Immediate vs. deferred therapy with protease inhibitors

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A. Study purpose and rationale

HIV has three main genes- env, gag and pol. The pol gene codes for enzymes responsible for viral maturation and spread of infection. In order to be active, precursor polyproteins must undergo cleavage carried out by a viral proteinase. Protease inhibitors, the newest intervention in the treatment of HIV disease, inactivate this proteinase, making the viral products immature and non-infectious. The introduction of protease inhibitors have provided patients and clinicians with new hope in the management of HIV and AIDS.

Current theories on when illness develops in HIV-infected persons involves not only the CD4+ count, but the idea of a viral set point. When the body is initially infected by HIV, there is a high level of viral reproduction, with infection and perhap's some harboring of the virus within lymph nodes. Eventually an equilibrium is reached between the CD4+ cells and the amount of virus, or viral load, and this is known as the set point. The level of this set point helps to determine the rapidity of decline, with patients at higher set points having a more rapid course. Protease inhibitors have been shown to both decrease the load of HIV- I viral RNA and increase the CD4+ count, which has been shown to prolong life, and to prolong the time before illness occurs. Decreases in HIV-1 viral RNA titer generally occurs within four weeks of starting or changing antiretroviral treatment, at times to nearly undetectable levels.

The current recommendations for treatment initiation were given by an International panel in a consensus statement published in JAMA (July 1996). Current clinical data supports the initiation of therapy, a three drug regimen with two nucleoside analogs and a protease inhibitor, in all patients with symptomatic disease, asymptornatic patients with CD4+ counts less than 500, and patients with more than 30,000- 50,000 HIV-1 RNA copies/n-d. There is currently no available data to support therapy in subjects at CD4+ counts greater than 500. However, interest continues in antiretroviral therapies for HIV-infected persons with CD4 cell counts above 500, particularly since there is active viral proliferation during all stages of the disease. Given that viral replication likely continues in lymphoid tissue, even at lower rates, variation in the virions produced can be expected. Some of these variants include. those that have decreased susceptibility to anti viral therapy. This lends some support to initiating antiretroviral therapy earlier, for a more durable response before a broad array of drug resistant mutants would be expected to be present. Theoretically, the longer the virus is allowed to proliferate, the greater the number of wild type strains with resistance to these new drugs that might be produced.

In this study, I propose using triple drug therapy, including protease inhibitors, earlier in the course of the disease, when viral loads are lower, before the T-cell count is below 500, and the development of opportunistic infections. The theory behind this is that if used earlier in the course of disease, perhaps wild type strains with resistance that might naturally develop, will not yet have developed, and it might prolong the time before viral loads rise again and the CD4+ count drops. It has been shown that CD4+ counts remain

elevated for as long as viral loads are suppressed, and this is highly predictive of both progression to AIDS and death.

B. Design

The study will be a randomized, double.blind, placebo controlled, multi-center trial. All patients will receive two nucleoside analogs, zidovudine and lamivudine, and randomized to receive either a protease inhibitor, indinivir, or placebo. The patients will be randomized in blocks of twelve, with randomization occurring at each of the four study sites. The study will be divided into three periods: a screening phase, introduction of the nucleoside analogs, and a randomized, double blind placebo

controlled phase when the protease inhibitor is introduced. There is no plan to cross patients over, and they will be analyzed as intention to treat.

The primary endpoint to be measured is the rate of change of CD4+ count and viral load of the two groups, over a one year period; secondary endpoints include comparison between the study and control groups of mean CD4+ counts and viral loads at the end of the study period.

Ninety-six study subjects will be enrolled and followed for a one year period, with serial laboratory measurements (see below). The study has been designed to detect a standard deviation difference between placebo and intervention of two-thirds, with a power of 80%, and a type I error rate of 5%.

C. Procedures

During the screening phase, patients will have a baseline medical exam, with measurement of complete blood count with differential, platelet count, renal profile, and liver profile. In addition, an average CD4+ count will be garnered from three measurements over a three week period. HIV- I viral RNA load will be measured via branched chain DNA assay or PCR as needed.

Patients who pass the screening phase will be started on the two nucleoside analogs, and have an average CD4+ count measured at four weeks. Once therapy has been initiated, CD4+ counts and HIV- I viral RNA load will be measured at weeks 4,8,12,16, and 24, and every eight weeks thereafter. During the last weeks of the study, patients will again have an average CD4+ count measured from three values over a three week period. Typical clinical care at this time measures the CD4+ count every 12 weeks, and viral load is not measured as most laboratories do not have this assay available to them.

The likely duration of the study is for thirteen months post randomization, with each subject expected to remain for the entire period.

D. Study drugs

The three drugs to be used in this study are:

- **Zidovudine** (retrovir, AZT), 200mg q8 hours by mouth. Adverse effects are dose dependent and include nausea (50%), anorexia (20%), vomiting (17%), headache (62%), malaise (53%), anemia and macrocytosis.
- **Lamivudine** (3TC, epivir), 300mg q8 hours by mouth. Adverse effects include rash, insomnia, headache, diarrhea, hair loss. Indinivir, 800 mg q8 hours by mouth. Adverse effects include benign hyperbilirubinernia (12%) and nephrolithiasis (34%). Incidence of nephrolithiasis greatly reduced by intake of 48ozs of water a day.
- **Indinivir** has been selected over the other available protease inhibitors because of its good bioavailability, an easier dosing schedule when combined with the other medications, and the lower incidence of adverse effects.

The pharmaceutical companies will be solicited for donations of medications.

Medications will be distributed monthly, at designated sites, with more pills than needed for the month given. Compliance with the prescribed medical regimen will be monitored by counting left over pills and patient interviews. Two personal contacts through whom the subject can be reached will also be recorded to help with long term follow up.

E. Devices

not applicable

F. Questionnaires

not applicable

G. Subjects

Criteria for inclusion are as follows: age of 18 or older, documented HIV- I infection, average CD4+ count of 600-800, HIV-1 viral RNA load of- <25,000, no previous history of treatment with antiretroviral therapy, normal liver and renal function. Exclusion criteria are: anen-da, history of renal stones, on other experimental protocols, pregnancy or nursing, and inadequate birth control methods.

Recruitment for potential subjects will occur via HIV clinics, GMHC, methadone centers, and private physicians. Physicians will be informed of enrollment criteria, and asked to initially approach any patients who they feel are appropriate for the study, to see if they are willing to participate. Patients may also contact directly the investigators for enrollment. Further information regarding study purpose, required interventions, possible side effects of the medications and the understanding that they might receive placebo will be provided by a designated representative from the investigative group. Informed consent will be obtained, and those who pass the screening process will be enrolled.

H. Confidentiality

Confidentiality will be maintained by having each subject assigned a coded number under which all information will be stored. All personal information will be available only to the investigators.

I. Study site

All phases will be in the outpatient setting, at teaching institutions within New York City.

J. Risks/ Benefits

The potential risks involve the adverse events described previously with the medications. Possible benefits include prolongation of life, deferment of illness, and the potential to alter management recommendations.

K. Alternative therapies

The alternative for asymptomatic patients at this T-cell count is no therapy at all. Possible disadvantages of waiting for lower T cell counts before initiating antiretroviral therapy is that the immune system is burned out, and therapy will have little effect on the course of the disease. Possible disadvantages for starting therapy earlier is the development of therapy specific resistance, with decreased efficacy of the medications at higher viral loads.

L. Compensation and costs

The patients will incur no costs other than transportation to and from centers for laboratory evaluation and pill distribution monthly. Compensation involves free medical care, laboratory testing, and medications. In addition, to encourage compliance and a diversity of the study population, a small monetary compensation will be made for each follow up visit, and for completing the study.

M. Minors

N/A

N. Radiation

N/A