUARY - JUNE, 1986

John L. Ziegler, M.D.
Director

Paul Volberding, M.D.
Deputy Director

ORGANIZATION

The AIDS Clinical Research Center (ACRC) at the University of California, San Francisco, was established by the State of California in 1983 to support a network of clinics and to create a Specimen Bank and Computer Center to register and analyze specimens and clinical data from patients with AIDS and ARC. In January 1986, the Center expanded its role to plan, coordinate and conduct clinical trials in AIDS. Funding was provided by the State of California through the Universitywide Task Force on AIDS. This report describes the progress of the first six months of this endeavor and proposes plans for the future.

The Clinical Center comprises the AIDS treatment units (both inpatient wards and outpatient clinics) in the three UCSF teaching hospitals -- San Francisco General, Moffitt-Long and the Veterans Administration Medical Center. Supported by the Clinical Trials State Grant are personnel assigned to specific clinical, laboratory, and administrative duties related to AIDS clinical trials.

Governance of the Center is accomplished by an Executive Committee, which meets twice monthly, and the AIDS Advisory Committee, appointed by the Dean of the School of Medicine. In addition, protocol development groups meet regularly to address treatment problems in specific generic areas. For example, one inter-hospital working group directed by Dr. Connie Wofsy organizes treatment of *Pneumocystis carinii* pneumonia, a common infection in AIDS patients. Another interdisciplinary group of

specialists headed by Dr. Mark Rosenblum meets regularly to coordinate clinical trials on neurological manifestations of AIDS.

The Center integrates five support programs:

- (1) Clinical Trials Coordinating Unit, which manages protocol development, data collection and analysis, and statistical consultation.
- (2) Laboratory Support for specific trials that require specimen storage, immunologic monitoring, or special viral diagnostic procedures.
- (3) Community Consortium, a network of Bay Area physicians who treat AIDS patients and who enter patients in controlled clinical studies.
- (4) Clinical Specialties that treat AIDS patients (Pediatrics, Neurology, Oral Medicine, Dermatology, Infectious Disease, Pulmonary, Gastroenterology, Oncology and Behavioral Medicine.)
- (5) Administration, which governs the Center, plans and projects budgets, manages project review and awards, and conducts educational programs.

UCSF has recruited an outstanding clinical epidemiologist, Dr. R. Palmer Beasley, to head a newly created Division of AIDS Epidemiology and Communicable Diseases, located at San Francisco General Hospital. Dr. Beasley will play a major role in the ACRC in developing and coordinating clinical and epidemiological studies in AIDS. Pioneering the use of hepatitis immune globulin

and hepatitis vaccine in Taiwan, Dr. Beasley will be in an ideal position to introduce comparable interventions in AIDS as they are developed.

PROGRESS

Since January, 1986, the ACRC has initiated and supported twenty-one clinical trials, which will be summarized here by category.

Primary Prevention

HIV seropositive individuals are identified and counseled as to behavior that causes spread of the virus in two large seroepidemiologic trials conducted by Drs. Andrew Moss and Richard Chaisson. These studies are aimed at two high risk groups (gay men and IV drug abusers, respectively) and examine the behavioral effects of notification of seropositivity.

Pediatric AIDS, though now comprising only one percent of the cases nationwide, is likely to increase. The Center now supports a coordinated approach to this problem in prevention, diagnosis, and treatment. Potential HIV seropositive mothers are identified through a variety of screening projects in San Francisco (AWARE, FACET, Alternative Test Centers) and counseled about pregnancy. Pregnant seropositive mothers are identified and placed on a careful observation program led by Dr. Mort Cowan aimed at early diagnosis of HIV in the infant. The development

of a neutralizing antiserum is underway and will be tested in affected infants when ready.

At least half of AIDS patients have neurologic abnormalities, ranging from mild alterations in mental status to severe encephalopathy and myelopathy. Two ACRC efforts have begun in this area. One under Dr. Dave Seigal, will identify neurologic abnormalities in various cohorts of gay men who participate in an epidemiologic study of the natural history of AIDS being conducted by Dr. Warren Winklestein of UC-Berkeley. Another will create an AIDS Neurology Board that will evaluate and assign protocol treatments of AIDS patients with identified neurologic manifestations. To this end, protocol therapy for patients with peripheral neuropathy, toxoplasmosis, and primary CNS lymphoma will commence in July, 1986.

Prevention of Progression.

Many individuals known to be HIV seropositive become symptomatic over time. The exact role of the virus (dose, pathogenicity) versus the host (cofactors such as infections, lifestyle, stress, genetics) in this process is unknown. Several trials supported by the ACRC are now aimed at detecting and interrupting this clinical decline.

Since it is known that HIV infects the CD4 (T4) lymphocyte and that the number of CD4 lymphocytes bears an inverse relationship to disease severity, it is logical to assume that the virus destroys its target cell. Thus, antiviral therapy should avert this process.

At San Francisco General Hospital, ACRC-supported trials under the direction of Dr. Paul Volberding explore a therapeutic role for compounds that inhibit HIV. Thus far, the results with three such drugs (suramin, ribavirin, and HPA-23) are disappointing. A present trial using AZT has not yet been completed. To date, 75 patients have been treated with antiviral drugs. Future trials will continue to explore antiviral strategies as promising agents become available.

Other attempts at preventing disease progression are aimed at putative cofactors. To this end, antiviral treatments of cytomegalovirus (CMV) and Epstein-Barr virus (EBV) are underway. Both of these herpesviruses are immunosuppressive and are frequently "activated" in ARC and AIDS patients. Fifty patients with oral hairy leukoplakia (an EBV-associated lesion) are under treatment by Dr. John Greenspan with BW B75911, and lesions are clearly regressing in some patients. Two studies (one using DHPG, the other isoprinosine) will begin soon in an attempt to suppress CMV infections in AIDS.

Finally, stress has been implicated as a potential cofactor that suppresses immune resistance. The effects of systematic stress reduction is testing this hypothesis in a controlled study of 60 gay men under the direction of Drs. Thomas Coates and Leon McKusick.

Treatment and Prevention of Infection and Neoplasms.

Pneumocystis carinii pneumonia (PCP) is the most common opportunistic infection in AIDS. Seven trials in this disease are currently coordinated and supported by the ACRC and are itemized on the chart which follows.

Treatment trials are aimed at improving control of the infections while avoiding drug toxicity. Two studies introducing dapsone will involve over 150 participants. Patients who fail standard treatments will be studied with new agents (such as trimetrexate) or novel methods of delivery (such as aerosolized pentamidine).

Two important studies that exemplify trial coordination by the ACRC will begin in July, 1986. One is a controlled study of fansidar, dapsone or pentamidine as prophylaxis for PCP. This will involve a collaborative effort of the community and the University, and will enroll 240 patients. A second trial under development will test the ability of high dose steroids to avert acute mortality in patients with PCP who have severe hypoxemia.

Management of the neoplasms that accompany AIDS is particularly challenging since standard treatments are often immunosuppressive. The ACRC supports a trial of interferon alpha with or without vinblastine in Kaposi's sarcoma. These regimens are well tolerated, reasonably effective and not immunosuppressive.

Another trial, instituted statewide in collaboration with UCLA, treats AIDS-associated non-Hodgkin's lymphoma with a novel combination chemotherapy regimen.

On the following three pages are a summary of studies currently being conducted.

JUNE 1986
SUMMARY OF AIDS CLINICAL TRIALS
(CURRENT STUDIES)

Primary Prevention

TITLE (DRUG/INTERVENTION)	DATE OPEN	P.I.	# OF PATIENTS # OF OPENINGS	RESULTS TO DATE
Identification and Coun- selling of HIV Positive Drug Addicts	01/86	Chaisson	<u>15</u> 100	In progress
Effect of Seropositivity Notification on Behavior in High Risk Population	01/86	Moss	<u>200</u> 450	In progress
Identification and Anti- viral treatment of Children of HIV Sero- positive Mothers	05/86	Cowan/ Wara	<u> </u> ?	Too early

Prevention of Progression

Randomized Double-Blind Placebo Controlled Study of Ribavirin in Pts with Symptomatic Virocytemic AIDS Related Conditions (ARC)	04/21/86	Volberding	<u>21</u> 30	No antiviral effects noted
Randomized Double-Blind Placebo Controlled Study of Azidothymidine (compound S) in Pts with ARC and S/P 1st Episode PCP	03/26/86	Volberding	<u>20</u> 20	In analysis
Effect of Stress Reduction on Immune Response	05/86	Coates/ McKusick	<u> </u> 60	Too early

Treatment of Aids-Associated Diseases

TITLE (DRUG/INTERVENTION)	DATE OPEN	P.I.	# OF PATIENTS # OF OPENINGS	RESULTS TO DATE
Randomized Maintenance Study of DHPG in AIDS related CMV Infection (primarily retinitis)	01/25/85	Mills	$\frac{25}{60}$	Appears to stabilize infection; neutropenia
Alpha Interferon with or without Vinblastine in AIDS related Kaposi's Sarcoma	01/13/86	Volberding	$\frac{5}{40}$	Too early; fever, fatigue; some partial responses
Randomized Double-Blind Study of Dapsone/Trimethoprim vs. Trimethoprim/Sulfamethoxazole in 1st Episode PCP	03/17/86	Wofsy	$\frac{18}{60}$	Too early. No unexpected toxicity
Chemotherapy for AIDS Associated Non-Hodgkins Lymphoma with Pentamidine for PCP Prophylaxis (Drugs: Vincristine, Cytosine, Methotrexate, Leucovorin, VP-16, Ara-C)	03/06/86	Kaplan/ Ziegler	$\frac{4}{20}$	Three CR; two relapsed
Therapy of AIDS related Kaposi's Sarcoma with Immunoabsorption using Protein A (Plasmapheresis)	09/04/85	Kiprov/ Abrams	$\frac{6}{10}$	Not effective; serum sickness, fatigue, myalgia
Effect of Pentamidine Prophylaxis of PCP in Oral Hairy Leukoplakia	02/86	Greenspan/ Conte	$\frac{\quad}{60}$	Too early
Use of Aerosolized Pentamidine in Pts with PCP	02/86	Hopewell	$\frac{2}{10}$	Too early

Treatment of AIDS-Associated Diseases (cont)

TITLE (DRUG/INTERVENTION)	DATE OPEN	P.I.	# OF PATIENTS # OF OPENINGS	RESULTS TO DATE
Chemotherapy and Radiation therapy of AIDS Pts with Primary CNS Lymphomas	07/86	Rosenblum/ Wara	<u>15</u>	Too early
Effect of BW A515U on EBV-Induced Oral Hairy Leukoplakia	01/86	Greenspan	<u>15</u> 50	Some regressions noted
Treatment of CMV with Isoprinosine in Pts with AIDS/ARC	07/86	Conant/ Drew	<u>40</u>	Too early
Pharmacokinetics of Pentamidine	02/86	Conte	<u>15</u>	Too early
Community Consortium Trial of Fansidar, Dapsone, Pentamidine (randomized, controlled)	07/86	Abrams	<u>240</u>	Too early
Treatment of AIDS-Associated ITP with Chloroquine	07/86	Stricker	<u>10</u>	Too early
Treatment of PCP failures with Dapsone-Trimethoprim	07/86	Wofsy	<u>30</u>	Too early
Pharmacokinetics of Dapsone and TMP/SMX	07/86	Benowitz	<u>60</u>	Too early

TOTAL NUMBER OF PATIENTS TREATED ON CURRENT AIDS CLINICAL TRIALS = 331 PTS

TOTAL NUMBER OF OPENINGS ON CURRENT AIDS CLINICAL TRIALS = 1360 OPENINGS

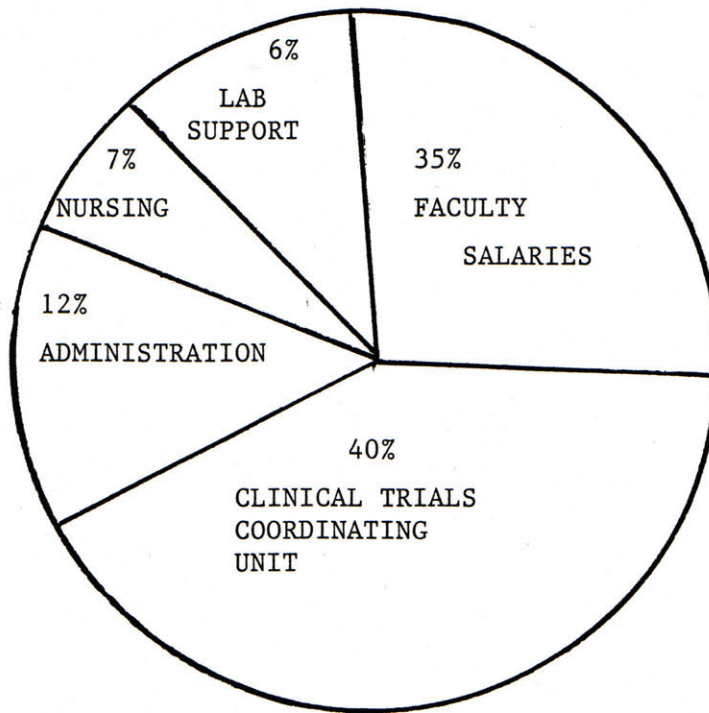
BUDGET

A total of approximately \$1.6 million in state funds was awarded by the Universitywide Task Force on AIDS to the ACRC for clinical trials for the 18-month period from January, 1986, through June, 1987.

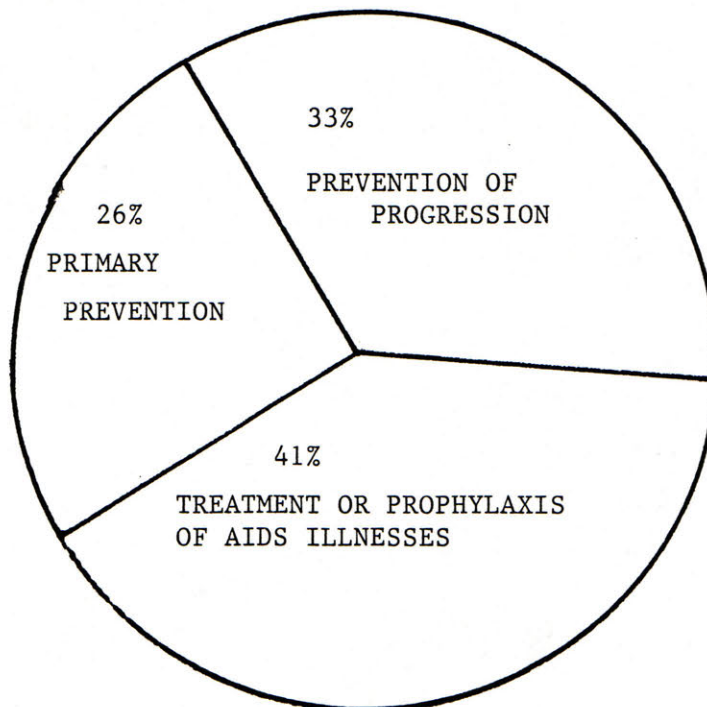
For administrative and accounting purposes, the ACRC clinical trials budget is divided into two components, core and project. The core budget provides stable funding for staff salaries and other resources needed to conduct comprehensive, multi-center clinical trial programs. The project budget is allocated competitively as full or partial support for trials which the ACRC and Dean's Advisory Committee deem promising. Most of these studies are partially funded with the aim of placing investigators in a more competitive position to achieve larger grants from other sources.

A chart illustrating the approximate budget allocation and a summary of the budget projection for the period July 1, 1986 - June 30, 1987 appear below.

CORE BUDGET



PROJECT BUDGET



AIDS CLINICAL RESEARCH CENTER

BUDGET 1986-87

CORE FUNDING - 86-87:

VA Medical Center (Office of the Director)

Faculty Salaries	20,246
Nursing Salary	22,918
Administration	72,840
Supplies	26,000

	142,004

San Francisco General Hospital

Faculty Salaries	194,632
Nursing Salaries	98,748
Clinical Trials Unit	210,281
Computer Center	44,193

	547,854

Moffitt - Long Hospital

Faculty Salaries	120,667
Specimen Bank	130,000

	250,667

UC Davis

Nursing Salary	19,407

	19,407

Total CORE funding FY 86-87	959,932
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Clinical Trials awarded FY 86-87	400,000
Clinical Trials funded FY 86-87	-368,766

Funds remaining for	
Clinical Trials	FY 86-87
	31,234

RELATED PROJECTS AND FUTURE PLANS

The ACRC serves as an important resource for pilot studies and novel treatment approaches where funds from conventional sources would be unavailable. UCSF faculty utilize the ACRC as an "umbrella" to secure funding for promising prevention, treatment and education projects. In addition, the ACRC helps to generate research proposals, coordinate educational activities, and recommend statewide treatment programs where feasible.

Some examples of these projects include:

- (1) The Center for Substance Abuse and Mental Health, a proposal by Dr. Stephen Hulley and others to the National Institute of Mental Health. (Site Visit July 21, 1986).
- (2) Statewide mental health provider training, a contract awarded by the State of California Department of Mental Health to Drs. John Ziegler and Leon McKusick.
- (3) A five-year, \$16 million grant proposal for laboratory and clinical studies of AIDS under the direction of Dr. Paul Volberding pending at the National Institutes of Health.
- (4) Sponsorship of various professional education conferences on subjects such as neurological manifestations on AIDS, intravenous drug abuse and ethnic minority issues.
- (5) Provision of a mainframe computer and other data support for AIDS-related projects.

- (6) Collaboration with basic science researchers to develop treatment or prevention strategies and clinical trials.
- (7) Oral Manifestations of AIDS, a program project proposal from the School of Dentistry by Dr. John Greenspan.
- (8) A contract for a drug treatment evaluation center from the National Institute of Allergies and Infectious Diseases, under the direction of Drs. Paul Volberding and John Mills.
- (9) Coordination of health care worker education programs with Dr. Philip Lee, sponsored by the Robert Wood Johnson Foundation.
- (10) Collaboration with the Langley Porter Institute for a Grant on Mental Health Aspects of AIDS (in preparation).

Plans for the coming year include an increased emphasis on prevention studies, with special attention to emerging risk groups in the San Francisco Bay Area (intravenous drug abusers, prostitutes, children of seropositive mothers, heterosexuals). A special effort will be made to involve all participating hospitals in clinical trials. Expansion of the patient registry will assist greatly in demographic studies and in establishing a data base for the natural history of AIDS-associated illness. Finally, the ACRC will coordinate continuous interchange with basic scientists to enable swift clinical tests of promising leads from the laboratory.

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FORMAT FOR AD HOC REVIEW OF GRANT SUBMISSIONS TO
THE UCSF AIDS CLINICAL RESEARCH CENTER

Title of Proposal: Reduced Dosage of Parenteral Pentamidine or
Aerosolized Pentamidine for the Treatment of
Pneumocystis carinii Pneumonia with AIDS: A Pilot Study

Principal Investigator: John Conte, MD, 1378 3rd AVE, Bx 0208

Reviewer: Judd Shellito, MD; VAMC 111 D

General Guidelines: Please critique the proposal assigned to you according to the following categories. Do not summarize the grant. Be brief and concise.

1. Significance of study relative to preventive or interventive clinical trials in AIDS.

Important clinical problem. Reasonable approach to improved therapy.

2. Methods

Straightforward

3. Ability to carry out project

Qualified investigators.

4. Likelihood of gaining important new knowledge from the project.

I am concerned that a dose of 4mg/kg pentamidine as an aerosol may be too low. Most studies of aerosolized material have shown that less than 30% of the aerosolized drug reaches the lower respiratory tract. The patients on aerosol may all fail, not because the delivery system is inadequate, but because the dose is too small.

5. Priority (based on 1-4, above):

1	2	3	4	5
Outstanding	Very Good	Average	Poor	Reject

As written. I would provide some information about changing the dose of aerosolized drug based upon the blood and urine pentamidine levels. If no detectable tissue levels are recorded after aerosolized pentamidine at 4mg/kg, the dose could be increased much higher without running the risk of toxicity.

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FORMAT FOR AD HOC REVIEW OF GRANT SUBMISSIONS TO
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Title of Proposal: Treatment of Cryptococcal Meningitis in AIDS using
Intrathecal Amphotericin B, Oral 5 F-C, and Oral
Ketoconazole

Principal Investigator: Neil Flynn, MD 2115 Stockton Blvd Sacramento CA 95817

Reviewer: Peter Jensen, MD; VAMC

General Guidelines: Please critique the proposal assigned to you according to the following categories. Do not summarize the grant. Be brief and concise.

1. Significance of study relative to preventive or interventive clinical trials in AIDS. It is not likely to be a significant study because it is asking two questions at the same time: (1) is intrathecal AMB, alone, therapeutically equivalent or superior to the intravenous form and (2) does ketoconazole have any role in the treatment of cryptococcal meningitis? There is no way to derive any meaningful answer to either question with this study design.
2. Methods
Monitoring is to be only by PE and activity level assessment; conventional indicators include such parameters as CSF cell count, latex agglutination titers, etc.
3. Ability to carry out project Study demands adequate neurosurgical support for implantation of Ommaya reservoirs; availability of this is not mentioned in the proposal. The results of the initial three patients are not encouraging: there was only a 33% success rate, simply because of patient non-compliance. Then, there is the well-known mechanical and infectious failure rate of Ommayas, variously reported to be as high as 85%.
4. Likelihood of gaining important new knowledge from the project.
Low; keto adds additional toxicity and untested efficacy and is not controlled for in this design. See #1 above.
5. Priority (based on 1-4, above):

1
Outstanding

2
Very Good

3
Average

4
Poor

5
Reject

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FORMAT FOR AD HOC REVIEW OF GRANT SUBMISSIONS TO
THE UCSF AIDS CLINICAL RESEARCH CENTER

Title of Proposal: Early Detection of AIDS: An Educational Trial for Dentists

Principal Investigator: Barbara Gerbert, PhD

Reviewer: William B. Wescott, DMD, MS

General Guidelines: Please critique the proposal assigned to you according to the following categories. Do not summarize the grant. Be brief and concise.

1. Significance of study relative to preventive or interventive clinical trials in AIDS. There is a definite need for dentists to be aware of the early oral manifestations of HIV infection and further education is essential. There are educational programs available such as the ones from Southern Illinois Univ. although I have not reviewed them. The funding requested will be used to validate instruments and methodology in preparation for a larger study for which other funding has been requested. (May or may not be funded). I would like to see more emphasis on infection control pro-

2. Methods ----- / cedures in conjunction with the project; however, that is another / issue.

Very Good

3. Ability to carry out project

Excellent

4. Likelihood of gaining important new knowledge from the project.

The recipients will gain a great deal and the researchers will have a better understanding of the generalized need for better educational programs for dentists in relation to HIV associated lesions.

5. Priority (based on 1-4, above):

1
Outstanding

2
Very Good

3
Average

4
Poor

5
Reject

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FORMAT FOR AD HOC REVIEW OF GRANT SUBMISSIONS TO
THE UCSF AIDS CLINICAL RESEARCH CENTER

Title of Proposal: Early Detection of AIDS: An Educational Trial for Dentists

Principal Investigator: Barbara Gerbert, Ph.D.

Reviewer: Timothy P. Carmody, Ph.D.

General Guidelines: Please critique the proposal assigned to you according to the following categories. Do not summarize the grant. Be brief and concise.

1. Significance of study relative to preventive or interventive clinical trials in AIDS.

The intervention to be pilot tested in this study may contribute to early detection of AIDS/ARC and to decreased disease morbidity.

2. Methods

The assessment methodology relies on self-report (survey) regarding subjects' knowledge, attitudes, and behavior. However, the validity/accuracy of these data will be examined in the proposed auxiliary study. No methods are described to compare dentists who join vs. those who do not to assess the generalizability of the results.

3. Ability to carry out project

This team of investigators and consultants appears to have both the resources and competence to carry out ^{at} this project. They also have experience in analyzing practitioner survey data.

4. Likelihood of gaining important new knowledge from the project.

These educational techniques have been used successfully with physicians in other content areas. This project is likely to determine the impact of these intervention strategies on the attitudes and behaviors of dentists related to early detection of AIDS.

5. Priority (based on 1-4, above):

1	2	3	4	5
Outstanding	Very Good	Average	Poor	Reject

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FORMAT FOR AD HOC REVIEW OF GRANT SUBMISSIONS TO
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Title of Proposal: Phase I Trial of Vinblastine Infusion in Patients with
Epidemic Kaposi's Sarcoma

Principal Investigator: Craig A. Lindquist

Reviewer: Thomas B. Bradley, M.D.

General Guidelines: Please critique the proposal assigned to you according to the following categories. Do not summarize the grant. Be brief and concise.

1. Significance of study relative to preventive or interventive clinical trials in AIDS.

The study may well point the way to an effective therapy for KS in AIDS.

2. Methods

My calculations indicate a maximum dose of 0.95 rather than 1.05 mg/m²/day. I have some concern about the criteria for dosage escalation and the frequency of hematologic studies. Hematologic nadirs after bolus vinblastine occur at about one week. Would weekly observations suffice in a patient whose WBC fell from 4000 to 2100 and who therefore qualified for dose escalation?

3. Ability to carry out project

Both patients and techniques are amply available for this project.

4. Likelihood of gaining important new knowledge from the project.

See #1 above.

Gratuitous comment: Nice word processor. It's too bad it doesn't have a spell check option.

5. Priority (based on 1-4, above):

1
Outstanding

2
Very Good

3
Average

4
Poor

5
Reject

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THE UCSF AIDS CLINICAL RESEARCH CENTER

Title of Proposal: Phase I Trial of Vinblastine Infusion in Patients with
Epidemic Kaposi's Sarcoma

Principal Investigator: Craig Linquist

Reviewer: B. Jensen, VAMC

General Guidelines: Please critique the proposal assigned to you according to the following categories. Do not summarize the grant. Be brief and concise.

1. Significance of study relative to preventive or interventive clinical trials in AIDS. This study involves an interesting innovative use of what many consider to be a standard drug in the therapy of epidemic KS. The laboratory studies of KS cell lines underscore the potential benefit on kinetics of prolonged drug exposure.
2. Methods I see no problem with either the methodology or the feasibility of completing this project. Because one of the objectives of the study is to define [toxicity and because there are many underlying neurologic abnormalities in this patient population, I wonder if more detailed neurologic evaluation (such as nerve conduction studies) should be performed as part of the initial evaluation. Since the study [cited Ratain and Vogelang found that serum levels predicted for cytoperria, and serum.
3. Ability to carry out project level will be obtained weekly, I wonder if [these will be used to determine dose.
4. Likelihood of gaining important new knowledge from the project.
High
5. Priority (based on 1-4, above):

1	2	3	4	5
Outstanding	Very Good	Average	Poor	Reject

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FORMAT FOR AD HOC REVIEW OF GRANT SUBMISSIONS TO
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Title of Proposal: The Efficacy of Intralesional Velban in the
Treatment of Oral Kaposi's Sarcoma

Principal Investigator: Francina Lozada-Nur, DDS, MS UCSF S-657; Marcus Conant MD

Reviewer: Dr. Diessereth VAMC

General Guidelines: Please critique the proposal assigned to you according to the following categories. Do not summarize the grant. Be brief and concise.

1. Significance of study relative to preventive or interventive clinical trials in AIDS.

Intralesional Velban for oral Kaposi's is illogical when an effective means (radiation) exists for its management. This program lacks any redeeming values, and will be morbid as well.

2. Methods

Intralesional administration of Velban will be conducted on 1/2 of palate. The other half will serve as control.

3. Ability to carry out project

The PI's choice of intralesional administration of a chemotherapeutic agent suggests he has no experience with chemotherapy.

4. Likelihood of gaining important new knowledge from the project.

This is a throw-back to the DCG Era. It will be morbid, and will be unlikely to control the disease. It will be associated with local toxicity. I recommend disapproval.

5. Priority (based on 1-4, above):

1	2	3	4	(5)
Outstanding	Very Good	Average	Poor	Reject

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THE UCSF AIDS CLINICAL RESEARCH CENTER

Title of Proposal: The Efficacy of Intralesional Velban in the Treatment of
Oral Kaposi's Sarcoma

Principal Investigator: Lozada-Nur

Reviewer: William Wescott, DMD VAMC

General Guidelines: Please critique the proposal assigned to you according to the following categories. Do not summarize the grant. Be brief and concise.

1. Significance of study relative to preventive or interventive clinical trials in AIDS. Velban may well control the expansile oral KS lesions and reduce ulceration, bleeding and trauma to the lesion as well as improve patients ability to eat. The undesirable side effects of radiation would be eliminated.
2. Methods OK for monitoring the lesions. (assume injections precautions, side-effects, etc. have been covered).
3. Ability to carry out project
Excellent; experienced investigators
4. Likelihood of gaining important new knowledge from the project.
Excellent; if successful there would be great benefit to many patients.
5. Priority (based on 1-4, above):

<u>1</u>	2	3	4	5
Outstanding	Very Good	Average	Poor	Reject

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FORMAT FOR AD HOC REVIEW OF GRANT SUBMISSIONS TO
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Title of Proposal: Will Indomethacin Alleviate "B" Symptoms in Patients
with ARC and AIDS?

Principal Investigator: Frank H. Valone, VAMC

Reviewer: Marc Goldyne, MD VAMC

General Guidelines: Please critique the proposal assigned to you according to the following categories. Do not summarize the grant. Be brief and concise.

1. Significance of study relative to preventive or interventive clinical trials in AIDS. Because some of the debilitating symptoms of AIDS or ARC could be caused by eicosanoids susceptible to inhibition by indomethacin (fever, diarrhea, etc.) it makes sense to evaluate the potential benefit of this drug (based also on the data from the Lancet (1986)2:570 as paliative therapy.
2. Methods
The methods seem appropriate for the goals of this proposal.
3. Ability to carry out project Dr. Valone is a well-established independent investigator with experience in dealing with various aspects of arachidonic acid metabolism. I have no doubt he is fully capable of carrying out the proposed studies.
4. Likelihood of gaining important new knowledge from the project.
If these trials support the literature experience in regard to inomethacin alleviating some of the debilitating symptoms of AIDS or ARC, it will be a worthwhile accomplishment.
5. Priority (based on 1-4, above):

1	2	3	4	5
Outstanding	Very Good	Average	Poor	Reject

CONFIDENTIAL

RETURN TO: Dr. John L. Ziegler, MD
VAMC - 141; Campus Mail

or hand deliver to:
ACRC
V A M C
4150 Clement St.
Bldg 4 - Room 203

**FORMAT FOR AD HOC REVIEW OF GRANT SUBMISSIONS TO
THE UCSF AIDS CLINICAL RESEARCH CENTER**

Title of Proposal: Will Indomethacin Alleviate "B" Symptoms in Patients with
ARC and AIDS?

Principal Investigator: Frank H. Valone, MD; VAMC

Reviewer: William Seaman; VAMC x2104

General Guidelines: Please critique the proposal assigned to you according to the following categories. Do not summarize the grant. Be brief and concise.

1. Significance of study relative to preventive or interventive clinical trials in AIDS.

The studies are of significance in that they will test one therapeutic role of indomethacin in relation to certain symptoms of patients with ARC

2. Methods The methods are deficient in defining a limited number of objective variables to be assessed. There is no power analysis and it is almost certainly not possible that the number of patients is sufficient to test outcome in one large number of variables, many of which are poorly defined.

3. Ability to carry out project

The investigators have the ability to carry out the project.

4. Likelihood of gaining important new knowledge from the project.

No meaningful results can be obtained until clearly defined endpoints are detailed. "Peridontal disease" is too vague and is not likely to be significantly altered in three weeks. The CBC and SMA-12 provide a very large number of variables. I suggest daily temperature as one defineable variable.

5. Priority (based on 1-4, above):

1	2	3	4	5
Outstanding	Very Good	Average	Poor	Reject

As currently defined, I would reject the proposal. With appropriate revisions, I would give it a high priority. A statistician should be consulted.

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FORMAT FOR AD HOC REVIEW OF GRANT SUBMISSIONS TO
THE UCSF AIDS CLINICAL RESEARCH CENTER

Title of Proposal: Immunologic Parameters and Concurrent infection
associated with Heterosexual Transmission of HIV

Principal Investigator: Warren Winklestein, Epid Prog; 140 Warren Hall UC-B

Reviewer: Dr. David Wofsy; VAMC 111 R

General Guidelines: Please critique the proposal assigned to you according to the following categories. Do not summarize the grant. Be brief and concise.

1. Significance of study relative to preventive or interventive clinical trials in AIDS. The study that this grant will supplement is an important one, but the supplement itself is little more than window dressing. Object #1 (enumeration of T cell subsets) is very unlikely to add to knowledge from previous studies of homosexual men and hemophiliacs. Objective #2 (distinction of HSV-1 from HSV-2, detection of gonorrhea and trichomonas) is a worthwhile improvement on the original study design.

2. Methods

Appropriate

3. Ability to carry out project

Good

4. Likelihood of gaining important new knowledge from the project.

Main Study - High
This Supplement - Low

5. Priority (based on 1-4, above):

1
Outstanding

2
Very Good

3
Average

4
Poor

5
Reject

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4150 Clement St.
Bldg 4 - Room 203

FORMAT FOR AD HOC REVIEW OF GRANT SUBMISSIONS TO
THE UCSF AIDS CLINICAL RESEARCH CENTER

Title of Proposal: Immunologic Parameters and Concurrent Infection
Associated with Heterosexual Transmission of HIV

Principal Investigator: Warren Winkelstein, Epid Prog, 140 Warren Hall UC-B

Reviewer: Dr. Warren Browner, VAMC

General Guidelines: Please critique the proposal assigned to you according to the following categories. Do not summarize the grant. Be brief and concise.

1. Significance of study relative to preventive or interventive clinical trials in AIDS. I can't figure out what has been proposed well enough to be able to say! However, it's not at all clear that any of the immunologic tests would be helpful in preventing AIDS.

2. Methods

I think that if I can't figure out what is proposed, then the investigators don't really know either. It's hard to tell whether they propose a case-control study of "infected" cases versus "non-infected" controls, or a follow-up of "high risk" controls.

3. Ability to carry out project

The power of the study is extremely low (can only detect relative risks of G-7), and that's before adjusting for confounders like IVDA.

4. Likelihood of gaining important new knowledge from the project.

. Seems low

5. Priority (based on 1-4, above):

1	2	3	4	5
Outstanding	Very Good	Average	Poor	Reject

But could be anywhere from 1 to 5!! I just can't tell.