The Effects Of Antiretroviral Therapy On Bone Mineral Density In Hiv Infected Patients

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A. Study Purpose and Rationale

The introduction of highly active antiretroviral therapy (HAART) in recent years has dramatically improved the prognosis of patients infected with HIV. As a result, several complications of long term HIV infection as well as metabolic complications related to these new medications are emerging. Among these complications are alterations in bone metabolism and subsequent changes in bone mineral density.

Several studies before the era of HAART have examined the association between HIV infection and bone metabolism, by utilizing markers of bone turnover as well as measurements of bone mineral density (BMD). Decreased rates of bone formation, as well as increased rates of bone resorption have been reported using biochemical and histomorphometric data. In addition, levels of osteocalcin, a marker of bone formation, and 1,25 (OH) Vitamin D have both been found to correlate with CD4+ lymphocyte count.

The majority of studies examining BMD changes in HIV infected patients have found lower values for BMD in HIV patients compared with controls. The mechanism of bone loss in these patients has yet to be elucidated. Factors including decreased physical activity, malnutrition and hypogonadism all contribute to bone loss in this population, particularly in those patients with advanced AIDS.

Several recent studies of the relationship between HAART, protease inhibitors in particular, and bone metabolism have yielded conflicting results. Although many researchers have found decreases in BMD, particularly at the lumbar spine, in patients taking HAART, others have not found significant changes. It has been suggested by that observed differences in BMD may be related to duration of infection and changes in body mass index. One recent study found that patients with HIV taking the protease inhibitor indinivir had increased BMD. Most of these studies are small cross-sectional analyses, further complicating interpretation of their results.

In this study, the effects of HAART on bone metabolism will be further elucidated using newly diagnosed, treatment-naïve HIV patients with CD4 counts >300. Changes in BMD will be measured in those started on HAART and compared with those who are not over a two year period. Using this relatively healthy population and longitudinal design will better control for some of the above mentioned confounding factors. The study hypothesis is that patients taking HAART will have decreased BMD when compared to controls at the end of a two year period.

B. Study Design and Statistical Analysis

In this prospective longitudinal study, subjects will be divided into two parallel arms, those receiving HAART and those not receiving any treatment. The decision whether or not to begin treatment will be made by each patient and their physician, prior to study enrollment. In the population of HIV patients with CD4 counts above 300 the decision to start treatment is complex and based upon several factors including viral load, co-morbid illnesses as well as patient and physician preference. While many patients in this group are started on treatment, a significant number elect to wait until they exhibit signs of disease progression, and these patients will serve as the control group for this study. Equal numbers of patients in each group will be recruited.

The number of subjects included in this study is limited by the relatively small number of newly diagnosed patients with HIV seen each month at our medical center. We can expect to recruit approximately 40 patients total for the study, approximately 25 currently in our system, not yet treated and approximately 2 or 3 patients diagnosed each month, according to information provided by the HIV

clinic. Because of this size limitation, a power analysis was performed to determine detectable effect size based upon a set number of 20 subjects per group. The formula for the unpaired student's t-test with a power of 80% and $p<0.05$ was utilized. Based upon normative lumbar spine bone mineral density from current literature, a value of 1.22 +/- a standard deviation of 0.12 was used in this calculation. It was determined that an effect size of 0.15 or 13% could be detected. This change, given the presumed normal BMD of our population at baseline, was felt to be clinically significant.

There is expected to be a small amount of cross-over in this study. Subjects in the group not receiving treatment may begin treatment for various reasons during the two year period, including clinical deterioration. As a result, the actual effect will be larger than the observed effect in this study.

The statistical analysis in this study will be performed using an unpaired student's t-test and subsequently an ANOVA to control for possible confounding differences between the groups including age, gender and ethnic background.

C. Study Procedure

Upon enrollment in the study, demographic information including age, gender, and ethnic background will be collected on all participants. Data on height and weight will also be collected. Subjects will provide information regarding medical history and current medications. They will be asked to update their medication lists every six months. Initial BMD measurements will be made from the lumbar spine L2-L4 and right total hip using dual X-ray absorptiometry scans. These scans will all be performed by the same technician and read by the same individual, who will both be blinded to study groups. BMD will be classified according to the World Health Organization (WHO) Criteria, defining osteopenia as a T score, compared with a young adult of the same gender, of <-1.0 and osteoporosis as a T score of <-2.5. Blood samples will also be collected upon entry for measurement of calcium, phosphorus, intact parathyroid hormone, 25(OH)D, 1,25(OH)D and osteocalcin. Urine samples for N-telopeptide will also be collected. Initial Viral load, (HIV RNA by measured by reverse transcriptase polymerase chain reaction assay) and CD4 counts will be determined on all patients. Repeated measurements of BMD, the above described biochemical markers of bone metabolism, CD4 count and viral load will be taken at six month intervals over a two year period. The usual duration of CD4 and viral load monitoring in these patients is every three months. The other laboratory analyses would not otherwise be done in this population. The total length of the study is expected to be approximately three years, as each subject's participation will be for two years and it will require approximately one year to recruit the desired number of subjects.

D. Study Drugs

The following antiretroviral medication regimen will be used in the study:

1. Trizivir (Zidovudine, Lamivudine, Abacavir)
2. Combivir(Zidovudine and Lamivudine) and Nelfinivir
3. Combivir and Kaletra (Lopinivir and Ritonovir)
4. Combivir and Efavarenz

These medications have all been approved for use in HIV infected patients. The method and route of administration, as well as the dosage regimen, utilized in this study are standard. Please refer to the attached documents for detailed information regarding the safety profiles of these drugs including their known side effects and expected frequency.

E. Medical Device

Not applicable.

F. Study Questionnaires

As described above, demographic information as well medical history and medication will be collected on all patients. In addition, every 6 months patients will complete questionnaires measuring medication compliance as well as dietary intake of calcium and vitamin D, see appendix B.

G. Study Subjects

Subjects for this study will be selected from the patient population of Columbia Presbyterian Medical Center. Eligible subjects will include men and women between the ages of 18 and 45 who are HIV positive as determined by an enzyme-linked immunosorbent assay (ELISA) and confirmed by a Western Blot. In order to participate in this study, patients must have blood CD4+ lymphocyte counts greater than 300 at the time of entry and be treatment naïve in regards to antiretroviral therapy. Exclusion criteria for this study will include: recent history of extended bed rest or immobility, previous diagnosis of metabolic bone disease, renal failure, end stage liver disease, endocrine disease, hypogonadism, and moderate to severe malnutrition, 20% or more beneath their ideal weight. In addition, patients taking medications known to affect bone metabolism, including bisphosphonates, vitamin D, glucocorticoids, anticonvulsant medications, anti-coagulants, fluoride and lithium will be excluded.

H. Recruitment of Subjects

Subjects will be recruited by referral from the practitioners in the HIV clinic, as well as flyers placed around the medical center.

I. Confidentiality of Study Data

All data will be organized according to unique study numbers assigned to each patient in order to ensure patient confidentiality.

J. Potential Conflict of Interest

There is no conflict of interest for the investigator of this study.

K. Location of the Study

This study will be conducted at the Columbia Presbyterian Medical Center, in the HIV clinic as well as the bone mineral density unit.

L. Potential Risks

This study involves minimal risk to patients, through measurement of BMD, see below, as well as serial blood draws five times during the course of the experiment.

M. Potential Benefits

There are several potential benefits to participants in this study. Any subject who has a BMD in the osteoporotic range (T score <-2.5) will be referred to osteoporosis specialists at our institution for further management and treatment. Since participants and their physicians will determine treatment regimen prior to study entry, observed changes will occur regardless of study participation. Therefore, our study will provide patients with screening tests to which they would otherwise not have had access. Although individual patients may or may not benefit as a result of participation in this study, the results

may prove beneficial to the HIV population as a whole. If antiretroviral medications are shown to adversely affect bone density, appropriate changes can be made regarding screening, prophylaxis and treatment of osteopenia in this population.

N. Alternative Therapies

Not applicable.

O. Compensation to Subjects

Subjects will be compensated $200 for participating in this study. They will receive checks for $40 at the start of the study and at 6 month intervals until its completion.

P. Costs to Subjects

There will be no cost to subjects as a result of participating in this study.

Q. Minors as Research Subjects

Not applicable.

R. Radiation or Radioactive Substances

Patients will be exposed to a minimal amount of radiation during measurement of BMD through dual x-ray absorptiometry. These measurements will be taken at 6 month intervals a total of five times throughout the course of the experiment.

S. References

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Teichmann, J., Stephan, E., Discher, T. et al. Changes in calciotropic hormones and biochemical markers of bone metabolism in patients with human immunodeficiency virus infection. Metabolism 2000, 49:1134-1139.

Calcium Checklist

Record the number of servings you ate on a typical day in the last week.

Food Group	Servings # daily	X	Calcium (mg)
A. Milk and Dairy			
1 oz or 6 Tbsp. Cheese.		X 200	
½ cup Cottage cheese		X 50	
2 Tbsp. Cream cheese, nonfat		X 100	
1 cup Ice cream, frozen yogurt, or milkshake		X 200	
½ cup Custard, pudding, or cream pie		X 150	
1 cup Milk or cocoa		X 300	
1 cup Soy milk		X 10	
1 cup Calcium fortified soy or rice milk		X 300	
1 cup Yogurt		X 350	
1 cup Cream soups/sauces		X 200	
1 cup Macaroni & cheese; 1/8 of 5" pizza; 1/8 of 8" quiche		X 250	
Milk Total			_____ mg
B. Fruits and Vegetables			
½ cup Broccoli, cooked greens (beet, turnip, greens, kale, collards, spinach)		X 100	
½ cup Other vegetables		X 30	
½ cup or 1 small Fruit		X 30	
1 cup Calcium fortified orange juice		X 300	
5 medium Figs, dried		X 126	
½ cup Raisins seedless		X 48	
Fruit and Vegetable Total			_____ mg
C. Animal Protein, Beans, Nuts			
3 oz Meat, fish, poultry		X 10	
3 oz Salmon with bones		X 150	
3 oz Sardines with bones		X 400	
3 oz Shrimp or 7 – 9 oysters		X 100	
1 cup Dried beans, cooked (navy, pinto, kidney)		X 50	
½ cup Peanuts, 1 egg		X 30	
½ cup Soybean nuts		X 136	
½ cup almonds shelled		X 168	
1 Tbsp. Peanut butter		X 5	
4 oz Tofu		X 276	
Protein Total			_____ mg
D. Breads, Cereals, Rice, Pasta			
1 slice Bread, 1 oz cereal, 2" biscuit, 6" corn tortilla		X 20	
3" Muffin, corn bread, donut		X 40	
1 cup Rice, noodles, pasta		X 20	
1 medium Pancake, waffle, or French toast		X 100	
Bread Total			_____ mg

Bread Total			_____ **mg**
E. Other			
1/16 of 9" Cake		X 40	
12 oz Beer		X 10	
12 oz Cola		X 10	
1 oz Chocolate		X 50	
1 Tbsp. Blackstrap molasses		X100	
Other Total			_____ **mg**
Total A – E			_____ **mg**

Ref: Hartzler, PhD, RD and Fray, PhD. A Dietary Calcium Rapid Assessment Method (RAM) *Top Clin Nutr*, 1994;9(3):76-85.

The Irving Center for Clinical Research
Nutrition Unit

Vitamin D Content of Certain Foods
(Advanced Nutrition and Metabolism, Hunt & Groff)

Food	**Vitamin D content ("ug /100g)**
Nonfortified	
Butter	0.8
Milk- winter	0.03
Milk- summer	0.13
Cheese	0.2-0.3
Liver	0.1-0.2
Herring	22 .0
Canned pilchards	8.0
Tuna	6.0
Sardines	7.5
Fortified	
Milk (USA)	1.0
Margarine (USA)	11.0

To convert ug to IU: ug ÷ .025 = IU

BASELINE CLIENT INTERVIEW-SELF REPORT

HATS ID 10 UID 0504887118JA1 Close Form

Interview Date 4/7/1999 Interview Number Baseline Interviewer Ana Rojas

○ Check if client is not on Antiretroviral therapy

Step 1 Name of antiretroviral drugs	Step 2 # Pills each time (pills each dose)	Step 3 # times per day (doses per day)	How many doses did you miss.. (write "dk" if the response is don't know) Step 4 Yesterday	Step 5 Day before Yesterday	Step 6.... three days ago
Saquinavir	2	2	2	2	2
Ritonavir	1	2	2	2	2
Viramune	1	2	2	2	2