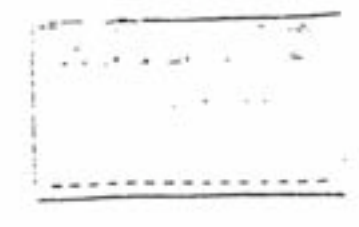

A Pilot Study of

INDUCED MALARIA THERAPY IN 30 HUMAN IMMUNODECIFICIENCY VIRUS POSITIVE INDIVIDUALS

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PRINCIPAL INVESTIGATORS

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PROTOCOL FOR:
INDUCED MALARIA as THERAPY
for HIV Infection

1.0 INTRODUCTION

The Human Immunodeficiency Virus Type 1 (HIV-1) is the etiological agent of Acquired Immune Deficiency Syndrome (AIDS). AIDS is characterized by a profound breakdown in the host's cellular and humoral immunity and increased susceptibility to a wide range of opportunistic infections. One of the consequences of this immune dysfunction is a marked depletion in absolute CD4+ cells in HIV-infected individuals. Some of the current research efforts are directed toward exploring vaccines, antivirals, immune modulators and antisera as approaches to the antiviral and immunotherapy of AIDS. Recent insights into immune system responses to any given pathogen have illustrated the importance of TH1 and TH2 or cell mediated and humoral immune activation and control, respectively.

The World Health Organization current estimate of the number of HIV infected individuals world wide is 19, 000, 000.

1.1 BACKGROUND

The technique of deliberately giving a disease to cure or prevent another disease is well known in the history of medicine. Examples include cowpox vaccination to prevent smallpox, and the Sabin live polio vaccine to prevent polio.

Induced Malaria Therapy (IMT) consists of inoculating a patient with a curable form of malaria (usually *Plasmodium vivax*) to cure another disease that is otherwise incurable. It was pioneered by Wagner-Jauregg who was awarded the Nobel Prize in 1927 for his discovery that IMT cured neurosyphilis. It has been determined that syphilis pathology is advanced by a premature TH1/TH2 immunological switch (Fitzgerald, TJ Infection and Immunity, Sept. 1992). HIV pathology is also advanced by a premature TH1/TH2 switch, i.e. cell mediated immune response predominance is replaced by humoral immune response predominance.

Research studies conducted at UC Berkeley, Walter Reed Army Institute of Research, and Heidelberg University independently demonstrated that malaria induces production of various cytokines, including interleukins and tumor necrosis factor. These cytokines regulate the TH1/TH2 response which are responsible for the escape of HIV and syphilis from the immune system defenses.

Because of the dramatic burst of interferon gamma (INFγ) produced by the immune system's response to IMT, it is postulated that TH1 predominance will be restored. Strong TH1 responses are associated with stabilization of HIV symptomatology.

1.2 RATIONALE

At the 1990 conference on AIDS in Florence, Italy, a study was presented by researchers at a children's medical office. The team 112 children with HIV, 41 also had malaria and 71 did not.

At the end of two years, 25 (35%) of the 71 children with AIDS and no malaria were dead. During the same time period, the 41 children with malaria and AIDS were all living and well. None of the malaria infected AIDS patients died during this two year period.

A second significant study, published in the *New England Journal of Medicine*, was carried out in Venezuela by researchers from the University of Nebraska. They reported that a group of Venezuelans with malaria were seropositive for HIV antibodies, but never developed symptoms of AIDS.

2.0 OBJECTIVES

2.1 To determine the safety of IMT in persons with HIV disease.
2.2 To monitor immune system functioning before and after the administration of IMT.
2.3 To monitor febrile responses of IMT on HIV-1 viability.
2.4 To monitor viral load in patients' peripheral blood mononuclear cells prior to beginning, during and post IMT treatments.
2.5 To monitor cytokine responses of IMT in study participants.
2.6 To monitor the course or incidence of opportunistic infections in the study participants.
2.7 To monitor the affect of IMT on cutaneous lesions in those study participants who have Kaposi's sarcoma.
2.8 To detect a shift in immune predominance response (TH2 to TH1).
2.9 To monitor the affect of anti-malaria drugs on HIV proliferation.

3.0 CLINICAL ENDPOINTS

To determine if IMT may be of therapeutic benefit for widespread use in HIV disease based on the following criteria:

3.1 Changes in HIV load or concentration as indicated by quantified RNA-PCR in peripheral blood mononuclear cells (PBMC).
3.2 Changes in p24 antigen level.
3.3 Changes in complete blood cell count.
3.4 Changes in T cell enumeration panel.
3.5 Changes in CD-88 (natural Killer cells).
3.6 Changes in the key cytokines including but not limited to:
  3.6a Interleukin 2 (IL2)
  3.6b Interleukin 12 (IL12)
  3.6c Tumor Necrosis Factor alpha (TNFα)

3.5d Interferon gamma (INFγ)

3.7 Changes in incidence rate for new opportunistic infections.

3.8 Changes in cell mediated immunity (CMI) as measured by intra dermal antigen skin test (Muti-test CMI).

3.9 Changes in the size, color, intensity, and palpable skin characteristics of cutaneous Kaposi's sarcoma lesions.

4.0 METHODS

The methods of treatment we will use are well established and based on the more that 60 years that IMT has been used. Each HIV positive patient will receive a natural inoculation containing malaria parasites. Malaria fever typically occurs every other day after approximately a two week incubation period. One the first day fever occurs, the patient will be admitted to the medical facility. After the indicated number of fevers have occurred as determined by their group, antimalarial medications will be administered. In all the years that IMT has been utilized, there is not a single report of a failure to cure this deliberately induced malaria.

Patients will be followed closely and periodically re-evaluated by members of the clinical research team.

Laboratory draws will take place at baseline, weekly during febrile response to malaria and three and six weeks after antimalaria treatment has begun.

4.1 MATERIALS

Malaria will be induced in the study participants utilizing the natural mode of transmission. Antimalaria treatment will consist of, "appropriate antimalarial medication".

4.2 STUDY GROUP

30 HIV+ patients will be enrolled as participants in the open-label controlled trial of IMT.

4.2a Inclusion Criteria

1) At least 18 years of age.

2) HIV seropositivity; confirmation of this from previous treating physicians in the form of medical records is acceptable.

3) A CD4+ lymphocyte count of at least 100/mm for Group 1; CD4+ count of at least 300/mm for Group 2. Two previous T-cell panels must

be provided to the study coordinator. This criteria will be confirmed by base line counts performed at enrollment by the principal investigator.

4) Have the following baseline laboratory values:

Hemoglobin > 9 gm/dl
WBC > 1,500 per ul
PMN > 500 per ul
Platelets > 25,000 per ul
Bilirubin < 2.0 mg/dl
SGOT, SGPT, alk. phos. < 3x the upper limit of normal
Creatinine < 1.5 mg/dl
Karnofsky > 70
Life Expectancy of > 6 months

5) Use of suitable contraception for women of child bearing age.
6) Willing and capable to provide informed consent.

4.2b Exclusion Criteria

1) Patients with prior exposure to malaria or who show a positive reaction to the intradermal test dose of malaria. Such a reaction consists of an area of redness or swelling > 10 mm in diameter, fever, dyspnea, change in blood pressure, or the development of rash within 48 hours. Such patients will be included if it can be demonstrated that they are still susceptible to different acceptable strains.

2) No change in antiretroviral therapy for the previous two months. Previous treatment with chemotherapeutic agents (other than intralesional) within eight weeks of enrollment.

3) History of or active presence of a major or life threatening opportunistic infection.

4) Active substance abuse which, in the Principal Investigator's opinion, might prevent compliance with the study's requirements.

5) Pregnancy or breast feeding.

6) Cardiac disease is a contraindication to malariotherapy.

4.3 BASELINE DATA COLLECTION

After a patient has qualified for the study, details of the study will be discussed and the patient given an opportunity to ask questions. Informed consent will be obtained prior to treatment.

Baseline evaluation will consist of a brief medical history including detailed information about the course of the patient's HIV infection, previous and current medications and treatment, and a physical exam. Included also are the following laboratory tests:

Chemistry panel 24
Complete Blood Cell Count
T-Cell Panel
Interleukin 2, 12
Tumor Necrosis Factor alpha
Interferon gamma
Cell Mediated Immunity Skin Test
Beta – 2 Microglobulin
Urinanalysis
P-24
P-24 (AOD)
Quanative RNA PCR
Temperature

4.4 STUDY TIME LINE AND TREATMENT PHASE

There are two treatment groups of 15 individuals each.

Group 1 will receive inoculation of *vivax* malaria. When symptoms of paracytemia are evident they will be allowed to continue untreated by anti-malaria drugs for 14 days.
Group 2 will receive inoculation of *vivax* malaria. When symptoms of paracytemia are evident they will be allowed to continue untreated by anti-malaria drugs for 28 days.

Each group is further divided into three groups of 5:

Group A will not have their symptoms treated with anti-pyretics unless their fevers rise above 41° C.
Group B will receive non-steriod anti-inflamitory (*sic*) for the resolution of mild to moderate symptoms attributed to malaria.
Group C will be treated only with 2 mg of oral alpha Interferon Q1D.

5.0 SIDE EFFECTS AND ADVERSE REACTIONS

The side effects and adverse reactions of inducing malaria therapy may include, but are not limited to the following: fever, chills, fatigue, nausea, vomiting, headache, flushing,

tightness of the chest, back pain, myalgia, sweating, hypotension, anaphylaxis, even death, serum sickness, muscle weakness, and potential progression of the symptoms of HIV/AIDS.

In case of any medical problems the patient should contact his or her primary care physician for treatment. If it is believed that the problem is related to the study, the study coordinator and/or the principal investigator must be notified.

6.0 DATA MONITORING AND EVALUATION

Maintenance of the highest standards of medical and laboratory care shall be adhered to at all times throughout the study.

All data will be collected and reviewed by the study monitor and the Principal Investigator. The study coordinator shall be responsible for collection of the laboratory data, final reports as they become available and their transmission to the PI and the monitor.

Statistical analysis will be performed to determine significant changes from baseline assessments of the clinical endpoints.

Assessment of the efficacy of this therapeutic modality shall be based upon percentage differences in assessments between baseline and interim values and baseline and final values. The goals of the research and this protocol are to determine safety and efficacy, to determine whether the results revealed from this study are encouraging enough to proceed to a large scale clinical trial.

7.0 MODIFICATION OF PROTOCOL

There may be clear indications for modification of this protocol as the study proceeds. These indications will be documented as they occur but they will be reported to the study monitor within 48 hours of their occurrence.

8.0 CONFIDENTIALITY

All information with regard to the above described study, as well as any associated information, shall be treated as confidential. Report forms and all written communications will be maintained under adequate security and restricted accessibility.

9.0 PUBLICATION/PRESENTATION

All research information generated by this study is confidential. The investigator and the study monitor shall mutually agree upon publication or presentation of the results.

10.0 TERMINATION

The Principal Investigator reserves the right to terminate the clinical study at any time. Should such action occur, the Principal Investigator shall notify all study participants of the reason for such termination and shall provide a set of final instructions for the participants.