

Inpatient versus Outpatient Treatment Initiation for High-Risk HIV Populations: a Prospective Randomized Controlled Trial Investigating Optimal Timing for Instatement of HAART

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A. Study Purpose and Rationale

Although numerous studies have reported increased mortality among HIV-positive patients who begin highly active antiretroviral therapy (HAART) only after their CD4 counts fall below 200 (1,2), the initiation of HAART among hospitalized patients even with extremely low CD4 counts typically is delayed until outpatient follow-up and patient adherence can be established. Current guidelines from the National Institutes of Health (NIH) highlight this tension, affirming that all patients with CD4 counts less than 200 should be started on antiretroviral therapy, but simultaneously asserting that “the likelihood of patient adherence to a long-term drug regimen should be discussed and determined by the patient and clinician before therapy is initiated” (3). However, given that overall in-hospital mortality for HIV-related hospitalizations has been reported as approximately 12% (4), the possibility of reducing inpatient deaths by initiating HAART during hospitalization has been minimally studied. A small retrospective cohort study in 2003 by Morris et al. (5) noted that patients requiring intensive care for *Pneumocystis carinii* pneumonia (PCP) experienced a reduction in mortality from 63% to 25% if they were either receiving HAART at the time of admission or were started on HAART while hospitalized. While this study was not randomized, it does seem to support the implementation of HAART as a potentially life-saving measure among critically ill HIV patients. The need for prospective studies to clarify this question is clear.

This study will examine a slightly healthier group of patients: HIV-positive inpatients who are not requiring ICU-level care, but who, despite CD4 counts less than 200, are not taking antiretroviral therapy. This subgroup of patients likely includes some of the highest-risk populations among HIV-positive patients: they have essentially failed outpatient management, likely due to some combination of noncompliance, comorbid illnesses, social stressors, and the conclusion by their outpatient physician, if they have one, that they will be unable to adhere to treatment. Indeed, patients with CD4 counts less than 200 have been shown to have a two-year mortality rate of approximately 20% (1). This study's hypothesis is that patients with CD4 counts less than 200 who are randomized to early initiation of HAART, while they are inpatients, will experience improvements in both their 30-day and 2-year mortality rates compared with those randomized to the standard of care, in which they will be started on HAART after discharge in an outpatient clinic.

B. Study Design and Statistical Analysis

The study will be a multi-center trial involving five sites in the United States, and will recruit 1735 patients for enrollment.

Subjects will be randomized to two arms, one of which will start HAART in the hospital and the other of which will be the traditional “standard of care” arm, in which patients will be encouraged to go to clinic and to start HAART as an outpatient following discharge. The randomization will be stratified by age and by presence or absence of active IV drug use, because both of these factors have been independently associated with increased mortality among HIV patients (6). Patients will be given whichever of the approved HAART regimens is deemed optimal for them (based on individual characteristics including comorbidities, concurrent medications, adherence potential, and history of prior

antiretroviral therapy) by either the inpatient ID attending or their outpatient ID physician, and each regimen will be checked by the study coordinators prior to medication administration to ensure that it is among the current optimal treatment regimens described by the NIH (3). On discharge, both groups of subjects will be encouraged to follow up in an HIV outpatient clinic for the continuation or initiation of HAART.

Patients will be followed from their index date of randomization to primary endpoints of 30-day and 2-year mortality. Based on an estimated in-hospital mortality rate of 12%, this study would need to enroll 1735 patients in order to have 80% power (at $p=0.05$) to detect a 3% difference in 30-day mortality. This number of patients would also provide 80% power with a p of 0.05 to detect a 3% difference in 2-year mortality, which is estimated from a previously-reported value of 20%. A chi-square test will be used to determine mortality differences between the two groups, with a multivariate logistic regression model to investigate the effects of homelessness, gender, CD4 count at the time of study enrollment, viral load at time of study enrollment, and comorbid illness as quantified by the Charlson Comorbidity Index (7) using ICD-9 codes (8).

C. Study Procedure

Patients admitted to CPMC who meet the criteria for enrollment in this study will be approached by the study team following a referral from their inpatient care team. If they provide informed consent to participate in the study, they will be randomized either to begin HAART the following day, or to be followed by the study group and to begin HAART as an outpatient. These groups will be matched by age within 2 years and by active substance abuse (defined as using any illicit drug at least once weekly within the month prior to hospital admission). Patients will also be asked about housing status at the time of randomization. Charlson Comorbidity Index will be calculated from ICD-9 codes, and no additional blood draws will be necessary provided that the patient's CD4 count and viral load have been measured on this hospitalization.

On discharge, the patients will be given a follow-up appointment with an outpatient Infectious Disease physician, and will be encouraged to follow up either by continuing HAART or by beginning HAART in the near future. Patients' charts will be reviewed for the two years following randomization to the study. They will not be required to participate in any additional visits, blood draws, or procedures.

While each individual patient's participation in the study will last just two years, the study itself will likely require slightly less than 7 years total (5 years of recruitment, given that each center will be expected to recruit approximately 75 patients per year, with two years for follow-up following enrollment of the final patient).

D. Study Drugs

The only treatment drug regimens that will be used in this study will be those that are included among the current recommendations for treatment of HIV infection. This includes approximately 20 medications that fall into four general classes. Side effects for antiretroviral medications are numerous and vary from mild to severe, but the drugs are tested rigorously and recommendations by the NIH are updated frequently.

E. Medical Device

No medical devices will be used in this study.

F. Study Questionnaires

No questionnaires will be used in this study.

G. Study Subjects

Patients eligible for the trial will be inpatients hospitalized at New York Presbyterian-Columbia Campus who have CD4 counts of less than 200, who are either HAART-naïve or who have not taken HAART for the past six months. While patients who are in the intensive care unit will not be eligible for study participation, those patients who have been transferred from an ICU and remained on a medical floor for greater than 48 hours will be eligible for inclusion in this study. Patients with new diagnoses of HIV during the same hospital admission will be included in the study as they also in some way represent a high-risk group in which HIV was not diagnosed until it had progressed to an advanced stage of disease. Patients must be able to give consent for their participation in the study.

Patients who are unable to take medications by mouth will be excluded from this trial, as will patients less than 18 years of age. No patients will be excluded on the basis of gender, race, ethnicity, concurrent illness, or substance abuse.

H. Recruitment of Subjects

Subjects will be referred by their inpatient physicians for participation in this study. After verifying that the patient is willing to discuss the study with the research team, the study investigator on call will approach the patient in order to explain the study and to obtain informed consent.

In order to increase housestaff referrals, a brief overview of the study will be presented for the first 15 minutes of noon conference, with an emphasis on patient eligibility and ease of referral to the study. A clinical investigator will also present the study briefly to rotating housestaff teams on the infectious disease service every four weeks, when a new team of interns begins the clinical rotation. All members of the housestaff will be given a pocket card detailing inclusion criteria and study protocol. One of the study investigators will be available by pager at all times in order to answer questions and collect referrals in conjunction with the study.

I. Confidentiality of Study Data

Study data will be coded and labeled only with a unique identifier, in accordance with IRB standard procedures. The key to the code will be stored in a separate, secure location from study data that will be accessible only to the study investigators.

J. Potential Conflict of Interest

None.

K. Location of the Study

This will be a multicenter trial, and to be conducted in five academic hospitals in the United States. The study itself will occur both in the inpatient units of each hospital, as well as in their outpatient infectious disease clinics.

L. Potential Risks

Because outcomes are unknown, it is possible that patients randomized to begin HAART while they are hospitalized may experience worsened mortality or progression of their disease compared with those in the other group. In particular, patients randomized to begin HAART in the hospital who subsequently do not continue therapy as outpatients will be at risk for development of viral resistance, which may cause their HIV disease to be more difficult to treat adequately in the future. It is possible that this problem could ultimately cause this nonadherent subgroup of patients to have an increased mortality

compared with those in either group who do adhere to medications, or even compared with those who never start HAART at all.

Patients who begin HAART in either group will be at risk of experiencing a wide variety of side effects from these antiretroviral medications; between 25 and 50% of patients taking HAART report side effects. These range from mild to severe in nature, and different risks are associated with different medications and medication combinations. Several of the more common side effects include nausea, diarrhea, rash, fat redistribution, fatigue, insomnia, loss of appetite, elevated cholesterol, numbness in the hands and feet, headache, kidney damage or kidney stones, impairment of the bone marrow, dizziness, and elevated blood sugar. Rarer and more serious complications of some of these medications include extreme sensitivity to a particular medication, lactic acidosis (development of blood acidity, which can have serious organ-damaging complications), damage to the liver which may be irreversible, inflammation of the pancreas, and death. It is important to note that the Federal Drug Administration (FDA) and the National Institutes for Health carefully monitors drug reactions and toxicities, and alters its recommendations as new data emerges. Moreover, the potential of these medications to provide potentially live-saving treatment is felt by these governing bodies to outweigh the risks that may occur with their administration.

M. Potential Benefits

This study hypothesizes that patients randomized to begin HAART during their hospitalization will experience a reduction in both their 30-day and 2-year mortality rates. HAART has been shown to prolong life, increase CD4 counts, decrease hospitalizations, and improve quality of life in patients who take this medication correctly, so this study will potentially benefit all study participants who begin and continue HAART for treatment of their advanced HIV disease.

N. Alternative Therapies

The study drugs are not experimental, and initiation of antiretroviral therapy recommended by the NIH for treatment of patients who have CD4 counts less than 200.

O. Compensation to Subjects

Subjects will not be compensated monetarily for their participation in this trial; however, their antiretroviral therapy will be provided free-of-charge for the duration of the study. Patients will also be given routine follow-up and treatment by outpatient infectious disease physicians at no cost, regardless of insurance status.

P. Costs to Subjects

None.

Q. Minors as Research Subjects

No minors will participate in this study.

R. Radiation of Radioactive Substances

None.

S. References

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- (5) Morris A, Wachter RM, Luce J, Turner J, Huang L. Improved survival with highly active antiretroviral therapy in HIV-infected patients with severe *Pneumocystis carinii* pneumonia. *AIDS* 2003; 17:73-80.
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**Columbia Presbyterian Medical Center
Consent to Participate in a Research Study**

The purpose of this consent form is to provide you with the information you need to consider in deciding whether to participate in this research study.

Study Title: Inpatient versus Outpatient Treatment Initiation for High-Risk HIV Populations: a Prospective Randomized Controlled Trial Investigating Optimal Timing for Instatement of HAART

Study Purpose

You are invited to participate in a research study in which differences in benefits related to the time that highly active antiretroviral therapy (HAART) is started for the treatment of patients with advanced HIV disease will be studied. Current recommendations from the National Institutes of Health state that all patients who have CD4 (T-cell) counts less than 200 should be started on HAART. The guidelines also suggest that patients should start HAART after they, together with their outpatient physician, feel that they will be able to take the medications as prescribed, without missing doses. However, because a small but significant percentage of patients who are hospitalized for HIV-related reasons may die while in the hospital, recent studies are beginning to investigate whether patients who are started on HAART while they are hospitalized may have better outcomes. The purpose of this study is to compare the outcomes between two groups of patients with advanced HIV disease who agree to start HAART. Patients will be randomly divided into two groups, and one of these groups will begin taking HAART in the hospital. The other group will be encouraged to begin HAART under the supervision of their outpatient physician after they are discharged from the hospital. This study plans to enroll 1735 patients at five academic hospitals throughout the United States.

You were referred by the physicians taking care of you during this hospital stay as a patient who would qualify for participation in this study. You qualify as a possible participant because you have a CD4 (T-cell) count of less than 200 and either have never taken HAART, or have not taken HAART in the past six months. You also qualify as long as you are not in the intensive care unit now, and as long as you have been out of the intensive care unit for at least 48 hours.

Study Procedures

If you agree to participate in this study, you will first be given a random identification number, and from this point on, the code to link your study information to your personal identifying information will be kept in a secure, locked location. You will then be assigned by chance to one of two groups: either to the group that will start HAART treatment the day after you agree to participate, or to the group that will be encouraged to start HAART after discharge from the hospital. In either case, the specific HAART regimen you start will be chosen as the optimal one for you by board-certified Infectious Disease physicians (either those involved in your hospital care, or your outpatient physician) in conjunction with the guidelines from the National Institutes of Health. Regardless of which group to which you are assigned, you will be given follow-up appointments with an outpatient Infectious Disease specialist. This person will coordinate your care and start or change your HAART medications as necessary.

You will permit the study investigators to have access to your records and your personal data both prior to this hospitalization and for the next two years after you agree to participate in this study. You will have no questionnaires, extra blood tests, or other requirements for participation in this study. We will ask you at the time you sign the consent form whether you are an active IV drug user (defined as using illegal drugs at least once a week for the month leading up to this hospitalization), what your race/ethnicity is, and whether you have housing difficulties (defined as living on the street, living in a shelter, or living in an SRO) for the purposes of making sure that differences among the two groups of patients in this study are not the cause of differences in their outcomes.

Study Risks

Your participation in this study involves the risk that the study group to which you are assigned will not do as well as the other group. If this does happen, there is a possibility that your condition may worsen as a result. In addition, between one quarter and one half of patients who take antiretroviral medications experience side effects, and these range from mild to severe in nature. Several of the more common effects include nausea, diarrhea, rash, fat redistribution, fatigue, loss of appetite, elevated cholesterol, numbness in the hands and feet, headache, kidney damage or kidney stones, impairment of the bone marrow, dizziness, and elevated blood sugar. Rarer and more serious complications of some of these medications include extreme sensitivity to one particular medication, lactic acidosis (development of blood acidity, which can have serious organ-damaging complications), damage to the liver which may be irreversible, inflammation of the pancreas, and death. It is important to note that not all medications have risks of causing all of these effects, and that the National Institutes for Health carefully monitors drug reactions and alters its recommendations as new data emerges. If you would like, we will be happy to provide you with information from the National Institutes of Health regarding specific risks associated with each drug.

Study Benefits

You may or may not benefit personally from this study. Benefits to you may include prolonged life, a slower progression of your HIV disease, increased CD4 (T-cell) counts and decreased viral loads, decreased need for repeat hospitalizations, and improvement in your overall wellbeing and quality of life.

Benefits to society as a result of your participation may include a better understanding of how best patients with low CD4 counts who are not taking HAART medications can be treated, which may ultimately prolong life for countless people worldwide suffering from HIV/AIDS.

Alternatives

If you choose not to participate in this study, you will still be given a follow-up appointment with an outpatient Infectious Disease specialist, who may decide to recommend HAART treatment. You do not have to participate in this study to start HAART treatment as an outpatient. The risks associated with the medications remain unchanged. If you choose not to participate in this study, you also have the alternative of not starting antiretroviral therapy at all.

Costs

There are no costs to you as a result of participating in this study.

Compensation

You will not receive any money for participating in this study, but you will receive free HAART medications beginning either in the hospital or in the outpatient clinic following discharge. The free medications will continue for the entire two years that you participate in this study. You will also receive free treatment by an Infectious Disease specialist for the two years that you participate in this study.

Confidentiality

Any information obtained during this study and identified with you will remain confidential. All of your information will be coded by a unique identification number, which will be stored in a secure location that is separate from the study data that we collect. The Federal Drug Administration (FDA) may have access to medical records related to this study in order to permit monitoring of the effects of medications.

Participation is Voluntary

Your participation in this study is voluntary. You can refuse to participate, or can freely withdraw from the study at any time. Either of these decisions will in no way affect your medical care at Columbia-Presbyterian Medical Center or at any of the other academic institutions participating in this study, now or in the future. Signing this form does not waive any of your legal rights.

If you do choose to withdraw from this study, we will do our best to ensure that you are able either to continue to see your outpatient Infectious Disease physician, or to have your records sent to another physician of your choosing. If you develop adverse reactions to medications, you may continue to participate in this study; your physician will work with you to change and/or adjust medications as needed. Any new findings which may affect your willingness to continue in the study will be communicated to you.

Questions

If you have any questions, please ask, and we will do our best to answer them. If you have additional questions in the future, you can reach Dr. Downs at _____ at any time. If you have any questions on your rights as a research subject, you can call the Institutional Review Board at (212) 305-5883 for information.

Statement of Consent

I have discussed this study with _____ to my satisfaction. I understand that my participation is voluntary and that I can withdraw from the study at any time without prejudice. I have read the above and agree to enter this research study. Signing this form does not waive any of my legal rights.

I have been informed that if I believe that I have sustained injury as a result of participating in a research study, I may contact the Principal Investigator, Dr. Downs, at _____, or the Institutional Review Board at (212) 305-5883, so that I can review the matter and identify the medical resources which may be available to me.

I understand that:

- a) The Presbyterian Hospital will furnish that emergency medical care determined to be necessary by the medical staff of this hospital;
- b) I will be responsible for the cost of such care, either personally or through medical insurance or other form of medical coverage;
- c) No monetary compensation for wages lost as a result of injury will be paid to me by Columbia-Presbyterian Medical Center, and;
- d) I will receive a copy of this consent form.

Signatures:

Participant	Date
Investigator Eliciting Consent	Date

The solicitation of subjects into this study has been approved by the Columbia-Presbyterian Medical Center Institutional Review Board.