

A Double Blind, Placebo Controlled Trial of Salvage Highly Active Antiretroviral Therapy for HIV-Infected Individuals Who have Failed One Previous Protease Inhibitor-Containing Regimen

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A. Study Purpose and Rationale

Since the development and widespread usage of Highly Active Antiretroviral Therapy (HAART) the morbidity and mortality of Human Immunodeficiency Virus (HIV) infection has declined dramatically. However, the rate of new HIV infections has not changed. For example, the mortality among patients has declined from 29.4 per 100 person-years in 1995 to 8.8 per 100 person-years in the second quarter of 1997.¹ The incidence of opportunistic infections has declined from 21.9 to 3.7 per 100 person-years in the same time period but the rate of infection is estimated at 40,000 new infections/ year. The dramatic effects on morbidity and mortality depend on patients medically tolerating the components of HAART, strict compliance with medications, and maintained efficacy of the antiretroviral treatment. Randomized-controlled, clinical trials have shown that the maintenance of an undetectable viral load, which is measured by the reverse transcriptase-coupled polymerase chain reaction (RT-PCR) technology, leads to increased survival and less AIDS defining events.^{2,3} There are a number of reports suggesting that the immune^{4,5} system may also be reconstituted after prolonged therapy (greater than 1-2 years). These data highlight the value of maintaining absolute viral suppression for as long as tolerable. The current FDA approved lower limit of detection is < 500 HIV RNA copies/ml by PCR-RT. In a National Institute of Health (NIH)^{6,7} report defining the principals of therapy of HIV infection, and its update, at least a three drug regimen is recommended for all people with the Acquired Immunodeficiency Syndrome (AIDS). Patients without 3 symptoms, but with CD4 T cells < 500/mm³, or, an HIV RNA > 20,000 copies/ml should also be offered treatment. Patients without symptoms and have > 500 CD4 T Cells and HIV RNA < 20,000 copies/ml may be offered treatment but some experts would wait and observe off therapy until either the CD4 count fell or the viral load increased.

There are a significant number of patients who fail first-line therapy. While many definitions of failure exist, typically the goal is to get the viral load below detectable limits and failure in not meeting this -defining illness or death. In one of the initial studies that documented the benefit of a threegoal, an AIDS 2 drug regimen over a two-drug regimen, the number of people who failed was 40%. In a similar randomized, controlled, study, the failure rate was 10%.³ When patients are followed in prospective cohorts studies, the number of people who maintain an undetectable viral load ranges from 30-50% at six months to one year.^{8,10} While there are 12 approved drugs for the treatment of HIV Infection, resistance to one drug in one class may confer resistance to other drugs in the same class. Hence, a patient's chance of sustained viral suppression is maximal the first time they are treated. The current recommendations for first-line HAART suggest a protease inhibitor (PI) be combined with two drugs of the nucleoside reverse transcriptase inhibitor class (NRTI). A third class of drugs used is the non-nucleoside reverse transcriptase inhibitors (NNRTI). However, the first two drugs in this class are not generally recommended as first-line therapy because the chance of a durable response is less than when a patient is on a regimen with a pl.^{6,1}

For the clinician, there is little randomized, controlled data to guide treatment in the patient who fails first-line HAART. At the AIDS Conference in Geneva (June 28 - July 3, 1998), several investigators have examined salvage HAART for people with extensive prior antiretroviral experience. For many patients, they have been switched from mono-therapy to double, then triple therapy and have tried multiple PIs and at least one NNRTL. When this group of patients is given four or five drugs, the percent

of people who have an undetectable viral load is approximately 25% at 16 to 24 weeks. The rate of adverse events, either clinically, or, from the laboratory, has been as high as 34-92%¹¹. Given the difficulty in compliance with multiple drugs and the danger of drug resistance, the simplest regimen to take with the best efficacy is the most desired goal. Currently, there is no randomized, controlled trial looking solely at people who have failed their first HAART. There is one small series of patients given a salvage therapy of ritonavir plus saquinavir reported. Only 4/14 (29%) patients had a sustained response.

However, a recent randomized trial using a new drug in the NNRTI class, called efavirenz, has shown surprising efficacy when used as first-line HAART. One group of patients received standard therapy: indinavir (a PI), zidovudine and lamivudine. The other group got zidovudine, lamivudine and efavirenz. The later group at 24 weeks had an undetectable viral load in 75% versus 54% in the PI group. The efavirenz group also tolerated their regimen better than the PI group. One flaw in the study was the high dropout rate in the PI group. It was also an open label design. However, these results suggest that a PI-sparing regimen with comparable efficacy may be possible to implement.

Therefore, this study examines two salvage therapies in people who have failed first line HAART that included the PIs indinavir or nelfinavir. In addition, subjects should be naive to the NNRTI class of drugs. Subjects would be randomized to either an efavirenz + two new NRTIs or saquinavir + ritonavir + two new NRTIs. Patients will be followed for one year and the percent of patients who remain with undetectable viral load will be compared between the groups.

B. Study Design and Statistical Analysis

This is a multi-center, randomized, double blind, phase II study of the efficacy of the two arms of the salvage therapy. The first arm will contain two new NRTIs + efavirenz, the second arm will have saquinavir + ritonavir + two new NRTIs. The patients enrolled in the study will be on a PI-containing regimen including nelfinavir or indinavir plus two NRTIs and they must have failed this therapy. Pretreatment failure is defined as detectable viral load (> 500 HIV RNA copies/ml by PCR-RT), measured at least twice. The second viral load must be at least $> 20,000$ HIV RNA copies/ml. Each measurement must be at least 7 days apart and no more than 30 days apart. The patient must not have had an illness during these viral RNA determinations or had an immunization within the past month.

Assuming that a response rate of approximately 30% of the patients in the double PI arm maintain an undetectable viral load at six months, then this study is designed to find a 10% increase in efficacy in the efavirenz arm. Assuming 80% power, and alpha of 0.05 for a two-tailed test of the difference between two proportions, each arm will need 500 subjects. The groups can be compared using Kaplan-Meier survival analysis. Subjects who do not attain an undetectable viral load at 16 weeks or who have not shown at least a 2 log decrease in viral load will be considered failures. These subjects may crossover to the other treatment arm at that time or withdraw from the study.

Patients who exhibit toxicity to the study medications may require a change in dose of a drug. If the adverse event is severe enough that the physician must change the medications then the subject will still be kept blind to the study medications. The appropriate change will be made.

C. Study Procedures

At baseline a complete history and physical exam will be taken. There will be a total of ten visits. Standard of care is a minimum of five visits. At the baseline visit, all records documenting the inclusion & exclusion criteria will be reviewed, the informed consent will be signed and labs will be drawn. After the baseline visit adverse events will be reviewed with the patient at each visit.

Baseline	History & Physical, CBC with differential, Chem20, amylase, lipase, HIV RNA, CD4 count, ICON
Week 2	History & Physical, pill count

Week 4	History & Physical, CBC with differential, Chem20 HIV RNA, CD4 count, pill count
Week 8	History & Physical, pill count
Week 16	History & Physical, CBC with differential, Chem20, HIV RNA, CD4 count, pill count
Week 24	History & Physical, CBC with differential, Chem20, amylase, lipase, HIV RNA, CD4 count, pill count
Week 32	History & Physical, pill count
Week 40	History & Physical, CBC with differential, Chem20, HIV RNA, CD4 count, pill count
Week 48	History & Physical, pill count
Week 52	History & Physical, CBC with differential, Chem20, amylase, lipase, HIV RNA, CD4 count, pill count

D. Study Drugs

Zidovudine: NRTI
 Lamivudine: NRTI
 Didanosine: NRTI
 Zalcitabine: NRTI Stavudine: NRTI
 Efavirenz: NNRTI
 Saquinavir soft gel cap: PI
 Ritonavir: PI
 Adefovir: a nucleotide RT inhibitor

E. Dose of Study drugs

Zidovudine 300 mg po bid
 Lamivudine 150 mg po bid
 Didanosine 200 mg po bid if weight < 60 kg; 400mg, po qd if weight > 60 kg
 Zalcitabine 0.375-0.75 mg po tid
 Stavudine 20-40mg po bid
 Efavirenz 600mg po qhs
 Saquinavir soft gel cap 400 mg po bid
 Ritonavir 400 mg po bid
 Adefovir 60mg po qd or 120 mg po qd + L-carnitine 500 mg po qd

F. Medical Devices

None.

G. Study Questionnaires

None.

H. Study Subjects

- a. Inclusion criteria**
- Documented HIV positive serology

- Previous document history of at least 16 weeks of HAART including nelfinavir or indinavir and at least two NRTIs.
- These patients must have two documented detectable HIV RNA viral loads > 1000 copies/ml. Each measure must be done at least seven days apart but no more than 30 days apart.
- The patient must not have been clinically ill with and AIDS defining illness during these viral load assessments or had an immunization .5
- A negative pregnancy test and a method of contraception

b. Exclusion criteria

- Previous use of saquinavir, ritonavir or any NNRTI.
- Current malignancy 8.2.3 Pregnancy
- A absolute WBC < 1000 8.2.5
- A total WBC < 2000 Platelets < 60,000 8.2.7
- AST or ALT > three times the normal value 8.2.8
- Creatinine > 1.5 8.2.9
- Alleraies to any of the study medications

I. Recruitment of Subjects

Subjects will be recruited from the HIV/AIDS clinic at the Columbia Presbyterian Medical Center. Other center from the ACTG will be asked to participate.

J. Confidentiality of Study Data

All data with be confidential as per the policies at each institution. Each patient and their physician will be blinded to the treatment arm. Only the Data Management center located at CPMC will know the unblinded data.

K. Potential Conflict of Interest

None.

L. Location of the Study

Initially at CPMC then at other institutions in the ACTG.

M. Potential Risks

Drug toxicity from the study medications which can include organ failure and death.

N. Potential Benefits

The major benefits include prolonged life, decreased number of AIDS defining opportunistic infections and potential immune restitution.

O. Alternative Therapies

There are many alternative drug combinations possible. However, it is not known which of the combinations is the best combination.

P. Compensation to Subjects

None.

Q. Costs to Subjects

Subjects will be provided with the study drugs free of charge or thire insurance will pay for all these FDA approved medications. Subjects will have to provide their own transportation to the study center.

R. Minors as Research Subjects

No patients under the age of 18 will be allowed to enrolled.

S. Radiation or Radioactive Substances

Not applicable.