A Prospective, Randomized, Placebo-Controlled Trial of Alendronate for the Treatment of Osteopenia in Postmenopausal Women with HIV

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A. Study Purpose and Rationale

The advent of highly active antiretroviral therapy (HAART), in conjunction with improved standard prophylactic regimens, has dramatically changed the clinical course of HIV infection. As persons with HIV infection live longer, previously unknown metabolic complications of HIV infection have been coming to light. Paton et al. demonstrated, for the first time, a decrease in BMD in persons with HIV infection [1]; since then, a growing number of studies have been published which confirm this association.

Although the specific etiology and pathogenesis of low BMD in patients with HIV is not clearly understood, there are several postulated factors. These include the direct effect of the virus on osteogenic cells; expression of inflammatory cytokines, such as tumor necrosis factor-a (TNF-a), interleukin-1 (IL-l), and interleukin-6 (IL-6), which stimulate osteoclast differentiation [2]; alterations in the metabolism of vitamin D and its derivatives [3]; secondary effects on nutrition and weight loss of chronic disease and opportunistic infections; and a high incidence of established risk factors for osteopenia/osteoporosis in the HIV population [4].

The majority of studies that have reported an increased prevalence of reduced BMD among persons with HIV infection have been conducted in men. Fewer studies have focused exclusively in women. In one cross-sectional study of fifty ambulatory, normal weight, HAART-naive HIV+ women who were predominantly premenopausal, BMD was reduced as compared with age-matched HIV-negative controls [5]. Using BMD at the lumbar spine, and the World Health Organization (WHO) definitions of osteopenia (t-score -1.0 to -2.5 SD below normal) and osteoporosis (t-score < -2.5 SD below normal), 14 percent of HIV+ women had osteoporosis and 62 percent had osteopenia, as compared to none and 4 percent of HIV-negative women respectively. A larger cross-sectional study in 84 HAARTexperienced HIV+ women also demonstrated reduced BMD in women with HIV infection as compared to those who were NW negative [6]. The differences in BMD between the HIV+ and HIV- women in the lumbar spine (1.02 ± 0.02 versus 1.07 ± 0.02 g/cm^2, $p = 0.03$) and total hip (0.93 ± 0.01 versus 0.99 ± 0.01 g/cm^2, $p = 0.004$), though statistically significant, were relatively modest. However, these findings still translated to osteopenia being present in 54 versus 30 percent ($p = 0.004$) of HIV-infected versus control subjects, and in a multivariate model accounting for age, race, menstrual function, and body mass index (BMI), was 2.5 times more likely in women with HIV infection versus controls.

A recent cross-sectional study with a much larger study population of 263 women with HIV infection with 232 NW-negative controls with similar behavioral risk factors demonstrated similar results [7]. Femoral neck BMD and lumbar spine BMD were reduced in women with HIV infection, compared with women without HIV infection (femoral neck BMD, 1.01 ± 0.13 g/cm^2 versus 1.05 ± 0.13 g/cm^2, p -- 0.001; lumbar spine BMD, 1.21 ± 0.17 g/cm^2 versus 1.24 ± 0.17 g/cm^2, $p = 0.04$).

Finally, a cross-sectional study specifically in HIV+ postmenopausal women demonstrated a higher prevalence of osteoporosis in the 31 HIV+ women as compared with 186 historical controls, matched for age, ethnicity, and postmenopausal status (LS spine, 42 versus 23 percent, p 0.03; total hip, 10 versus 1 percent, $p = 0.003$) [8]. Among the women with HIV infection, time since menopause and weight were significant predictors of BMD, whereas duration or class of HAART, nadir CD4 count, and duration of HIV diagnosis were not.

In terms of treatment for osteopenia/osteoporosis in general, alendronate is a once-weekly bisphosphonate approved for the treatment of osteoporosis in both men and women. One trial in the

literature has looked at the use of alendronate in individuals with HIV and osteopenia/osteoporosis [9]. In this prospective, randomized trial, a total of 31 HIV-infected persons with evidence of osteopenia or osteoporosis (i.e., with LS spine BMD t-scores < -1.0 on DEXA) who had been on HAART for a minimum of 6 months were recruited from a large university AIDS clinical trial unit and the Infectious Diseases outpatient practice. Patients were then randomized to receive either 70 mg of alendronate once a week or no study drug for a total of 48 weeks; all subjects received calcium (1000 mg daily) and vitamin D (400 llJ daily) supplements. The results of this study demonstrated a significant difference between the two groups; alendronate in combination with vitamin D and calcium increased LS spine BMD by 5.2 percent (95% confidence interval: 1.3 to 6.4) at 48 weeks compared with an increase of 1.3 percent (95% confidence interval: -2.4 to 4.0) in subjects receiving vitamin D and calcium alone. Furthermore, there were no adverse effects seen with the use of alendronate in this population.

Given the high prevalence of osteopenia reported among HIV-infected individuals, the results of this study seem particularly promising. It is important to note however that the majority of subjects enrolled (almost 90 percent) were men. Therefore, this proposed study is designed as a prospective, randomized, placebo-controlled trial which aims to evaluate the efficacy and safety of alendronate in postmenopausal, HIV-infected women with osteopenia.

B. Study Design and Statistical Analysis

This study is designed *as a* prospective, randomized, double-blinded, placebo-controlled trial in postmenopausal women with HIV infection and evidence of osteopenia. It will evaluate the efficacy and safety of alendronate as part of a treatment regimen in such women. Approval by the hospital's institutional review board will be obtained.

There will be two study groups, one of whom will receive alendronate 70 milligrams *once a* week, the other group to receive a matching placebo. Both groups will receive calcium (1000 mg) and vitamin D (400 IU) supplements as per clinical standard-of-care. After informed consent is obtained by the study investigators, each subject will be randomized to either alendronate or placebo via computer-generated methods. Follow-up drug counts will be monitored by the designated pharmacist; he or she will also dispense the study drug and vitamin supplements for self-administration. The subjects, their physicians, and the study investigators will all be blinded to the subject assignments.

The primary outcome will be change in BMD at the LS spine after a 12-month period. Secondary outcomes will include change in BMD at the total hip, as well as changes in markers of bone metabolism (osteocalcin, bone-specific alkaline phosphatase, 25-OH-vitamin D, 1,25-OH vitamin D, N-telopeptide) after a 12-month period.

The power analysis and calculation of sample size is based on the primary outcome, change in BMD at the LS spine at 12 months. Using prior published data to estimate standard deviation of the change in LS spine BMD at 12 months in individuals taking calcium and vitamin D supplements, SD is set at 4.5%. Furthermore, the smallest difference (or treatment effect) of clinical interest (SDCI) was chosen to be a relative BMD change between the two groups of 3%. In clinical practice, and according to the American Society of Endocrinologists, it is common for a BMD difference of 3% to 5% at the spine to be considered clinically significant. Of note, precision error rates for DEXA are estimated at <1% for the anterior-posterior spine and 1% to 2% for the hip [10, 111

Therefore, in order for the study to have an 80% power to detect a 3% difference between the two groups, the average number of persons in each group should be 36. Using prior published data, the approximate drop-out rate for this particular population is estimated at 15%. Therefore, we will attempt to recruit approximately 45 subjects for each group. Statistical analysis will be performed using an unpaired t-test with alpha of 0.05.

Because the number of subjects in each group is relatively small, adequate randomization will necessarily be difficult. Therefore, to achieve appropriate randomization, patients will be stratified according to nadir CD4 cell count (<250 cells/nun^3 and >250 cells/m/11^3), a variable which has been

demonstrated in prior published studies to have a statistically significant effect on BMD in persons with HIV and osteopenia.

Finally, subjects in the alendronate group who discontinue the study drug, for whatever the reasons, will still be analyzed as part of the study drug group. Similarly, subjects in the placebo group who develop an indication during the course of the study to begin alendronate or another bisphosphonate, will still be analyzed *as* part of the placebo group. Thus, the analysis will be on an intention to treat basis.

In addition to nadir CD4 cell count, other confounding variables will be followed as well, including age, ethnicity, current or recent (<12 months) alcohol abuse, BMI, and duration of HIV diagnosis. Since all confounding variables will not be taken into account prior to randomization, a multiple regression analysis will be undertaken to determine those variables which are independent predictors of change in BMD.

C. Study Procedure

Subjects will meet with a study investigator at the time of enrollment in order to obtain informed consent and schedule all necessary follow-up visits, tests, and phlebotomy sessions. All subjects will have their blood drawn at time of enrollment for baseline data (basic metabolic chemistries, liver function tests, and complete blood counts). After informed consent is obtained, subjects will also have blood drawn for CD4 cell counts and HIV RNA viral loads. In addition, prior to enrollment, all subjects will undergo a dual-energy X-ray absorptiometry (DEXA) scan, and complete a medical and social history evaluation to determine eligibility. A radiologist who specializes in reading and interpreting DEXA scans at this institution will then determine which subjects meet the WHO criteria of osteopenia (t-score between -1.0 and -2.5 SDs) and therefore are eligible for inclusion in this study. This radiologist will be blinded to subject assignments. Furthermore, in order to minimize interobserver variability, this radiologist will also be the same person interpreting the follow-up DEXA scans at the conclusion of this 12-month study. Of note, subjects who are determined to have osteoporosis on the initial DEXA scan and therefore are not eligible for the study will have these results explained to them and transmitted to their primary medical care provider for further appropriate treatment; if the subject does not have a primary care provider, she will be given referrals for one.

Patients who are subsequently enrolled will receive additional clinical evaluations every 4 weeks for the first 8 weeks and then every 12 weeks thereafter to monitor for any adverse events. These clinical evaluations will be perforated by a blinded study investigator. All adverse events, including reasons for discontinuing study medications, will be reported by the investigators and will be monitored by an independent data safety monitoring board.

All subjects will have a DEXA at baseline and subsequently at 12 months after the end of the study. Of note, clinical consensus as well as recommendations from the American Society of Endocrinologists recommend following DEXA scans yearly for the first two years after initiation of treatment; measurements made sooner than a one year period are likely not clinically valuable *as* there will be a great deal of variability seen in this time period. Any subject who sustains a pathological fracture during the study period and is then determined to have osteoporosis on repeat DEXA scan and is not in the alendronate arm of the study, will subsequently be placed on alendronate for appropriate treatment. However, as mentioned above, the data from these subjects will still be included in the placebo group according to an intention to treat analysis.

Finally, bone metabolism parameters (osteocalcin, bone-specific alkaline phosphatase, etc.) will be obtained at baseline after an overnight fast, and subsequently at 24-week intervals (approximately 10 cc of whole blood per session). Safety laboratory parameters, including a complete blood cell count, serum electrolytes, and liver function tests, will be obtained at study enrollment and at 12-week intervals (approximately 6 cc of whole blood per session).

D. Study Drugs

Alendronate (FOSAMAX, Merck USA) is a nitrogen-containing drug *in* the bisphosphonate class. It is currently approved by the FDA for prevention of bone loss in recently menopausal women (for example, those with osteopenia), treatment of established postmenopausal osteoporosis, and treatment of glucocorticoid-induced osteoporosis.

The approved dosages of alendronate for treatment of postmenopausal osteoporosis are 10 mg orally daily or, as will be used in this study, 70 mg orally once a week. Of note, once-weekly dosing has been shown to be equivalent to daily dosing as reflected by changes in BMD and biochemical markers, and is more commonly used in clinical practice because of ease of dosing.

Participants in this trial will be fully instructed in the proper administration of alendronate; that is, it should be taken with plain water on an empty stomach, at least half an hour before the first food, beverage, or medication of the day. In order to avoid irritation of the esophagus, alendronate should be taken with approximately 8 ounces of water, and the patient should remain upright (seated or standing) until food has been eaten.

Alendronate has been shown in prospective, randomized, double-blind, placebo-controlled trials to prevent bone loss and increase BMD at the spine and hip by 5 to 10%. Alendronate therapy has also been show to reduce the risk of fractures of the spine and nonvertebral sites such as the hip and wrist by 40 to 50%. Furthermore, the effects of alendronate on BMD at the spine and hip are maintained for at least 2 years after use of the drug is discontinued in older patients.

Side effects of alendronate are generally mild and primarily affect the upper gastrointestinal system. In large-scale clinical trials, no apparent difference in tolerability has been noted between alendronate and placebo. In clinical practice, however, upper gastrointestinal symptoms such as heartburn, indigestion, and substemal discomfort can occur, and rare instances of esophageal erosion, ulceration, or bleeding have been described. Serious problems however have been reported only in approximately 1 in 10,000 (0.01%) of alendronate users and can often be explained by patient selection or dosing errors.

E. E Medical Devices

All subjects will have a DEXA scan at baseline and at the end of the 12-month study period. The DEXA machine used will be a QDR 4500 bone densitometer (Hologic, Waltham, MA, USA). DEXA is considered the gold standard for determination of BMD because it is the most extensively validated test for predicting fracture outcomes.

F. Study Questionnaires

Questionnaires will be administered at the time of enrollment by a study nurse/assistant, and will include relevant clinical and social history: duration of HIV diagnosis, age, ethnicity, smoking history, current and lowest weight, CD4 count (both current and nadir), viral load, history of HAART, and history of prior opportunistic infections.

G. Study Subjects

Eligible subjects include women over the age of 50 with a known diagnosis of HIV/AIDS and who meet defined hormonal or age criteria for postmenopausal status (age>50 and amenorrheic for at least one year, or serum follicular stimulating hormone [FSH] >30 mIU/nd, or FSH >20 mIU/ml with estradiol <30 pg/tnl, or age >55). Furthermore, subjects will have been maintained on HAART for a minimum of 6 months prior to enrollment. Subjects thus screened will then be enrolled based on the finding of osteopenia as defined by the WHO criteria on their initial DEXA scans.

Exclusion criteria include absolute or relative contraindications to bisphosphonates, including: peptic ulcer disease, esophagitis, prior allergic reaction to a bisphosphonate, or a creatinine clearance of <30 cc/minute (as defined by the Cocicrauft-Gault formula). Additional exclusion criteria include a known metabolic bone disorder (i.e., Paget's disease, multiple myeloma, Cushing's disorder, primary

hyperparathyroidism, hyperthyroidism), recent prolonged bed rest (>3 months), known malignancy, current opportunistic infection, current use of hormonal replacement therapy, or concurrent use of drugs with known effects on bone metabolism (i.e., heparin, foscamet, anticonvulsants, growth hormone, glucocorticoids).

H. Recruitment of Subjects

Patients will be recruited at Columbia Presbyterian Medical Center, both at the Associates in Internal Medicine (AIM) practice, as well as the Infectious Diseases Clinic. Based on each clinic protocol, flyers will be posted throughout public clinic space, and physicians will be reminded through flyers and emails. Patients will approach or be approached by their physicians for possible enrollment in this study. Subsequently, the subject will meet with a study investigator to discuss the study and to obtain informed consent.

I. Confidentiality of Study Data

All study data will be strictly confidential. Subjects will be identified by a unique code, and all patient identifying information corresponding to the subject's code will be kept in a secure, locked location.

J. Potential Conflict of Interest

There are no conflicts of interest in this study. None of the study investigators hold stock in or have been paid for lectures or endorsements by Merck, USA.

K. Location of the Study

CPMC, and potentially other HIV clinics in New York City.

L. Potential Risks

Patients will be made aware that they may be receiving a placebo instead of alendronate for the study period of 12 months. All subjects however will receive current clinical standard-of-care, vitamin D and calcium supplementation. There may be an increased risk of adverse GI side effects in subjects receiving alendronate as described above.

M. Potential Benefits

Patients will be made aware that they may or may not benefit personally from this study, i.e., in receiving vitamin D and calcium supplementation with or without alendronate in terms of BMD. The data accumulated will be beneficial for HIV-infected persons in general in regards to further understanding the effect of HIV infection on BMD and potential therapy.

N. Alternative Therapies

All study subjects will receive current clinical standard-of-care for osteopenia, vitamin 13 and calcium supplementation.

O. Compensation to Subjects

Patients will be compensated for travel costs by way of pre-paid metrocard. They will also receive a meal voucher for each visit.

P. Costs to Subjects

Subjects should not incur any costs for participation in this study. All costs for study visits, medications, laboratory testing, and DEXA scans, will be paid for by the study.

Q. Minors as Research Subjects

No minors will be involved as research subjects in this study.

R. Radiation or Radioactive Substances

Joint Radiation Safety Committee (JRSC) approval will be obtained for administration of DEXA scans. Radiation exposure to subjects during a DEXA scan is minimal, and less than that received from a chest X-ray.

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