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TREATMENT OF HERPES VIRUS INFECTIONS
WITH ZOVIRAX® (ACYCLOVIR) OR CONDYLOMA ACUMINATA
WITH WELLFERON® (HUMAN LYMPHOBLASTOID INTERFERON)
IN PATIENTS WITH UNEXPLAINED LYMPHADENOPATHY SYNDROME

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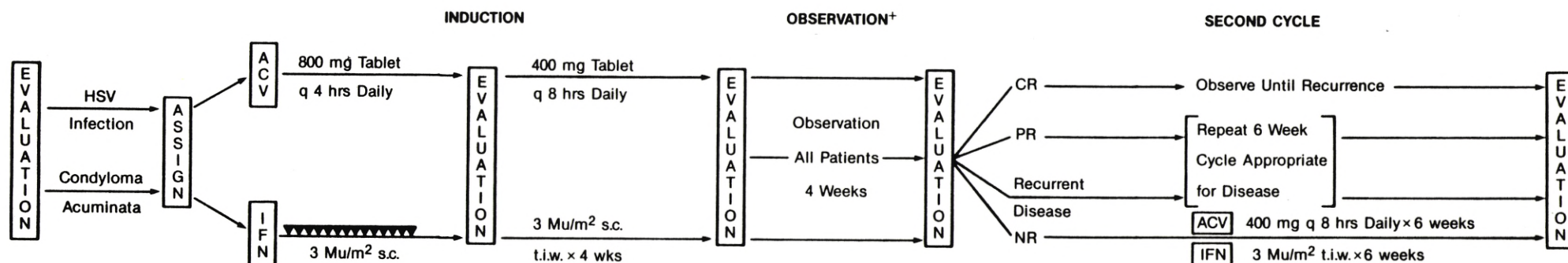
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**WELLFERON® FOR CONDYLOMA ACUMINATA
ZOVIRAX® FOR HERPES SIMPLEX
IN PATIENTS WITH UNEXPLAINED LYMPHOADENOPATHY SYNDROME**

PRIMARY OR RECURRENT HSV
SEVERE/RESISTANT CONDYLOMATA
(30)

UCLA MEDICAL CENTER
BURROUGHS WELLCOME CO.



WEEK:	Entry	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
EVALUATIONS	*			*		*		*		*		*		*		*		*
HEMATOLOGY	*		*	*		0		*		0		*		*		0		*
CHEMISTRIES	*		*	*		0		*		0		*		*		0		*
BIOPSIES/ ISOLATES	*							*										*

+:Patients developing disease other than original diagnoses may cross to other arm.
0:Optional-to be repeated if previous laboratory values abnormal.

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WELLFERON® OR ZOVIRAX® FOR VIRAL INFECTIONS
IN UNEXPLAINED LYMPHADENOPATHY SYNDROME

1.0 OBJECTIVES

- 1.1 To determine response patterns of condyloma acuminata of LAS patients to 6 weeks of treatment with human lymphoblastoid interferon (WELLFERON).
- 1.2 To characterize response of herpes virus infections in LAS patients to oral acyclovir (ZOVIRAX) administration.
- 1.3 To determine the tolerance and toxicity of acyclovir or human lymphoblastoid interferon in patients with LAS.
- 1.4 To measure response rates and patterns of recurrent/resistant condyloma acuminata or recurrent herpes virus infections to a second six-week course of human lymphoblastoid interferon or acyclovir, respectively.
- 1.5 To determine the effectiveness of combined acyclovir and interferon treatment for disease that does not respond to initial acyclovir or interferon therapy alone.
- 1.6 To study the molecular virology of herpes viruses and condyloma acuminata which do and do not respond to acyclovir or interferon therapy.

2.0 BACKGROUND AND RATIONALE

2.1 Prolonged Unexplained Lymphadenopathy Syndrome

The acquired immunodeficiency syndrome (AIDS) is defined as biopsy-confirmed Kaposi's Sarcoma and/or the occurrence of one or more life-threatening opportunistic infections in persons with no previously documented immune deficiency (1). Patients with AIDS have prominent defects in cell-mediated immunity. Clinical manifestations may include anergy, marked reduction in T-helper cell numbers, inversion of T-helper/T-suppressor cell ratios, depressed mitogen and antigen responses and depressed natural killer cell activity (2, 3). Retrospective studies and analyses of newly occurring cases have demonstrated the existence of major groups at high risk of acquiring AIDS. These are: homosexual and bisexual men, intravenous drug abusers,

persons born in Haiti and now living in the U.S., patients with hemophilia, and recipients of blood transfusions.

The first report of AIDS was in the Spring of 1981. As of December, 1983, 3000 cases that meet the current definition of AIDS had been reported by physicians and health departments in the U.S. (4). Of these reported cases, 1283 or 43% of patients are known to have died. One of the striking epidemiologic features of AIDS is the age factor; 90% of reported patients are between 20 and 49 years old. Although the rate of increase of diagnosed cases appeared lower during the last half of 1983, this may reflect a longer lag-time in reporting cases to local, state, and national health agencies.

Simultaneous with the AIDS epidemic, a syndrome of prolonged unexplained generalized lymphadenopathy (LAS) was recongized in the same population groups at increased risk for AIDS (5). These patients exhibit lymphadenopathy which may be associated with low grade fevers, night sweats, weight loss, and/or fatigue. Lymph node biopsies reveal follicular hyperplasia (6). Peripheral blood T-helper/T-suppressor ratios are typically reduced in some cases due to reduced numbers of T-suppressor/cytotoxic cells. These patients may have an unusual acid-labile form of human leukocyte, or alpha, interferon in their serum (7). Persons with LAS and immune deficiency appear to be at increased risk for development of AIDS (8).

One of the major problems for AIDS patients is the high number of opportunistic and virus infections, often occurring concomitantly. Virus infections, in particular Cytomegalovirus and Epstein-Barr virus, occur in nearly 100% of these patients. Due to suppressed immunity, herpes simplex infections of the genital or perianal area can become quite severe and/or chronic. Volberding and colleagues (9) have reported that 17/20 patients, in their initial trial with human IFN- α_2 , developed herpes simplex infections during the course of study. Another virus-associated disease, condyloma acuminata, was observed in 7/20 patients entered in that study (9). Because virus infections

pose such a problem for these patients, intervention with antiviral agents at early stages of disease development seems logical for prevention of severe infections and possible viral dissemination.

Acyclovir (ZOVIRAX®) is a potent antiviral that has been marketed for intravenous or topical application as treatment of mucocutaneous herpes simplex virus infections. In addition, an oral capsule formulation is being evaluated extensively in on-going clinical trials. Human lymphoblastoid interferon (WELLFERON®) is a highly purified preparation of a mixture of alpha interferons and presently is under clinical development for viral and oncologic indications. A pilot study and multicenter Phase II study have demonstrated that this interferon is effective in treating severe resistant/recurrent condyloma acuminata in males and females. It is the purpose of the present study to employ these two agents, at doses and schedules known to be effective, for the treatment of these two types of viral diseases in LAS patients. ZOVIRAX will be given orally to patients with herpes virus infections and WELLFERON will be administered subcutaneously to patients with condyloma acuminata of the genital area, perianal or rectal mucosa.

2.2 Interferons

2.2.1 Description

Interferon was the term used originally for an inducible cellular factor which protected eukaryotic cells against influenza virus infection (10). Today it is known that this agent is a protein secreted by cells in response to viral or other stimuli (e.g., mitogens, antigens) and that it elicits a number of biological responses. Some of the properties associated with interferon, in addition to antiviral activity, include immunomodulatory and antiproliferative effects.

2.2.2 Biologic Properties

Three major types of interferons have been identified and differ in their molecular weight, antigenicity, stability and other biochemical properties. Current nomenclature refers to human interferons as alpha (HuIFN- α), beta (HuIFN- β) and gamma (HuIFN- γ) which were formerly leukocyte, fibroblast and immune interferons, respectively. Cells induced to make interferon by viral or other stimuli commonly synthesize more than one type but a preparation is usually identified by the predominant component. The following table outlines the known human interferons:

NOMENCLATURE OF HUMAN INTERFERONS

<u>Current</u>	<u>Former</u>	<u>No. of Genes</u>	<u>Chromosome</u>	<u>Properties</u>
HuIFN- α	Leukocyte	12-13	9	Acid-stable; Virus-induced.
HuIFN- β	Fibroblast	1	9	Acid-stable; Virus-induced.
HuIFN- γ	Immune	1	12	Acid-labile; Mitogen-induced.

The numerous bacteria-derived human alpha subtypes differ in their antiviral properties (11) and they are distinct from HuIFN- β and HuIFN- γ . The identification of these multiple interferons with different biological properties has led to the identification of what is now referred to as "the interferon system" (12).

Interferon for clinical evaluation may be produced from blood leukocytes, from cell lines of fibroblasts or lymphoblasts, all stimulated with virus, or by recombinant DNA techniques. The interferon to be administered in this study, WELLFERON®, is purified from supernatants of cultures of human lymphoblastoid cells, Namalwa, after Sendai virus stimulation (See Section 4.1). The

purification process results in a product containing multiple subtypes of HuIFN- α . Its chemical, physical, immunologic and biologic properties closely resemble those of the most widely used native interferon, the leukocyte interferon prepared by the Finnish Transfusion Service from buffy coat cells of donated blood.

2.2.3 Antiviral Activities of Interferons

A substantial database documenting in vitro and in vivo antiviral properties of interferons has been reviewed comprehensively in other sources (13, 14). In brief, studies performed principally in vitro have revealed that:

- a. most cell types can produce an interfering substance and can respond to it by the development of an antiviral state.
- b. the substance is not virucidal but rather confers protection by inducing expression of certain cellular genes.
- c. the antiviral effect is not virus specific.
- d. exquisitely small amounts are required for protection.
- e. the protection of cells may show some degree of species specificity.

Interferon is also important in the control of viral infections in vivo. The appearance and level of interferon correlate with host recovery and that correlation is better than for other elements of host defense systems (15). Its role was more clearly established when anti-interferon antibody was shown to compromise host recovery from viral infection (16). Numerous therapeutic models have been developed in which the application of exogenous interferon or the induction of endogenous interferon modulates viral infection. Consistent with the in vitro findings, interferon is active against a wide spectrum of viruses in a variety of animal hosts.

2.2.4 Interferon in the Treatment of Human Viral Diseases

Although interferons were identified originally by their antiviral nature, clinical evaluation in viral diseases has been limited. Appropriate studies have been hampered by the practical problems of limited supplies and the fact that interferon is most effective as an antiviral when administered prophylactically. A growing body of evidence from studies carried out at relatively low doses is demonstrating that exogenous interferon can produce antiviral effects in man.

Some of the most significant responses to interferon in virus-associated disease have been reported in patients with laryngeal papillomas. These epithelioproliferative growths afflict the larynx and airways of both children and adults and contain viral DNA from a unique subtype of human papilloma virus, HPV-11. Four reported studies utilizing leukocyte-derived interferon have shown that systemic administration of low doses of interferon causes regression and/or growth control of these warty lesions (17, 18, 19, 20).

Hepatitis B virus has been treated with alpha or beta interferon in several studies. Weimar et al. (21) reported daily treatment with 12 Mu and weekly maintenance at 50% dose decrements produced a decrease only in DNA polymerase levels. Work by Merigan and colleagues has addressed the question of combined therapy in the treatment of chronic hepatitis. Studies employing adenine arabinoside, leukocyte interferon or a combination of these have shown that multiple cycles of the two agents were most effective in eradicating serum DNA polymerase activity (22). Treated patients also had improved liver biopsies and reduced serum transaminase levels (23).

A variety of herpesvirus infections has also been treated with interferon. In cutaneous varicella zoster, disease improvement has been observed at the higher

doses tested (24). Disease dissemination, new vesicle formation, acute pain, post-herpetic neuralgia and visceral complications were all reduced. However, short-term therapy (48 hours) at the same dose resulted in only modest effects on the symptoms observed (25). In a separate study, 44 immunocompromised children with cancer were treated with leukocyte interferon resulting in a diminished spread of infection in the skin and visceral complications (26). The value of prophylactic interferon against HSV-1 infections was demonstrated in patients undergoing trigeminal nerve surgery (27). Both virus shedding and the incidence of recurrent herpes labialis was reduced. Topical application of interferon showed limited efficacy in herpetic dendritic keratitis but significantly reduced healing time and virus shedding when combined with debridement (28) or trifluorothymidine (29). Immunocompromised homograft recipients are at high risk for viral infection and many develop HSV and CMV infections. Interferon therapy post-transplant has shown limited efficacy (30); whereas, IFN prophylaxis for 14 weeks in 20 transplant recipients resulted in significant reduction of clinical signs of CMV infection (31).

2.3 Acyclovir

2.3.1 Description

Acyclovir [9-(2-hydroxy ethoxy methyl) guanine] is an acyclic purine nucleoside analog that is a potent inhibitor of herpes simplex virus (HSV), types 1 and 2, replication. This compound is highly selective in inhibiting viral enzyme and has extremely low toxicity for host cells. A very substantial database has been established on the mechanism of action of this agent and preclinical testing of safety and efficacy. The very high therapeutic index of this compound can be explained by a number of differences between cellular

and virus-encoded enzymes (32). Experimental work has shown that:

- a. herpesvirus-encoded thymidine kinase phosphorylates acyclovir; cellular thymidine kinase does not.
- b. HSV-infected cells contain 40-100 times greater amounts of acyclo-GTP than uninfected cells.
- c. viral polymerases are more sensitive to acyclo-GTP inhibition than cellular DNA polymerases.
- d. acyclo-GTP is a much better template for viral polymerases.
- e. viral DNA polymerase has a 50-fold greater affinity for acyclo-GMP-terminated template.

The sum total of these selective inhibitions is a 300 to 3000-fold difference in the toxicity of acyclovir to herpes viruses and to the cell (32).

2.3.2 Antiviral Properties of Acyclovir

Numerous in vitro studies have demonstrated acyclovir's activity against HSV, Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Varicella zoster virus (HZV), and other herpes virus infections. Studies in nonhuman primates, guinea pigs, rabbits, and mice have documented its antiviral activities in vivo. The results of such experimentation have been reviewed thoroughly in the proceedings of a recent symposium (33). In brief, pre-clinical animal studies have demonstrated that:

- a. topical application is effective against cutaneous herpes simplex in guinea pigs.
- b. genital herpes virus type 2 infection of mice and guinea pigs can be treated successfully by topical therapy.
- c. oral or subcutaneous administration at 10 mg/kg is effective against herpetic encephalitis in mice.
- d. application of 1, 2, or 3% ointment is effective in treating herpetic keratitis in rabbits.

- e. intravenous or intramuscular dosing effectively inhibits similar varicella virus infection.
- f. murine cytomegalovirus is exquisitely sensitive to acyclovir both in vitro and in vivo.

These results coupled with extensive toxicologic studies in animals have confirmed the high selectivity of acyclovir for herpes viruses and its low toxicity for uninfected cells.

2.3.3 Use of Acyclovir in Humans

Acyclovir has been approved for intravenous and topical use for treatment of mucocutaneous herpes simplex virus infections. Intravenously administered acyclovir has shown clinical efficacy in a number of studies of patients with herpes simplex and varicella zoster virus infections (33). At present, an oral capsule formulation is being studied extensively in clinical trials. This orally administered form has demonstrated clinical efficacy in first-episode and recurrent genital herpes simplex infections (34, 35). Its efficacy for other mucocutaneous herpes infections, varicella zoster, and Epstein-Barr virus infections is currently under investigation.

2.4 Interferon in Treatment of Condyloma Acuminata

Condyloma acuminata, or genital warts, are benign fibro-epithelial tumors of suspected viral etiology. Viral particles in condyloma tissue were demonstrated first by electron microscopy and were classified as members of the papillomavirus group (36, 37). Human papilloma viruses (HPV) are a heterogeneous group consisting of at least eighteen distinct types (38, 39). Types 1, 2, 3, 4 and 7 have been associated with benign skin warts. The type found in condyloma tissue is designated HPV-6 (40) and DNA hybridization and restriction enzyme analyses have shown it to have 25% homology with laryngeal papilloma virus DNA, HPV-11 (41, 42). Hybridization studies using cloned HPV-6 genomic sequences have shown that 93 percent of all genital warts screened contained DNA sequences homologous to HPV-6 (41).

Condyloma acuminata has a preference for moist mucosal surfaces. These epithelial proliferations have a predilection for the genital area and are found frequently in sexually active males and females. The disease presents in females as verrucous lesions on the perineum, vaginal mucosa or portio-vaginalis of the cervix and in males on the genitalia, perianal or rectal mucosa. Each small exophytic keratinized vegetation arises separately from the skin or mucosa. The low power microscopic appearance suggests fronds of actively growing epithelium. Each frond is supported by a thin connective tissue branch which bears vessels leading to the epithelial layer. The condyloma is infiltrated with inflammatory cells throughout the subepithelial zone and epithelial cells occasionally exhibit atypical hyperplasia and dysplasia.

Early studies first reported nearly a decade ago demonstrated the utility of topical application of a vaseline-lanolin ointment containing crude human leukocyte interferon (43, 44). The results of this and other studies are outlined in the following table:

	Results Reported from Study of:			
	<u>Ikie et al. (43)</u>	<u>Ikie et al. (44)</u>	<u>Wallach et al. (45)</u>	<u>Gall et al. (46)</u>
Disease Severity:	Unknown	Unknown	Unknown	Resistant/ severe
Prior Therapy:	Unknown	Unknown	Unknown	Podophyllin
Interferon:	Leukocyte	Leukocyte	Fibroblast	WELLFERON®
Route:	Topical	Topical	i.m./s.c.	i.m.
Formulation:	Ointment	Ointment	Solution	Solution
Dose:	.04 Mu/gm	.04 Mu/gm	5 Mu	5 Mu/m ²
Schedule:	5-6 x daily	5-6 x daily	t.i.w.	daily x 28; then t.i.w.
Duration:	2-8 wks	2-8 wks	6 wks	6 wks
Complete Responses:	36/40	4/10	5/5	8/16
Partial Responses:	Unknown	6/10	0/5	7/16

Interpretation of results from the three earliest studies (43, 44, 45) is difficult because prior therapy, history, and extent of disease were not reported.

A 17 patient pilot study has examined the effects of systemic WELLFERON® on genital warts in women who have failed a minimum of 10 Podophyllin treatments (46). WELLFERON was administered at 5 Mu/m²/day intramuscularly for 28 days followed by three doses per week for 2 weeks. Sixteen patients completed therapy; one patient withdrew from the study after 1 week due to side effects of the interferon. Eight of 16 had complete regression (CR), 7 had good partial responses (PR) and one patient did not respond to treatment. All patients on this study required dose reductions to 3 Mu/m² due to decreased WBC's and/or side effects such as headaches, nausea and vomiting.

A Phase II study to examine the efficacy of 1 vs. 3 Mu/m² of WELLFERON given intramuscularly or subcutaneously to patients with resistant disease is being performed at four institutions. The study design requires daily injections for 14 days followed by treatment three times weekly for one month. Patients experiencing partial regression may continue for an additional month and nonresponding patients have doses escalated from 1 to 3 or 3 to 5 Mu/m². To date, the most experience has been gained at Duke Medical Center where 28 patients (24F/4M) have received the full six weeks of therapy. Responses are: 9 CR, 12 PR, 4 S and 2 NR. One patient withdrew from the study before completing an adequate course of treatment. Ten of 14 patients started at 1 Mu/m² have required dose escalations in order to achieve optimal responses. Only 4 patients treated at 3 Mu/m² have been escalated to 5 Mu/m² after 6 weeks of therapy.

Based on these significant responses with WELLFERON in Phase I and II studies, the present Phase III/IV trial is being undertaken to establish the effects of systemic administration of 3 Mu/m² of WELLFERON on the regression of severe recurrent genital warts. The antiviral effects of human lymphoblastoid interferon

will be measured in LAS patients with recurrent/resistant disease on a dose and schedule known to be effective; namely, 3 Mu/m²/day x 14 followed by 3 doses per week for an additional 4 weeks.

2.5 Acyclovir for Herpes Virus Infections

The rationale for the use of acyclovir (ZOVIRAX®) in treating herpes virus infections in LAS patients is based on its high selectivity for these viruses. Extensive clinical trials have demonstrated the safety and efficacy of topical administration of ZOVIRAX for recurrent herpes labialis and genitalis. In addition, studies with intravenous administration have proven its effectiveness in treating acute viral infections in both immunocompetent and immunocompromised patients. Multiple-dose studies have been performed to evaluate the efficacy, safety, pharmacokinetics and bioavailability of oral acyclovir as well.

Intravenous administration of ZOVIRAX Sterile Powder is efficacious for varicella and zoster infections in patients with competent and compromised immune status. A multicenter trial conducted in immunocompromised children with chickenpox infections resulted in 0/7 ZOVIRAX treated patients developing pneumonitis; whereas, 5/11 placebo recipients did. In a similar study, 94 patients with zoster infections (shingles) were evaluated. Fifty-two patients received acyclovir and 42 received placebo. ZOVIRAX therapy resulted in significant reductions in cutaneous dissemination, visceral dissemination, and the number of patients deemed treatment failures. Two controlled trials in immunocompetent patients with acute zoster infection or trigeminal zoster have corroborated these results. ZOVIRAX administered at a dose of 5 mg/kg every 8 hours for 5 days significantly shortened the time of new lesion formation, time to vesicle collapse, and time to complete crusting of lesions. Two additional randomized placebo-controlled trials at different doses of ZOVIRAX have shown that patients treated with acyclovir had a significantly abbreviated time of viral shedding when compared to placebo recipients.

ZOVIRAX® Capsules have been employed in controlled clinical trials in patients with initial and recurrent genital herpes. Proportional increases in bioavailability were observed through doses of 600 mg with higher than anticipated values at 800 mg doses. Oral administration of ZOVIRAX has shown significant decreases in healing time, severity and duration of pain, new lesion formation, and viral shedding when compared to placebo. In patients with initial episodes of genital herpes, inguinal adenopathy and headache resolved significantly faster in the ZOVIRAX treated group. Likewise, dysuria in females was resolved more quickly. Early treatments significantly improved time to crusting and complete healing in females and effectively reduced new lesion formation in both sexes. To date, data support that therapy should be initiated as early as possible following onset of signs and symptoms to maximize clinical benefit.

3.0 STUDY SUMMARY

This study will measure the efficacy of interferon in treating resistant/recurrent condyloma acuminata or acyclovir in treating primary or recurrent herpes virus infections in patients with LAS. Patients will be assigned to receive either ZOVIRAX (Regimen A) or WELLFERON® (Regimen B) according to their original disease diagnosis. The time course involved for regression of condyloma acuminata or healing of herpes lesions are critical portions of this study. Additionally, interferon-induced or acyclovir-associated side effects will be monitored at regular intervals during this trial. Disease responses will be recorded on schematic drawings and confirmed with photographs on an every two week schedule during the study. Patients assigned to WELLFERON will receive daily subcutaneous injections for 14 days then 3 x weekly for 4 weeks at a dose of 3 Mu/m² per injection. If a complete response (CR) has occurred within 6 weeks, the patients will be observed until recurrence. If a partial (PR) or no response (NR) has occurred after the first 6 weeks, the patient will be observed for 4 weeks. Patients who were PR after initial 6 weeks or experience recurrence during observation will receive a

second six-week course of ZOVIRAX® for herpes infection or WELLFERON® for condylomata. Patients who remain nonresponders (NR) after observation will receive combined therapy of acyclovir 400 mg tablets every 8 hours daily plus interferon 3 Mu/m² s.c. 3 x weekly for a total of 6 weeks. Any patient who develops disease, either herpes virus infection or condyloma acuminata, other than their original diagnosis may cross to the appropriate arm of study for that disease.

3.1 Patient Selection

Thirty homosexual male patients with the syndrome of prolonged unexplained lymphadenopathy and presenting with recurrent/resistant condyloma acuminata or herpes simplex infection will be entered on study. Patients will be under care in the AIDS clinic, UCLA Center for Health Sciences.

3.1.1 Eligibility Criteria

All patients must have:

- 1) Lymphadenopathy with pathologic, clinical appearance (1-3 cm diameter) and involving at least two regional chains above diaphragm
- 2) Lymphadenopathy for >6 months duration.
- 3) Biopsy proven follicular hyperplasia, and absence of involution and malignancy.
- 4) Symptoms of weight loss, night sweats, low grade fever, or prominent fatigue.
- 5) T-helper/T-suppressor ratio <0.8.
- 6) Diagnosis of condyloma acuminata or culture-proven herpes simplex or clinical herpes zoster.
- 7) Condylomata present for $\geq$ 3 months.
- 8) At least 2 previous podophyllin or equivalent treatments (cryo, laser, surgery) for condylomata.
- 9) Measurable condyloma or herpes lesions.
- 10) Signed informed consent.

3.1.2 Exlcusions

- 1) Less than 18 years old.
- 2) Patients with AIDS or oral candidiasis.
- 3) Malignant degeneration in excised tumor.

- 4) Immunological therapy within previous 3 months.
- 5) Renal insufficiency (serum creatinine >1.4).
- 6) Anemia (Hgb <10 gm/dl), leukopenia ($\leq 1500/\text{mm}^3$), thrombocytopenia ($<100,000/\text{mm}^3$), clinical or laboratory coagulopathy.
- 7) Impaired liver functions (SGOT >1.5 mg/dl).
- 8) Known hypersensitivity to Neomycin or Polymyxin B.
- 9) Significant cardiac, pulmonary, gastrointestinal, renal, or other conditions which may impair tolerance of acute pyrexial reactions or blood pressure changes associated with interferon administration.
- 10) Unavailability for 6 weeks treatment and 4 weeks observation.
- 11) Not accessible geographically for follow-up.
- 12) Patients receiving steroids, cytotoxic immunosuppressive agents or radiotherapy.

4.0 THERAPEUTIC AGENTS

4.1 WELLFERON® (Human Lymphoblastoid Interferon)

4.1.1 Product Description

WELLFERON is a purified preparation of human alpha interferons from cultured human lymphoblastoid cells. These cells are induced with Sendai virus which results in synthesis and secretion of interferons. WELLFERON is isolated, concentrated and purified from cell-free supernatants to $\geq 95\%$ purity. Human lymphoblastoid interferon has been purified to a level of 2×10^8 international units (IU) of human alpha interferon per mg protein.

Biological activity of WELLFERON is expressed in megaunits (Mu) where 10^6 IU equal 1 Mu. This unitage is determined in a viral cytopathic effect inhibition assay standardized against the international alpha interferon standard 69/19. Extensive experimental work has demonstrated that WELLFERON is nearly identical in

its chemical, physical, immunologic and biologic properties to interferon derived from buffy coat cells of human blood. It contains at least 12 human alpha interferon subtypes.

4.1.2 Formulation and Stability

WELLFERON® is formulated in tri-glycine buffered physiologic saline with human serum albumin added as stabilizer. Prior to blending, $\geq 95\%$ of the material is purified interferon protein. Because albumin accounts for 90% or more of the protein in the final product, the specific activity of the interferon becomes correspondingly reduced.

WELLFERON is supplied in 1.0 ml vials. Interferon content of final containers is determined by titration in an antiviral assay and expressed in mega units (Mu) per vial. WELLFERON vials are routinely filled at concentrations of approximately 3 or 10 Mu/vial; the precise unitage for each individual lot is specified on the carton label.

WELLFERON is supplied as a frozen solution. Storage must be at or below -20°C and WELLFERON must not be thawed and refrozen repeatedly. It may be stored frozen for up to 12 months. It contains no preservatives, antimicrobial or antifungal agents. Thawed WELLFERON may be stored in unentered vials at $4-8^{\circ}\text{C}$ for up to 6 months. Vials entered under pharmaceutically sterile conditions (laminar flow hoods) may be stored at $4-8^{\circ}\text{C}$ for up to 48 hours and may be re-entered.

4.1.3 Administration and Supply

WELLFERON will be injected subcutaneously on the anterior portion of the thigh in rotation of sites at a dose of 3 Mu/m^2 daily for 14 days and 3 x weekly for 4 weeks thereafter.

WELLFERON will be supplied in sequentially numbered vials. Records of drug used and carton labels will be

retained in a CTM Inventory folder supplied by B.W. Co. Vials should not be shaken or inverted as loss of drug may occur due to liquid being trapped in the small neck of the vial. All empty vials, vials with remaining drug, unused vials and CTM Inventory folder will be returned to Burroughs Wellcome Co. for accountability.

4.1.4 Pharmacology of WELLFERON®

WELLFERON has been studied in a series of Phase I trials employing doses from 0.1 to 50 Mu/m² administered by i.m. or i.v. routes. Doses as high as 200 Mu/m² have been given by continuous 24-hour infusions. Serum interferon pharmacokinetics have been studied systematically within the limits inherent in bioassays and differences in individual subjects.

In a Phase I study in which 40 patients received 0.1-50 Mu, serum interferon levels were detectable at doses of 5 Mu or greater by either route (47). The peak levels were dose related with i.v. peaks higher than their i.m. counterparts (compare Figs. 1 & 2 below).

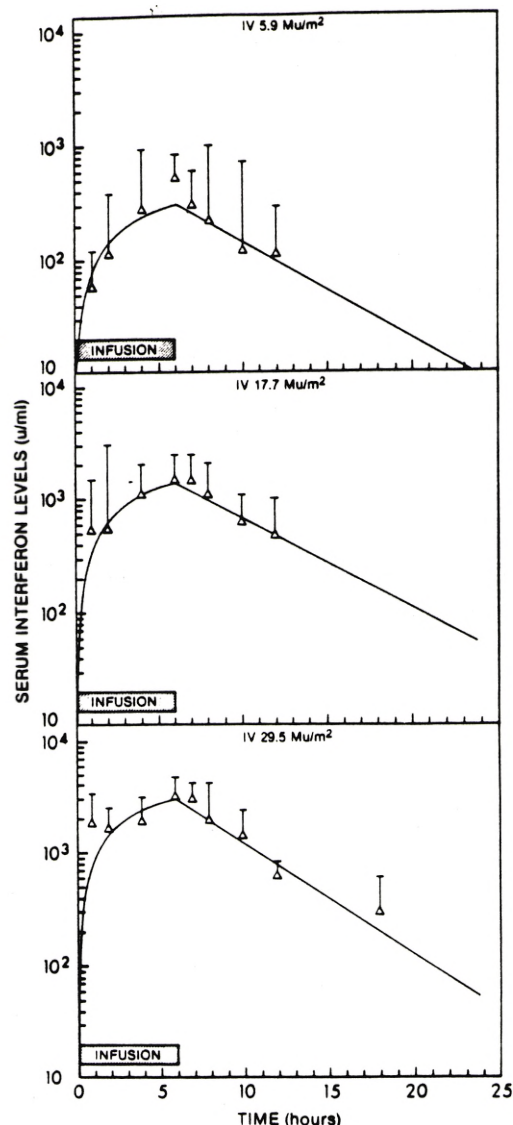


Fig. 1. Analyses of serum interferon levels following 6 hr intravenous infusions of WELLFERON® at 3 different doses (47). Interferon was administered in total doses of 10, 30 or 50 Mu which correspond to approximately 6, 12 and 30 Mu/m^2 , respectively. These curves represent the best fit as determined by a single compartmental pharmacokinetics model. Each point represents the mean of 13-20 individual values and the bars are S.E.M.

Peak levels following i.m. administration occur 6-7 hours after injection (Fig. 2) and this is consistent with earlier data reported for lower doses of WELLFERON. Following termination of intravenous infusions there is a rapid decline in serum interferon levels (Fig. 1). Analyses of the data plotted in Figures 1 and 2 indicate that areas under the curve are approximately 25% greater following i.m. injections at doses of 10 and 30 Mu. In another study in which daily 24-hour infusions were given, a plateau, which was dose related through 30 Mu/m^2 , was achieved (48). Infusions of 50-200 Mu/m^2 did not result in higher serum levels.

A comparison of data from several WELLFERON® studies supports several general conclusions:

- a. serum levels are dose related and the kinetics in serum show an initial fall-off with $T_{1/2}$ of 10-12 hrs following i.m. dosing.
- b. "accumulation" can occur as reflected by trough levels at 24 hours; this is dependent on the dose level and frequency of administration.
- c. individual patients develop somewhat variable levels of serum interferon activity with some patients consistently higher than others.

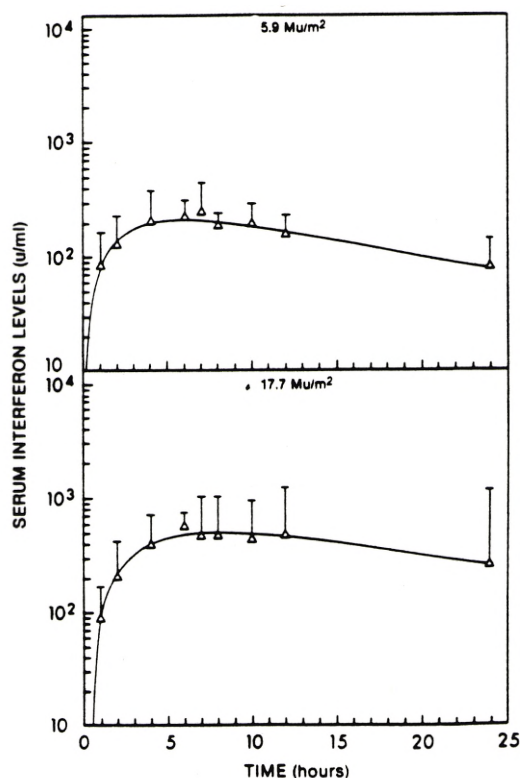


Fig. 2. Analyses of serum interferon levels following intramuscular injection of WELLFERON at 2 doses (47). The data are presented as described in the legend to Figure 1. Each point represents the average of 10 values.

The results described above for pharmacokinetic studies with WELLFERON demonstrate that the clearance rates and serum half-lives for this mixture of alpha interferons are similar to those reported for other interferons. Studies conducted with leukocyte-derived (49) or bacteria-derived (50) alpha interferons report similar findings at comparable doses.

4.1.5 Side Effects and Toxicity of WELLFERON®

The symptomatic side effects and toxicities related to WELLFERON administration are similar to those ascribed to both native leukocyte and recombinant DNA-derived interferons. Lists of these are recorded respectively in Tables I and II below.

TABLE I
WELLFERON SIDE EFFECTS

<u>Endotoxin Reaction</u>	<u>Flu Syndrome</u>
Fever +/- Chill	Anorexia
Tachycardia	Myalgia
Headache	Malaise, Fatigue
	Weight Loss
<u>Gastrointestinal</u>	<u>Neurologic</u>
Nausea +/- Emesis	Paresthesias
Diarrhea	Somnolence
Dysgeusia	Confusion
	Seizures (rare)
<u>Others</u>	
Alopecia	
Induration at Injection Site (rare)	

The most commonly occurring side effect of WELLFERON has been a febrile response. Intramuscular injections of WELLFERON at doses from 0.3 up to 30 Mu/m² resulted in temperature rises between 1 and 8 hours post-injection (47). These pyrexial responses subsided with subsequent injections and were ameliorated with salicylates. Malaise and fatigue have been the most common complaints from patients even at the lowest doses given. Nausea and vomiting have been controlled with antiemetics. Anorexia accompanied by weight loss has been a problem in two instances but both were juvenile patients who recovered after interferon was stopped. Several adult patients with hepatitis B virus infections and two pediatric

patients with laryngeal papillomatosis have reported significant hair loss during WELLFERON® treatment. Reports of local induration or irritation at the sites of injection have been rare.

TABLE II
WELLFERON TOXICITIES

<u>Hematologic</u>	<u>Neurologic</u>
Leucopenia	Weakness
Granulocytopenia	EEG Slowing
Thrombocytopenia	Delta Bursts
Coagulopathy (rare)	
<u>Gastrointestinal/Chemical</u>	<u>Cardiovascular</u>
Hepatic Enzyme ↑↑	Hypertension
BUN ↑ (rare)	Hypotension
Ca ↓ (rare, high dose)	

WELLFERON has been administered by intravenous infusions at doses escalating from 5 to 200 Mu/m²/day in Phase I studies (47, 48). Continuous i.v. infusion was adopted after initial attempts at bolus delivery produced some severe hypotensive episodes. Similar patterns of side effects and clinical toxicities were observed with severe neurological toxicities noted at doses of 150 and 200 Mu/m²/day (48). Other neurological abnormalities included paresthesias and mental state modifications such as lack of concentration and confusion. Documentation of CNS side effects has shown that continuous i.v. infusion of 100 Mu/m²/day for 7 days caused reversible EEG changes in all patients examined (51). These alterations were measured even when there was no clinical evidence of CNS disturbances. Transient changes in hepatic functions were observed in all patients with marked increases in alkaline phosphatase and transaminase levels (51). Nine pediatric patients with acute nonlymphocytic leukemia have been treated by continuous infusions

with 15, 20 or 30 $\text{Mu}/\text{m}^2/\text{day}$ of WELLFERON® for 10 days. All but one of these individuals developed coagulation abnormalities between days 4 and 8 of their infusion cycles. Measurement of coagulation parameters demonstrated elevations in PT and PTT values. One patient with advanced ovarian cancer experienced severe renal and hepatic dysfunction following high dose (20 $\text{Mu}/\text{m}^2/\text{day}$) continuous infusion of WELLFERON. Seven patients with advanced renal cell carcinoma have exhibited severe rises in SGOT levels or granulocytopenia requiring dose reductions or discontinuation of i.m. injections of 30 $\text{Mu}/\text{m}^2/\text{day}$.

The experience with WELLFERON to date indicates that most severe toxicities associated with human lymphoblastoid interferon treatment occur at relatively high doses ($>10 \text{ Mu}/\text{m}^2$). Many of these serious reactions appear to be related to the patient's underlying disease, previous therapy, age and performance status at the time of entering the interferon study. Several incidents in patients receiving low dose therapy of 5 Mu/m^2 require close attention to patients with neuroendocrine disorders as they may be relatively more sensitive to interferon's effects. In addition, chronic dosing with WELLFERON will require monitoring of white blood cell counts and observation for any long-term side effects on hepatic functions.

4.2 ZOVIRAX® (Acyclovir)

4.2.1 Product Description and Mechanism of Action

ZOVIRAX is an antiviral drug with potent activity against herpes viruses. It is a synthetic acyclic purine nucleoside analog with in vitro activity against herpes simplex types 1 and 2 (HSV-1 and HSV-2), varicella-zoster, Epstein-Barr and cytomegalovirus. Acyclovir is a white, crystalline powder with a molecular weight of 225 Daltons and a maximum solubility in water of 1.3 mg/ml.

The inhibiting activity of acyclovir is highly selective. Herpes simplex virus-coded thymidine kinase converts acyclovir into acyclovir monophosphate. Cellular thymidine kinase does not effectively use it as a substrate. The monophosphate form is further converted to diphosphate and triphosphate by a number of cellular enzymes. The acyclovir triphosphate interferes with Herpes simplex virus DNA polymerase and inhibits viral DNA replication.

4.2.2 Formulation and Stability

ZOVIRAX® Tablets conform to Burroughs Wellcome Pharmaceutical and Research Lab. CTM number _____. Each tablet contains 800 mg or 400 mg acyclovir with inert filler (lactose, magnesium stearate, sodium lauryl sulfate and corn starch). Tablets should be stored at room temperature in well-closed containers and should be dispensed in light-resistant bottles.

4.2.3 Administration

ZOVIRAX should be administered as one 800 mg tablet five times daily, every 4 hours, for 14 days; then, one 400 mg tablet three times daily, every 8 hours, for an additional 4 weeks. This treatment cycle may be repeated as described in Section 3.0.

4.2.4 Pharmacology

Acyclovir has been administered orally to both immunocompromised and immunocompetent patients in dose ranging studies. A summary of the pharmacokinetic data from these studies are outlined below:

<u>Dose</u>	Mean Peak Plasma Conc. at Steady State <u>µg/ml</u>	Mean Trough Plasma Conc. at Steady State <u>µg/ml</u>	AUC (Area under con- centration/ time curve)
Immunocompromised Patients			
200 mg q 4 hrs, 5 days	0.5	0.3	7.9
400 mg q 4 hrs, 5 days	1.2	0.6	16.7
600 mg q 4 hrs, 5 days	1.3	0.8	21.0
800 mg q 4 hrs, 5 days	2.7	1.8	63.8
Immunocompetent Patients			
400 mg q 4 hrs, 5 x day, 5 days	1.0	0.6	13.3
600 mg q 4 hrs, 5 x day, 5 days	1.5	0.7	19.1
800 mg q 6 hrs, 5 days	1.5	0.7	26.0

4.2.5 Side Effects and Toxicities

No significant side effects, other than occasional single episodes of nausea or diarrhea, have been observed in patients studied to date. Controlled clinical trials also have not produced evidence of acute toxicity resulting from oral administration of acyclovir.

The most frequent adverse reaction reported during controlled studies of ZOVIRAX® Capsules have been nausea and/or vomiting in 5 of 306 patients (1.7%) and headache in 3 of 306 (1%). In patients receiving placebo, 2 of 290 (0.7%) experienced nausea/vomiting, and 1 of 290 (0.4%) reported headaches. In all studies, there was no significant difference between the drug and placebo groups in the rate or type of reported adverse reactions. Additional adverse reactions have been reported in uncontrolled trials and have included nausea, headache, diarrhea and loose stools.

5.0 TREATMENT REGIMEN

5.1 Patient Entry/Assignment

Eligible LAS patients with resistant/recurrent condyloma acuminata or herpes simplex lesions will have entry and eligibility forms completed. Patients will then be to receive ZOVIRAX® (Regimen A) or WELLFERON® (Regimen B). Assignments will be made on the basis of the original disease diagnosis. All patients must meet the entry criteria for the syndrome of unexplained generalized lymphadenopathy.

5.2 Regimen A - ZOVIRAX for Herpes Simplex

Patients assigned to this arm of the study will receive ZOVIRAX orally as 800 mg or 400 mg tablets. ZOVIRAX will be administered as one 800 mg tablet q. 4 hrs. daily for 14 days followed by one 400 mg tablet q. 8 hrs. daily for 4 weeks.

Following six weeks of treatment, all patients will be observed for 4 weeks to document regression or recurrence of herpes simplex lesions.

5.3 Regimen B - WELLFERON for Condyloma Acuminata

Patients assigned to this arm of the study will receive WELLFERON by s.c. injections at a dose of 3 Mu/m² daily for 14 days followed by the same dose given 3 times per week for 4 weeks. Subcutaneous administration will be achieved by rotation of sites on the anterior aspect of the thigh in a volume of 0.5-1.0 ml per site. Following this 6 week period, all patients will be observed for 4 weeks to document regression or recurrence of disease.

5.4 Assessment of Response/Toxicities

Lesion measurements are to be recorded every two weeks and documented by photographs at the same intervals.

Condyloma lesions will be assessed by objective bidimensional measurements of anatomically localized warts and response will be graded by the criteria outlined in Section 8.0. Tissue biopsies should be obtained at entry for viral DNA subtyping. Repeat biopsies should be performed at week 7 and at the end of study in those patients with remaining wart tissue.

Side effects and toxicities related to interferon are to be assessed weekly during the first month of study and for the remainder of the study.

Herpes simplex lesions will be assessed by objective measurements of anatomically localized lesions. Responses will be graded by the criteria outlined in Section 8.0. Virus isolates will be obtained for characterization of HSV at entry. Repeat isolates, if available, should be obtained at week 7 and the end of study.

5.5 Additional Treatment of Disease

5.5.1 Second Course of Therapy

All patients experiencing a partial response during the initial 6 week treatment period and/or recurrence of disease while undergoing observation for 4 weeks are eligible to receive a second 6 week course of WELLFERON® or ZOVIRAX® as appropriate for their disease.

Any patient experiencing a complete regression and then recurrence of disease while off therapy is eligible for the second 6 week course of WELLFERON or ZOVIRAX.

5.5.2 Combined Interferon and Acyclovir Therapy

All patients experiencing no response (NR) to ZOVIRAX for Herpes simplex infections or to WELLFERON for Condyloma acuminata during the initial 6 week treatment and observation periods will be eligible for combined therapy. Nonresponders will receive ZOVIRAX as one 400 mg tablet q. 8 hours daily for six weeks concomitant with WELLFERON s.c. at 3 Mu/m²/injection 3 x weekly for 6 weeks.

5.5.3 Crossover to Other Treatment Arm

Any patient developing disease (either HSV infection or condyloma acuminata) other than their original diagnosis at any time during the course of study may crossover to the treatment arm appropriate for that disease.

5.6 Removal from Study

5.6.1 Toxicities - Patients developing unmanageable or life-threatening toxicities may be removed from the study at

the discretion of the physician, but Burroughs Wellcome Co. must be notified immediately (Dr. John K. Whisnant or Dr. Phillip K. Weck (919) 248-4160 or 248-4568, respectively). If after business hours, call the respective home numbers ((919) 942-3936 or 781-5771).

5.6.2 Patient refusal of further treatment; reasons must be noted on Data Collection Form.

5.6.3 Patients whose disease is progressing unacceptably will be removed in consultation with the Burroughs Wellcome monitor.

6.0 OBSERVATIONS/STUDIES TO BE RECORDED

6.1 Study Schedule

Laboratory studies, disease evaluations and other procedures/ observations are to be performed as outlined in the Activities Chart (see next page).

6.2 Prestudy Evaluations

Studies at entry should be performed within one week prior to initiation of interferon or acyclovir therapy.

6.3 Intervals for Disease Evaluations

Patients receiving WELLFERON® or ZOVIRAX® will be evaluated clinically with diagrams and photographs every two weeks. The patients' lesions will be mapped on a schematic drawing of the genital, perianal or rectal area and objective measurement will be by visual determination of the size and severity of lesions. Photographs will be used to confirm objective measurement.

6.4 Patient Performance/Side Effects

Karnofsky performance status should be determined prestudy and every other week thereafter. Drug-related side effects and disease symptoms should be evaluated at least biweekly. These side effects and symptoms will be recorded in a personal daily diary maintained by each patient.

ACTIVITIES CHART
STUDY OF WELLFERON® FOR CONDYLOMA ACUMINATA
OR ZOVIRAX® FOR HERPES SIMPLEX IN
PATIENTS WITH UNEXPLAINED LYMPHADENOPATHY SYNDROME

Month Week	Pre	1	2	1 3	4	5	6	2 7	8	9	3 10	11	13	4 15	17
Regimen A ACV		800 mg q 4 hr---/400 mg q 8 hr Daily-----/---Observe*-----/													
Regimen B IFN 3 Mu/m ² s.c.		Daily----/--t.i.w.-----/---Observe*-----/													
Physical Exam	X														X
Hematology															
WBC	X		X	X		[X]		X		[X]		X	X	[X]	X
Differential	X		X	X		[X]		X		[X]		X	X	[X]	X
Platelets	X		X	X		[X]		X		[X]		X	X	[X]	X
Hgb/Hct	X		X	X		[X]		X		[X]		X	X	[X]	X
Chemistries	X		X	X		[X]		X		[X]		X	X	[X]	X
Serum (IFN/Ab)	X							X							X
Tissue Biopsies	X							X							X
Virus Isolates	X							X							X
Disease Evaluation	X		X	X		X		X		X		X	X	X	X
Photographs	X		X	X		X		X		X		X	X	X	X

} May repeat cycle,
crossover, or start
combination, if
eligible.

[] Optional: to be performed if previous laboratory values abnormal.

*Crossover: patients developing disease other than original diagnosis may cross to other treatment arm.

6.5 Laboratory Data

Patients presenting with documented Condyloma acuminata or Herpes simplex will be evaluated by the following:

- 6.5.1 Hematology: Hemoglobin or hematocrit, WBC with differential, and platelet count at Entry, weeks 2, 3, and every two weeks.
- 6.5.2 Chemistry: SGOT, bilirubin, BUN, and creatinine at Entry, weeks 2, 3, and every two weeks.
- 6.5.3 Serum: For anti-interferon antibody studies, acid-labile interferon, and baseline interferon titers, 3.0 ml of serum will be obtained. Samples should be obtained at entry, day 1 hour 4, week 7 and end of study. The serum will be divided into 3 aliquots in 1.0 ml volumes and stored with proper identification at -20°C.
- 6.5.4 Tissue Specimens: Tissue for diagnosis of Condyloma acuminata must be obtained if not performed within last 6 months. If available, additional tissue will be obtained for DNA hybridization studies. All specimens will be snap-frozen in liquid nitrogen and stored at -80°C (see Appendix III).
- 6.5.5 Immunologic Studies: Blood will be drawn for quantitative immunoglobulin levels (IgG, IgA, and IgM) at entry, and end of study. Blood will be taken for determination of percentage and absolute numbers of T-helper and T-suppressor lymphocytes at entry, weeks 3, 7 and 11.
- 6.5.6 Virologic Studies: Specimens of urine, semen, and buffy coat cells obtained at entry, weeks 3, 7 and 11 will be cultured for CMV.
- 6.5.7 Lymph Node Biopsy: A finding of follicular hyperplasia in a node biopsy will be required prior to patient enrollment.

7.0 TREATMENT MODIFICATIONS/TOXICITY MANAGEMENT

7.1 General Principles

7.1.1 Supportive Management

Every effort will be made to manage constitutional symptoms and gastrointestinal toxicities with supportive care and appropriate therapeutics (e.g., antiemetics). If symptoms persist despite such efforts, dose modifications may be made as outlined below (Section 7.4). If dose modification is required for an abnormal laboratory finding, that test will be repeated in 72 hours.

An acute febrile response and related symptomatology commonly occurs following interferon exposure. It has been most pronounced with initial treatment and ameliorates with subsequent dosing. These physiologic and subjective disturbances are to be monitored on all patients throughout the entire trial period. Dose reductions may be made for such physiologic and symptomatic side effects when the grade is intolerable for a particular patient, considering the amelioration with daily dosing and symptomatic control with medication (see grading below).

7.1.2 Intervals for Dose Alterations

During the primary treatment period, dose modification for interferon-induced symptomatic toxicities will be made after that week's laboratory results are reviewed and will be based on the highest grade of toxicity observed during the previous week.

7.2 Severe or Life-Threatening Toxicities

Major toxicities may require patient withdrawal after consultation with the Study Monitor who must be notified of such occurrences immediately (see Section 5.6).

7.2.1 Hypotension and hypertension may occur on the first or subsequent dose of WELLFERON®. Clinically significant hypotension has been reported. Any rise or fall >20 mm Hg will be dealt with cautiously and proper supportive or pharmacologic management will be considered if changes in blood pressure persist or recur.

- 7.2.2 CNS toxicity, including grand mal seizure, has been reported, particularly in association with very high doses ($>100 \text{ Mu/m}^2/\text{day}$). Anticonvulsants may be used for control during continued interferon treatment. Lesser CNS toxicities include confusion, depression, diminished alertness and ability to concentrate normally.
- 7.2.3 Anaphylactic reaction. This has not been previously seen with WELLFERON®. If severe hypersensitivity (urticaria, bronchospasm) to interferon is seen, Study Monitor should be notified immediately.

7.3 Toxicity Grading for Dose Reductions

<u>Toxicity</u>	<u>Toxicity Grading</u>			
	(Mild) <u>Grade 1</u>	(Moderate) <u>Grade 2</u>	(Severe) <u>Grade 3</u>	(Life-threatening) <u>Grade 4</u>
Fever*	1°C over pretreat- ment to 38.6°C	38.7°C- 39.7°C	>39.7°C	
Chills*	mild to moderate shaking	severe shaking	rigors	
Fatigue*	100% P.S.- feeling fatigue	50-100 P.S. significant fatigue	<50% P.S., depression extreme dis- comfort lethargy	
Malaise*	[Flu-like syndrome (myalgia, arthralgia)]			
	<6 hrs duration	6-24 hrs duration	>24 hours duration	
Nausea/* vomiting	Nausea only	Emesis <6 no antiemetics	Emesis >6 with antiemetics	
Headache*	<2 hrs not requiring analgesic	>2 hrs, but less than 24 or requiring analgesic	>24 hrs with or without analgesic	
Granulocytes	1000-1500	500-999	<500	Grade 3 plus infection
Platelets	<100,000	50-75,000	25-49,999	Grade 3 plus bleeding
SGOT	<2 x normal or patient's baseline	<3 x normal or patient's baseline	>3 x normal or patient's baseline	
Creatinine	1.5-1.9	2.0-2.5	>2.5	

*Dose reductions may be made at the discretion of the investigator.

7.4 Dose Reductions (% of Starting Dose) by Toxicity Based on Highest Grade

<u>WELLFERON®</u>			
<u>100%</u>	<u>67%</u>	<u>33%</u>	<u>0</u>
1	2		
	(1)	3	
		(2)	
			4
			(3)

Number in parentheses indicates dose adjustments to be made only after a grade 2 or 3 toxicity occurs on two consecutive weeks at a given dose.

8.0 DISEASE ASSESSMENT

8.1 Disease Measurement

Condyloma acuminata or Herpes simplex lesions used for response determination must be bidimensionally measurable. Disease response will be followed by individual serial measurements performed every two weeks.

8.2 Definition of Response

8.2.1 Responders

Complete Response (CR) - complete disappearance of all objective evidence of disease; suspicious lesions will be biopsied.

Partial Response (PR) - decrease of 50% or more in sum of products of diameters of measurable lesions.

Minimal Partial Response (MPR) - decrease of 25-50% of sum of products of diameters of measurable disease.

Stable Disease (SD) - decrease of <25% or increase of <25% in sum of products of diameters of measurable disease.

8.2.2 Nonresponders (progression) - increase of ≥25% in sum of products of diameter of measurable lesions.

9.0 STATISTICAL CONSIDERATIONS

9.1 Experimental Design

This is a Phase III/IV study designed to test the therapeutic effectiveness of interferon alone in severe/resistant Condyloma acuminata or acyclovir alone in herpes virus infections in LAS patients. It will test combination therapy in patients who do not respond to acyclovir treatment for herpes virus infections. Patients will be assigned to treatment with acyclovir or interferon based on their original diagnosis. Patients will be excluded from efficacy analysis if they receive less than the 6 weeks of primary therapy due to toxicities or withdrawal from study.

9.2 Sample Size

Thirty patients with diagnosed unexplained lymphadenopathy syndrome (LAS) will be entered on this study. Every effort will be made to assign 15 patients to each arm of the study to evaluate the effectiveness of either acyclovir or interferon in the treatment of viral infections in patients with this syndrome.

10.0 STUDY MANAGEMENT AND REPORTING PROCEDURES

10.1 Patient Consent and IRB Approval

The investigator is responsible for patient care and consent by the patient or family. Written informed consent must be obtained prior to entry of any patient.

No patients are to be entered on this protocol until after the institution's Human Investigation Committee has approved it. A copy of this institutional approval will be provided to Burroughs Wellcome Co. before drug is provided.

10.2 Drug Acquisition and Inventory Control

10.2.1 WELLFERON®

Sufficient WELLFERON for the primary treatment course for two patients will be provided from Burroughs Wellcome Co. to each institution at the time of FDA registration. When the investigator's office notifies

the Company of patient entry, additional interferon will be sent to the study institution. Any requests for interferon should be directed through the Burroughs Wellcome study monitor.

A record for all WELLFERON® used in this study must be maintained by the Dispensing Pharmacy. A tear-off label will be attached to each WELLFERON carton, and it will be placed on the Clinical Trial Material Inventory Control Form for accounting of vials for individual patients. ALL unused drug and empty drug vials must be returned to a Burroughs Wellcome staff member.

10.2.2 ZOVIRAX®

ZOVIRAX supplies for the primary treatment of two patients will be made available from Burroughs Wellcome at time of registration with FDA. Additional tablets should be requested through the study monitor. All unused drug will be returned to Burroughs Wellcome Co. after completion of study.

10.3 Patient Records

10.3.1 Hospital Records

Hospital records for patients on this study are the responsibility of the investigator.

10.3.2 B.W. Data Collection Form

The Sponsor (Burroughs Wellcome Co.) will supply a booklet of information (Information for Investigators), a final protocol, and an individual data collection form (DCF) for each patient. These are the property of the Sponsor and are considered confidential. The completed original DCF will be collected by a Burroughs Wellcome staff member and a copy will be provided to the investigator.

10.4 Publications

The study of these patients, data on the use of WELLFERON and results of all laboratory studies are considered private

and confidential. The progress and results of this study will not be presented or published without agreement between the investigator and Wellcome Medical Staff at Research Triangle Park, NC. All abstracts and publications will be reviewed by the Wellcome Medical Staff prior to submission for publication or presentation.

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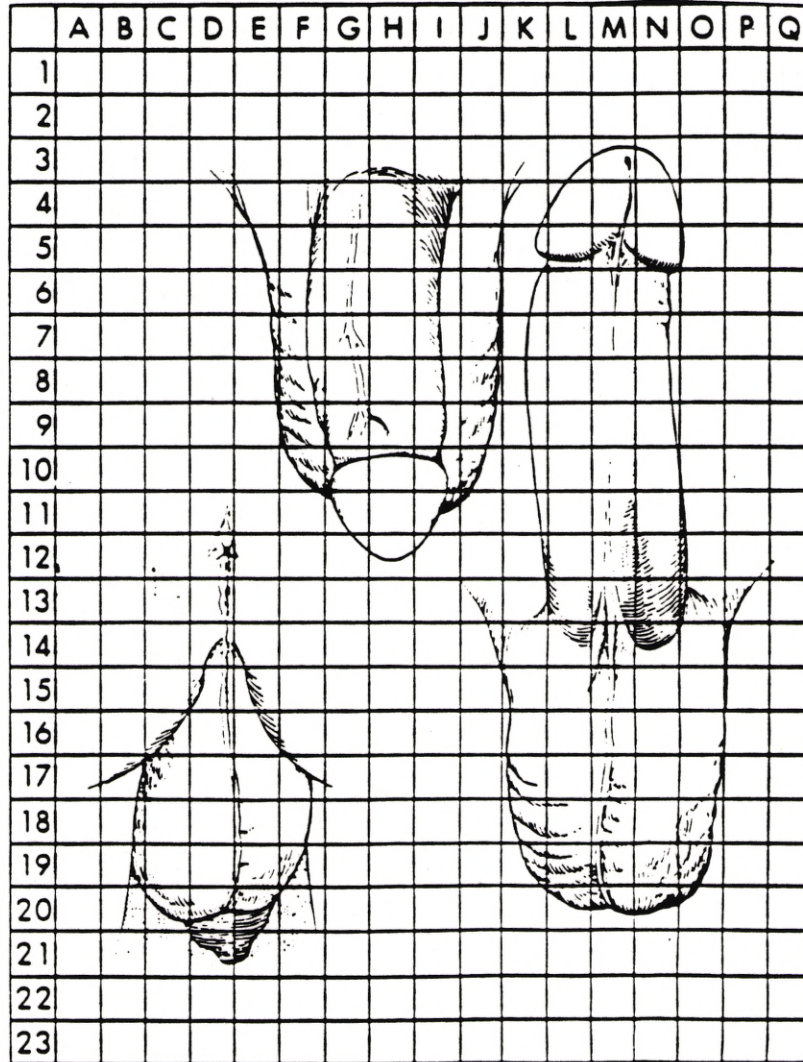
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APPENDIX I

SCHEMATIC OF MALE GENITALIA TO INDICATE LESION LOCATION

Schematic of the Male Genitalia



	Glans	Dorsal Shaft	Ventral Shaft	Anterior Scrotum	Posterior Scrotum	Exposed Prepuce	Occluded Prepuce	Perianal
No. of Lesions								
Surface Involvement								

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

	100 Normal; no complaints; no evidence of disease
Able to carry on normal activity; no special care is needed.	90 Able to carry on normal activity; minor signs or symptoms of disease
	80 Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; a varying amount of assistance is needed	70 Cares for self; unable to carry on normal activity or to do active work
	60 Required occasional assistance but is able to care for most of his needs
	50 Requires considerable assistance and frequent medical care
	40 Disabled; requires special care and assistance
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	30 Severely disabled; hospitalization is indicated although death not imminent
	20 Very sick; hospitalization necessary; active supportive treatment is necessary
	10 Moribund; fatal processes progressing rapidly
	0 Dead

APPENDIX III

PROCEDURE FOR COLLECTING AND FORWARDING CONDYLOMATA TISSUE SAMPLES

Note: Degradation of the DNA occurs if the excised tissue is not snap frozen immediately (as soon as possible) after removal.

The purpose of obtaining biopsies of the condylomata during the course of interferon therapy is to examine and quantify the papillomavirus genome present in the lesion as an aid in the assessment of disease. There are at least four different subtypes of human papillomavirus type 6 in genital warts which are distinguishable by hybridization analysis. It is possible to determine the number of copies of the papillomavirus genome per cell and we can therefore monitor the impact of interferon on replication of the virus. We also will be able to correlate viral subtype with resistance or sensitivity to interferon. In addition, since the patients are being selected from different regions of the United States, these studies will indicate if there are different viruses circulating in different geographic locations. Specimens will be collected prior to and during the course of interferon. For a successful analysis, it is necessary to snap freeze the tissue (not in saline) in liquid nitrogen as soon as possible after surgical excision.

1. Biopsies, collected in saline, should be removed from the saline and placed in a labelled Nunc vial or any similar small, sterile container which can withstand liquid nitrogen.
2. The vial is to be dropped in liquid nitrogen to snap freeze the tissue and then store at -70°C .
3. Tissue specimens are to be shipped with dry ice via Federal Express or Purolator to Burroughs Wellcome Co.

APPENDIX IV A

BODY SURFACE AREA (m²)

POUNDS/INCHES

Height (inches)	Weight (pounds)																							
	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125
20	0.27	0.33	0.38	0.43	0.47	0.51	0.55	0.58	0.62	0.65	0.68	0.70	0.73	0.76	0.78	0.81	0.83	0.86	0.88	0.90	0.92	0.94	0.97	0.99
22	0.28	0.34	0.40	0.45	0.49	0.53	0.57	0.61	0.64	0.67	0.70	0.73	0.76	0.79	0.82	0.84	0.87	0.89	0.92	0.94	0.96	0.98	1.01	1.03
24	0.29	0.36	0.41	0.47	0.51	0.55	0.59	0.63	0.66	0.70	0.73	0.76	0.79	0.82	0.85	0.87	0.90	0.93	0.95	0.97	1.00	1.02	1.04	1.07
26	0.30	0.37	0.43	0.48	0.53	0.57	0.61	0.65	0.69	0.72	0.76	0.79	0.82	0.85	0.88	0.90	0.93	0.96	0.98	1.01	1.03	1.06	1.08	1.10
28	0.31	0.38	0.44	0.50	0.55	0.59	0.63	0.67	0.71	0.75	0.78	0.81	0.84	0.87	0.90	0.93	0.96	0.99	1.01	1.04	1.06	1.09	1.11	1.14
30	0.32	0.39	0.46	0.51	0.56	0.61	0.65	0.69	0.73	0.77	0.80	0.84	0.87	0.90	0.93	0.96	0.99	1.02	1.04	1.07	1.10	1.12	1.15	1.17
32	0.33	0.40	0.47	0.53	0.58	0.62	0.67	0.71	0.76	0.79	0.82	0.86	0.89	0.92	0.96	0.99	1.02	1.04	1.07	1.10	1.13	1.15	1.18	1.20
34	0.34	0.41	0.48	0.54	0.59	0.64	0.69	0.73	0.77	0.81	0.85	0.88	0.92	0.95	0.98	1.01	1.04	1.07	1.10	1.13	1.16	1.18	1.21	1.23
36	0.34	0.42	0.49	0.55	0.61	0.66	0.70	0.75	0.79	0.83	0.87	0.90	0.94	0.97	1.00	1.04	1.07	1.10	1.13	1.16	1.18	1.21	1.24	1.26
38	0.35	0.43	0.50	0.57	0.62	0.67	0.72	0.76	0.81	0.85	0.89	0.92	0.96	0.99	1.03	1.06	1.09	1.12	1.15	1.18	1.21	1.24	1.27	1.29
	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130	135	140	145
40	0.63	0.69	0.74	0.78	0.82	0.87	0.91	0.94	0.98	1.02	1.05	1.08	1.12	1.15	1.18	1.21	1.24	1.27	1.29	1.32	1.35	1.38	1.40	1.43
42	0.65	0.70	0.75	0.80	0.84	0.88	0.92	0.96	1.00	1.04	1.07	1.11	1.14	1.17	1.20	1.23	1.26	1.29	1.32	1.35	1.38	1.40	1.43	1.46
44	0.66	0.71	0.77	0.81	0.86	0.90	0.94	0.98	1.02	1.06	1.09	1.13	1.16	1.19	1.23	1.26	1.29	1.32	1.35	1.38	1.40	1.43	1.46	1.49
46	0.67	0.73	0.78	0.83	0.88	0.92	0.96	1.00	1.04	1.08	1.11	1.15	1.18	1.22	1.25	1.28	1.31	1.34	1.37	1.40	1.43	1.46	1.49	1.51
48	0.69	0.74	0.79	0.84	0.89	0.94	0.98	1.02	1.06	1.10	1.13	1.17	1.21	1.24	1.27	1.31	1.34	1.37	1.40	1.43	1.46	1.49	1.51	1.54
50	0.70	0.75	0.81	0.86	0.91	0.95	1.00	1.04	1.08	1.12	1.15	1.19	1.23	1.26	1.30	1.33	1.36	1.39	1.42	1.45	1.48	1.51	1.54	1.57
52	0.71	0.77	0.82	0.87	0.92	0.97	1.01	1.05	1.10	1.14	1.17	1.21	1.25	1.28	1.32	1.35	1.38	1.41	1.45	1.48	1.51	1.54	1.57	1.59
54	0.72	0.78	0.83	0.89	0.94	0.98	1.03	1.07	1.11	1.15	1.19	1.23	1.27	1.30	1.34	1.37	1.41	1.44	1.47	1.50	1.53	1.56	1.59	1.62
56	0.73	0.79	0.85	0.90	0.95	1.00	1.04	1.09	1.13	1.17	1.21	1.25	1.29	1.32	1.36	1.39	1.43	1.46	1.49	1.52	1.55	1.59	1.62	1.64
58	0.74	0.80	0.86	0.91	0.97	1.01	1.06	1.10	1.15	1.19	1.23	1.27	1.31	1.34	1.38	1.41	1.45	1.48	1.51	1.55	1.58	1.61	1.64	1.67
	50	60	70	80	90	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280
60	0.98	1.08	1.16	1.25	1.32	1.40	1.47	1.54	1.60	1.66	1.72	1.78	1.84	1.89	1.95	2.00	2.05	2.10	2.15	2.19	2.24	2.29	2.33	2.38
62	0.99	1.09	1.18	1.26	1.34	1.42	1.49	1.56	1.62	1.69	1.75	1.81	1.86	1.92	1.97	2.03	2.08	2.13	2.18	2.23	2.27	2.32	2.36	2.41
64	1.01	1.11	1.20	1.28	1.36	1.44	1.51	1.58	1.65	1.71	1.77	1.83	1.89	1.94	2.00	2.05	2.11	2.16	2.21	2.26	2.30	2.35	2.40	2.44
66	1.02	1.12	1.21	1.30	1.38	1.46	1.53	1.60	1.67	1.73	1.79	1.85	1.91	1.97	2.03	2.08	2.13	2.18	2.24	2.28	2.33	2.38	2.43	2.47
68	1.03	1.13	1.23	1.31	1.40	1.47	1.55	1.62	1.69	1.75	1.82	1.88	1.94	2.00	2.05	2.11	2.16	2.21	2.26	2.31	2.36	2.41	2.46	2.50
70	1.04	1.15	1.24	1.33	1.41	1.49	1.57	1.64	1.71	1.78	1.84	1.90	1.96	2.02	2.08	2.13	2.19	2.24	2.29	2.34	2.39	2.44	2.49	2.54
72	1.06	1.16	1.26	1.35	1.43	1.51	1.59	1.66	1.73	1.80	1.86	1.92	1.98	2.04	2.10	2.16	2.21	2.27	2.32	2.37	2.42	2.47	2.52	2.57
	90	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300	310	320
74	1.45	1.53	1.61	1.68	1.75	1.82	1.88	1.95	2.01	2.07	2.13	2.18	2.24	2.29	2.35	2.40	2.45	2.50	2.55	2.60	2.64	2.69	2.74	2.78
76	1.46	1.55	1.62	1.70	1.77	1.84	1.90	1.97	2.03	2.09	2.15	2.21	2.26	2.32	2.37	2.43	2.48	2.53	2.58	2.63	2.67	2.72	2.77	2.81
78	1.48	1.56	1.64	1.72	1.79	1.86	1.93	1.99	2.05	2.11	2.17	2.23	2.29	2.34	2.40	2.45	2.50	2.55	2.61	2.65	2.70	2.75	2.80	2.84
80	1.50	1.58	1.66	1.73	1.81	1.88	1.95	2.01	2.08	2.14	2.20	2.26	2.31	2.37	2.42	2.48	2.53	2.58	2.63	2.68	2.73	2.78	2.83	2.87
82	1.51	1.60	1.68	1.75	1.83	1.90	1.97	2.03	2.10	2.16	2.22	2.28	2.34	2.39	2.45	2.50	2.56	2.61	2.66	2.71	2.76	2.81	2.86	2.90
84	1.53	1.61	1.69	1.77	1.85	1.92	1.99	2.05	2.12	2.18	2.24	2.30	2.36	2.42	2.48	2.53	2.58	2.64	2.69	2.74	2.79	2.84	2.89	2.93
86	1.54	1.63	1.71	1.79	1.86	1.94	2.01	2.07	2.14	2.20	2.27	2.33	2.39	2.44	2.50	2.56	2.61	2.66	2.71	2.77	2.82	2.87	2.91	2.96

APPENDIX IV B

BODY SURFACE AREA (m²)

KILOGRAMS/CENTIMETERS

Height (cm)	Weight (kg)																			
	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	44
50	0.25	0.31	0.36	0.40	0.44	0.48	0.51	0.54	0.57	0.60	0.63	0.66	0.68	0.71	0.73	0.75	0.78	0.80	0.82	0.86
55	0.26	0.32	0.37	0.42	0.46	0.50	0.53	0.57	0.60	0.63	0.66	0.68	0.71	0.74	0.76	0.78	0.81	0.83	0.85	0.90
60	0.27	0.33	0.39	0.43	0.48	0.52	0.55	0.59	0.62	0.65	0.68	0.71	0.74	0.76	0.79	0.81	0.84	0.86	0.88	0.93
65	0.28	0.34	0.40	0.45	0.49	0.53	0.57	0.61	0.64	0.67	0.70	0.73	0.76	0.79	0.82	0.84	0.87	0.89	0.91	0.96
70	0.29	0.36	0.41	0.46	0.51	0.55	0.59	0.63	0.66	0.69	0.73	0.76	0.79	0.81	0.84	0.87	0.89	0.92	0.94	0.99
75	0.30	0.37	0.42	0.48	0.52	0.57	0.61	0.64	0.68	0.71	0.75	0.78	0.81	0.84	0.87	0.89	0.92	0.95	0.97	1.00
80	0.31	0.38	0.44	0.49	0.54	0.58	0.62	0.66	0.70	0.73	0.77	0.80	0.83	0.86	0.89	0.92	0.95	0.97	1.00	1.05
85	0.31	0.39	0.45	0.50	0.55	0.60	0.64	0.68	0.72	0.75	0.79	0.82	0.85	0.88	0.91	0.94	0.97	0.99	1.02	1.05
90	0.32	0.40	0.46	0.51	0.56	0.61	0.65	0.70	0.73	0.77	0.81	0.84	0.87	0.91	0.94	0.97	0.99	1.02	1.05	1.10
95	0.33	0.40	0.47	0.53	0.58	0.63	0.67	0.71	0.75	0.79	0.83	0.86	0.89	0.93	0.96	0.99	1.02	1.05	1.07	1.13
	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	48	52	56
100	0.59	0.64	0.68	0.73	0.77	0.81	0.84	0.88	0.91	0.95	0.98	1.01	1.04	1.07	1.10	1.13	1.15	1.21	1.26	1.30
105	0.60	0.65	0.70	0.74	0.78	0.82	0.86	0.90	0.93	0.97	1.00	1.03	1.06	1.09	1.12	1.15	1.18	1.23	1.28	1.33
110	0.61	0.67	0.71	0.76	0.80	0.84	0.88	0.92	0.95	0.99	1.02	1.05	1.08	1.11	1.14	1.17	1.20	1.25	1.31	1.36
115	0.63	0.68	0.73	0.77	0.81	0.86	0.89	0.93	0.97	1.00	1.04	1.07	1.10	1.13	1.16	1.19	1.22	1.28	1.33	1.38
120	0.64	0.69	0.74	0.79	0.83	0.87	0.91	0.95	0.99	1.02	1.06	1.09	1.12	1.15	1.19	1.22	1.24	1.30	1.36	1.41
125	0.65	0.70	0.75	0.80	0.84	0.89	0.93	0.97	1.00	1.04	1.07	1.11	1.14	1.17	1.21	1.24	1.27	1.32	1.38	1.43
130	0.66	0.71	0.77	0.81	0.86	0.90	0.94	0.98	1.02	1.06	1.09	1.13	1.16	1.19	1.23	1.26	1.29	1.35	1.40	1.46
135	0.67	0.73	0.78	0.83	0.87	0.92	0.96	1.00	1.04	1.07	1.11	1.15	1.18	1.21	1.25	1.28	1.31	1.37	1.43	1.48
140	0.68	0.74	0.79	0.84	0.89	0.93	0.97	1.01	1.05	1.09	1.13	1.16	1.20	1.23	1.26	1.30	1.33	1.39	1.45	1.50
145	0.69	0.75	0.80	0.85	0.90	0.94	0.99	1.03	1.07	1.11	1.14	1.18	1.22	1.25	1.28	1.32	1.35	1.41	1.47	1.53
	30	34	38	42	46	50	54	58	62	66	70	74	78	82	86	90	94	98	102	106
150	1.12	1.20	1.27	1.34	1.40	1.46	1.52	1.58	1.63	1.69	1.74	1.79	1.84	1.88	1.93	1.98	2.02	2.07	2.11	2.15
155	1.14	1.21	1.29	1.35	1.42	1.48	1.54	1.60	1.65	1.71	1.76	1.81	1.86	1.91	1.96	2.00	2.05	2.09	2.14	2.18
160	1.15	1.23	1.30	1.37	1.44	1.50	1.56	1.62	1.68	1.73	1.78	1.84	1.89	1.94	1.98	2.03	2.08	2.12	2.17	2.21
165	1.17	1.25	1.32	1.39	1.46	1.52	1.58	1.64	1.70	1.75	1.81	1.86	1.91	1.96	2.01	2.06	2.10	2.15	2.19	2.24
170	1.18	1.26	1.34	1.41	1.48	1.54	1.60	1.66	1.72	1.78	1.83	1.88	1.94	1.99	2.04	2.08	2.13	2.18	2.22	2.27
175	1.20	1.28	1.35	1.43	1.49	1.56	1.62	1.68	1.74	1.80	1.85	1.91	1.96	2.01	2.06	2.11	2.16	2.20	2.25	2.30
180	1.21	1.29	1.37	1.44	1.51	1.58	1.64	1.70	1.76	1.82	1.88	1.93	1.98	2.04	2.09	2.13	2.18	2.23	2.28	2.32
	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104	108	112	116
185	1.42	1.49	1.56	1.63	1.69	1.75	1.81	1.87	1.93	1.98	2.03	2.08	2.13	2.18	2.23	2.28	2.33	2.37	2.42	2.46
190	1.44	1.51	1.58	1.65	1.71	1.77	1.83	1.89	1.95	2.00	2.06	2.11	2.16	2.21	2.26	2.31	2.35	2.40	2.44	2.49
195	1.45	1.53	1.60	1.67	1.73	1.79	1.85	1.91	1.97	2.02	2.08	2.13	2.18	2.23	2.28	2.33	2.38	2.43	2.47	2.52
200	1.47	1.54	1.62	1.68	1.75	1.81	1.87	1.93	1.99	2.05	2.10	2.15	2.21	2.26	2.31	2.36	2.40	2.45	2.50	2.54
205	1.49	1.56	1.63	1.70	1.77	1.83	1.89	1.95	2.01	2.07	2.12	2.18	2.23	2.28	2.33	2.38	2.43	2.48	2.52	2.57
210	1.50	1.58	1.65	1.72	1.79	1.85	1.91	1.97	2.03	2.09	2.14	2.20	2.25	2.30	2.36	2.41	2.45	2.50	2.55	2.60
215	1.52	1.59	1.67	1.74	1.80	1.87	1.93	1.99	2.05	2.11	2.17	2.22	2.27	2.33	2.38	2.43	2.48	2.53	2.58	2.62
220	1.53	1.61	1.68	1.75	1.82	1.89	1.95	2.01	2.07	2.13	2.19	2.24	2.30	2.35	2.40	2.45	2.50	2.55	2.60	2.65
	120	124	128	132	136	140	144	148	152	156	160	164	168	172	176	180	184	188	192	196
225	1.54	1.62	1.69	1.76	1.83	1.89	1.95	2.01	2.07	2.13	2.19	2.24	2.30	2.35	2.40	2.45	2.50	2.55	2.60	2.65
230	1.55	1.63	1.70	1.77	1.84	1.90	1.96	2.02	2.08	2.14	2.20	2.25	2.30	2.36	2.41	2.46	2.51	2.56	2.61	2.66
235	1.56	1.64	1.71	1.78	1.85	1.91	1.97	2.03	2.09	2.15	2.21	2.26	2.31	2.37	2.42	2.47	2.52	2.57	2.62	2.67
240	1.57	1.65	1.72	1.79	1.86	1.92	1.98	2.04	2.10	2.16	2.22	2.27	2.33	2.38	2.43	2.48	2.53	2.58	2.63	2.68
245	1.58	1.66	1.73	1.80	1.87	1.93	1.99	2.05	2.11	2.17	2.23	2.28	2.33	2.38	2.43	2.48	2.53	2.58	2.63	2.68
250	1.59	1.67	1.74	1.81	1.88	1.94	2.00	2.06	2.12	2.18	2.24	2.29	2.34	2.39	2.44	2.49	2.54	2.59	2.64	2.69
255	1.60	1.68	1.75	1.82	1.89	1.95	2.01	2.07	2.13	2.19	2.25	2.30	2.35	2.40	2.45	2.50	2.55	2.60	2.65	2.70
260	1.61	1.69	1.76	1.83	1.90	1.96	2.02	2.08	2.14	2.20	2.26	2.31	2.36	2.41	2.46	2.51	2.56	2.61	2.66	2.71
265	1.62	1.70	1.77	1.84	1.91	1.97	2.03	2.09	2.15	2.21	2.27	2.32	2.37	2.42	2.47	2.52	2.57	2.62	2.67	2.72
270	1.63	1.71	1.78	1.85	1.92	1.98	2.04	2.10	2.16	2.22	2.28	2.33	2.38	2.43	2.48	2.53	2.58	2.63	2.68	2.73
275	1.64	1.72	1.79	1.86	1.93	1.99	2.05	2.11	2.17	2.23	2.29	2.34	2.39	2.44	2.49	2.54	2.59	2.64	2.69	2.74
280	1.65	1.73	1.80	1.87	1.94	2.00	2.06	2.12	2.18	2.24	2.30	2.35	2.40	2.45	2.50	2.55	2.60	2.65	2.70	2.75
285	1.66	1.74	1.81	1.88	1.95	2.01	2.07	2.13	2.19	2.25	2.31	2.36	2.41	2.46	2.51	2.56	2.61	2.66	2.71	2.76
290	1.67	1.75	1.82	1.89	1.96	2.02	2.08	2.14	2.20	2.26	2.32	2.37	2.42	2.47	2.52	2.57	2.62	2.67	2.72	2.77
295	1.68	1.76	1.83	1.90	1.97	2.03	2.09	2.15	2.21	2.27	2.33	2.38	2.43	2.48	2.53	2.58	2.63	2.68	2.73	2.78
300	1.69	1.77	1.84	1.91	1.98	2.04	2.10	2.16	2.22	2.28	2.34	2.39	2.44	2.49	2.54	2.59	2.64	2.69	2.74	2.79

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DISEASE EVALUATION DIAGRAM Systemic Course - Week __

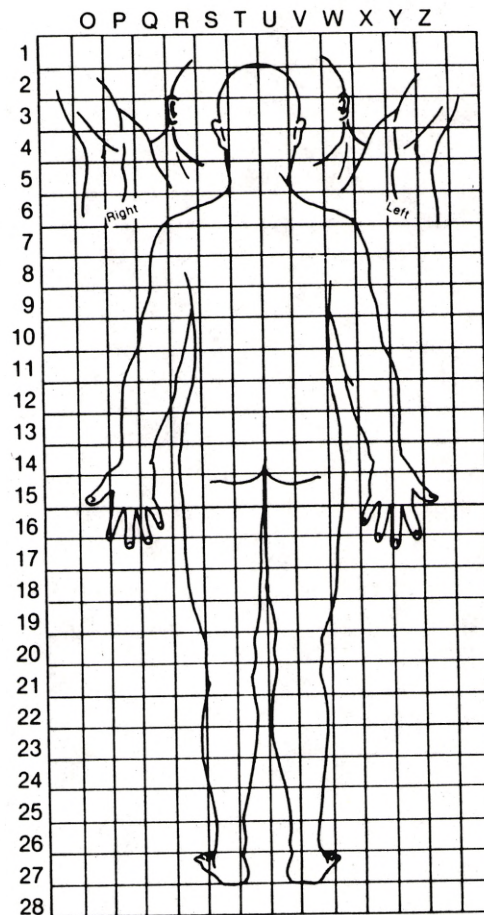
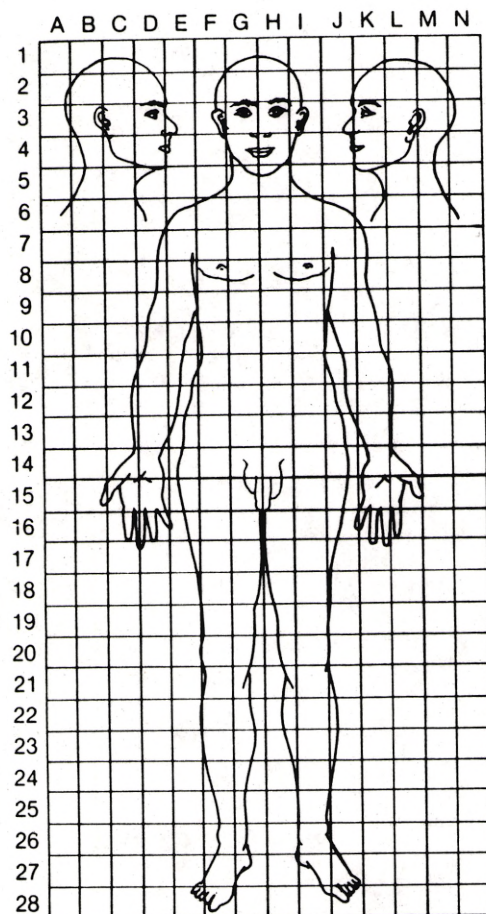
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Date ___ / ___ / ___
M D Y

BODY VIEW FOR HERPES ZOSTER



now file
~~IL-2~~ IL-2

Date 10-3-83

Clinical Project No. _____

To: Chairman, Clinical Research Committee

Recommended by: Michael M. Frank Clinical Director, NIAID
Michael M. Frank, M.D. and Chief, LCI, NIAID

From: H. Clifford Lane, M.D.
Anthony S. Fauci, M.D.

Project title: A phase I trial of Interleukin-2 (IL-2) in patients with the
Acquired Immune Deficiency Syndrome (AIDS)

Principal Investigators: Anthony S. Fauci, M.D. (LIR, NIAID)
H. Clifford Lane, M.D. (LIR, NIAID)
Henry Masur, M.D. (CCM, CC)

Associate Investigators: Edward Gelmann, M.D. (MB, NCI)
Dan Longo, M.D. (MB, NCI)
Gerald Quinlan, M.D. (DV, BB)

Estimated Duration of Study: 6 months

Number and Kind of Subjects needed: 4 patients with AIDS

Purpose of the Project: 1. To study the activity of IL-2 in AIDS.
2. To study the toxicity and tolerance of
IL-2 when given by intravenous injection.
3. To study the in vivo pharmacokinetics and
immunomodulatory properties of IL-2.

Introduction

Over the last 2 years a new syndrome has been described which consists of severe opportunistic infections, the development of neoplasms, predominantly Kaposi's sarcoma, and profound abnormalities of cellular immune function associated with a pronounced decrease in the number of circulating T cells which bear the helper/inducer phenotype. The disease was initially described in the male homosexual community where it has begun to reach epidemic proportions; however, it has more recently been described in Haitian immigrants, hemophiliacs, and intravenous drug users. Of great concern are the reports suggesting that the disease may be transmitted by blood products. This epidemiology, reminiscent of hepatitis B infection suggests that the disease may be due to a combination of an infectious, probably viral agent and a host with an abnormal immune response. If an infectious agent is involved, it is impossible to say at this time whether it is a persistent or a transient infection.

The individuals with this disease are left with essentially a non-functioning cellular immune system and are at great risk for

opportunistic infections and neoplasms. While antibiotic therapy exists for many of these infections, the failure of the hosts' immune systems to function adequately results in frequent, severe, and often eventually fatal infections. The mortality rate in this syndrome, as best we can tell at present, is an alarming 40%. It is possible, that as time goes on, the mortality will approach 100% since there have been, to date, no reports of reversibility of the immune defect.

IL-2 is a glycoprotein with a molecular weight of approximately 15,000. It is produced by normal T lymphocytes as part of a normal immune response following lymphocyte activation. This lymphokine is also produced by several primate tumor lines. The molecule is stable at pH 2 and has been reported to exist in various forms, presumably due to differences in glycosylation. IL-2 is important in the generation of an immune response predominantly as a messenger signal between lymphocytes. In vitro it has been shown to elicit clonal expansion as well as differentiation, particularly in the development of cytotoxic effector cell function.

While IL-2 has been administered to animals, its reported use in humans thus far has been restricted to a few anecdotal cases. Subcutaneous administration to a child with Nezeloff's syndrome was noted (at autopsy) to result in lymphoid hyperplasia in the draining lymph node. No serious side effects have been reported in the 3 patients known to us who have received IL-2 elsewhere. Potential side effects, observed in studies utilizing crude material include fever, leukocytosis, increased GH, increased ACTH, and peripheral lymphopenia.

In vivo mouse studies suggest that this compound has a half-life in vivo of approximately 4 minutes. In these studies, the drug was found to be excreted and metabolized predominantly by the kidneys. A concentration of 0.1-1.0 units/ml is generally felt to be a minimal stimulatory dose in vitro. In order to see IL-2-induced enhancement of cytotoxic effector cell function, cells may need to be preincubated with this lymphokine for periods exceeding 24 hours.

Virtually all cellular immune functions are suppressed or absent in patients with AIDS. In vitro studies in our laboratories have shown that the decreased cytotoxicity and mitogen responses can be augmented somewhat with immune interferon; however, the responses can be restored to close to normal with IL-2. It is for this reason that we are involved in clinical trials of IL-2 in patients with AIDS.

A combination phase I and phase II trial of an IL-2 preparation provided by Immuno Modulators Laboratories (IML) has recently been completed in 8 patients with AIDS. The results of this trial have been mixed. Definite immune enhancement of both in vivo (skin test reactivity) and in vitro (phytohemagglutinin responses, cytotoxic lymphocyte responses) immune responses were seen with the use of this agent. However, at doses exceeding 10,000 units per day, unacceptable side effects (severe peripheral phlebitis, decreased skin test reactivity, and decreased lymphocyte counts) were seen. It was our feeling that these side effects were most likely due to impurities in the IL-2 preparation rather than to a dose-limiting toxicity of IL-2 itself. This statement is based upon the in vitro observation that at high in vitro concentrations (30-100 units/ml), this product appeared to cause a decrease in lymphocyte blast transformation. This phenomenon was not seen with either Jerkat line IL-2 or recombinant IL-2. }

We have recently completed screening a variety of potential clinical sources of IL-2 to continue this work. Of all the samples screened, only one, that provided by Collaborative Research, Inc., did not demonstrate an in vitro toxicity at high in vitro concentrations (see attached graphs) and was of sufficient potency to be a viable clinical drug. This product is prepared from the supernatants of mitogen-stimulated normal human peripheral blood mononuclear cells and is purified by a variety of steps, including high-pressure liquid chromatography. The product is supplied in a lyophilized form at either 2,500 or 25,000 units per vial. The lyophilized product is stable for at least 6 months at 4°.

The trial will be conducted only when the product has obtained an IND approved by the Office of Biologics. This protocol will be used in filing for that IND.

Patient Eligibility

To be eligible to enter the study each patient must have a diagnosis of AIDS as evidenced by the clinical setting of an opportunistic infection and/or the development of Kaposi's sarcoma in a previously healthy individual who exhibits the characteristic inversion of the T4/T8 ratio of the peripheral blood T lymphocytes.

Age 18-60

Ability to sign an informed consent

Serum creatinine less than 2.0 mg/dl

Serum bilirubin less than 1.5 mg/dl

Omission of cytotoxic chemotherapy for at least 4 weeks prior to entry into the trial.

Omission of interferon or previous IL-2 therapy for at least 2 weeks prior to entry into the trial.

Therapeutic Protocol

Patients will be entered into the study on a single dose toxicity trial and following a 3-day wash-out period will move into an escalating dose trial.

For the single dose toxicity trial, each patient will receive a single intravenous bolus of IL-2 over 2 hours according to the following schedule:

Patient 1 - 250 units
Patient 2 - 2,500 units
Patient 3 - 25,000 units
Patient 4 - 250,000 units

If Grade II toxicity is seen at a given dose, the next 2 patients will receive the next lower dose. If both tolerate that dose, the next 2 patients will receive the dose which caused the initial toxicity. If either of those 2 patients develop toxicity, the single dose trial will be terminated at that point. If both tolerate the dose, then the next 2 patients will receive the next higher dose.

Following a 3-day wash-out period, each patient will be eligible to enter the escalating dose trial. In this phase of the study, patients will receive daily 24-hour infusions for 5 consecutive days of IL-2 in an escalating fashion as indicated in the Table. Medication will be infused Monday - Friday only.

Patients	Week			
	1	2	3	4
1, 2	250	2,500	25,000	250,000
3, 4	2,500	25,000	250,000	250,000

Weekly lymphocyte counts, cytotoxicity function, and mitogen responsiveness as well as routine laboratory studies will be performed during this time. This dose escalation will continue until toxicity is reached, at which point the patient will be dropped to the highest dose without unacceptable side effects (more than grade 1 toxicity).

Patients exhibiting significant improvement in clinical status or immune function following this therapy will be eligible to continue therapy with IL-2 as long as improvement is noted. Once improvement plateaus, dosage will be adjusted downward to the longest interval and lowest dose which maintain the patient's status.

If product administration is associated with a febrile response, patients will be administered acetaminophen either in response to fever or as a prophylactic measure. Neither aspirin nor other prostaglandin inhibitors will be administered to patients while receiving this product.

Serial Observations

	Pre-Study	24 Hours After Injection	Weekly After Injection	Off Study
History & physical exam	X	X ¹	X	X
CBC + differential, platelet count	X	X	X	X
PT, PTT	X	X	X	X
Urinalysis	X	X	X	X
SMA-12	X	X	X	X
CXR	X			X
EKG	X			X
X-rays, scan, tumor markers of evaluable disease	X			X
Immune parameters lymphocyte blastogenesis immunoglobulin production T-cell numbers (total subsets) NK and T-cell activity	X	X		X
Serum Interferon	X		X	
Serum IL-2	X	X ²	X	
Viral Cultures Blood, throat and urine	X	X	X	X

X¹ = Including vital signs and examination of injection site at 1, 2, 4, 6, 8, 12, 18, 24 hours after injection.

X² = Serum IL-2 levels at 0, 1, 2, 4, 6, 8, 12, 18, 24 hours and 7, 14, 21, 28 days.

Criteria of Response

For patients with opportunistic infections only:

1. Complete remission: Return of all immune parameters to normal. Resolution of any opportunistic infections.
2. Partial response: Improvement in T4/T8 ratio and/or resolution of any opportunistic infection.
3. Stable disease: No improvement in T4/T8 ratio, no new opportunistic infections.
4. Progression: Further decline in T4/T8 ratio or new opportunistic infection.

For patients with Kaposi's sarcoma:

1. Complete remission: Disappearance of all measurable and evaluable disease. Improvement in T4/T8 ratio to normal.
2. Partial response: Reduction by 50% or greater (in the sum of the products of 2 perpendicular diameters) of all measurable lesions, no increase in size of any measurable or evaluable lesion, no appearance of any new lesions.
3. Stable disease: Less than a partial response with no new lesions or less than a 25% increase in any measurable lesion.
4. Progression: Appearance of new lesions or an increase of 25% or greater in any measurable lesion.

Toxicity and Dose Modification (See table on next page)

- Grade I toxicity: Dosage may proceed as scheduled.
- Grade II toxicity: Dosage may proceed as scheduled or may be delayed until abnormal parameters return to baseline at discretion of the principal investigators.
- Grade III toxicity: Dosage must be delayed until abnormal parameters return to baseline.
- Grade IV toxicity: Off-study.
- Ungraded toxicity: Delay in dosage or off-study at discretion of the principal investigators.

Parameter	Grade of Toxicity			
	I (Mild)	II (Moderate)	III (Severe)	IV (Maximal or Life-threatening)
Fever	<103°F	103°F - 105°F (Transient <24 hours)	103°F - 105°F (Persistent >24 hours)	>105°F
Hematologic				
1. WBC				
2. PCV	1,500-2,000	1,000-1,500	1,000-2,000	<1000
3. Platelets	75,000-100,000	50,000-75,000	500-1,000 25,000-50,000	<500 <25,000
Hepatic				
1. Bilirubin	1.5-2.5	2.0-3.0	3.0-4.0	>4.0
2. SGOT	50-150	150-300	300-600	>600
Renal				
1. Creatinine	2.0-2.5	2.5-3.0	3.0-4.0	>4.0
2. Proteinuria	1+	2+ - 3+	4+ (<1g/24 hr)	4+ (>1g/24 hr)
Gastrointestinal				
1. Nausea/vomiting	nausea	<5 emesis/d	>5/d	Intractable, requiring IV fluids
2. Diarrhea	3-4 stools/d	5-7/d	>7/d	Intractable, requiring IV fluids
Neurologic				
1. Central	difficulty in concentration or memory	mild confusion or lethargy	disorien- tation or stupor	coma seizures
2. Peripheral	decreased DTR, mild paresthesia	absent DTR, moderate paresthesia	motor weakness severe paresthesia	paralysis
Fatigue	No impairment of APL	In bed <50% day	In bed >50% day	Unable to care for self

Previously unrecognized toxicity: To be reported to the principal investigators.

Off-Study Criteria

1. Unacceptable toxicity (see preceeding section).
2. Patient non-compliance or refusal.
3. Intercurrent illness precluding further therapy at the discretion of the principal investigator.

Product Information

Human IL-2 is supplied by Collaborative Research, Inc., and is currently awaiting IND license and approval. The material will be supplied in vials, each containing an amount of IL-2 appropriate for the phase of the trial. The product is stored lyophilized at 4 degrees centigrade and is reconstituted with preservative-free isotonic saline.

The material will be infused intravenously in 250 ml normal saline containing 5 gm% albumin over 8 hours.

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MEDICAL RECORDS

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

• Adult Patient or • Parent, for Minor Patient

INSTITUTE:

National Institute of Allergy and Infectious Diseases

STUDY NUMBER:

PRINCIPAL INVESTIGATOR:

Anthony S. Fauci

H. Clifford Lane

STUDY TITLE:

Phase I trial of human interleukin 2 (IL-2)

Henry Masur

In patients with the acquired immune deficiency syndrome (AIDS)

INTRODUCTION

We invite you (or your child) to take part in a research study at the National Institutes of Health. It is important that you read and understand several general principles that apply to all who take part in our studies: (a) taking part in the study is entirely voluntary; (b) personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others; (c) you may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled. The nature of the study, the risks, inconveniences, discomforts, and other pertinent information about the study are discussed below. You are urged to discuss any questions you have about this study with the staff members who explain it to you.

The disease you have (AIDS) is a disease syndrome consisting of unusual infections and/or an unusual form of cancer (Kaposi's sarcoma) which is presumably due to an acquired defect in your immune system. While therapies exist for many, but not all of the infections one with this syndrome might contract, there is no known cure for the immunologic defects. Thus, patients with this syndrome are prone to recurrent, and at times fatal infections. The purpose of this study is to see whether or not IL-2 is of value in treating any or all of the immunologic abnormalities associated with this syndrome.

IL-2 is a biologic substance produced by human lymphocytes (white blood cells). While it has not been proven to be of benefit in your disease, there are reasons to believe, based upon laboratory studies, that it may be helpful. However, it is important for you to realize that little is known about the toxicity of this compound (IL-2) in animals or man.

You will receive IL-2 on an experimental basis to determine the best dose of this medication, what side effects it may cause, and how well it works in the treatment of AIDS. During the first phase, you will receive a single intravenous dose of the medication over a 2-hour period to determine your tolerance for the product. Three days later you will be started on a dose escalation trial in which the drug will be given as a continuous intravenous infusion from Monday through Friday with the dose increasing 10-fold each week until either a therapeutic effect is seen or unacceptable side effects occur.

PATIENT IDENTIFICATION

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

• Adult Patient or • Parent, for Minor Patient

NIH 2514-1 (6-82)

DA. 00 00 0000

STUDY NUMBER: _____

CONTINUATION SHEET for either:
NIH 2514-1, Consent To Participate In A Clinical Research Study
NIH 2514-2, Minor Patient's Assent To Participate In A Clinical Research Study

CONTINUATION: page _____ of _____ pages.

This second phase of the study will last 28 days. Since the best dose for this drug is not currently known, you may be receiving a lower or higher total IL-2 dose than what is later determined to be the most helpful. You will be hospitalized for some or all of the 28 days of treatment. During the study, frequent blood and urine specimens will be taken to determine the level of IL-2 in your body. The total amount of blood taken during this study will be no more than 450 ml or 1 pint.

You will be asked not to use aspirin, alcohol, or barbiturates during this study because of possible adverse reactions in association with IL-2. The side effects of IL-2 in humans are not known at this time. Based upon studies with other types of lymphocyte products, these side effects may include, but are not necessarily limited to, fever, chills, loss of appetite, fatigue, mild nausea and vomiting, lowering of blood counts with increased risk of infection or bleeding, and abnormalities in blood tests of liver function. Patients receiving a similar medication were noted to have an increased incidence of vein inflammation at the site of the intravenous injections. Your treatment may need to be modified or even stopped if serious side effects of the medication occur.

It is not possible to predict whether any personal benefit will result from treatment with IL-2. If a therapeutic response is seen, you will be eligible to continue therapy until such time as no further improvement is noted. Treatment will be stopped if unacceptable side effects occur. If you should develop life-threatening progressive Kaposi's sarcoma while on the trial, appropriate therapy will be instituted, and you will be removed from the trial.

PATIENT IDENTIFICATION

CONTINUATION SHEET for either:
NIH-2514-1 (6-82)
NIH-2514-2 (6-82)

STUDY NUMBER: _____

OTHER PERTINENT INFORMATION

- Confidentiality.** When results of a study such as this are reported in medical journals or at meetings, the identification of those taking part is withheld. Medical records of Clinical Center patients are maintained according to current legal requirements, and are made available for review, as required by the Food and Drug Administration or other authorized users, only under the guidelines established by the Federal Privacy Act.
- Policy Regarding Research-Related Injuries.** The Clinical Center will provide short-term medical care for any physical injury resulting from your participation in research here. Neither the Clinical Center nor the Federal government will provide long-term medical care or financial compensation for such injuries, except as may be provided through whatever remedies are normally available under law.
- Payments.** You will not be paid for taking part in this study. The Clinical Center does not charge for medications, doctors' care or hospitalization. Exceptions for Normal Volunteers are guided by Clinical Center and Normal Volunteer Office policies.
- Problems or Questions.** Should any problem or question arise with regard to this study, with regard to your rights as a participant in clinical research, or with regard to any research-related injury, you should contact the principal investigator, _____, or these other staff members also involved in this study.

Building 10, Room 11B-09. Telephone: (301) 496-1124.
National Institutes of Health
Bethesda, Maryland 20205

Consent Document. It is suggested that you retain a copy of this document for your later reference and personal records.

COMPLETE APPROPRIATE ITEM BELOW, A or B:Adult Patient's Consent.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient & Date Signed _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s) & Date Signed _____

(If other than parent, specify relationship _____)

Signature of Investigator & Date Signed _____

Signature of Witness & Date Signed _____

PATIENT IDENTIFICATIONCONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY
• Adult Patient or • Parent, for Minor Patient

NIH 2514-1 (6-82)

PA: 09-25-0099

EXECUTIVE SUMMARY
RECOMMENDATIONS FOR PREVENTING TRANSMISSION OF INFECTION
WITH HUMAN T-LYMPHOTROPIC VIRUS TYPE III/
LYMPHADENOPATHY-ASSOCIATED VIRUS

This information and recommendations contained in these guidelines have been developed with particular emphasis on health-care workers and others in related occupations in which exposure might occur to blood from persons infected with HTLV-III/LAV, the "AIDS virus". Because of public concern about the purported risk of transmission of HTLV-III/LAV by persons providing personal services and those preparing and serving food and beverages, this document also addresses personal-service and food-service workers. Finally, it addresses "other workers"-- persons in settings, such as offices, schools, factories, and construction sites, where there is no known risk of AIDS virus transmission.

Because AIDS is a bloodborne, sexually transmitted disease that is not spread by casual contact, these guidelines do not recommend routine HTLV-III/LAV antibody screening for the groups addressed. Because it is not transmitted through preparation or serving of food and beverages, the guidelines state that food-service workers known to be infected with AIDS should not be restricted from work unless they have another infection or illness for which such restriction would be warranted.

These guidelines contain detailed recommendations of precautions appropriate to prevent transmission of all bloodborne infectious diseases to people exposed- in the course of their duties- to blood from persons who may be infected with HTLV-III/LAV. They emphasize that health-care workers should take all possible precautions to prevent needlestick injury. The guidelines are based on the well-documented modes of HTLV-III/LAV transmission and incorporate a "worst case" scenario, the hepatitis B model of transmission. Because the hepatitis B virus is transmitted in a similar manner as the AIDS virus and is both harder and more infectious than HTLV-III/LAV, guidelines that would prevent transmission of hepatitis B will also prevent transmission of AIDS.

Formulation of specific recommendations for health-care workers who perform invasive procedures is in progress.

Persons at increased risk of acquiring infections with human T-lymphotropic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV), the virus that causes acquired immunodeficiency syndrome (AIDS), include homosexual and bisexual men, intravenous (IV) drug abusers, persons transfused with contaminated blood or blood products, heterosexual contacts of persons with HTLV-III/LAV infections, and children born to infected mothers. HTLV-III/LAV is transmitted through sexual contact, parenteral exposure to infected blood or blood components, and perinatal transmission from mother to neonate. HTLV-III/LAV has been isolated from blood, semen, saliva, tears, breast milk and urine and is likely to be isolated from other body fluids, secretions and excretions, but epidemiologic evidence has implicated only blood and semen in transmission. Studies of nonsexual household contacts of AIDS patients indicate that casual contact with saliva and tears does not result in transmission of infection. Spread of infection to household contacts of infected persons has not been detected when the household contacts have not been sex partners or infants of infected mothers. The kind of nonsexual person-to-person contact that generally occurs among workers and clients or consumers in the workplace does not pose a risk for transmission of HTLV-III/LAV.

As in the development of any such recommendations, the paramount consideration is the protection of the public's health. The following recommendations have been developed for all workers, particularly workers in occupations in which exposure might occur to blood from individuals infected with HTLV-III/LAV. These recommendations reinforce and supplement the specific recommendations that were published earlier for clinical and laboratory staffs (1) and for dental-care personnel and persons performing necropsies and morticians services (2). Because of public concern about the purported risk of transmission of HTLV-III/LAV by persons providing personal services and by food and beverages, these recommendations contain information and recommendations for personal-service and food-service workers. Finally, these recommendations address workplaces in general where there is not known risk of transmission of HTLV-III/LAV (e.g. offices, schools, factories, construction sites). Formulations of specific recommendations for health-care workers (HCWs) who perform invasive procedures to prevent HTLV-III/LAV transmission in prisons, other correctional facilities, and institutions housing individuals who may exhibit uncontrollable behavior (e.g. custodial institutions). In addition, separate recommendations have already been developed for children in schools and day-care centers (3).

HTLV-III/LAV-infected individuals include those with AIDS (4); those diagnosed by their physician(s) as having other illnesses due to infection with HTLV-III/LAV; and those who have virologic or serologic evidence of infections with HTLV-III/LAV but who are not ill.

Some of these recommendations are based on the well-documented modes of HTLV-III/LAV transmission identified in epidemiologic studies. Other recommendations are based on the hepatitis B model of transmission.

THE HEPATITIS B MODEL

The epidemiology of HTLV-III/LAV infection is similar to that of hepatitis B virus (HBV) infection, and much that has been learned over the last 15 years related to the risk of acquiring hepatitis B in

the workplace can be applied to understanding the risk of HTLV-III/LAV transmission in the health-care and other occupational settings. Both viruses are transmitted through sexual contact, parenteral exposure to contaminated blood or blood products, and perinatal transmission from infected mothers to their offspring. Thus, some of the same major groups at high risk for HBV infection (e.g. homosexual men, IV drug users, persons with hemophilia, infants born to infected mothers) are also the groups at highest risk for HTLV-III/LAV infection. Neither HBV nor HTLV-III/LAV has been shown to be transmitted by casual contact, contaminated food or water, or airborne or fecal-oral routes (5).

HBV infection is an occupational risk for HCWs, but this risk is related to degree of contact with blood or contaminated needles. HCWs who do not have contact with blood or needles contaminated with blood are not at risk for acquiring HBV in the workplace (6-8).

In the health-care setting, HBV transmission has not been documented between hospitalized patients, except in hemodialysis units, where blood contamination of the environment has been extensive or where HBV-positive blood from one patient has been transferred to another patient through contamination of instruments. Evidence of HBV transmission from HCWs to patients has been extremely rare and limited to situations in which the HCWs exhibited high concentrations of virus in their blood (at least 100,000,000 circulating virus particles per ml of serum), and the HCWs sustained a puncture wound while performing traumatic procedures on patients or had exudative or weeping lesions that allowed virus to contaminate instruments or open wounds of patients.

In regard to the comparison of HBV with HTLV-III/LAV transmission in health-care settings, current evidence indicates that, despite epidemiologic similarities, the risk of acquiring HBV infection following a needlestick injury from an HBV carrier ranges from 6% to 30% (12,13), far in excess of the documented risk of HTLV-III/LAV infections following a needlestick involving a source patient infected with HTLV-III/LAV, which is less than 1%. In addition, all persons who have been shown to transmit HBV infection in health-care settings have belong to the subset of chronic HBV carriers who, when tested, have exhibited evidence of exceptionally high concentrations of virus (greater than 100,000,00 infectious virus particles per ml) in their blood. Chronic carriers who have substantially lower concentrations of virus in their blood have not been implicated in transmission in the health-care setting (9-11,14). The HBV model thus represents a "worst case" condition in regard to transmission in health-care and other related settings. Therefore, recommendations for the control of HBV infection should also effectively prevent spread of HTLV-III/LAV. Whether additional measures are indicated for those HCWs who perform invasive procedures will be addressed in the recommendations currently being developed.

Routine screening of all patients or HCWs for evidence of HBV infection has never been recommended. Control of HBV transmission in the health-care setting has emphasized the implementation of recommendations for the appropriate handling of blood, other body fluids, and items soiled with blood or other body fluids.

HEALTH CARE WORKERS

HCWs include, but are not limited to, nurses, physicians, dentists and other dental workers, optometrists, podiatrists, chiropractors, laboratory and blood bank technologists and technicians, phlebotomists, dialysis personnel, paramedics, emergency medical technicians, medical examiners, morticians, housekeepers, laundry workers and others whose work involves contact with patients, their blood or other body fluids, or corpses. Additional recommendations are being developed for HCWs who perform invasive procedures.

Recommendations for HCWs emphasize precautions appropriate for preventing transmission of bloodborne infectious diseases, including HTLV-III/LAV and HBV infections. Thus, these precautions should be enforced routinely, as should other standard infections-control precautions, regardless of whether HCWs or patients are known to be infected with HTLV-III/LAV or HBV. In addition to being informed of these precautions, all HCWs, including students and housestaff, should be educated regarding the epidemiology, modes of transmission, and prevention of HTLV-III/LAV infection.

Management of parenteral and mucous membrane exposures. If a HCW has a parenteral (e.g. needlestick or cut) or a mucous membrane (e.g. splash to the eye or mouth) exposure to blood or other body fluids, the source patient should be assessed clinically and epidemiologically to determine the likelihood of HTLV-III/LAV infection. If the source patient has AIDS or other evidence of HTLV-III/LAV infection, declines testing, or has a positive test, the HCW should be evaluated clinically and serologically for evidence of HTLV-III/LAV infection as soon as possible after the exposure, and, if seronegative, retested after 6 weeks and on a periodic basis thereafter (e.g. 3, 6, and 12 months following exposure) to determine if transmission has occurred. During this follow-up period, especially the first 6 weeks, when most infected persons are expected to seroconvert, exposed HCWs should receive counseling about the risk of infection and follow U.S. Public Health (PHS) recommendations for preventing transmission of AIDS (15,16). If the source patient is seronegative and has no other evidence of HTLV-III/LAV infection, no further follow-up of the HCW is necessary. If the source patient cannot be identified, decisions regarding appropriate follow-up should be individualized based on the type of exposure and the likelihood that the source patient was infected. If a patient has a parenteral or mucous membrane exposure to blood or other body fluids of a HCW, the patient should be informed of the incident and the same procedure outlined above should be followed. Management of this type of exposure will be addressed in more detail in the recommendations for HCWs who perform invasive procedures.

Serologic testing of patients. Routine serologic testing of all patients for antibody to HTLV-III/LAV is not recommended to prevent transmission of HTLV-III/LAV infection in the workplace, because results of such testing are unlikely to further reduce the risk of transmission, which, even with documented needlesticks, is already extremely low. Furthermore, the risk of needlestick and other parenteral exposures could be reduced by emphasizing and more consistently implementing routinely recommended infection control precautions (e.g. not recapping needles). Moreover, results of routine serologic testing would not be available for emergency cases

and patients with short lengths of stay, and additional tests to determine whether a positive test was a true or false positive would be required in populations with a low prevalence of infection. However, this recommendations is based only on considerations of occupational risks and should not be construed as a recommendation against other uses of the serologic test, such as for diagnosis or to facilitate medical management of patients. Since the experience with infected patients does vary substantially among hospitals (75% of all AIDS cases have been reported by only 280 of the more than 6,000 acute-care hospitals in the United States), some hospitals in certain geographic areas may deem it appropriate to initiate serologic testing of patients.

Risk of HCWs acquiring HTLV-III/LAV in the workplace. Using the HBV model, the highest risk for transmission of HTLV-III/LAV in the workplace would involve parenteral exposure to a needle or other sharp instrument contaminated with blood of an infected patients. The risk to HCWs of acquired HTLV-III/LAV infections in the workplace has been evaluated in several studies. In five separate studies, a total of 1,498 HCWs have been tested for antibody to HTLV-III/LAV. In these studies, 666 (44.5%) of the HCWs had direct parenteral (needlestick or cut) or mucous membrane exposure to patients with AIDS or HTLV-III/LAV infection. Most of these exposures were to blood rather than to other body fluids. None of the HCWs whose initial serologic tests were negative developed subsequent evidence of HTLV-III/LAV infection following their exposures. Twenty-six HCWs in these five studies were seropositive when first tested; all but three of these persons belonged to groups recognized to be at increased risk for AIDS (17). Since one was tested anonymously, epidemiologic information was available on only two of these three seropositive HCWs. Although these two HCWs were reported as probable occupationally related HTLV-III/LAV infection (17,18), neither had a preexposure nor an early postexposure serum sample available to help determine the onset of infection. One case reported from England describes a nurse who seroconverted following an accidental parenteral exposure to a needle contaminated with blood from an AIDS patient (19).

In spite of extremely low risk of transmission of HTLV-III/LAV infection, even when needlestick injuries occur, more emphasis must be given to precautions targeted to prevent needlestick injuries in HCWs caring for any patient, since such injuries continue to occur even during the care of patients who are known to be infected with HTLV-III/LAV.

Precautions to prevent acquisition of HTLV-III/LAV infection by HCWs in the workplace. The precautions represent prudent practices that apply to preventing transmission of HTLV-III/LAV and other bloodborne infections and should be used routinely (20).

1. Sharp items (needles, scalpel blades and other sharp instruments) should be considered as potentially infective and be handled with extraordinary care to prevent accidental injuries.
2. Disposable syringes and needles, scalpel blades, and other sharp items should be placed into puncture-resistant containers located as close as practical to the area in which they were used. To prevent needlestick injuries, needles should not be recapped, purposefully bent, broken, removed from syringes or otherwise manipulated by hand.

3. When the possibility of exposure to blood or other body fluids exists, routinely recommended precautions should be followed. The anticipated exposure may require gloves alone, as in handling items soiled with blood or other equipment contaminated with blood or other body fluids, or may also require gowns, masks, and eye-coverings when performing procedures involving more extensive contact with blood or potentially infective body fluids, as in some dental or endoscopic procedures or postmortem examinations. Hands should be washed thoroughly and immediately if they accidentally become contaminated with blood.
4. To minimize the need for emergency mouth-to-mouth resuscitation, mouth pieces, resuscitation masks, or other ventilation devices should be strategically located and available for use in areas where the need for resuscitation is predictable.
5. HCWs who are or might become pregnant should be counselled regarding potential risk to the fetus due to work assignment and preventive measures that will reduce these risks (21). Pregnant HCWs are not known to be at greater risk of contracting HTLV-III/LAV infections than those who are not pregnant; however, if a HCW develops HTLV-III/LAV infection during pregnancy, the infant is at increased risk of infection resulting from perinatal transmission. Because of this risk, pregnant HCWs should be especially familiar with precautions for the preventing of HTLV-III/LAV transmission.

Sterilization, disinfection, housekeeping, and waste disposal to prevent transmission of HTLV-III/LAV. Sterilization and disinfection procedures currently recommended for use (22,23) in health-care and dental facilities are adequate to sterilize or disinfect instruments, devices, or other items contaminated with the blood or other body fluids from individuals infected with HTLV-III/LAV. Instruments or other nondisposable items that enter normally sterile tissue or the vascular system or through which blood flows should be sterilized before reuse. Surgical instruments used on all patients should be decontaminated after use rather than just rinsed with water. Decontamination can be accomplished by machine or by hand cleaning by trained personnel wearing appropriate protective attire (24) and using appropriate chemical germicides. Instruments or other nondisposable items that touch intact mucous membranes should receive high-level disinfection.

Several liquid chemical germicides commonly used in laboratories and health-care facilities have been shown to kill HTLV-III/LAV at concentrations much lower than are used in practice (25). When decontaminating instruments or medical devices, chemical germicides that are registered and approved by the U.S. Environmental Protection Agency (EPA) as "sterilants" can be used either for sterilization or for high-level disinfection depending on contact time; germicides approved for use as "hospital disinfectants" and are mycobactericidal when used at appropriate dilutions can also be used for high-level disinfection of devices and instruments. Germicides that are mycobactericidal are preferred because mycobacteria represent one of the most resistant groups of microorganisms; therefore, germicides that are effective against mycobacteria are also effective against other bacterial and viral pathogens. When chemical germicides are

used, instruments or devices to be sterilized or disinfected should be thoroughly cleaned before exposure to the germicide, and the manufacturer's instructions for the use of the germicide should be followed.

Laundry and dishwashing cycles commonly used in hospitals are adequate to decontaminate linens, dishes, glassware, and utensils. When cleaning environmental surfaces, housekeeping procedures commonly used in hospitals are adequate; surfaces exposed to blood and body fluids should be cleaned with a detergent followed by decontamination using an EPA-approved hospital disinfectant that is mycobactericidal. Individuals cleaning up such spills should wear disposable gloves. Information on specific label claims of commercial germicides can be obtained by writing to the Disinfectants Branch, Office of Pesticides, Environmental Protection Agency, 401 M Street S.W., Washington, DC, 20408.

In addition to hospital disinfectants, a freshly prepared solution of sodium hypochlorite (household bleach) is an inexpensive and very effective germicide. Concentrations ranging from 5,000 ppm (a 1:10 dilution of household bleach) to 500 ppm (a 1:100 dilution) sodium hypochlorite are effective, depending on the amount of organic material (e.g. blood, mucus, etc.) present on the surface to be cleaned and disinfected.

Sharp items should be considered as potentially infective and should be handled and disposed of with extraordinary care to prevent accidental injuries. Other potentially infective waste (23) are adequate for disposal of waste contaminated by HTLV-III/LAV. Blood and other body fluids may be carefully poured down a drain connected to a sanitary sewer.

Risk of transmission of HTLV-III/LAV infection from HCWs to patients. Although there is no evidence that HCWs infected with HTLV-III/LAV have transmitted infection to patients, a risk transmission of HTLV-III/LAV infection from HCWs to patients would exist in situations where there is both (1) a high degree of trauma to the patient that would provide a portal of entry for the virus (e.g. during invasive procedures) and (2) access of blood or serous fluid from the infected HCW to the open tissue of a patient as could occur if the HCW sustains a needlestick or scalpel injury during an invasive procedure. HCWs known to be infected with HTLV-III/LAV who do not perform invasive procedures need not be restricted from work unless they have evidence of other infection or illness for which any HCW should be restricted. Specific recommendations for HCWs who perform invasive procedures are being developed.

Precautions to prevent transmission of HTLV-III/LAV infection from HCWs to patients. These precautions apply to all HCWs, regardless of whether they perform invasive procedures.

1. All HCWs should wear gloves for direct contact with mucous membranes or nonintact skin of all patients.
2. HCWs who have exudative lesions or weeping dermatitis should refrain from all direct patient care and from handling patient care and from handling patient-care equipment until the condition resolves.

Serologic testing of HCWs. Routine Serologic testing of HCWs who do not perform invasive procedures (including providers of home and prehospital emergency care) is not recommended to prevent transmission of HTLV-III/LAV infections. The risk of transmission is extremely low

and can be further minimized when routinely recommended infection control precautions are followed. However, serologic testing should be available to HCWs who may wish to know their HTLV-III/LAV infection status. Indications for serologic testing of HCWs who perform invasive procedures will be addressed in the recommendations being developed for these individuals.

Risk of transmission to HCWs during home care of persons infected with HTLV-III/LAV. Persons infected with HTLV-III/LAV can be safely cared for in home environments. Studies of family members of patients infected with HTLV-III/LAV have found no evidence of HTLV-III/LAV transmission to adults who were not sexual contacts of the infected patients or to children who were not at risk for perinatal transmission (3). HCWs providing home care face the same risk of transmission of infection as HCWs in hospitals and other health-care settings, especially if there are needlesticks or other parenteral or mucous membrane exposures to blood or other body fluids.

Precautions for HCWs during home care of persons infected with HTLV-III/LAV. When providing health-care service in the home to persons infected with HTLV-III/LAV, measures similar to those used in hospitals are appropriate. As in the hospital, needles should not be recapped, purposefully bent, broken, removed from syringes, or otherwise manipulated by hand. Needles and other sharp items should be placed into puncture-resistant containers and disposed of in accordance with local regulations for solid waste. Blood and other body fluids can be flushed down the toilet. Other items for disposal that are contaminated with blood or other body fluids that cannot be flushed down the toilet should be wrapped securely in a plastic bag before being discarded in a manner consistent with local regulations for solid waste disposal. Spills of blood or other body fluids should be cleaned with soap and water or a household detergent. As in the hospital, individuals cleaning up such spills should wear disposable gloves. A disinfectant solution or a freshly prepared solution of sodium hypochlorite (household bleach, see above) should be used to wipe the areas after cleaning.

Risk of occupational acquisition of other infectious diseases by HCWs infected with HTLV-III/LAV. HCWs who are known to be infected with HTLV-III/LAV and who have defective immune systems are at increased risk for acquiring or experiencing serious complications of other infectious diseases. Of particular concern is the risk of severe infection following exposure to patients with infectious diseases that are easily transmitted if appropriate precautions are not taken, e.g. tuberculosis. HCWs infected with HTLV-III/LAV should be counseled about the potential risk associated with taking care of patients with transmissible infections and should continue to follow existing recommendations for infection control to minimize their risk of exposure to other infectious agents (20,21). The HCW's personal physician, in conjunction with their institutions' personnel health services or medical directors, should determine on an individual basis whether the infected HCWs can adequately and safely perform patient-care duties and suggest changes in work assignments, if indicated. In making this determination, recommendations of the Immunization Practices Advisory Committee and institutional policies concerning requirements for vaccinating HCWs with the live virus vaccines should also be considered.

Risk of occupational transmission of HTLV-III/LAV to providers of prehospital emergency health care. Providers of prehospital emergency health care include the following: paramedics, emergency medical technicians, law enforcement personnel, firefighters, lifeguards, and others whose jobs might require them to provide first-response medical care. The risk of transmission of infection, including HTLV-III/LAV infection, from infected persons to providers of prehospital emergency health care should be no higher than that for HCWs providing emergency care in the hospital if appropriate precautions are taken to prevent exposure to blood or other body fluids.

Precautions for providers of prehospital emergency care. Providers of prehospital emergency health care should follow the precautions outlined above for other HCWs. No transmission of HBV infections during mouth-to-mouth resuscitation has been documented. However, because of the theoretical risks of salivary transmission of HTLV-III/LAV during mouth-to-mouth resuscitation, special attention should be given to the use of disposable airway equipment or resuscitation bags and the wearing of gloves when in contact with blood or other body fluids. Resuscitation equipment and devices known or suspected to be contaminated with blood or other body fluids should be used once and disposed of or be thoroughly cleaned and disinfected after each use.

PERSONAL-SERVICE WORKERS

Personal-service workers (PSWs) are defined as individuals whose occupations involve close personal contact with clients (e.g. hairdressers, barbers, estheticians, cosmetologists, manicurists, pedicurists, massage therapists). PSWs whose services (tattooing, ear piercing, acupuncture, etc.) require needles or other instruments that penetrate the skin should follow precautions indicated for HCWs. Although there is no evidence of transmission of HTLV-III/LAV from clients to PSWs, from PSWs to clients, or between clients of PSWs, as risk of transmission would exist from PSWs to clients and vice versa in situations where there is both (1) trauma to one of the individuals that would provide a portal of entry for the virus and (2) access of blood or serous fluid from one infected person to the open tissue of the other, as could occur if either sustained a cut. A risk of transmission from client to client exists when instruments contaminated with blood are not sterilized or disinfected between clients. However, HBV transmission has been documented only rarely in acupuncture and tattoo establishments and never in other personal-service settings, indicating that any risk for HTLV-III/LAV transmission in personal-service settings must be extremely low.

Serologic testing of PSWs. Routine serologic testing of PSWs for antibody to HTLV-III/LAV is not recommended to prevent transmission from PSWs to clients.

Precautions for PSWs. All PSWs should be educated about transmission of bloodborne infections, including HTLV-III/LAV and HBV. Such education should emphasize principles of good hygiene, antisepsis, and disinfection. This education can be accomplished by national or state professional organizations, with assistance from state and local health departments, using lectures at meetings or self-instructed materials. Licensure requirements should include evidence of such educations. Instruments that are intended to penetrate the skin (e.g. tattooing and acupuncture needles, ear

piercing devices) should be used once and disposed of or be thoroughly cleaned and sterilized after each use using procedures recommended for use in health-care institutions. Instruments not intended to penetrate the skin but which may become contaminated with blood (e.g. razors), should be used for only one client and be disposed of or thoroughly cleaned and disinfected after use using procedures recommended for use in health-care institutions. Any PSW with exudative lesions or weeping dermatitis, regardless of HTLV-III/LAV infection status, should refrain from direct contact with clients until the condition resolves. PSWs known to be infected with HTLV-III/LAV need not be restricted from work unless they have evidence of other infections or illnesses for which any PSW should also be restricted.

FOOD-SERVICE WORKERS

Food-service workers (FSWs) are defined as individuals whose occupations involve the preparation or serving of food or beverages (e.g. cooks, caterers, servers, waiters, bartenders, airline attendants).

Risk of transmission from FSWs to consumers. All epidemiologic and laboratory evidence indicates that bloodborne and sexually transmitted infections are not transmitted during the preparation or serving of food or beverages, and no instances of HBV or HTLV-III/LAV transmission have been documented in this setting.

Serologic testing of FSWs. Routine serologic testing of FSWs for antibody to HTLV-III/LAV is not recommended to prevent disease transmission from FSWs to consumers.

Precautions for FSWs. All FSWs should follow recommended standards and practices of good personal hygiene and food sanitation (26). All FSWs should exercise care to avoid injury to hands when preparing food. Should such an injury occur, both aesthetic and sanitary considerations would dictate that food contaminated with blood be discarded. FSWs known to be infected with HTLV-III/LAV need not be restricted from work unless they have evidence of other infection or illness for which any FSW should also be restricted.

ALL OTHER WORKERS

Risk of transmission of HTLV-III/LAV among workers sharing the same work environment. No known risk of transmission to co-workers, clients, or consumers exists from HTLV-III/LAV-infected workers in settings not previously discussed (e.g. offices, schools, factories, construction sites). This infection is spread by sexual contact with infected persons, injection of contaminated blood or blood products, and by perinatal transmission. Workers known to be infected with HTLV-III/LAV should not be restricted from work solely based on this finding. Moreover, they should not be restricted from using telephones, office equipment, toilets, showers, eating facilities, and water fountains. Equipment contaminated with blood and other body fluids of any worker, regardless of HTLV-III/LAV infection status, should be cleaned with soap and water or a detergent. A disinfectant solution or a fresh solution of sodium hypochlorite (household bleach, see above) should be used to wipe the area after cleaning.

OTHER ISSUES IN THE WORKPLACE

The information and recommendations contained in this document do not address all of the potential issues that may have to be considered when making specific employment decisions for persons with HTLV-III/LAV infection. The diagnosis of HTLV-III/LAV infection may evoke unwarranted fear and suspicion in some co-workers. Other issues that may be considered include the need for confidentiality, applicable federal, state or local laws governing occupational safety and health, civil rights of employees, workers' compensation laws, provisions of collective bargaining agreements, confidentiality of medical records, informed consent, employee and patient privacy rights, and employee right-to-know status.

DEVELOPMENT OF THESE RECOMMENDATIONS

The information and recommendations contained in these recommendations were developed and compiled by the CDC and other PHS agencies in consultation with individuals representing various organizations. The following organizations were represented: Associated of State and Territorial Health Officers. Conference of State and Territorial Epidemiologists. Association of State and Territorial Public Health Laboratory Directors. National Association of County Health Officials. American Hospital Association. United States Conference of Local Health Officers. Association for Practitioners in Infection Control. Society for Hospital Epidemiologists of America. American Dental Association. American Medical Association. American Nurses' Association. American Association of Medical Colleges. American Association of Dental Schools. National Institutes of Health. Food and Drug Administration. Food Research Institute. National Restaurant Association. National Hairdressers and Cosmetology Association. National Gay Task Force. National Funeral Directors and Morticians Association. American Association of Physicians for Human Rights. National Association of Emergency Medical Technicians. The consultants also included a labor union representative, an attorney, a corporate medical director, and a pathologist. However, these recommendations may not reflect the views of the individual consultants or the organizations they represented.

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Effectiveness of IMREG-1 in the Treatment
of AIDS Related Complex
and Acquired Immune Deficiency Syndrome

Protocol for Phase III Clinical Trial
November 12, 1986

Imreg, Inc. Laboratory Procedures

See Page 13, B item 7, Pretreatment evaluation - Cellular Immune Studies

Page 14, D - On Therapy Examination
Item 6 (T-Cell Subsets), 7 (Cellular Immune Studies), and 8 (Blood Requirement)

Page 22, Cellular Immunology Mitogen Stimulation
of Lymphocyte Proliferation, and T-Cell Subsets Production

SEPARATION OF LYMPHOCYTES FROM WHOLE BLOOD

Reagents:

Saline: 0.9% NaCl

Ficoll-Paque* or equivalent

Procedure:

- (1) Under aseptic conditions dilute heparinized blood 1:1 (a 1/2 dilution) with saline.
- (2) Add 10ml Ficoll-Paque solution into 50ml conical tubes.
- (3) Overlay 25ml diluted blood onto Ficoll-Paque surface, being careful to maintain a sharp interface between the two liquids.
- (4) Centrifuge 25 minutes at room temperature at 400xg at the interface.
- (5) Using a sterile pasteur pipet, carefully aspirate the lymphocytes from the interface area between top layer (plasma) and middle layer (LSM).
- (6) Wash the interface cells 3 times in saline before use.

* Pharmacia, Inc.
Laboratory Separation Division
800 Centennial Avenue
Piscataway, NJ 08854
(800) 526-3618
(201) 457-8000

PHA-INDUCED PROLIFERATIVE RESPONSE

Reagents:

RPMI 1640 Medium (Hepes buffered, glutamine added) - M.A. Bioproducts*
12-115B or equivalent.

PSN Antibiotic Mixture (100x) - Gibco** #600-5640 or equivalent.

Fetal Bovine Serum (FBS) - K.C. Biological*** #3000 or equivalent.

Phytohaemagglutinin (PHA) - Wellcome**** HA16

Tritiated Thymidine 2 Ci/mmol - New England Nuclear***** NET-027A

Procedure:

- (1) Prepare mononuclear cells by density gradient centrifugation on Ficoll-Paque or equivalent.
- (2) Concentrate cells to 1×10^6 /ml in RPMI 1640-10% FBS-2% PSN.
- (3) Dispense 0.2ml/well aliquots of cells to the wells of 96 well flat-bottomed microtiter plates (suggest Falcon microtest III).
- (4) Add to triplicate sets of wells either 20ul/well of RPMI-1640 (unstimulated control) or 20ul/well of PHA in RPMI-1640 to give the following final concentrations of PHA (use Wellcome HA 16 PHA only):
 - 0.125 ug/ml PHA
 - 0.25 ug/ml PHA (Note: Stock PHA will be 11x)
 - 0.5 ug/ml PHA
 - 1.0 ug/ml PHA
- (5) Incubate for a total of 72 hours at 37°C, 5% CO₂. For the terminal 18 hours of the culture period, add 20ul/well of 20uCi/ml solution tritiated thymidine in RPMI-1640.
- (6) Harvest cells on a cell harvester unit using water washes. Dry filter strips before counting. Determine cpm incorporated by liquid scintillation counting, and report cpm/well for each test concentration. Note: Scintillation fluid - Use the same throughout the study. Do not use nonaromatic fluids.

* Whittaker M.A. Bioproducts
P. O. Box 127 Briggs Ford Rd.
Walkersville, MD 27193
(800) 638-8174
(301) 898-7025

**** Wellcome Diagnostics
3030 Cornwallis Rd.
Research Triangle Park, NC 27709
(800) 334-9332
(919) 758-3436

** Gibco-Life Technologies
421 Merrimack Street
Lawrence, MA 01843
(800) 343-8156

*****E.I. duPont de Nemours & Co.
Biomedical Products Dept.
NEN Products
549 Albany Street
Boston, MA 02118
(800) 225-1572
(617) 482-9595

*** K.C. Biologicals
Lenexa, KS 06215
(800) 255-6032

PWM-INDUCED PROLIFERATIVE RESPONSE

Reagents:

RPMI 1640 (Hepes buffered, glutamine added) - M.A. Bioproducts 12-115B or equivalent.

PSN Antibiotic Mixture (100x) - Gibco #600-5640 or equivalent.

Fetal Bovine Serum (FBS) - K.C. Biological #3000 or equivalent.

Pokeweed Mitogen (PWM) - Gibco 670-5360

Tritiated Thymidine 2 Ci/mmol - New England Nuclear NET-027A

Procedure:

- (1) Prepare mononuclear cells by density gradient centrifugation on Ficoll-Paque or equivalent.
- (2) Concentrate cells to 1×10^6 /ml in RPMI 1640-10% FBS-2% PSN.
- (3) Dispense 0.2ml/well aliquots of cells to the wells of 96 well flat-bottomed microtiter plates (suggest Falcon microtest III).
- (4) Add to triplicate sets of wells either 20ul/well of RPMI-1640 (unstimulated control) or 20ul/well of PWM in RPMI to give the following final concentrations of PWM (use GIBCO* 670-5360 PWM only):
 - 1/800 PWM
 - 1/400 PWM
 - 1/200 PWM
 - 1/100 PWM
 - 1/50 PWM(Note: Stock PWM will be 11x)
- (5) Incubate for a total of 96 hours at 37°C, 5% CO₂. For the terminal 18 hours of the culture period, add 20ul/well of a 20uCi/ml solution of tritiated thymidine in RPMI 1640.
- (6) Harvest on a cell harvester unit using water washes. Dry filter strips before counting. Determine cpm incorporated by liquid scintillation counting, and report mean cpm/well for each test concentration. Note: Use the same scintillation fluid throughout the study. Do not use non-aromatic fluids.

GENERATION OF PHA-INDUCED INTERLEUKIN-2

Reagents:

RPMI 1640 Medium (Hepes buffered, glutamine added) - M.A. Bioproducts 12-115B or equivalent.

PSN Antibiotic Mixture (100x) - Gibco #600-5640 or equivalent.

Fetal Bovine Serum (FBS) - K.C. Biological #3000 or equivalent.

Phytohaemagglutinin (PHA) - Wellcome HA16

Procedure:

- (1) Prepare human mononuclear cells by density gradient centrifugation on Ficoll-Paque or equivalent.
- (2) Concentrate cells to 1×10^6 /ml in RPMI 1640 with 10% FBS and 2% PSN.
- (3) Dispense 0.2ml/well aliquots to 96 well flat-bottomed microtiter plates (Falcon Microtest III).
- (4) Add to quadruplicate sets of wells either 20 ul/well RPMI-1640 or 20 ul/well Wellcome* HA16) to give the desired final concentrations.
0.125 ug/ml PHA
0.25
0.5
1.0
NOTE: Stock PHA will be 11x
- (5) Incubate for 24 hours at 37°C, 5% CO₂.
- (6) After incubation, harvest and pool replicate samples with a sterile pasteur pipette. Pellet cells, transfer SNs to fresh tube and store at -20°C until they can be shipped on dry ice to Imreg, Inc.

NOTE: IL-2 assay requires a total volume of 800ul of pooled supernatants. If at the end of the incubation period 4 wells produce less than this, then in future studies add a well and run each sample in quintuplicate rather than quadruplicate.

STAINING OF HUMAN MONONUCLEAR CELLS
FOR ANALYSIS BY FACS OR FLUORESCENCE MICROSCOPY
PHASE III CLINICAL TRIAL

- (1) Prepare mononuclear cells by density gradient centrifugation on Ficoll-Paque or equivalent.
- (2) One x 10⁶ mononuclear cells (in a 1.5ml microfuge tube) are centrifuged at 400xg for 7 min. at 4°C.
- (3) Supernate is aspirated and the cell pellet resuspended in the proper dilution of monoclonal antibody or appropriate control (see manufacturers instructions).
- (4) Incubate cells on ice for 20 minutes.
- (5) After 20 minutes, add one ml of cold PBS - 2%FCS. Centrifuge at 400xg, 7 minutes, 4°C.
- (6) Aspirate supernate, resuspend pellet in one ml of cold PBS - 2%FBS. Centrifuge at 400xg, 7 minutes, 4°C.
- (7) If monoclonal antibody is directly conjugated with FITC* or PE** the cell pellet may be resuspended in 1ml 1% paraformaldehyde for analysis.
- (8) If monoclonal antibody is not directly conjugated, the cell pellet is resuspended in FITC-conjugated, goat anti-mouse IgG, followed by 20 minute incubation on ice, washing 2x with PBS - 2% FBS and fixation with 1ml 1% paraformaldehyde, as above.

Recommended stains to be used on patient's cells: (Phase III Protocol Pg. 13)

Lymphocyte Subjects to be Stained	Stain	Cluster Designation	Cell Population	Becton Dickinson Catalog No.
T8 ⁺	Anti-Leu 2a PE	(CD-8)	T-cytotoxic/Suppressor	7317
T4 ⁺	Anti-Leu 3a PE	(CD-4)	T-helper/inducer	7327
T3 ⁺	Anti-Leu 4 PE	(CD-3)	T-cells (mitogenic)	7347
Leu 11 ⁺	Anti-Leu 11a PE	(CD-16)	NK/neutrophils	7617
T10 ⁺	Anti-Leu 17 PE	-	Thymocytes/NK cells	7687
			Activated T cells/B cell subsets.	
IgG control	IgG ₁ PE (control)	-		9043

* FITC = Fluorescence isothiocyanate
** PE = Phycoerythrin

Becton Dickinson Immunocytometry Systems
P. O. Box 7375
Mountain View, CA 94039
(800) 223-8226
(800) 821-9796 (in CA)

PREPARATION OF 4% PARAFORMALDEHYDE

- (1) Paraformaldehyde (2g) is added to 42.5ml sodium phosphate buffer, 0.1M, pH 7.4.
- (2) Heat to 70°C with stirring. Requires 15 to 20 minutes at 70°C to dissolve.
- (3) After dissolving, add 2.4ml of 0.001M CaCl_2 .
- (4) Let cool. Filter through #1 Whatman filter. Add 5ml of sodium phosphate buffer.
- (5) Prepare 1% paraformaldehyde by dilution of 4% stock solution with sodium phosphate buffer immediately prior to use.
- (6) 4% stock solution may be kept for two weeks in the refrigerator.
- (7) Sodium phosphate buffer, 0.1M, pH 7.4

NaH_2PO_4	H_2O	1.31g
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Na_2HPO_4	$7\text{H}_2\text{O}$	10.8g
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Distilled water to 500ml.

- (8) After cells have been reacted with antibodies and fixed with paraformaldehyde, they should not be frozen but should be maintained at 4°C.

EFFECTIVENESS OF IMREG-1 IN THE TREATMENT
OF AIDS RELATED COMPLEX
AND ACQUIRED IMMUNE DEFICIENCY SYNDROME
FINAL
PROTOCOL FOR PHASE III CLINICAL TRIAL

Prepared by Imreg, Inc.
New Orleans, Louisiana

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PROTOCOL PHASE III CLINICAL TRIAL

Effectiveness of IMREG-1 in the Treatment of ARC/AIDS

I. INTRODUCTION

A. Background

The Acquired Immunodeficiency Syndrome (AIDS) is a recently described disorder which, in the United States, predominates in male homosexuals and intravenous drug users. The natural history of AIDS includes a high risk for the development of life-threatening opportunistic infections, Kaposi's sarcoma, and short-term relative survival. The underlying pathologic mechanism in AIDS is associated with a deficiency in cell-mediated immunity. The early phases of AIDS can be identified as AIDS Related Complex (ARC), and is characterized by persistent generalized lymphadenopathy (PGL) and seropositivity to the virus HTLV-III/LAV.

As defined by the HHS, "ARC is a clinical and laboratory syndrome characterized by minor conditions clinically associated with immunosuppression (e.g., oral thrush) and laboratory evidence of immunosuppression probably associated with HTLV-III infection. The clinical syndromes in ARC include unexplained idiopathic thrombocytopenia and a variety of non-life-threatening fungal, viral and bacterial infectious processes that probably represent manifestations of virus-induced immunologic perturbation associated with HTLV-III infection. These manifestations are sometimes termed lesser AIDS (1)".

AIDS is caused by a retrovirus that is lymphotropic for helper T-cells ($T4^{+}$) and impairs the function of these cells, resulting in increased susceptibility to opportunistic infections (2, 3). Reversal of the immune

dysfunction does not occur spontaneously in patients with AIDS, and the syndrome has a high mortality rate.

B. Preliminary Studies

In previous reports, we have called attention to the existence of low molecular weight modulators of human cell-mediated immunity present in human leukocyte dialysates which exert their activity in an antigen-non-specific fashion (4). One of these modulators, IMREG-1, a low molecular weight amplifier of human cell-mediated immune responses, has been purified from normal human peripheral blood lymphocytes (5). IMREG-1 has the ability to augment and accelerate delayed-type hypersensitivity (DTH) responses in normal subjects in an antigen-dependent, antigen-nonspecific manner. In vivo, IMREG-1 may be an endogenous regulator of cell-mediated immunity.

Subsequent to the description of the in vivo immunoamplifying activity of IMREG-1, in vitro assay systems were developed to characterize the mechanisms of action of this low molecular weight modulator (5). In initial studies, the effect of IMREG-1 on the production of antigen-induced leukocyte migration inhibition factor (LIF) and macrophage migration inhibitor factor (MIF) was investigated, on the basis of the known correlation between response in the assay system and DTH. Addition of IMREG-1 to cultures was observed to both accelerate and augment production of antigen induced migration inhibitory activity, with the characteristics of the in vitro modulation closely resembling those observed in vivo. Furthermore, by selectively enriching peripheral blood mononuclear cells for T-cell subsets, it was possible to demonstrate that the target cell for IMREG-1 amplification of LIF/MIF production belong to the helper (OKT4/Leu3a⁺) T-cell subset, suggesting that modulation of helper cell lymphokine (LK) production may be at least partially responsible for the in vivo activity of IMREG-1.

In more recent studies, IMREG-1 has been examined for both its effect on production of T-cell-derived LKs other than LIF/MIF, and for its ability to augment production of specific cytolytic lymphokines (6). Inclusion of IMREG-1 in a standard culture system clearly enhances production of interleukin-2 (IL-2) by normal lymphocytes, particularly at suboptimal concentrations of the agent used for IL2 induction, which can be either a mitogen or alloantigen. As was the case for LIF/MIF production, augmentation of IL2 production by IMREG-1 is directed by the human helper T-cell subset.

Preliminary studies indicate that IMREG-1 modulates production of interferon-gamma under conditions where IL2 production is augmented, with this effect appearing 24 hours later than IL2 modulation. Immunomodulation of IL2 and interferon-gamma production by IMREG-1 are most likely responsible for the observed ability of this agent to enhance the generation of specific cytolytic lymphocytes (CTL) to either alloantigenic or tumor cell targets. This aspect of IMREG-1 activity is also dependent on the presence of functional helper T-cells. Considering the known ability of both IL2 and interferon-gamma to potentiate CTL generation, modulation of helper cell production of the LKs remains the most reasonable explanation for IMREG-1 activity. Moreover, addition of IMREG-1 increases the number of IL2 receptors by 60% to 150% over baseline by 24 hours; in contrast, a similar increase in IL2 receptors is observed at 48 to 72 hours in cultures from normal individuals not containing IMREG-1. These observations indicate that IMREG-1 accelerates the expression of the IL2 receptor (Farmer JL and Gottlieb AA, unpublished observations). Of additional interest is the observation that IMREG-1 potentiates the generation of anti-tumor CTLs of two distinct phenotypes (OKT8+ and Leu 11a+).

The ability of IMREG-1 to augment helper cell function in vitro suggested that this modulator might function as an immunopotentiating agent in immunodeficiencies characterized by a defect in this T-cell subpopulation. One

such condition, AIDS, is accompanied by a severe decrease in the number of circulating T-helper cells, with corresponding impairment in T-cell dependent immune functions (e.g. IL2 production). To determine if IMREG-1 might augment immune reactivity in AIDS, lymphocytes from 6 patients, both AIDS and ARC, were examined for their ability to produce IL2 in response to phytohemagglutinin (PHA), in the presence and absence of IMREG-1. All subjects exhibited significant increases in IL2 production in the presence of IMREG-1 (6). In addition, IMREG-1, when administered in combination with isologous HLA-identical leukocytes to a patient with Kaposi's sarcoma and severe constitutional symptoms, resulted in a transient, though striking, enhancement of proliferation responses and IL2 production in response to mitogen. An increase in $T4^{+}$ cells to normal levels was also observed after IMREG-1 administration. Administration of isologous HLA-identical leukocytes alone produced none of these effects in this patient.

As a result of these studies, small clinical trials were initiated to examine the effect of in vivo IMREG-1 administration on systemic immunity in AIDS patients. The observations to date are summarized as follows:

1. IMREG-1 has been shown to return DTH to tetanus toxoid in over fifty percent of the patients with AIDS/ARC enrolled in clinical protocols and who had become anergic to tetanus toxoid (and other antigens) as a result of the disease process. This return and enhancement of DTH has been consistently demonstrated by those who have been actively working with IMREG-1 in AIDS/ARC. Return of DTH has also been demonstrated following IMREG-1 treatment in selected cancer patients who had also become anergic.

2. Extensive testing of IMREG-1 using multiple doses over a three-month period, and in some cases for over one year, in some 90 patients has failed to show any toxicity or adverse effects resulting from such treatment.

3. In addition, some beneficial clinical effects have been shown, following only three months or less of treatment of patients whose cell mediated immune system had been severely compromised prior to treatment. These patients were anergic to several skin test antigens prior to treatment with IMREG-1. Many, also, had oropharyngeal candida infections which were resistant to treatment and had experienced significant weight loss. Most were AIDS patients so classified by having Kaposi's Sarcoma and/or a life-threatening opportunistic infection. In addition to the return of DTH in over fifty percent of patients, clinical effects observed included resolution of candida infection in over fifty percent, weight loss stopped in most, and in many patients weight gain was observed. In general, the greater the number of residual $T4^{+}$ (helper) cells, the more predictable was the clinical improvement. A residual of as little as fifteen to twenty percent (100) $T4^{+}$ (helper) cells (normal= 32% to 56%, or greater than 750 cells) was associated with the greatest improvement. In a few cases, $T4^{+}$ helper cell number and total lymphocyte count was seen to increase. In general, there was a decrease in serum uric acid and creatine phosphokinase levels suggesting decreased cell and muscle cell destruction, respectively. Except for patients who were also being treated with Fansidar, liver enzymes that were abnormally elevated prior to IMREG-1 treatment appeared to decrease toward normal levels.

4. IMREG-1 also reliably increased mitogen stimulated lymphocyte proliferation and interleukin-2 production in those patients with a minimum residual of as little as fifteen to twenty percent $T4^{+}$ cells (100).

As these early observations have been conducted in uncontrolled trials and in view of these early positive clinical observations, associated improvement in immunologic function parameters, lack of observed toxicity and no alternative successful therapy, a phase III, randomized double blind clinical trial will be undertaken with IMREG-1.

C. References

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II. OBJECTIVES

A. To evaluate the clinical efficacy of IMREG-1 (versus placebo) therapy to interrupt the natural history of ARC and AIDS as follows:

1. reduce the frequency and/or duration of the following constitutional symptoms:
 - a. oral thrush
 - b. intermittent or continuous fever (2-3 x /wk, >38.5°C)
 - c. repeated night sweats
 - d. debilitating fatigue
 - e. persistent diarrhea
 - f. weight loss
2. reduce the occurrence of opportunistic infections
3. reduce the occurrence or progression of Kaposi's sarcoma
4. reduce the occurrence of total and cause specific mortality

B. To evaluate in vivo effects of IMREG-1 therapy on:

1. number and function of $T4^{+}$ lymphocytes
2. reconstitution of delayed hypersensitivity reactions to cutaneous antigens

C. To evaluate the correlation between improvement in clinical outcomes and in-vitro immunologic function.

D. To evaluate the safety of IMREG-1 as measured by the above mentioned clinical outcomes and toxicity tests.

III. HYPOTHESIS

Calculation of sample size was based on the hypothesis that administration of IMREG-1 would return delayed type hypersensitivity (DTH) in six months in fifty percent of subjects compared to ten percent of placebo controls. This was based on the observation that in uncontrolled studies of over fifty patients, DTH was returned in over 50 percent of IMREG-1 treated patients in three months. It is well-known that DTH does not return spontaneously, unless

the reason for immune suppression is removed. The significance level to be achieved was $p < 0.05$, power 90 percent.

Return of DTH is highly correlated with other evidence of cell-mediated immune system function. Decrease in constitutional symptoms listed in IA 1 and 2, is expected to be highly correlated with the return of DTH. Therefore the a priori hypothesis is that treatment of anergic AIDS/ARC patients with constitutional symptoms with IMREG-1 will result in the significant return of DTH and/or a significant reduction of the symptoms associated with this condition. Alternatively we will disprove that no improvement in these parameters will occur as a result of treatment.

Given the changing epidemiologic data on the natural history of HIV disease, because of advances in medical diagnosis and earlier treatment of infections, return of DTH response appears to be the most specific end-point from which to determine sample size.

IV. STUDY DESIGN - Sample Size

One hundred-forty-four adults who meet the entry criteria defined in Section IV will be enrolled and complete therapy in this multi-center double blind, placebo controlled, randomized clinical trial. Volunteer patients who meet eligibility criteria will be randomized to either IMREG-1 or placebo groups and baseline laboratory and clinical evaluation will proceed. Each subject is expected to receive six-months of treatment. The enrollment of all subjects is expected to be completed within a three-month period. Stratification of eligible patients on the presence or absence of Kaposi's sarcoma will occur such that 81 patients with constitutional symptoms, and with or without lymphadenopathy and without Kaposi's Sarcoma will be enrolled, and 63 patients with slowly progressive Kaposi's Sarcoma and constitutional symptoms will be enrolled.

Each enrolled patient will be randomly allocated to IMREG-1 or placebo in a 2:1 ratio to minimize the exposure of subjects to placebo treatment while maintaining adequate power to detect clinically significant differences in relevant outcomes. For example, this sample size will result in a power of 0.90 for the following expected outcome: for placebo controls, amplification of delayed type hypersensitivity will occur in fewer than ten percent of the enrolled subjects while in the IMREG-1 group such amplification will occur in at least fifty percent over a three-month period.

At study entrance, during, and following treatment, evaluation of clinical and laboratory parameters will be performed at regular intervals as described below.

V. STUDY POPULATION

It is anticipated that a total of 144 patients will complete this trial. Approximately 16 to 32 patients will be enrolled in each of at least five different centers. () patients who meet the entrance criteria will be enrolled at:

(Center).

- A. A completed patient is defined as one
 - 1. who meets the eligibility criteria specified below
 - 2. who receives the randomized therapy and completes all of the requirements specified in the Treatment Program and Study Procedures sections of this protocol and
 - 3. for whom a completed Case Report Form and Informed Consent Form have been received and accepted by the Sponsor, Imreg, Inc.
- B. Criteria For Eligibility (prospective patients must meet all criteria)
 - 1. HTLV-III/LAV antibody positive (confirmed Western Blot documentation of HTLV-III virus would be desirable, and if available should be included in the record)
 - determined once prior to initiation of treatment

2. Reduced immunologic function as determined by:
 - a. $T4^+/T8^+$ ratio of 0.7 or less and,
 - b. $T4^+$ cell numbers ranging from 100-400/mm³
 - c. Partial or complete anergy to skin test antigens as defined by less than a 10mm induration, after 24 hours, to at least one antigen in which a prior history of sensitivity is reported. (PPD, tetanus toxoid, candida, histoplasmin, mumps)
3. Presence of any one constitutional symptom with or without lymphadenopathy or slowly progressive Kaposi's sarcoma with constitutional symptoms (defined as less than 10 new lesions per week for four weeks). Constitutional symptoms as defined by:
 - a. intermittent or continuous fever $\geq 38.5^\circ\text{C}$ for the prior month or,
 - b. significant weight loss of $\geq 10\%$ of body weight in the last three months or
 - c. three or more episodes of diarrhea per day for two or more weeks or,
 - d. debilitating fatigue in the prior month or,
 - e. repeated night sweats (twice a week for at least two weeks) or,
 - f. oral candidiasis* or
 - g. herpes zoster
4. Male (Female, if patient is not using oral contraceptives and if she will agree not to become pregnant during the period of the Trial.)
5. 18-60 years of age
6. Karnofsky performance status of 70% or greater
7. Anticipated compliance and reliability; with documented local residence and telephone number
8. Informed written consent obtained

* If oral pharyngeal candida uncontrolled by Nystatin is present at screening, treatment with 400 mg per day of ketoconazole should be initiated for two weeks and then 200 mg per day for two weeks.

Treatment with ketoconazole should be continued until four weeks after the first dose of IMREG-1. Thereafter Nystatin troches can be used by the patient. A drug use diary will be kept by the patient to record the use of medication for candida.

C. Criteria for Exclusion (for patients meeting all eligibility criteria)

1. Unstable ARC/AIDS status as evidenced by:
 - a. progressive Kaposi's sarcoma indicated by 10+ new lesions per week for the prior 4 weeks or,
 - b. prior or concurrent life-threatening opportunistic infection other than oral thrush (i.e., esophageal thrush as determined by symptoms and requiring treatment with Amphotericin B)
 - c. miliary tuberculosis
2. Concurrent disease or therapy which may interfere with IMREG-1 evaluation as follows:
 - a. Significant renal, hepatic, cardiac or other visceral dysfunction as defined by:
 - 1) serum creatinine >2mg%, or
 - 2) serum bilirubin >2mg%, or
 - 3) serum transaminase three times the normal value, or
 - 4) myocardial infarction in prior six months, or
 - 5) hematology profile which shows
 - Platelets: < 50,000/mm³
 - White Blood Count: < 3,000/mm³
 - Hematocrit: < 30%
 - b. Systemic lupus erythematosus, rheumatoid arthritis or other collagen vascular disease or,
 - c. Granulomatous diseases or,
 - d. Malignancy other than Kaposi's Sarcoma or,
 - e. Immune suppressive disease other than AIDS/ARC or,
 - f. Esophageal candidiasis requiring treatment with Amphotericin B or,
 - g. Concurrent or recent therapy which includes any one of the following:
 - 1) immunomodulatory therapy in the prior three months
 - 2) steroids, non-steroidal anti-inflammatory agents in prior two weeks, anti-viral medication, or Cimetadine and H₂ receptor antagonists in the prior 4 weeks, (Aspirin and acetaminophen are allowed).

- 3) treatment with Fansidar, Dapsone or Pentamidine less than 4 weeks prior to evaluation. Amphotericin B, Rifampin, Ansamycin are excluded, as are prophylactic treatment with Bactrim for opportunistic infections and chronic methadone treatment. (Nystatin and ketoconazole preparations are acceptable.)
 - 4) any packed red cell transfusion in the prior four weeks, or for treatment of the underlying condition in the prior three months.
 - 5) any prior cancer chemotherapy or radiation therapy.
3. Clinical evidence that patient is a current intravenous drug abuser.
 4. Patients who have clear clinical evidence of AIDS associated encephalopathy who have been progressively withdrawn with markedly impaired recent memory.
 5. Positive Pregnancy Test.

VI. STUDY PROCEDURES (see Table 1 which follows)

A. Pretreatment Evaluation (Visit 1) - within four weeks prior to initiation of therapy

At the initial examination (Visit 1) each patient will have evaluations performed by the investigator that will document the diagnosis of ARC/AIDS. This examination will be conducted within four weeks prior to the initiation of therapy to allow for completion of all laboratory parameters.

Based on the results of the medical history, physical examination and tests leading to a diagnosis of ARC/AIDS, the investigator will determine the eligibility of each prospective patient to participate in the study. All examinations and laboratory tests must be completed and the results known to the investigator and evaluated by the sponsor before the patient may be considered for entry into the study. Determinations to be made during this visit include the following:

1. $T4^{+}$ (helper) and $T8^{+}$ (suppressor) cell count.
2. Four skin Tests to evaluate delayed type hypersensitivity using Squibb fluid tetanus toxoid, Purified Protein Derivative, Candida, and Histoplasmin or mumps, depending on the likely appropriate prior sensitivity.
3. History and physical examination to determine eligibility and exclusion criteria.

4. HTLV III/LAV antibody test.
5. Blood chemistry - Ca, P inorg., Total Protein, Albumin, SGOT, SGPT, Alkaline Phosphatase, LDH, Total Bilirubin, Direct Bilirubin, Uric Acid, Creatinine, BUN, Creatine Phosphokinase, Na⁺, K⁺, Cl⁻, CO₂ and Fasting Glucose, Quantitative Immune Globulins (IgG, IgA, IgM).
6. Hematology (CBC with differential) with platelets.
7. Urinalysis - including microscopic examination.
8. Pathologic or Microbiologic Studies to exclude malignancies or opportunistic infections.

B. Pre-treatment Evaluation (Visit 2) - within approximately 2 weeks prior to therapy

To obtain a more accurate baseline prior to study, the immunological studies, skin testing and hematology will be repeated two weeks prior to initiation of therapy. Determinations to be made during the visit include:

1. Medical history- per protocol
2. Physical examination per protocol including vital signs (blood pressure, pulse, respiration, and body temperature)
3. CBC with differential and platelet count
4. Blood chemistry: Ca, P inorg., Total Protein, Albumin, SGOT, SGPT, Alkaline phosphatase, LDH, Total Bilirubin, Direct Bilirubin, Uric acid, Creatinine, BUN, Creatine phosphokinase, Na⁺, K⁺, Cl⁻, CO₂, Fasting Glucose, Quantitative Immune Globulins, (IgG, IgA, IgM)
5. Chest X-ray
6. Skin-Test to Tetanus toxoid, PPD, Candida and Histoplasmin or mumps
7. Cellular immune studies
 - a. Total T-lymphocytes and subsets T4⁺, T8⁺, T3⁺, T10⁺, Leu 11⁺
 - b. Mitogen stimulation studies
 - (1) PHA stimulation of cell proliferation and preparation of supernatants to be shipped to Imreg, Inc. to do interleukin-2 production
 - (2) PWM stimulation of cell proliferation

C. Entry Into Study (Day 0) (Visit 3)

Once eligibility to participate in the study and sponsor agreement has been established, the patient will be randomized to receive either the study medication or placebo.

D. On Therapy Examination (See Table 1)

Examination will be conducted while on therapy at intervals to evaluate the safety and efficacy of the medication in each patient. These examinations will be at selected intervals as follows:

1. Complete History and Physical Examination
At baseline, and two weeks after the final dose. Interval history and relevant physical examinations will be done with every dose.
2. Skin-Test will be done as follows:

On opposite fore-arm to that in which treatment is given

In addition to the two evaluations before baseline:
 - a. Tetanus toxoid on days 64, 134 (weeks 9, and 19)
 - b. The four skin-tests selected and performed at screening and at baseline, tetanus toxoid, PPD, Candida, and Histoplasmin or mumps on day 176 (week 25) Skin-Tests should be read at seven hours 24 and 48 hours. The 24-hour reading will be read by the staff.
3. Hematology including platelets will be done on days 15, 64, 92, 120, 176, and 197, (weeks 2, 9, 13, 17, 25 and 28).
4. Clinical chemistries including quantitative immune globulins will be done on days 15, 64, 120, 176 and 197, (weeks 2, 9, 17, 25 and 28).
5. Urinalysis will be done on day 197, (week 28).
6. T-Cell subsets will be done on days 64, 120, 176 and 197, (weeks 9, 17, 25 and 28).
7. Cellular immune studies will be done on days 8, 15, 64, 71, 120, 127, 176 and 197, (weeks 1, 2, 9, 10, 17, 18, 25, and 28).
These studies will include:
 - a. PHA and PWM stimulated lymphocyte proliferation
 - b. PHA stimulated interleukin-2 production (Supernates from PHA cultures for interleukin-2 assays will be frozen and regularly sent to the Central Laboratory according to an agreed upon schedule).

8. Blood Requirement:

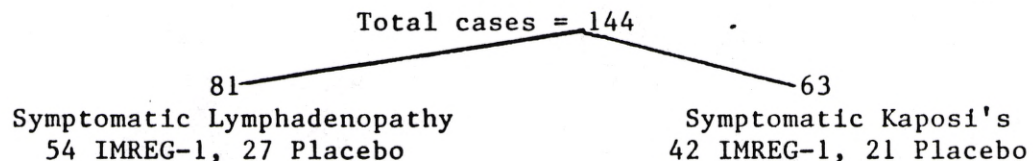
Fifty ml of heparinized blood is required for Cellular Immunology Studies. Also 1cc of blood is required for hematology and 5cc clotted blood for chemistries. At each visit at which blood is taken, an additional three ml of serum will be obtained from each patient and frozen. This will be sent periodically to Imreg, Inc. according to an agreed upon schedule. These will be stored and will be available by agreement for other analyses.

VII. TREATMENT PROGRAM

A. Treatment Plan

Patients will be randomized to receive bi-weekly intradermal injections of either placebo (normal saline 0.1 ml) or 400,000 cell equivalents (0.1 ml of a 10^{-2} dilution of IMREG-1 in normal saline). This will be continued for six months (thirteen treatments).

Each center will be expected to identify subjects for each of the two groups of patients (Kaposi's with Constitutional Symptoms and constitutional symptoms with and without lymphadenopathy). Approximately 44 percent of the subjects will be from the Kaposi's group. Each center will call the sponsor after eligibility has been determined for each patient to receive the blind treatment assignment. The randomization procedure will stratify the patient types and randomize treatments within types in blocks of three patients, having randomized one of the three patients to the placebo group. The schematic layout of the design is found below:



B. Study Medication

The following test and control materials will be supplied by Imreg, Inc., New Orleans, Louisiana.

- a. IMREG-1 and placebo will be supplied in blinded five dose 1 ml vials. Vials should be kept at -70°C and can be thawed and refrozen twice. Therefore, each vial will yield three doses. Following the administration of the final dose in each vial, investigators are required to send to the sponsor the remainder of the vial contents to test for potency. (These vials should be batched and shipped on dry ice periodically) Each new vial should be diluted with 0.5 ml sterile saline and mixed well. It should be refrozen after each use. For each three randomized patients, thirteen vials of drug uniquely marked with the specific patient code will be supplied.
- b. Sterile 0.9% sodium chloride Injection USP Diluent will be supplied. This will be used to add to the bottles of drug and placebo.
- c. Skin-Test Antigens (Squibb fluid tetanus toxoid, PPD, candida Histoplasmin and mumps).
- d. Sealed envelopes containing the code for the study assignment of each patient.
- e. Data forms to record patient information.

All test materials will be prepackaged in pre-coded, randomized medication packages for each subject and delivered to the hospital pharmacist, or the principal investigator who agrees to and has the facilities to maintain an appropriate drug log. The hospital pharmacist (or principal investigator) will be responsible for storing and dispensing the drug to the investigators according to protocol, in addition to maintaining an accurate drug log which will be provided by IMREG-1. The investigator must keep current records of supplies dispensed to patients participating in this study.

C. Administration of Study Medication:

All patients will be randomized to receive either IMREG-1 or the placebo. 0.1 ml of IMREG-1 or the placebo will be injected intradermally into the volar surface of the left forearm. Skin test antigens will be administered, according to schedule, intradermally into the volar surface of the right forearm.

D. Emergency Identification of Study Medication

It is the responsibility of the Principal Investigator to immediately notify the Sponsors of any problem which may require identification of the treatment in use for a particular patient. This will be done only after the decision to terminate the subject from the study has been made, and according to the criteria which follows:

E. Treatment of Patients and Placebo Controls with IMREG-1 at End-Point and at the Completion of the Study

At the time of the removal of a patient from the study because an end-point has been reached, the code will be broken. If the patient has been receiving a placebo, IMREG-1 will be provided by the Company, at no cost to him, if he is able to be treated according to a protocol acceptable to the FDA, and a physician acceptable to the FDA is willing to provide the treatment.

At the end of the study, and the code has been broken, those who have been in the placebo group will be offered IMREG-1 which will be provided by the Company. Likewise, patients who request continued treatment will be provided IMREG-1 by the Company for at least six months or until IMREG-1 is available from other sources, whichever is longer. The group that received placebo treatment will have first priority for receiving IMREG-1.

VIII. CRITERIA FOR EARLY REMOVAL FROM THE STUDY

Patients will be removed from the study in the event of any of the following and following discussion with the Sponsor:

- A. Any adverse experience (Grade III or IV toxicity - see Appendix) or development of other concurrent disease*, which in the opinion of the investigator, would endanger the welfare of the patient by continuing on the study.

*
Note:

For patients who develop other concurrent illnesses but who will be maintained in the trial, standard therapy protocols will be used. In the case of illnesses for which no standard therapy protocol has been developed, investigators, in concert with the sponsor, will develop such a protocol and be used for subsequent patients developing such an illness.

- B. Non-compliance to study schedules and/or procedures (two consecutive doses clinical or immunologic assessments missed during six months).
- C. Development of pneumocystis carinii pneumonia or similar opportunistic infections which would require treatment. (Oral or esophageal candidiasis does not constitute reasons for removal).
- D. A rapid and significant increase in the number of skin lesions of Kaposi's sarcoma (greater than 10 new lesions per week for a period of one month).
- E. Development of other diseases as follows:
 - (1) malignancy (other than Kaposi's sarcoma)
 - (2) requirement for transfusion
 - hematocrit $< 25\%$
 - platelets $< 50,000/\text{mm}^3$

IX. DROPOUTS - Patients who fit in the following categories will not be counted for determination of efficacy.

- a. Patients who are removed from the study before the completion of four weeks of therapy will be replaced according to the guidelines in section IV.
- b. Patients who are dropped out of the study because of non-compliance on two consecutive visits.

If a subject has dropped out of the protocol, he shall not be eligible for re-entry.

In order to insure that sufficient numbers of subjects complete this study, additional study medication, case report forms and consent forms will be provided for the addition of new subjects as replacements.

X. ADVERSE REACTIONS

All adverse effects occurring while on therapy will be recorded and followed.

The patient must be observed and the patient questioned regarding the occurrence of possible adverse reactions. These interviews should be conducted with due regard to objectivity and in particular, the investigator must note if information concerning a specific symptom or complaint is offered spontaneously by the patient or elicited only by direct questioning.

The investigator should carefully evaluate the response and comments of the patient in order that he may judge whether or not it is a genuine adverse reaction and, if so, its nature and severity. In this regard, particular attention should be paid to symptoms or complaints voiced by or elicited from the patient during the screening and baseline evaluations, as symptoms occurring during the study treatment period and ascribed to drug effect, may well have existed prior to administration of the study drug. In any event, the question of the relationship of the adverse reaction to drug administration will be determined by the investigator after thorough consideration of all the facts available and then record the findings on the patient's case report form.

Adverse reaction information is to be completed by the investigator listing each adverse reaction (either observed by the investigator or reported by the patient), severity of the adverse reaction, whether or not the adverse

reaction was due to study medication, date of onset, duration, course and outcome of the adverse reaction. Adverse reactions may also include laboratory values which become significantly out of range for individual patients. These should be re-analyzed immediately and followed-up until the patient's safety is not at risk.

All adverse experiences will be immediately (within 24 hours) reported on Case Report Form to the Sponsor - and discussed by telephone call with the Director of Clinical and Regulator Affairs, Marise S. Gottlieb, M.D., (504) 523-2875, as soon as possible.

XI. EVALUATION OF IMREG-1

A. Safety

Evaluation of safety will include comparison of treatment and control groups on the following measurements or changes in measurement during the course of the trial:

1. adverse reactions
2. medical history
3. physical exam
4. chest x-ray
5. vital signs
6. Laboratory
 - hematology
 - SMA-21
 - Urinalysis

B. Clinical Efficacy - Constitutional Symptoms with or without

Lymphadenopathy-without Kaposi's Sarcoma

1. Complete positive clinical response would be indicated by clearing of oral candidiasis, disappearance of constitutional symptoms, weight gain to ideal body weight, no occurrences of opportunistic infections and fewer sick days, no Kaposi's Sarcoma lesions after one month of therapy, stabilization of hematologic parameters and absence of any clinically detectable residual disease after treatment in the treated compared with the placebo group.
2. Partial clinical response would be fewer candida infections and partial clearing of severe candida infections and constitutional symptoms, reduced weight loss, fewer occurrences of opportunistic infections and sick days and a less rapid decline in the hematologic parameters in the treated compared with the placebo groups.
3. Minor response would be indicated by a trend to improvement in the listed parameters but without significant difference in the treated versus the placebo group.
4. No response would be indicated by no difference in the two groups.

C. Clinical Efficacy - with regard to Kaposi's Sarcoma

1. Complete response- absence of any detectable residual disease after treatment.

2. Partial response- 50 percent or greater decrease in the number or size, or both, of previous lesions after at least two months of treatment.
3. Stable disease- less than 50 percent reduction in tumor size or number in the same time period.
4. Progressive disease- increase in tumor size or number after at least 12 weeks or treatment.

The precise definition of clinical response is a major difficulty in describing patients with AIDS related Kaposi's sarcoma. Spontaneous regression of skin lesions has been reported. In addition, whereas a 50% decrease in the area or number of measured lesions is readily acceptable as a partial response, allowance must also be made for changes in tumor nodularity, pigmentation, or both. For this reason a subjective component is allowed in a definition of partial response. This subjective assessment may obviously introduce a bias in assessing response rates, but it seems to be an unavoidable area of difficulty in all clinical trials in this disease.

D. Immunologic Response

1. Complete Response is defined as complete return of DTH to tetanus toxoid; and or one other skin-test antigen, sustained increase in mitogen stimulated lymphocyte proliferation and interleukin-2 production.
2. Partial response is defined as some return of DTH to tetanus toxoid; or one other skin-test antigen, some increase in mitogen stimulated lymphocyte proliferation and interleukin-2 production.
3. Minor response is defined as a limited correction in some immunologic parameters.
It is difficult to assess how to evaluate the measurable number of T4⁺ cells in peripheral blood. Functional immune parameters are a better measure of drug effect.

XII.

OBLIGATIONS OF PRINCIPAL INVESTIGATORS

- A. Approval by Institutional Review Board of Protocol and Informed Consent Form- copies of both should be submitted to Imreg, Inc.
- B. Case Report Forms
The Investigator will be responsible for the timeliness, completeness and accuracy of the information on the case report forms. All entries must be legibly recorded in black ink with

cross-outs initialled and dated. All pages should be signed by the person who completes them. (This should be a principal investigator or one of the co-investigators named on FDA Form 1573).

Within one week of visit and/or receipt of data copies of forms must be sent to Imreg, Inc. Copies must be duplicated at sufficient intensity to be read legibly. The Investigator will assure that staff members are properly qualified to conduct the trial, and will assure their availability and cooperation in the training activities.

- C. Regularly review quality of laboratory and clinical data that is collected to identify problems as soon as possible to ensure a minimum loss of data points.
- D. Periodically, representatives of the Sponsor will expect to monitor the program and assess records, drug dispensing and other related procedures.
- E. All facilities will meet the standards for good medical practice.
- F. The investigator will provide normal laboratory values to Imreg, Inc. for the parameters being measured locally.
- G. The investigator will maintain a record on forms provided by the Sponsor of all patients evaluated for inclusion in the study and provide specific reasons for non-inclusion e.g. unwillingness to be randomized, and specific reasons for ineligibility.
- H. By Federal Regulation the investigator is required to retain study records for:
 - (1) A period of five years following the date on which the results of the study are submitted to the FDA in an IND or NDA.
 - (2) A period of two years following the date in which the entire clinical investigation is terminated or discontinued by either the company or the FDA.
 - (3) A period of two years following the data on which the drug is approved by the FDA for marketing for the purposes which were the subject of the clinical investigation.

XIII. DATA ANALYSIS

Data will be analysed by the Sponsor and will be reported to each center in a timely manner. Data analysis will proceed as follows:

- a. Analysis of comparability of treatment and control groups
- b. Analysis of toxicity in treatment and control groups
- c. Analysis of clinical outcomes in treatment and control groups within grade groups. Adjust for covariates as is necessary.

Combine grade groups if effectiveness is equivalent between the grades. Test effect of study center on outcome.

- d. Analysis of in-vitro changes in immunologic responses between treatment and control using repeated measures design.

XIV.

LABORATORY WORK

Routine Clinical Laboratory

Clinical laboratory work should be performed locally in a sponsor approved laboratory. This should include CBC with differential and platelets, urinalysis and clinical chemistries which will include Ca^{++} , P inorg., Alkaline Phosphatase, LDH, Total Bilirubin, Direct Bilirubin, Creatine Phosphokinase, SGOT, SGPT, Uric acid, Creatinine, BUN, Total protein, Albumin, and IgG, IgA, and IgM (quantitative immune globulins), fasting blood glucose, Na^+ , K^+ , CO_2 , Cl^- .

Skin Tests

Skin Tests will be performed by personnel trained in intradermal tests. Training sessions will be held for all persons to whom this responsibility is allocated to insure uniformity of technique and interpretation.

Cellular Immunology Laboratory

Mitogen Stimulation of Lymphocyte Proliferation and T-cell Subsets Production

To insure the uniformity of laboratory procedures, training sessions will be conducted on site, for those institutions that will be doing these studies. This capability must be available within the city that the study is being conducted.

Cell culture supernates for interleukin-2 will be shipped and will all be done at the Sponsor's central laboratory. T-cell subsets must be done at a laboratory at the study site or in the same city. The laboratory must be acceptable to Imreg, Inc.

In order to insure that there is comparability among the immunology laboratories, the same protocol will be followed, the same reagents including batch numbers will be utilized. Before the first patient samples are processed, laboratories will exchange selected normal bloods for analysis. This will be repeated periodically during the course of the trial (at monthly intervals).

RECOMMENDATIONS FOR GRADING OF ACUTE AND SUBACUTE TOXIC EFFECTS

	<SEVERE (Grade 0)	<SEVERE (Grade 1)	<SEVERE (Grade 2)	<SEVERE (Grade 3)	LIFE-THREATENING (Grade 4)
Hematological (Adults)					
Hemoglobin	>11.0 g/100 ml >110 g/l >6.8 mmol/l	9.5-10.9 g/100 ml 95-109 g/l 5.6-6.7 mmol/l	8.0-9.4 g/100 ml 80-94 g/l 4.95-5.5 mmol/l	6.5-7.9 g/100 ml 65-79 g/l 4.0-4.9 mmol/l	<6.5 g/100 ml <65 g/l <4.0 mmol/l
Leukocytes (1000/mm ³)	>4.0	3.0-3.9	2.0-2.9	1.0-1.9	1.0
Granulocytes (1000/mm ³)	>2.0	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
Platelets (1000/mm ³)	>100	75-99	50-74	25-49	<25
Hemorrhage	None	Petechiae	Mild blood loss	Gross blood loss	Debilitating blood loss
Gastrointestinal					
Bilirubin	<1.25 x N ^a	1.26-2.5 x N ^a	2.6-5 x N ^a	5.1-10 x N ^a	>10 x N ^a
Transaminases (SGOT, SGPT)	<1.25 x N ^a	1.26-2.5 x N ^a	2.6-5 x N ^a	5.1-10 x N ^a	>10 x N ^a
Alkaline phosphatase	<1.25 x N ^a	1.26-2.5 x N ^a	2.6-5 x N ^a	5.1-10 x N ^a	>10 x N ^a
Oral	No change	Soreness/erythema	Erythema, ulcers; can eat solids	Ulcers; requires liquid diet only	Alimentation not possible
Nausea/Vomiting	None	Nausea	Transient	Vomiting requiring therapy	Intractable Vomiting
Diarrhea	None	Transient<2 days	Tolerable, but >2 days	Intolerable, requiring therapy	Hemorrhagic dehydration
Renal					
Blood urea nitrogen or Blood urea creatinine	<1.25 x N ^a	1.26-2.5 x N ^a	2.6-5 x N ^a	5-10 x N ^a	>10 x N ^a
Proteinuria	No change	1+ <0.3 g% <3 g/l	2-3+ 0.3-1.0 g% 3-10 g/l	4+ >1.0 g% >10 g/l	Nephrotic Syndrome
Hematuria	No change	Microscopic	Gross	Gross + clots	Obstructive
Pulmonary	No change	Mild symptoms	Exertional dyspnea	Dyspnea at rest	Complete bsd rest required
Fever with drug	None	Fever <38 C	Fever 38 C-40 C	Fever >40 C	Fever with hypotension
Allergic	No change	Edema	Bronchospasm; no parenteral therapy required	Bronchospasm; parenteral therapy required	Anaphylaxis
Cutaneous	No change	Erythema	Dry desquamation, vesiculation, pruritus	Molt desquamation, ulceration	Exfoliative dermatitis; necrosis requiring surgical intervention
Hair	No change	Minimal hair loss	Moderate, patchy alopecia	Complete alopecia, but reversible	Non-reversible alopecia
Infection (Specify site)	None	Minor infection	Moderate infection	Major infection	Major infection
Cardiac					
Rhythm	No change	Sinus tachycardia, 110 at rest	Unifocal PVC atrial arrhythmia	Multifocal PVC	Ventricular tachycardia
Function	No change	Asymptomatic, but abnormal cardiac sign	Transient symptomatic dysfunction; no therapy required	Symptomatic dysfunction responsive to therapy	Symptomatic dysfunction non-responsive to therapy
Pericarditis	No change	Asymptomatic effusion	Symptomatic; no tap required	Tamponade; tap required	Tamponade; surgery required
Neurotoxicity					
State of communication	Alert	Transient lethargy	Somnolence 50% of waking hours	Somnolence 50% of waking hours	Coma
Peripheral	None	Paresthesias and/or decreased tendon reflexes	Severe paresthesias and/or mild weakness	Intolerable paresthesias and/or marked motor loss	Paralysis
Constipation ^b	None	Mild	Moderate	Abdominal distention	Distention and vomiting
Pain ^c	None	Mild	Moderate	Severe	Intractable

^a N = upper limit of normal value of population under study.

^b This does not include constipation resultant from narcotics.

^c Only treatment related pain is considered, not disease-related pain.

The use of narcotics may be helpful in grading pain, depending upon the tolerance level of the patient.

Appendix B

NEW DRUG OR PROCEDURE CONSENT FORM
CONSENT FORM FOR THE USE OF LEUKOCYTE DIALYSATES IN
PATIENTS WITH ACQUIRED IMMUNE DEFICIENCY SYNDROME
(AIDS OR AIDS RELATED COMPLEX)

(Name of Institution)
NEW DRUG OR PROCEDURE CONSENT FORM
CONSENT FORM FOR THE USE OF LEUKOCYTE DIALYSATES IN
PATIENTS WITH ACQUIRED IMMUNE DEFICIENCY SYNDROME
(AIDS OR AIDS RELATED COMPLEX)

I am being asked to volunteer to be a subject in a research study. This form is designed to provide me with information which I should know about this study.

1. PURPOSE OF THE RESEARCH

I have been invited to participate in a research study investigating the effect of IMREG-1 which is made from leukocyte extracts (natural products from blood cells) as treatment for the immunologic disorder of the Acquired Immunodeficiency Syndrome (AIDS) or AIDS Related Complex (ARC), a condition I have been diagnosed as having. Preliminary studies indicate that IMREG-1 is able to improve immune function (ability to prevent and fight infections) of patients with AIDS and generalized lymphadenopathy (enlarged lymph nodes) based on blood and skin tests which measure how well the immune system works.

This study is designed as a prospective, randomized trial. This means that I will receive either the drug or a placebo (a substance with no expected effect). The treatment I receive will be determined by chance. This study is being sponsored by Imreg, Inc., New Orleans, Louisiana, (504) 523-2875.

2. PROCEDURES

Prior to the beginning of the study, I will undergo a physical examination as well as have blood tests performed which means I will have a needle inserted into my vein from which blood will be drawn. Three samples of blood (less than 5 tablespoons each) will be drawn over 4 weeks for measuring the effects of treatment on my immune cells, as well as blood cells and other organs. This procedure will be repeated every six and seven weeks after treatment is initiated for the duration of treatment. Prior to the beginning of the study, a small amount of

blood will be tested for the presence of HTLV-III/LAV antibody. As the HTLV-III/LAV virus has been associated with AIDS, this test will determine if I have been exposed to the virus. The HTLV-III/LAV results will be recorded only in the records for this study and will be kept strictly confidential.

Another test that I will have is a skin-test which will measure how well my immune system works or my ability to prevent and fight infections. A small amount of material from a standard skin-testing system will be injected under my skin (like a TB test). I will experience some itching and swelling where the material was injected which will fade in a few hours. This test will be done five times during the trial.

0.1 ml (less than a hundredth of a teaspoon) of either the drug or the placebo, will be injected under my skin every 14 days. This will be continued for up to 6 months. Throughout this period, I will be checked by the doctors in charge by physical examination and blood tests. If at any time my doctor decides that I need additional forms of treatment, the study treatment will be discontinued.

3. RISKS AND/OR DISCOMFORTS

No side effects have been reported to date. However, my participation in the project may involve the following risks: (1) irritation and burning at the site of injection; (2) the remote possibility of infection at the site of injection; (3) IMREG-1 derived from human blood, may transmit hepatitis (an infection involving the liver) although the product has been screened for infectious agents that may affect my liver and lymph nodes; (4) blood letting may be associated with local pain, and the remote possibility of bleeding and/or infection. I understand that the research study treatment may not be successful and that my condition may worsen even with the study treatment.

4. BENEFITS

Benefits for my participation in this study may include a better way to treat people with AIDS and generalized lymphadenopathy (ARC). I may directly benefit if I receive IMREG-1 and it improves my body's ability to fight infection, although this is not proven. If I complete the trial and have been given the placebo treatment I understand that if I choose, my physician will be given IMREG-1 doses, free of charge, sufficient to treat me for 6 months.

5. ALTERNATIVE TREATMENTS

At this time no other treatments have been shown to be effective in improving my condition. At such time as other treatments become clinically indicated, my doctor will discuss this with me.

6. CONFIDENTIALITY

The results of this study may be published, but my name and identity will be kept confidential within these limits. Because an investigational drug subject to U.S. Food and Drug Administration regulations is being used, it may be necessary for this consent form and other medical records to be reviewed by representatives of the Food and Drug Administration and the company providing the test substance for the purposes of assuring that my rights have been protected and that real people have received the test medication.

7. MEDICAL CARE

I understand that in the event of physical injury resulting from research procedures used in this study only immediate essential medical treatment as determined by the Hospital will be available for the injury without charge to me personally; there will be no monetary compensation.

8. CRITERIA FOR DISCONTINUATION OF PATIENT FROM STUDY

Patients who: 1) for any reason have not adhered to study schedules and procedures as defined in the schedule of study procedures, and/or 2) exhibit any adverse effects which in the opinion of the investigator will endanger their welfare with the continued use of the study medication will be discontinued from the study.

9. VOLUNTARY PARTICIPATION

I clearly understand that my participation is voluntary and that I may withdraw from the study at any time under no penalty of loss of benefits to which I am otherwise entitled. I further understand that at any time during treatment I am free to discuss with Dr. (name of investigator) (phone #) or Dr. (name of investigator) (phone #) or their designee my participation in this study or any side effects that might occur.

10. I have read the above statements and I fully understand the information in these statements. I do hereby authorize Dr. (name of investigator), Dr. (name of investigator), or their designee to administer the extracts. I voluntarily consent to participate in this study.

Patient Signature

Date

Witnessing Doctor

Date

Signature of Investigator

Date

TABLE I

SCHEDULE OF VISITS AND DETERMINATIONS

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33		
Day (relative to baseline)	-28	-27	-26	-14	-13	-12	1	7	14	28	42	56	63	64	65	70	84	91	98	112	119	126	133	134	135	140	154	168	175	176	177	182	193		
Week	-21	-20	-19	-10	-9	-8	0	1	2	3	4	5	6	7	8	9	9	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	
Procedures																																			
Screening History and Physical	↑			↑			↑		↑	↑	↑				↑		↑		↑			↑				↑		↑		↑			↑		
TLV III/LAV	↑																																		
Kin Test	↑		↑										↑										↑						↑						
1 hr. reading	↑		↑										↑										↑							↑					
4 hr. reading		↑			↑									↑											↑						↑				
8 hr. reading			↑			↑									↑												↑								
Immunology MA-21	↑			↑					↑				↑					↑				↑								↑				↑	
Immune Globulins	↑			↑					↑				↑									↑								↑				↑	
Heat X-ray				↑																															↑
Urinalysis	↑																																		↑
T-Cell Subsets	↑			↑									↑																		↑				↑
Cellular Immune Studies				↑				↑	↑				↑			↑						↑	↑							↑				↑	
FEATMENT							↑		↑	↑	↑					↑	↑		↑			↑				↑		↑		↑					
Load Required																																			

EXECUTIVE SUMMARY
RECOMMENDATIONS FOR PREVENTING TRANSMISSION OF INFECTION
WITH HUMAN T-LYMPHOTROPIC VIRUS TYPE III/
LYMPHADENOPATHY-ASSOCIATED VIRUS

This information and recommendations contained in these guidelines have been developed with particular emphasis on health-care workers and others in related occupations in which exposure might occur to blood from persons infected with HTLV-III/LAV, the "AIDS virus". Because of public concern about the purported risk of transmission of HTLV-III/LAV by persons providing personal services and those preparing and serving food and beverages, this document also addresses personal-service and food-service workers. Finally, it addresses "other workers"-- persons in settings, such as offices, schools, factories, and construction sites, where there is no known risk of AIDS virus transmission.

Because AIDS is a bloodborne, sexually transmitted disease that is not spread by casual contact, these guidelines do not recommend routine HTLV-III/LAV antibody screening for the groups addressed. Because it is not transmitted through preparation or serving of food and beverages, the guidelines state that food-service workers known to be infected with AIDS should not be restricted from work unless they have another infection or illness for which such restriction would be warranted.

These guidelines contain detailed recommendations of precautions appropriate to prevent transmission of all bloodborne infectious diseases to people exposed- in the course of their duties- to blood from persons who may be infected with HTLV-III/LAV. They emphasize that health-care workers should take all possible precautions to prevent needlestick injury. The guidelines are based on the well-documented modes of HTLV-III/LAV transmission and incorporate a "worst case" scenario, the hepatitis B model of transmission. Because the hepatitis B virus is transmitted in a similar manner as the AIDS virus and is both harder and more infectious than HTLV-III/LAV, guidelines that would prevent transmission of hepatitis B will also prevent transmission of AIDS.

Formulation of specific recommendations for health-care workers who perform invasive procedures is in progress.

Persons at increased risk of acquiring infections with human T-lymphotropic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV), the virus that causes acquired immunodeficiency syndrome (AIDS), include homosexual and bisexual men, intravenous (IV) drug abusers, persons transfused with contaminated blood or blood products, heterosexual contacts of persons with HTLV-III/LAV infections, and children born to infected mothers. HTLV-III/LAV is transmitted through sexual contact, parenteral exposure to infected blood or blood components, and perinatal transmission from mother to neonate. HTLV-III/LAV has been isolated from blood, semen, saliva, tears, breast milk and urine and is likely to be isolated from other body fluids, secretions and excretions, but epidemiologic evidence has implicated only blood and semen in transmission. Studies of nonsexual household contacts of AIDS patients indicate that casual contact with saliva and tears does not result in transmission of infection. Spread of infection to household contacts of infected persons has not been detected when the household contacts have not been sex partners or infants of infected mothers. The kind of nonsexual person-to-person contact that generally occurs among workers and clients or consumers in the workplace does not pose a risk for transmission of HTLV-III/LAV.

As in the development of any such recommendations, the paramount consideration is the protection of the public's health. The following recommendations have been developed for all workers, particularly workers in occupations in which exposure might occur to blood from individuals infected with HTLV-III/LAV. These recommendations reinforce and supplement the specific recommendations that were published earlier for clinical and laboratory staffs (1) and for dental-care personnel and persons performing necropsies and morticians services (2). Because of public concern about the purported risk of transmission of HTLV-III/LAV by persons providing personal services and by food and beverages, these recommendations contain information and recommendations for personal-service and food-service workers. Finally, these recommendations address workplaces in general where there is not known risk of transmission of HTLV-III/LAV (e.g. offices, schools, factories, construction sites). Formulations of specific recommendations for health-care workers (HCWs) who perform invasive procedures to prevent HTLV-III/LAV transmission in prisons, other correctional facilities, and institutions housing individuals who may exhibit uncontrollable behavior (e.g. custodial institutions). In addition, separate recommendations have already been developed for children in schools and day-care centers (3).

HTLV-III/LAV-infected individuals include those with AIDS (4); those diagnosed by their physician(s) as having other illnesses due to infection with HTLV-III/LAV; and those who have virologic or serologic evidence of infections with HTLV-III/LAV but who are not ill.

Some of these recommendations are based on the well-documented modes of HTLV-III/LAV transmission identified in epidemiologic studies. Other recommendations are based on the hepatitis B model of transmission.

THE HEPATITIS B MODEL

The epidemiology of HTLV-III/LAV infection is similar to that of hepatitis B virus (HBV) infection, and much that has been learned over the last 15 years related to the risk of acquiring hepatitis B in

the workplace can be applied to understanding the risk of HTLV-III/LAV transmission in the health-care and other occupational settings. Both viruses are transmitted through sexual contact, parenteral exposure to contaminated blood or blood products, and perinatal transmission from infected mothers to their offspring. Thus, some of the same major groups at high risk for HBV infection (e.g. homosexual men, IV drug users, persons with hemophilia, infants born to infected mothers) are also the groups at highest risk for HTLV-III/LAV infection. Neither HBV nor HTLV-III/LAV has been shown to be transmitted by casual contact, contaminated food or water, or airborne or fecal-oral routes (5).

HBV infection is an occupational risk for HCWs, but this risk is related to degree of contact with blood or contaminated needles. HCWs who do not have contact with blood or needles contaminated with blood are not at risk for acquiring HBV in the workplace (6-8).

In the health-care setting, HBV transmission has not been documented between hospitalized patients, except in hemodialysis units, where blood contamination of the environment has been extensive or where HBV-positive blood from one patient has been transferred to another patient through contamination of instruments. Evidence of HBV transmission from HCWs to patients has been extremely rare and limited to situations in which the HCWs exhibited high concentrations of virus in their blood (at least 100,000,000 circulating virus particles per ml of serum), and the HCWs sustained a puncture wound while performing traumatic procedures on patients or had exudative or weeping lesions that allowed virus to contaminate instruments or open wounds of patients.

In regard to the comparison of HBV with HTLV-III/LAV transmission in health-care settings, current evidence indicates that, despite epidemiologic similarities, the risk of acquiring HBV infection following a needlestick injury from an HBV carrier ranges from 6% to 30% (12,13), far in excess of the documented risk of HTLV-III/LAV infections following a needlestick involving a source patient infected with HTLV-III/LAV, which is less than 1%. In addition, all persons who have been shown to transmit HBV infection in health-care settings have belong to the subset of chronic HBV carriers who, when tested, have exhibited evidence of exceptionally high concentrations of virus (greater than 100,000,00 infectious virus particles per ml) in their blood. Chronic carriers who have substantially lower concentrations of virus in their blood have not been implicated in transmission in the health-care setting (9-11,14). The HBV model thus represents a "worst case" condition in regard to transmission in health-care and other related settings. Therefore, recommendations for the control of HBV infection should also effectively prevent spread of HTLV-III/LAV. Whether additional measures are indicated for those HCWs who perform invasive procedures will be addressed in the recommendations currently being developed.

Routine screening of all patients or HCWs for evidence of HBV infection has never been recommended. Control of HBV transmission in the health-care setting has emphasized the implementation of recommendations for the appropriate handling of blood, other body fluids, and items soiled with blood or other body fluids.

HEALTH CARE WORKERS

HCWs include, but are not limited to, nurses, physicians, dentists and other dental workers, optometrists, podiatrists, chiropractors, laboratory and blood bank technologists and technicians, phlebotomists, dialysis personnel, paramedics, emergency medical technicians, medical examiners, morticians, housekeepers, laundry workers and others whose work involves contact with patients, their blood or other body fluids, or corpses. Additional recommendations are being developed for HCWs who perform invasive procedures.

Recommendations for HCWs emphasize precautions appropriate for preventing transmission of bloodborne infectious diseases, including HTLV-III/LAV and HBV infections. Thus, these precautions should be enforced routinely, as should other standard infections-control precautions, regardless of whether HCWs or patients are known to be infected with HTLV-III/LAV or HBV. In addition to being informed of these precautions, all HCWs, including students and housestaff, should be educated regarding the epidemiology, modes of transmission, and prevention of HTLV-III/LAV infection.

Management of parenteral and mucous membrane exposures. If a HCW has a parenteral (e.g. needlestick or cut) or a mucous membrane (e.g. splash to the eye or mouth) exposure to blood or other body fluids, the source patient should be assessed clinically and epidemiologically to determine the likelihood of HTLV-III/LAV infection. If the source patient has AIDS or other evidence of HTLV-III/LAV infection, declines testing, or has a positive test, the HCW should be evaluated clinically and serologically for evidence of HTLV-III/LAV infection as soon as possible after the exposure, and, if seronegative, retested after 6 weeks and on a periodic basis thereafter (e.g. 3, 6, and 12 months following exposure) to determine if transmission has occurred. During this follow-up period, especially the first 6 weeks, when most infected persons are expected to seroconvert, exposed HCWs should receive counseling about the risk of infection and follow U.S. Public Health (PHS) recommendations for preventing transmission of AIDS (15,16). If the source patient is seronegative and has no other evidence of HTLV-III/LAV infection, no further follow-up of the HCW is necessary. If the source patient cannot be identified, decisions regarding appropriate follow-up should be individualized based on the type of exposure and the likelihood that the source patient was infected. If a patient has a parenteral or mucous membrane exposure to blood or other body fluids of a HCW, the patient should be informed of the incident and the same procedure outlined above should be followed. Management of this type of exposure will be addressed in more detail in the recommendations for HCWs who perform invasive procedures.

Serologic testing of patients. Routine serologic testing of all patients for antibody to HTLV-III/LAV is not recommended to prevent transmission of HTLV-III/LAV infection in the workplace, because results of such testing are unlikely to further reduce the risk of transmission, which, even with documented needlesticks, is already extremely low. Furthermore, the risk of needlestick and other parenteral exposures could be reduced by emphasizing and more consistently implementing routinely recommended infection control precautions (e.g. not recapping needles). Moreover, results of routine serologic testing would not be available for emergency cases

and patients with short lengths of stay, and additional tests to determine whether a positive test was a true or false positive would be required in populations with a low prevalence of infection. However, this recommendations is based only on considerations of occupational risks and should not be construed as a recommendation against other uses of the serologic test, such as for diagnosis or to facilitate medical management of patients. Since the experience with infected patients does vary substantially among hospitals (75% of all AIDS cases have been reported by only 280 of the more than 6,000 acute-care hospitals in the United States), some hospitals in certain geographic areas may deem it appropriate to initiate serologic testing of patients.

Risk of HCWs acquiring HTLV-III/LAV in the workplace. Using the HBV model, the highest risk for transmission of HTLV-III/LAV in the workplace would involve parenteral exposure to a needle or other sharp instrument contaminated with blood of an infected patients. The risk to HCWs of acquired HTLV-III/LAV infections in the workplace has been evaluated in several studies. In five separate studies, a total of 1,498 HCWs have been tested for antibody to HTLV-III/LAV. In these studies, 666 (44.5%) of the HCWs had direct parenteral (needlestick or cut) or mucous membrane exposure to patients with AIDS or HTLV-III/LAV infection. Most of these exposures were to blood rather than to other body fluids. None of the HCWs whose initial serologic tests were negative developed subsequent evidence of HTLV-III/LAV infection following their exposures. Twenty-six HCWs in these five studies were seropositive when first tested; all but three of these persons belonged to groups recognized to be at increased risk for AIDS (17). Since one was tested anonymously, epidemiologic information was available on only two of these three seropositive HCWs. Although these two HCWs were reported as probable occupationally related HTLV-III/LAV infection (17,18), neither had a preexposure nor an early postexposure serum sample available to help determine the onset of infection. One case reported from England describes a nurse who seroconverted following an accidental parenteral exposure to a needle contaminated with blood from an AIDS patient (19).

In spite of extremely low risk of transmission of HTLV-III/LAV infection, even when needlestick injuries occur, more emphasis must be given to precautions targeted to prevent needlestick injuries in HCWs caring for any patient, since such injuries continue to occur even during the care of patients who are known to be infected with HTLV-III/LAV.

Precautions to prevent acquisition of HTLV-III/LAV infection by HCWs in the workplace. The precautions represent prudent practices that apply to preventing transmission of HTLV-III/LAV and other bloodborne infections and should be used routinely (20).

1. Sharp items (needles, scalpel blades and other sharp instruments) should be considered as potentially infective and be handled with extraordinary care to prevent accidental injuries.
2. Disposable syringes and needles, scapel blades, and other sharp items should be placed into puncture-resistant containers located as close as practical to the area in which they were used. To prevent needlestick injuries, needles should not be recapped, purposefully bent, broken, removed from syringes or otherwise manipulated by hand.

3. When the possibility of exposure to blood or other body fluids exists, routinely recommended precautions should be followed. The anticipated exposure may require gloves alone, as in handling items soiled with blood or other equipment contaminated with blood or other body fluids, or may also require gowns, masks, and eye-coverings when performing procedures involving more extensive contact with blood or potentially infective body fluids, as in some dental or endoscopic procedures or postmortem examinations. Hands should be washed thoroughly and immediately if they accidentally become contaminated with blood.
4. To minimize the need for emergency mouth-to-mouth resuscitation, mouth pieces, resuscitation backs, or other ventilation devices should be strategically located and available for use in areas where the need for resuscitation is predictable.
5. HCWs who are or might become pregnant should be counselled regarding potential risk to the fetus due to work assignment and preventive measures that will reduce these risks (21). Pregnant HCWs are not known to be at greater risk of contracting HTLV-III/LAV infections than those who are not pregnant; however, if a HCW develops HTLV-III/LAV infection during pregnancy, the infant is at increased risk of infection resulting from perinatal transmission. Because of this risk, pregnant HCWs should be especially familiar with precautions for the preventing of HTLV-III/LAV transmission.

Sterilization, disinfection, housekeeping, and waste disposal to prevent transmission of HTLV-III/LAV. Sterilization and disinfection procedures currently recommended for use (22,23) in health-care and dental facilities are adequate to sterilize or disinfect instruments, devices, or other items contaminated with the blood or other body fluids from individuals infected with HTLV-III/LAV. Instruments or other nondisposable items that enter normally sterile tissue or the vascular system or through which blood flows should be sterilized before reuse. Surgical instruments used on all patients should be decontaminated after use rather than just rinsed with water. Decontamination can be accomplished by machine or by hand cleaning by trained personnel wearing appropriate protective attire (24) and using appropriate chemical germicides. Instruments or other nondisposable items that touch intact mucous membranes should receive high-level disinfection.

Several liquid chemical germicides commonly used in laboratories and health-care facilities have been shown to kill HTLV-III/LAV at concentrations much lower than are used in practice (25). When decontaminating instruments or medical devices, chemical germicides that are registered and approved by the U.S. Environmental Protection Agency (EPA) as "sterilants" can be used either for sterilization or for high-level disinfection depending on contact time; germicides approved for use as "hospital disinfectants" and are mycobactericidal when used at appropriate dilutions can also be used for high-level disinfection of devices and instruments. Germicides that are mycobactericidal are preferred because mycobacteria represent one of the most resistant groups of microorganisms; therefore, germicides that are effective against mycobacteria are also effective against other bacterial and viral pathogens. When chemical germicides are

used, instruments or devices to be sterilized or disinfected should be thoroughly cleaned before exposure to the germicide, and the manufacturer's instructions for the use of the germicide should be followed.

Laundry and dishwashing cycles commonly used in hospitals are adequate to decontaminate linens, dishes, glassware, and utensils. When cleaning environmental surfaces, housekeeping procedures commonly used in hospitals are adequate; surfaces exposed to blood and body fluids should be cleaned with a detergent followed by decontamination using an EPA-approved hospital disinfectant that is mycobactericidal. Individuals cleaning up such spills should wear disposable gloves. Information on specific label claims of commercial germicides can be obtained by writing to the Disinfectants Branch, Office of Pesticides, Environmental Protection Agency, 401 M Street S.W., Washington, DC, 20408.

In addition to hospital disinfectants, a freshly prepared solution of sodium hypochlorite (household bleach) is an inexpensive and very effective germicide. Concentrations ranging from 5,000 ppm (a 1:10 dilution of household bleach) to 500 ppm (a 1:100 dilution) sodium hypochlorite are effective, depending on the amount of organic material (e.g. blood, mucus, etc.) present on the surface to be cleaned and disinfected.

Sharp items should be considered as potentially infective and should be handled and disposed of with extraordinary care to prevent accidental injuries. Other potentially infective waste (23) are adequate for disposal of waste contaminated by HTLV-III/LAV. Blood and other body fluids may be carefully poured down a drain connected to a sanitary sewer.

Risk of transmission of HTLV-III/LAV infection from HCWs to patients. Although there is no evidence that HCWs infected with HTLV-III/LAV have transmitted infection to patients, a risk transmission of HTLV-III/LAV infection from HCWs to patients would exist in situations where there is both (1) a high degree of trauma to the patient that would provide a portal of entry for the virus (e.g. during invasive procedures) and (2) access of blood or serous fluid from the infected HCW to the open tissue of a patient as could occur if the HCW sustains a needlestick or scalpel injury during an invasive procedure. HCWs known to be infected with HTLV-III/LAV who do not perform invasive procedures need not be restricted from work unless they have evidence of other infection or illness for which any HCW should be restricted. Specific recommendations for HCWs who perform invasive procedures are being developed.

Precautions to prevent transmission of HTLV-III/LAV infection from HCWs to patients. These precautions apply to all HCWs, regardless of whether they perform invasive procedures.

1. All HCWs should wear gloves for direct contact with mucous membranes or nonintact skin of all patients.
2. HCWs who have exudative lesions or weeping dermatitis should refrain from all direct patient care and from handling patient care and from handling patient-care equipment until the condition resolves.

Serologic testing of HCWs. Routine Serologic testing of HCWs who do not perform invasive procedures (including providers of home and prehospital emergency care) is not recommended to prevent transmission of HTLV-III/LAV infections. The risk of transmission is extremely low

and can be further minimized when routinely recommended infection control precautions are followed. However, serologic testing should be available to HCWs who may wish to know their HTLV-III/LAV infection status. Indications for serologic testing of HCWs who perform invasive procedures will be addressed in the recommendations being developed for these individuals.

Risk of transmission to HCWs during home care of persons infected with HTLV-III/LAV. Persons infected with HTLV-III/LAV can be safely cared for in home environments. Studies of family members of patients infected with HTLV-III/LAV have found no evidence of HTLV-III/LAV transmission to adults who were not sexual contacts of the infected patients or to children who were not at risk for perinatal transmission (3). HCWs providing home care face the same risk of transmission of infection as HCWs in hospitals and other health-care settings, especially if there are needlesticks or other parenteral or mucous membrane exposures to blood or other body fluids.

Precautions for HCWs during home care of persons infected with HTLV-III/LAV. When providing health-care service in the home to persons infected with HTLV-III/LAV, measures similar to those used in hospitals are appropriate. As in the hospital, needles should not be recapped, purposefully bent, broken, removed from syringes, or otherwise manipulated by hand. Needles and other sharp items should be placed into puncture-resistant containers and disposed of in accordance with local regulations for solid waste. Blood and other body fluids can be flushed down the toilet. Other items for disposal that are contaminated with blood or other body fluids that cannot be flushed down the toilet should be wrapped securely in a plastic bag before being discarded in a manner consistent with local regulations for solid waste disposal. Spills of blood or other body fluids should be cleaned with soap and water or a household detergent. As in the hospital, individuals cleaning up such spills should wear disposable gloves. A disinfectant solution or a freshly prepared solution of sodium hypochlorite (household bleach, see above) should be used to wipe the areas after cleaning.

Risk of occupational acquisition of other infectious diseases by HCWs infected with HTLV-III/LAV. HCWs who are known to be infected with HTLV-III/LAV and who have defective immune systems are at increased risk for acquiring or experiencing serious complications of other infectious diseases. Of particular concern is the risk of severe infection following exposure to patients with infectious diseases that are easily transmitted if appropriate precautions are not taken, e.g. tuberculosis. HCWs infected with HTLV-III/LAV should be counseled about the potential risk associated with taking care of patients with transmissible infections and should continue to follow existing recommendations for infection control to minimize their risk of exposure to other infectious agents (20,21). The HCW's personal physician, in conjunction with their institutions' personnel health services or medical directors, should determine on an individual basis whether the infected HCWs can adequately and safely perform patient-care duties and suggest changes in work assignments, if indicated. In making this determination, recommendations of the Immunization Practices Advisory Committee and institutional policies concerning requirements for vaccinating HCWs with the live virus vaccines should also be considered.

Risk of occupational transmission of HTLV-III/LAV to providers of prehospital emergency health care. Providers of prehospital emergency health care include the following: paramedics, emergency medical technicians, law enforcement personnel, firefighters, lifeguards, and others whose jobs might require them to provide first-response medical care. The risk of transmission of infection, including HTLV-III/LAV infection, from infected persons to providers of prehospital emergency health care should be no higher than that for HCWs providing emergency care in the hospital if appropriate precautions are taken to prevent exposure to blood or other body fluids.

Precautions for providers of prehospital emergency care. Providers of prehospital emergency health care should follow the precautions outlined above for other HCWs. No transmission of HBV infections during mouth-to-mouth resuscitation has been documented. However, because of the theoretical risks of salivary transmission of HTLV-III/LAV during mouth-to-mouth resuscitation, special attention should be given to the use of disposable airway equipment or resuscitation bags and the wearing of gloves when in contact with blood or other body fluids. Resuscitation equipment and devices known or suspected to be contaminated with blood or other body fluids should be used once and disposed of or be thoroughly cleaned and disinfected after each use.

PERSONAL-SERVICE WORKERS

Personal-service workers (PSWs) are defined as individuals whose occupations involves close personal contact with clients (e.g. hairdressers, barbers, estheticians, cosmetologists, manicurists, pedicurists, massage therapists). PSWs whose services (tattooing, ear piercing, acupuncture, etc.) require needles or other instruments that penetrate the skin should follow precautions indicated for HCWs. Although there is no evidence of transmission of HTLV-III/LAV from clients to PSWs, from PSWs to clients, or between clients of PSWs, as risk of transmission would exist from PSWs to clients and vice versa in situations where there is both (1) trauma to one of the individuals that would provide a portal of entry for the virus and (2) access of blood or serous fluid from one infected person to the open tissue of the other, as could occur if either sustained a cut. A risk of transmission from client to client exists when instruments contaminated with blood are not sterilized or disinfected between clients. However, HBV transmission has been documented only rarely in acupuncture and tattoo establishments and never in other personal-service settings, indicating that any risk for HTLV-III/LAV transmission in personal-service settings must be extremely low.

Serologic testing of PSWs. Routine serologic testing of PSWs for antibody to HTLV-III/LAV is not recommended to prevent transmission from PSWs to clients.

Precautions for PSWs. All PSWs should be educated about transmission of bloodborne infections, including HTLV-III/LAV and HBV. Such education should emphasize principles of good hygiene, antisepsis, and disinfection. This education can be accomplished by national or state professional organizations, with assistance from state and local health departments, using lectures at meetings or self-instructed materials. Licensure requirements should include evidence of such educations. Instruments that are intended to penetrate the skin (e.g. tattooing and acupuncture needles, ear

piercing devices) should be used once and disposed of or be thoroughly cleaned and sterilized after each use using procedures recommended for use in health-care institutions. Instruments not intended to penetrate the skin but which may become contaminated with blood (e.g. razors), should be used for only one client and be disposed of or thoroughly cleaned and disinfected after use using procedures recommended for use in health-care institutions. Any PSW with exudative lesions or weeping dermatitis, regardless of HTLV-III/LAV infection status, should refrain from direct contact with clients until the condition resolves. PSWs known to be infected with HTLV-III/LAV need not be restricted from work unless they have evidence of other infections or illnesses for which any PSW should also be restricted.

FOOD-SERVICE WORKERS

Food-service workers (FSWs) are defined as individuals whose occupations involve the preparation or serving of food or beverages (e.g. cooks, caterers, servers, waiters, bartenders, airline attendants).

Risk of transmission from FSWs to consumers. All epidemiologic and laboratory evidence indicates that bloodborne and sexually transmitted infections are not transmitted during the preparation or serving of food or beverages, and no instances of HBV or HTLV-III/LAV transmission have been documented in this setting.

Serologic testing of FSWs. Routine serologic testing of FSWs for antibody to HTLV-III/LAV is not recommended to prevent disease transmission from FSWs to consumers.

Precautions for FSWs. All FSWs should follow recommended standards and practices of good personal hygiene and food sanitation (26). All FSWs should exercise care to avoid injury to hands when preparing food. Should such an injury occur, both aesthetic and sanitary considerations would dictate that food contaminated with blood be discarded. FSWs known to be infected with HTLV-III/LAV need not be restricted from work unless they have evidence of other infection or illness for which any FSW should also be restricted.

ALL OTHER WORKERS

Risk of transmission of HTLV-III/LAV among workers sharing the same work environment. No known risk of transmission to co-workers, clients, or consumers exists from HTLV-III/LAV-infected workers in settings not previously discussed (e.g. offices, schools, factories, construction sites). This infection is spread by sexual contact with infected persons, injection of contaminated blood or blood products, and by perinatal transmission. Workers known to be infected with HTLV-III/LAV should not be restricted from work solely based on this finding. Moreover, they should not be restricted from using telephones, office equipment, toilets, showers, eating facilities, and water fountains. Equipment contaminated with blood and other body fluids of any worker, regardless of HTLV-III/LAV infection status, should be cleaned with soap and water or a detergent. A disinfectant solution or a fresh solution of sodium hypochlorite (household bleach, see above) should be used to wipe the area after cleaning.

OTHER ISSUES IN THE WORKPLACE

The information and recommendations contained in this document do not address all of the potential issues that may have to be considered when making specific employment decisions for persons with HTLV-III/LAV infection. The diagnosis of HTLV-III/LAV infection may evoke unwarranted fear and suspicion in some co-workers. Other issues that may be considered include the need for confidentiality, applicable federal, state or local laws governing occupational safety and health, civil rights of employees, workers' compensation laws, provisions of collective bargaining agreements, confidentiality of medical records, informed consent, employee and patient privacy rights, and employee right-to-know status.

DEVELOPMENT OF THESE RECOMMENDATIONS

The information and recommendations contained in these recommendations were developed and compiled by the CDC and other PHS agencies in consultation with individuals representing various organizations. The following organizations were represented: Associated of State and Territorial Health Officers. Conference of State and Territorial Epidemiologists. Association of State and Territorial Public Health Laboratory Directors. National Association of County Health Officials. American Hospital Association. United States Conference of Local Health Officers. Association for Practitioners in Infection Control. Society for Hospital Epidemiologists of America. American Dental Association. American Medical Association. American Nurses' Association. American Association of Medical Colleges. American Association of Dental Schools. National Institutes of Health. Food and Drug Administration. Food Research Institute. National Restaurant Association. National Hairdressers and Cosmetology Association. National Gay Task Force. National Funeral Directors and Morticians Association. American Association of Physicians for Human Rights. National Association of Emergency Medical Technicians. The consultants also included a labor union representative, an attorney, a corporate medical director, and a pathologist. However, these recommendations may not reflect the views of the individual consultants or the organizations they represented.

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The one outstanding agreement among AIDS researchers is need for prevention. Prevention is also in the enlightened self interest of our State government. We are not going to have a cure for AIDS for years. A vaccine is 2-3 years away and it will be of value only to those who have not been exposed. Prevention is the ~~only~~ logical long term course of action in the foreseeable future.

Must do all we can to encourage VACCINE developers.

The primary role of the AAC has been in developing information and education campaigns. For this fiscal year it has developed a comprehensive, coordinated cost-effective prevention campaign which can be implemented statewide using proven contractors and messages developed over the past two years. *including several highly effective organizations*

I will briefly describe the 1985-86 RFP process - early '85 RFP went out from DHS - approached it as NIH does - give us a comprehensive AIDS prevention plan - received proposals in April

The Committee received ~~41 projects totalling 5.9 mil~~ - staff conducted technical reviews and reduced total \$ to 4.25 proposals worthy of funding including an excellent proposal from the SD AIDS Project. This clearly exceeded the 1.237 allocated in the Governors budget.

such as So. Calif. and LA SD Riverside Orange Ctries.

In meantime as part of an independent process an AIDS Budget Task Force was convened by Assemblyman John Vasconcellos to plan a budget strategy for the AIDS crisis. This had a well-developed cross section of physicians, researchers, educators, legislators and administration representatives. Vasco Task Force met 7 times between March 4 and April 8.

Vasco met with Gov June 6. The 4 governors appointees to the AAC wrote or met with him on the need to increase funding particularly in the I & E area.

a 12% increase by

On June 28 the Governor signed a 33.9 bil budget that does not require a tax increase and maintains a 1 bil reserve. The general fund commitment to health and welfare totals 8.8 bil, a 12% increase over 1984-5.

2.9 AIDS research

2.0 DHS for personnel, I&E grants, epi surveillance and state lab

4.9 million tagged for

16.635 in augmentations added by legislature

11.623 eliminated by Gov

5.012 more than in original budget

	Gov	Leg	
Prevention/Education	2.0	7.4	4.25 (+3.012)
Research	2.9	9.3	4.9 (+2.0)

Testing/Mental Health	5.0	6.6	5.0
MediCal	0	3.7	
	9.9	27.0	14.15

Blue lined:

0.1	ombudsman
1.5	block grant community support
.085	education related to HTLV test
1.5	train crisis center staff re test
1.0	mental health services for PWA
9.2	research

The AIDS augmentations which were cut could theoretically be overridden by the Legislature, however they were contained in 4 separate budget items.

Dept.	AIDS Augmentation Cut	Total Item Cut
U.C.	4.3	6.0
Dept. of HS (gen)	3.3	11.0
Dept. of HS (cty)	3.0	15.0
Dept of Mental Hlth	1.0	40.0

In order to override the Gov's cuts the legislature must pick up all the augmentations in that item.

Budget proposal from the legislature indicated a need for 4.25. Many individuals lobbied Gov. All 4 AAC appointees advised him to augment I & E, *and he did by 3 million \$.*

Gov used the document provided by the AAC indicating how the 4.25 would be spent in making the decision not to blue line the education and information augmentation. The Committee and the contractors were ecstatic about the augmentation and met last Friday in S.F. to make final recommendations to the Department.

But an unanticipated problem arose. Despite the approval of the AAC plan for allocation of funds to the community based organizations and HD's, DHS under Dr Kizer has indicated disagreement and proposed to undertake additional analysis. Thus there will be delays in funding of the prevention programs and more cases of AIDS will occur as a result. The matter is now in hands of Secretary (Swoap), Dir DHS (Kizer), Dir of Finance and appointees.

The epidemic is the most significant public health issue facing our country in this century yet there are some in this Administration who appear not to realize this. Years from now history will look back at our role in responding to the AIDS crisis. ~~AIDS must not become this administrations medfly. At 100,000/case 10,000 cases would dry up the states 1 billion surplus.~~

~~I really don't know what will be the outcome of the present~~

snafu. We are hopeful that it is all a misunderstanding which can be rapidly rectified by the Governor by directive to his staff. If it is not, and the funding is diverted or significantly delayed I am afraid that AIDS will become a political issue which could be costly to the Administration.

is a continued
There may yet be a need for political clubs, political action committees and AIDS organizations to establish a presence in Sacramento on AIDS issues.

In the meantime I can assure you that Mr. Decker, Mr. Filante and all the Committee members will stay on top of this particular situation. In summary my service on the AAC has been demanding but rewarding experience. In this capacity I will do all that I can to represent the needs of Southern California in this crisis. I hope that you will call on me and assist me in staying current with the needs here in S.D. Thank you.

AB 403 signed by Gov April 4. Delay of 60 d from effective date to date at which provisions become operative.

Mandatory Reporting Requirements

Requires that all blood donors be given a blood test for antibodies, that labs which make the test be approved, and that donors be notified of test results. BB's and PC's required after retesting for confirmation to provide a list of identities of + donors to DHS. Physicians and hospitals must also report all cases of tx-associated A to local county health officer. Donor deferral register list will be distributed to blood banks twice monthly.

Written Consent

Requires written consent of all test subjects unless the test is performed at alt sites established for voluntary testing according to state guidelines that req anon

AB488

Provides for civil penalties of at least 1,000 for negligent disclosure and up to 5000 for the wilfull disclosure of test results which identify subjects. Wilful or neg disclo is also a misdemeanor and exposes the disclosing party to liability for damages if disclosure results in harm to the test subject. Prohibits use of test results for determininh insurability or suitability for employment.