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DEPARTMENT OF MEDICINE
UCLA Center For Clinical AIDS Research And Education (CARE)
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Paul K. Bronston, MD, FACEP
Ethics and Policy Committee
American College of Medical Quality
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VIA: FAX 310-823-2433

Dear Paul:

I am writing in response to your request for comments regarding the proposed induced malaria therapy (IMT) study for the treatment of patients with AIDS. I have received a copy of the synopsis on this treatment from you and have already spoken to you regarding this approach in previous phone conversations.

Let me state at the outset that as a clinical research investigator involved in clinical trials research in AIDS-related diseases since the early 1980's, that I have encouraged many research scientists and individuals with ideas regarding HIV therapy to publish their data and to fully investigate new therapeutic approaches through scientific clinical trials. Studies which we have been involved in have been fully sanctioned and reviewed both by scientific peer review groups such as the ACTG, our local IRB and the FDA which are both responsible for assuring the safety of patients and the reasonableness of the clinical protocol in answering the specific scientific questions posed.

The material which you provided me causes me considerable concern in that it proposes to infect immunosuppressed patients with HIV with a known infectious pathogen (Plasmodium vivax) to induce the production of various immune substances, specifically interleukins and tumor necrosis factor. It is postulated that this treatment may in some way be beneficial to the HIV-infected patients by prolonging life and reducing progression of diseases.

From a theoretical standpoint this approach makes very little sense in that both TNF and interleukin-1, as well as a number of other cytokines may up regulate HIV replication and may in fact cause further progression of disease. The interaction of HIV with immune cells and the regulation of cytokine production and their subsequent effects in patients is extremely complicated, and the net effect of a biologic approach on inducing these substances cannot be predicted and therefore needs to be studied in a very controlled manner. The use of infectious pathogens rather than inert inducing substances or the cytokines themselves will make it difficult to assess their hypotheses as well as subject patients to considerable risk associated with the infection.

It is my understanding that hyperthermia has also been directly evaluated in patients with HIV infection and found to have no beneficial effect on HIV replication, or on Kaposi's

~~complications~~, sarcoma in a small group of patients treated in Louisiana. In vitro work by Tony Fauci and others have shown that increased temperature may actually induce heightened HIV replication in certain HIV-infected cell lines.

It was also indicated that Plasmodium vivax is easily treated and has no major sequela. I would differ with this statement in that P. vivax can not only induce high fevers, chills and rigors but may also be responsible for anemia with its attendant complications, splenomegaly with the risk of rupture and, if not completely eradicated with treatment, hepatic transaminase elevations, renal vascular diseases, microthrombi and cerebral vascular complications.

Aside from these scientific and patient-related concerns is a significant ethical concern about conducting this study in Mexico rather than in the United States where it may not be approved due to patient safety concerns. I would have concerns about taking a therapy which has not been well evaluated laboratory or preclinical testing and which may not be approvable in the United States due to safety and scientific concerns to a country where therapy for HIV may be less available and where the issues of coercion and ability to give true informed consent may be more problematic.

Overall I share your concerns about this study and would hope that the investigators would more fully disclose their intended study design and scientific rationale prior to initiating this trial either in a foreign country or within the USA. The materials which I have seen are certainly not convincing enough to me and have sufficient potential danger to patients that I would be very concerned about allowing this study to move forward without additional information which should be reviewed by the appropriate regulatory agencies.

I commend you for your actions regarding this study to and hope that you can convey this concern to others who may have more authority over this trial.

Sincerely yours,

Ronald T. Mitsuyasu, MD
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