IMPACT OF ORAL ALENDRONATE THERAPY ON BONE MINERAL DENSITY IN HIV-INFECTED CHILDREN AND ADOLESCENTS WITH LOW BONE MINERAL DENSITY

A Multicenter, Domestic Trial of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)

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and
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IMPAACT P1076 PROTOCOL TEAM ROSTER

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### GLOSSARY

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>3TC</td>
<td>lamivudine</td>
</tr>
<tr>
<td>ALN</td>
<td>Alendronate</td>
</tr>
<tr>
<td>ART</td>
<td>Antiretroviral therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral</td>
</tr>
<tr>
<td>AZT</td>
<td>Zidovudine</td>
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<tr>
<td>BMC</td>
<td>Bone Mineral Content</td>
</tr>
<tr>
<td>BMD</td>
<td>Bone Mineral Density</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BUA</td>
<td>Broadband ultrasound attenuation</td>
</tr>
<tr>
<td>D4T</td>
<td>Stavudine</td>
</tr>
<tr>
<td>DDI</td>
<td>Didanosine</td>
</tr>
<tr>
<td>DXA</td>
<td>Dual energy X-ray absorptiometry</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Efavirenz</td>
</tr>
<tr>
<td>EIA or ELISA</td>
<td>Enzyme immunoassay</td>
</tr>
<tr>
<td>FN</td>
<td>Femoral neck</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly active antiretroviral therapy</td>
</tr>
<tr>
<td>IGF-I</td>
<td>Insulin-like growth factor-I</td>
</tr>
<tr>
<td>I.U.</td>
<td>International Units</td>
</tr>
<tr>
<td>JON</td>
<td>Jaw osteonecrosis</td>
</tr>
<tr>
<td>LS</td>
<td>Lumbar spine</td>
</tr>
<tr>
<td>N.B.</td>
<td>Nota bene (please take note)</td>
</tr>
<tr>
<td>NFV</td>
<td>Nelfinavir</td>
</tr>
<tr>
<td>NTx</td>
<td>Cross-linked N-telopeptides of type I collagen</td>
</tr>
<tr>
<td>OCP</td>
<td>Oral contraceptive pills</td>
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<tr>
<td>OI</td>
<td>Osteogenesis imperfecta</td>
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<tr>
<td>OPG</td>
<td>Osteoprotegerin</td>
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<tr>
<td>PBM</td>
<td>Peak Bone Mass</td>
</tr>
<tr>
<td>PHACS</td>
<td>Pediatric HIV/AIDS Cohort Study</td>
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<tr>
<td>PHV</td>
<td>Peak Height Velocity</td>
</tr>
<tr>
<td>PI</td>
<td>Protease inhibitor</td>
</tr>
<tr>
<td>QCT</td>
<td>Quantitative Computed Tomography</td>
</tr>
<tr>
<td>QUS</td>
<td>Quantitative Ultrasound</td>
</tr>
<tr>
<td>RANKL</td>
<td>Receptor Activator for Nuclear Factor κ B Ligand</td>
</tr>
<tr>
<td>SOS</td>
<td>Speed of sound</td>
</tr>
<tr>
<td>TBLH</td>
<td>Total body less head</td>
</tr>
<tr>
<td>TDF</td>
<td>Tenofovir Disoproxil Fumarate</td>
</tr>
<tr>
<td>TH</td>
<td>Total hip</td>
</tr>
</tbody>
</table>
SUMMARY OF CHANGES


All changes in this version appear in boldface type. Major changes are listed below. Editorial changes, including corrections of typographical errors and other changes required to update information not affecting regulatory issues or the Sample Informed Consent may also be included. Information from Letter of Amendment #1 (July 14, 2009) and Letter of Amendment #2 (October 19, 2009) are included.

1. The protocol IND#, 105,570, is included on the cover page.
2. The team roster has been updated.
3. The glossary is updated.
4. The background and rationale are updated with additional data references.
5. Schema, the following language was added to the POPULATION section: “within the prior 12 months.”
6. Schema, Section 3.0, Section 4.15, Section 6.6, and Appendix I-A (footnote #9): The LS DXA BMD z-score eligibility criteria is changed from -2.0 (qualifying pre-study LS DXA and screening LS DXA) -1.8 (entry visit LS DXA) to -1.5.
7. Schema, Section 3.1, and Section 4.11: The upper age limit eligibility criterion is increased from < 21 years to < 25 years.
8. Section 1.0, Introduction (Background and Rationale), is modified to include additional reference data.
9. Section 3.2: The criteria for identifying subjects at high risk of low BMD are revised.
10. Section 3.2, Section 4.5, and Appendix I-A (footnote #1): Includes guidance on how to manage subjects with screening failures.
11. Section 3.2 and Section 6.3: Link to IMPAACT Unblinding SOP (SDM-4001-01) is updated to: http://www.impaactgroup.org/files/sops/SDM-4001-01.doc
12. Section 4.12: This inclusion criterion is updated to include the new IMPAACT HIV definition.
13. Section 4.5: Indicates that sites must have the ability locally to interpret DXA scans.
14. Section 5.0 and Appendix VI: The indication of “chewable” has been deleted from the description of the calcium/vitamin D formulation.
15. Section 5.2:
   • Indicates that other calcium/vitamin D formulations that appear equivalent in dosing of calcium and vitamin D may be permitted upon review and approval by the P1076 protocol team.
   • The following sentence is deleted from this section, “The calcium is derived from calcite and not from oyster shells.”
16. Section 6.3: The RCC website hyperlink is updated to: http://rcc.technology/safetyandpharmacovigilance/.
17. Section 6.6: for consistency, the following language was added to the first bullet in this section “within the prior 12 months”
18. Section 7.0: This section is updated with the revised adverse event language per DAIDS guidance.
19. Section 8.5: Indicates that the study will now monitor screening failures.
20. Section 9.0 (3rd paragraph, 1st sentence): Is revised to indicate that subjects eligible for this study must have a standardized LS BMD at least 1.5 standard deviations below average.
21. Section 9.1: References to Appendices are modified accordingly.
22. Section 9.21, Confidential Testing Results for Adolescents, is added.
23. Section 12.0: Includes additional references.
24. Appendix I-A (Footnote #8) and Appendix III: Additional guidance is provided regarding DXA scans.
25. Appendix I-A (Footnote #13): Is added to indicate that an optional Dentist Brochure (Appendix IV) can be completed at any study dental visit to relay dental related study findings to the subject’s primary dentist.
26. Appendix I-A (Footnote #17): The hyperlink to the P1076 Protocol Specific Webpage is updated.
27. Appendix I-A (Footnote #18): Includes a sentence indicating the timing of availability of entry LS DXA results.
28. Appendix IV- Dentist Brochure is added. Note: The addition of this appendix shifted the numbering of the subsequent appendices, which are adjusted accordingly.
29. Appendix V (Sample Informed Consent):
   a. “You/your child” is updated accordingly throughout the sample informed consent.
   b. INTRODUCTION (2nd paragraph, 5th sentence) is modified to read: “If you agree to take part or agree to allow your child to take part in this study, you will be asked to sign this consent form.”
   c. WHAT DO I/DOES MY CHILD HAVE TO DO IF I AM/HE/SHE/IS IN THIS STUDY? (Screening):
      - The 3rd bullet indicates that the subject will complete a form about smoking, which is estimated to take about 15 minutes to complete.
      - The last paragraph in this section includes the following additional sentence related to sharing of screening information: “Even if you/your child are/is not eligible to enter the study, the results of the screening tests will be used by the protocol team in their research on bone density in HIV-infected youth.”
   d. OTHER INFORMATION: The following sentence is added to this section: “Information provided throughout this study about smoking and alcohol use and sexual activity will not be shared with parents or caretakers of adolescent participants.”
   e. WHAT ARE THE RISKS OF THE STUDY? The risk list for alendronate is updated.
   f. ARE THERE RISKS RELATED TO PREGNANCY? The following paragraph is added as the last paragraph to this section: “Pregnancy test results will be
shared confidentially with participants, even if a parent or other adult is consenting for the child’s participation in the study. If the pregnancy test is positive, the study staff will refer pregnant participants to their primary provider for counseling about pregnancy and pregnancy care. [Sites should modify the preceding language about confidentiality of pregnancy test results to conform to their local practice, regulations and IRB requirements.]

30. Appendix VI (Sample Assent Form):
   a. If you agree to join this study, you will be asked to: the 6th bullet is added, and reads, “Information you provide in this study about sexual activity, smoking, and alcohol use will not be shared with your parents or caretakers without your permission.”
   b. If you are a girl who can become pregnant, then here is some additional information that you need to know: The 5th bullet is revised to read, Information you provide in this study about sexual activity and pregnancy test results will not be shared with your parents or caretakers without your permission. [Sites should modify the preceding language about confidentiality of pregnancy test results and sexual activity information to conform to their local practice, regulations and IRB requirements.]
SCHEMA

IMPACT OF ORAL ALENDRONATE THERAPY ON BONE MINERAL DENSITY IN HIV-INFECTED CHILDREN AND ADOLESCENTS WITH LOW BONE MINERAL DENSITY

DESIGN: Randomized, placebo-controlled, double-blind, pilot study

SAMPLE SIZE: 51 subjects (to ensure 45 evaluable subjects)

POPULATION: HIV-infected boys and girls, $\geq$11 to $<$ 25 years of age, no antiretroviral or on stable antiretrovirals, HIV infection acquired before puberty, and DXA lumbar spine BMD z-score $<$ -1.5 OR history of fragility fracture within the prior 12 months.

REGIMEN: Fifty-one subjects will be randomized equally into three Groups:
- Group 1a will receive alendronate for 96 weeks
- Group 1b will receive alendronate for 48 weeks followed by 48 weeks on placebo
- Group 2 will receive placebo for 48 weeks followed by 48 weeks on alendronate.

To ensure adequate balance in enrollment by gender, no more than 70% of the subjects can be one gender within each Group.

TREATMENT DURATION:
- Group 1a will receive alendronate for 96 weeks
- Group 1b will receive alendronate for 48 weeks followed by 48 weeks on placebo
- Group 2 will receive placebo for 48 weeks followed by 48 weeks on alendronate.

All three Groups will be followed off treatment for an additional 48 weeks.

STUDY DURATION: Each subject will be on study for 144 weeks from the time of entry including a 48 week period after the subject has completed the 96 weeks of study treatment.
OBJECTIVES:

Primary:

1. To estimate and compare changes from pre-treatment levels in BMD of the lumbar spine after 24 and 48 weeks of alendronate treatment versus placebo.

2. To assess the safety of 48 weeks of alendronate use as measured by the incidence of new ≥ Grade 3 hematology or chemistry laboratory values, signs or symptoms, or new cases of jaw osteonecrosis (JON), atrial fibrillation or non-healing fractures.

Secondary:

1. To estimate and compare changes from pre-treatment levels in whole body BMD after 24 and 48 weeks of alendronate treatment versus placebo.

2. To estimate and compare changes from pre-treatment levels in whole body and lumbar spine BMD after 96 weeks of alendronate treatment versus 48 weeks of alendronate followed by 48 weeks of placebo.

3. To assess the safety of 96 weeks of alendronate use as measured by the incidence of new ≥ Grade 3 hematology or chemistry laboratory values, signs or symptoms, or new cases of jaw osteonecrosis (JON), atrial fibrillation or non-healing fractures.

4. To assess the effect of other known bone mineral determinants (age, gender, race/ethnicity, steroid use, Depo-Provera, tenofovir, pubertal stage, bone age, vitamin D status) and inflammatory cytokine levels on changes in BMD after 24 and 48 weeks of alendronate treatment.

5. To assess changes in BMD over a 48 and 96-week period after completion of 48 weeks of alendronate therapy.

6. To characterize the alterations in pre-treatment bone marker turnover, RANKL/OPG ratio, central fat content (by whole body DXA) at baseline compared to levels after 48 weeks of alendronate therapy and determine if the changes in these outcomes correlate with changes in BMD.

7. To evaluate the effect of alendronate therapy on changes in HIV status (as measured by changes in viral load, CD4% and CDC disease category) and determine if the changes in these outcomes correlate with changes in BMD.

8. To estimate the duration of detectable urinary alendronate in adolescent subjects who have completed 48 and 96 weeks of alendronate therapy.
1.0 INTRODUCTION

1.1 Background

Normal Bone Mineralization

Developmental Issues:

Puberty is a time when the foundation is laid for healthy bone mass. Over the course of puberty, 26% of bone mass is established in the 4-year period of peak height velocity (PHV) and up to 60% of adult peak bone mass is established (1,2). Factors that affect normal bone mineralization include calcium intake, vitamin D status, degree of physical and weight bearing activities, hormones, genetics, body weight and general health and nutrition status (1).

Bailey et al. used six annual DXA (Hologic 2000) measurements to study calcium accretion in healthy white adolescents (2). Of the 113 boys and 115 girls initially enrolled, 60 boys and 53 girls who had PHV and peak BMC velocity values were used in this longitudinal analysis. The mean peak bone mineral accrual rate was 407 g/year for boys (SD, 92 g/year; range, 226–651 g/year) and 322 g/year for girls (SD, 66 g/year; range, 194–520 g/year). These corresponded to peak calcium accretion rates of 359 mg/day for boys (81 mg/day; 199–574 mg/day) and 284 mg/day for girls (58 mg/day; 171–459 mg/day), 7–34% higher than what was reported by the same authors in their previous cross-sectional analysis in which reported mean values were 282 mg/day for boys and 212 mg/day for girls. The mean age of peak calcium accretion was 14.0 years for the boys (1.0 years; 12.0–15.9 years), and 12.5 years for the girls (0.9 years; 10.5–14.6 years). The average dietary calcium intake, as determined by diet histories, was 1140 mg/day (SD, 392 mg/day) for boys and 1113 mg/day (SD, 378 mg/day) for girls. The authors conclude that about 26% of adult calcium is laid down during the two adolescent years of peak skeletal growth and that more efficient use of dietary calcium during this period makes more calcium available for accretion during this period of rapid growth (2).

Abnormal bone mineralization frequency and consequences:

Adult bone mass is the strongest predictor of osteoporotic fracture risk and the result of the peak bone mass (PBM) attained in early adulthood less the subsequent bone loss. Based on studies examining risk factors associated with bone loss, many fracture prevention strategies attempt to reduce or reverse bone loss, primarily through drugs, exercise, and dietary supplementation. Interventions to enhance PBM have not been as well studied and are made more difficult by controversy as to the age of attainment of PBM. There has been no adequate longitudinal investigation of bone mass accumulation before PBM (2).
Decreased bone mineral density (BMD) has been highly correlated to the risk of osteoporotic fractures in postmenopausal women. The association with fractures in healthy children is not as strong, though a recent prospective study in healthy children confirmed the association between low BMD (especially low volumetric BMD) and subsequent fracture risk (3). Another study in healthy children demonstrated a 53% increased risk of subsequent forearm fracture for each one-unit decrease in standard deviation (corresponds to -1.0 Z-score unit) of lumbar spine BMD at baseline (4). However, the association is less well studied for children with chronic illness (1).

Osteoporosis is defined as a disease of low bone mineral density. It may present as an acute fracture (most commonly of the wrist, ribs, hip, or spine), asymptomatic thoracic wedge or lumbar compression fracture, or generalized osteopenia on a radiograph. The majority of patients presenting with compression fractures are asymptomatic (5). In children, the diagnosis of osteoporosis must include clinical features and not rest solely on low bone density measurements (5).

Bone development in adolescence and childhood:

Bone deposition and absorption is a dynamic process and attains some special characteristics during peak height velocity during puberty. This dynamic process may lead to temporary periods of increased bone fragility with an increased risk of fractures.

In children and adolescents, the BMD z-score (derived from comparing patient values to mean values of a population matched for age, sex and ethnicity) is predictive of distal forearm fractures (most common fracture site during pubertal growth spurt) in a dose-response fashion, though the association is not as strong as it is for adults (6). Reduced bone mineral content (BMC) and BMD, especially in the distal radius, are more common in children with fractures. Osteopenia (defined as Z score below -1), was more common in cases than controls (p < 0.05) in the forearm, spine, and hip, with one third of fracture cases having low spinal density (7).

The high incidence of fractures in adolescence may be related to a period of relative skeletal fragility resulting from dissociation between bone expansion and bone mineralization during the growing years (8). BMD decreased significantly before the age of PHV and then increased until 4 years after PHV. The peak rates in radial fractures (reported from previous work) in both boys and girls coincided with the age of negative velocity in BMDs; the age of peak bone area velocity preceded the age of peak BMC velocity (PBMCV) by 0.5 years in both boys and girls (8). Thus, the results support the theory that there is a period of relative
skeletal weakness during the adolescent growth period caused, in part, by a draw on cortical bone to meet the mineral demands of the expanding skeleton resulting in a temporary increased fracture risk (8).

Low BMD in childhood and adolescence appears to be a risk factor for later development of osteoporosis in postmenopausal women (1;9), though it is uncertain if enhancing bone mass acquisition in adolescence will have an effect on adult osteoporosis risk (10). The prospective studies of children by Clark et al. (3) and Flynn (4) demonstrated that a low BMD by DXA, adjusted for height and weight, (age and sex, in the Flynn study) was associated with increased fracture risk during childhood and adolescence, suggesting that the risk of fracture in children with low BMD may increase well before older ages.

Risk factors for abnormal bone mineralization:

Chronic medical conditions (multifactorial etiologies), including prolonged immobilization, anorexia nervosa, asthma, celiac disease, cerebral palsy and other neuromuscular conditions, chronic renal failure, cranial irradiation (particularly pituitary), cystic fibrosis, bowel disease, malignancies, solid organ and bone marrow transplantation, rheumatologic diseases, sickle cell disease, thalassemia, and Turner syndrome have been associated with derangements in normal bone mineralization (1). Specific endocrinopathies, including Cushing syndrome (hypercortisolemia), growth hormone deficiency, hyperthyroidism, hyperparathyroidism, hyperprolactinemia, hypopituitarism, hypothyroidism, sex hormone deficiency/hypogonadism (acquired or genetic) can also have a negative effect on normal bone mineralization. Medications (medium- to long-term use), including anticonvulsants, glucocorticoids, cyclosporine A, gonadotropin-releasing hormone agonists, heparin, lithium, depot medroxyprogesterone acetate, methotrexate, and other chemotherapeutic agents also have a negative effect on bone mineralization. Deleterious behaviors, including female athlete triad (defined as the interrelationship among disordered eating, amenorrhea, and osteoporosis in female athletes competing in activities that emphasize a lean physique), have been negatively associated with bone mineralization as has excessive alcohol consumption and tobacco use (1).

Skeletal Effects of Oral Contraceptive Pills and Depo Provera

There have been several reports to date suggesting a deleterious effect of Depo Provera on bone density, especially in adolescent girls (11-14) and as discussed in a position statement by the Society for Adolescent Medicine (15). The loss in BMD is most significant during the first year of use, although losses are sustained. Because of increasing data showing this trend in bone density, especially in adolescents, the US Food and Drug Administration put a “black
box” warning label on its use, with special attention given to problems with skeletal losses among adolescent girls. The lingering question, especially with regard to its use in adolescents, is whether the skeletal effects of this agent are reversible, and if the achievement of peak bone mass is compromised. The effects of oral contraceptive pills (OCPs) have been extensively studied because of the large number of adolescents and young women who receive these agents. In general, combination OCPs containing both estrogen and progestin have no deleterious effect on bone density with the exception of ultra low-dose OCPs (i.e., which contain 20 mcg of ethinyl estradiol) which have been shown to be associated with a suppression of bone turnover and lower accretion of bone density (16-18).

Measurement of bone mineralization: Dual-energy x-ray absorptiometry (DXA)

Dual-energy x-ray absorptiometry (DXA) is the standard modality for bone assessment of adults. Normative data for DXA scan assessment of BMD in children have been developed, although not as extensively or as definitively as for adults. However, DXA is the preferred method for assessment of bone density in children with diseases that may affect bone health (19;20). The radiation exposure from DXA is low, equivalent to about 1/10 of the exposure of a single plain chest radiograph. Based on normative databases, t-score <-2.5 can establish the diagnosis of osteoporosis in older men and women (6). In children, however, osteoporosis is a clinical diagnosis, not a DXA diagnosis. When DXA is applied to children, t-score should not be used; z-scores adjusted for age, sex and ethnicity should be used. A z-score <-2.0 should be termed “low BMD for age” and not osteoporosis. The preferred sites for measurement of BMD by DXA in children are the spine and total body (6). A baseline DXA (of lumbar spine and whole body) is recommended for all children and adolescents with primary bone diseases or potential secondary bone diseases (e.g. due to chronic inflammatory diseases, endocrine disturbances, history of childhood cancer, or prior transplantation (non-renal)), spine and total body less head (TBLH) BMC and a real BMD should be measured at clinical presentation (20).

The three main limitations of DXA measurements in children have been
- the lack of a standardized pediatric normative database
- the lack of a meaningful clinical outcome measure related to DXA values in children
- inaccuracies resulting from growth-related variations in bone and body size and composition (21)

The lack of a standardized pediatric normative database has been resolved with the recent publication of the Bone Mineral Density in Childhood Study. However, normative DXA z-scores can only be applied to measurement on the same type of DXA used to derive the norms.
The Bone Mineral Density in Childhood Study, sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD), recruited 1530 boys and girls aged 6 to 16 years and from diverse ethnic backgrounds for longitudinal bone studies (21). Subjects underwent a baseline and three consecutive annual evaluations that include DXA measurements, a bone-age radiograph of the hand, sexual maturation staging, and growth measurements. The Hologic bone densitometers - QDR4500A, QDR4500W and Delphi A models – were used to measure whole body, PA lumbar spine (L1-L4), non-dominant forearm, and left proximal femur yearly in all participants. BMC and BMD were higher for blacks than non-blacks at all sites. BMC and BMD measurement and variation both increased with age; measurement values did not seem to plateau out to the age range followed thus far (16 year old girls; 17 year old boys). This study has established age, race and sex specific reference curves that can be used to help identify children with bone deficits, and for monitoring changes in bone in response to chronic diseases or therapies. Continued annual evaluations of these study participants is expected to allow for development of age, race and sex-specific reference curves through age 20, the time by which male and female BMD reaches >95% of peak adult values.

Inaccuracies resulting from growth-related variations in bone and body size and composition are another major limitation to the use of DXA in children. Bone-mass measurements using DXA are based on a two-dimensional projection of a three-dimensional structure. The results are influenced by many skeletal and extraskeletal parameters including the size of the bone, the volume (tissue density) of the bone, and the material density of the bone being examined, as well as the amount and distribution of soft tissues around the bone. The inability of DXA to account for the influence of variations in these anatomic measures markedly hinders the accuracy and reproducibility of bone determinations in the growing bones of a child. There have been numerous correction factors proposed to correct for variation in bone size but there is no clear consensus for which adjustment performs best in different pediatric populations (21).

Thoracic wedge or lumbar compression fractures (usually asymptomatic) can elevate local readings of BMD by DXA (5). Thus, a thoracic wedge or lumbar compression fracture, even in the face of LS DXA BMD results not suggestive of low BMD, meets criteria for osteoporosis diagnosis, since this type of fracture may cause a falsely elevated LS DXA BMD reading (5).

Low BMD in HIV infected populations:

A. Adults
In an ARV comparison study, Gallant et al found that about 23-28% of HIV infected adults (mean age 36 years, range 18-64) had osteopenia by DXA at baseline. Lower baseline lumbar spine T scores correlated with lower weight, male sex, and increased age. Treatment with tenofovir was associated with a greater, albeit modest, decrease in spine BMD than non-tenofovir highly active antiretroviral therapy (HAART); the decrease progressed over the first 2 years and then appeared to stabilize (22).

Mondy et al. (23) followed 93 HIV infected adults (mean age, 42 years) who were mostly male (86%), white (84%), and on a PI-based HAART regimen (68%). 46% of patients met criteria for osteopenia or osteoporosis at baseline. In multivariate analysis, baseline predictors of low BMD included smoking, steroid use, significant weight loss and low BMI but not HIV-1 RNA, CD4 cell count or antiretroviral agents. Longitudinal assessment showed an increase in spine and hip BMD; baseline virologic suppression and increasing CD4 cell count during follow-up were positive predictors of increase in BMD. PI-based HAART and non-PI-based HAART had similar associations with increasing BMD during follow-up, in contrast to prior cross-sectional studies suggesting that PIs were risk factors for loss of BMD. Other studies of HIV infected adults who were switched from PI-based to non-PI-based therapies failed to show an effect of change in drug regimen on BMD as well (24).

In multivariate analyses of data from a cohort of HIV-infected adult patients (mean age, 41 years) at clinics in Denver, Minneapolis, Providence, and St. Louis, low BMD was significantly associated with older age, male gender, lower body mass index, unemployment, and stavudine use; osteoporosis was associated with older age, non-white race, lower body mass index, longer duration since HIV diagnosis, and unemployment (25).

In a cohort of HIV infected women (mean age, 39-41 years) and HIV-negative healthy controls, abnormal bone mineral density was associated with low body weight, reduced lean mass, reduced androgen levels, and abnormal menstrual function. A significant difference was seen in bone mineral density among all 3 groups at the lumbar spine (0.97±0.01 g/cm² vs 1.02±0.02 g/cm² vs 1.07±0.01 g/cm², p = <0.0001), total hip (0.88±0.01 g/cm² vs 0.95±0.02 g/cm² vs 0.98±0.01 g/cm², p = <0.0001), and femoral neck (0.78±0.01 g/cm² vs 0.83±0.02 g/cm² vs 0.87±0.01 g/cm², p = <0.0001) (HIV-infected low weight, HIV-infected normal weight, and healthy control subjects, Clinical risk factors for osteopenia and osteoporosis in the HIV population included low free testosterone (< 1.1 pg/mL [lower limit of the normal range of the free testosterone assay for
women] (3.8 pmol/L) \( (p = 0.003) \), low weight \( (p = <0.0001) \), and oligiomenorrhea \( (p = 0.0006) \) \( (26) \).

In A5005s, the metabolic substudy of AIDS Clinical Trials Group (ACTG) 384, whole-body DXA scans were performed at entry and every 16 weeks thereafter in 157 adult subjects (age not provided). Participants were randomized to receive nelfinavir (NFV), efavirenz (EFV), or both drugs combined with open-label zidovudine (AZT) and lamivudine (3TC) or didanosine (ddI) and stavudine (d4T) (NRTI groups). Percentage change in total bone mineral content was the primary outcome variable. The initiation of ART was associated with a modest but statistically significant bone loss that was independent of the regimen used in this study. The amount of bone loss after ART initiation was greater in individuals with lower baseline CD4 cell count. The authors conclude that the findings suggest that the treatment effect of ART on bone was not a direct toxic effect, but might be mediated through the antiviral or immunological changes associated with the initiation of ART \( (27) \). However, lack of untreated controls makes it difficult to know if the pace of bone loss might have been even greater if no treatment were given.

Thus, low BMD is relatively common in HIV infected adults. In addition to the traditional risk factors for low BMD unrelated to HIV that may be present in these patients, antiretroviral treatment appears to confer an increased risk. D4t and tenofovir may confer some specific increased risk of low BMD, but previous concerns about specific effects of PIs have not been confirmed; ARV treatment may lead to lower BMD through indirect effects and not through ARV agent-specific direct effects on bone.

There have been case reports of HIV infected adults with fragility fractures associated with osteopenia or osteoporosis, but thus far, such cases have been very limited \( (28;29) \). A more recent analysis of a large adult database demonstrated a significantly higher prevalence of fracture – including of spine and hip fractures that are typical of fractures related to osteoporosis – in HIV-infected adults compared to HIV-uninfected adults \( (30) \). In the SMART study, HIV-infected adults assigned to continuous ART had a higher incidence of serious fractures than adults assigned to intermittent ART \( (31) \).

B. Children

HIV infected children, youth and adults have lower BMD than would be expected for healthy people of similar age, weight and race \( (32-35) \). As the majority of perinatally HIV infected US children are entering or in
adolescence, the potential for HIV-related impaired BMD during the adolescent peak of bone mass acquisition is of particular concern.

Data from the Pediatric HIV/AIDS Cohort Study (PHACS) cohort suggest that about 10% of children and adolescents with perinatally-acquired HIV infection have LS BMD z-scores < -1.5 and about 4% have LS BMD z-scores < -2.0 (36).

While complete understanding of the many factors contributing to abnormal BMD in HIV infection is lacking, major risk factors that have emerged from longitudinal studies include longer duration of HIV disease, low BMI, history of weight loss, and previous use of steroids. Tenofovir disoproxil fumarate (TDF) therapy has emerged as a significant risk factor for loss of BMD in children. In general, longitudinal studies have shown that initiation of HAART is associated with an improvement from low baseline BMD over time. Mora et al., in a study of 32 perinatally infected children receiving PI-based, non-TDF-containing HAART, demonstrated low BMD with biochemical evidence of increased bone turnover (increased formation and resorption) at baseline; BMD improved but bone turnover did not during the one year duration of the study (33).

Jacobsen et al. (37) studied 37 HIV infected children compared to nine sibling controls. When compared with population norms, HIV infected children had lower than expected age- and sex-adjusted bone mass by DXA. Independent predictors of low BMD in HIV infected children suggested contributions from delays in growth, sexual maturity, time (length of HIV infection), ethnicity and disease severity. Multivitamin use was strongly associated with better bone mineral density, but not with changes in BMD over time. Change in BMD z-score over time showed that BMD was stable or increased in controls but stable/increased BMD was observed in only 44% of the HIV-infected children, a trend that approached statistical significance (37).

While the association in cross-sectional studies between PIs and low BMD has not been consistently confirmed in longitudinal studies, the potential effect of TDF may be more concerning. Initiation of tenofovir-containing HAART has been associated with an initial decrease in BMD in adults (22) and children (38). In adults, the initial loss seems to stabilize over time, but the pattern is less clear in children. The effect of tenofovir may be partly attributable to its ability to cause a Fanconi-like syndrome with renal phosphate wasting and secondarily increased osteomalacia and bone resorption. The effects may be exaggerated in younger children, who may be receiving a disproportionately high dose of TDF. Hazra et al. (39) treated sixteen children and adolescents with perinatally-acquired HIV
infection with TDF and at least three other ARTs as part of a salvage regimen. Five of 15 evaluated at 48 weeks had experienced a greater than 6% decline in their absolute LS BMD despite linear growth, resulting in worse Z-scores than when they started the trial (since BMD would be expected to increase over time at these ages). All 5 of these subjects with BMD decline experienced >2 log_{10} copies per mL decreases in HIV plasma RNA levels at 48 weeks and high and sustained increases in CD4+ T cell counts. In additional studies of these five patients (38), two of the five patients with BMD declines discontinued TDF after 48 to 50 weeks because of significant decrease in BMD. In one patient, these decreases were seen in all three body sites assessed and were associated with a marked increase in urine calcium excretion. By 96 weeks, absolute BMD had returned to baseline; however, z scores remained lower. Similarly, in the second patient LS BMD showed near recovery by 96 weeks; however, TH and FN BMD continued to decline even after discontinuation of TDF. Both patients remained on other antiretrovirals throughout the follow up period, and HIV disease remained stable after discontinuation of TDF in both patients. The authors concluded that TDF should be used with caution in growing children, the long-term effects on bone are unknown, and careful monitoring (e.g., bone densitometry at baseline and every 6–12 months) of HIV-infected children receiving TDF is indicated.

While the Hazra/Gafni studies involved highly ARV experienced children, another study looked at 16 children undergoing a switch from d4t to tenofovir but whose HIV was well controlled for a long period of time (40). DXA BMD was measured in these children 12 months before the switch, at the time of the switch and then 12 months later. There was no apparent change in BMD increments during the two 1-year periods compared to healthy controls. The contradictory findings of studies of effect of TDF on BMD in children may be due to differences in study populations: the Giacomet study involved older, more mature, and possibly healthier children and adolescents with potentially lower tenofovir exposures secondary to lack of concomitant therapy with ritonavir and the use of lower relative doses of TDF.

Pitukcheewanont et al. (41) compared vertebral bone assessments in 58 5-19 year old perinatally HIV infected children to age-, gender- and ethnicity-matched controls, using both DXA (Delphi Hologic) and quantitative computed tomography (QCT). By DXA, HIV-1 infected children had significantly less bone area, lower bone mineral content (BMC), and lower BMD at the vertebral level and of the whole body compared to controls. In contrast, by QCT, HIV-1 infected children had similar vertebral BMD compared to controls, but smaller vertebral height and cross-sectional area. It appeared that the lower bone measurements by
DXA were primarily due to the decreased bone and body size of the HIV-infected children (41).

C. Pathophysiologic explanations

HIV appears to be associated with dysregulation of bone formation and bone resorption homeostasis; resorption is frequently increased, formation may be decreased and the processes appear to be uncoupled in untreated or advanced HIV. Factors that may mediate the association of HIV and decreased BMD include growth and pubertal delay, chronically elevated inflammatory cytokines, renal dysfunction and malnutrition. Other factors that are not HIV-specific but may occur in HIV infected children and contribute to abnormal BMD include poorly understood genetic determinants, inadequate calcium intake, vitamin D deficiency, generalized malnutrition, use of drugs that affect BMD, such as steroids, anticonvulsants, tobacco and drugs of abuse (heroin, ethanol). In particular, Depo-Provera injection, a popular contraceptive method for HIV infected female youth, is strongly associated with bone mineral loss. Systemic corticosteroids are a well-established risk factor, but even topical or inhaled steroids in youth receiving the CYP 3A4-inhibiting ritonavir may cause an exaggerated systemic corticosteroid exposure.

The mechanisms underlying the uncoupling in HIV are likely dependent on the OPG/RANK/RANKL system. Normally, osteoblasts express RANKL (receptor activator for nuclear factor kappa B ligand) which interacts with RANK, found on the cell surface of osteoclast precursors, thereby inducing osteoclast differentiation and proliferation. Thus, increased RANKL leads to increased osteoclast activity and bone resorption. As a control mechanism, osteoblasts also secrete a protein called osteoprotegerin (OPG) which binds to RANKL and prevents osteoclast activation. RANKL is also produced by activated T-cells. RANKL production is also stimulated by proinflammatory cytokines, such as IL-1 and TNF-alpha, potentially explaining how bone density loss due to increased bone resorption occurs in conditions (including HIV infection) with increase in these inflammatory cytokines (42).

In vitro studies have shown that HIV viral components themselves can also upregulate RANKL (43) and certain antiretroviral agents may enhance this effect (44). In a recently reported study of 27 vertically HIV-infected children and adolescents (aged 4.9 to 17.3 years) on long-term PI-based HAART (70±8 months) and 336 healthy children, aged 4.8 to 17.9 years, as controls, serum concentration of bone alkaline phosphatase (BAP), RANKL, and OPG were measured by enzyme immunoassay (EIA) assays and the concentration of NTx (a bone resorption index) was
measured by ELISA assay in timed urine samples. Altered bone metabolism was present in HIV-infected children and adolescents. The high bone resorption rate appeared to be the result of a profound modification of the factors regulating osteoclastogenesis (suggested by the ratio between OPG and RANKL). Furthermore, in vitro evidence indicates a role of HIV infection and antiviral treatment in the production of RANKL by T cells. Thus, these patients on long-term HAART had a high concentration of RANKL that may be in part due to the use of antiviral drugs (45).

Stagi et al. (46) characterized bone differences in 44 perinatally infected children (23 mildly symptomatic and 21 severely symptomatic). By calcaneal quantitative ultrasound (QUS), only patients with severe HIV symptoms have reduced QUS measurements of BMD, and low BMD was associated with reduction in serum total and free insulin-like growth factor-I (IGF-I).

Treatment of low BMD:

A. Calcium and/or Vitamin D

Calcium supplementation in prepubertal children and in adolescence improves BMD but there are conflicting pubertal study results on whether the effect is transient or sustained (2). Vitamin D deficiency has been linked to fracture and low BMD in adults; however, while vitamin D deficiency appears to be a common problem in adolescents with and without HIV infection (47), its deficiency has not been well-correlated with low BMD in this age group. Vitamin D supplementation of at least 200 IU daily has been recommended by the American Academy of Pediatrics for all adolescents (1). Vitamin D supplementation of vitamin D-deficient adolescents appears to improve some BMD measures in girls but not in boys (48).

In a small study, 9 HIV-infected children with initial BMD z-score <-2.0 received daily supplementation with calcium (< 9 years: 500mg; > 9 years: 1000 mg) and vitamin D (200 IU) for a median duration of 9 months (range 5.5-16.5). Their median z scores were -2.7 and -2.1 before and after supplementation, respectively (p = 0.13) (49). Multivitamin use was associated with lower baseline risk of low BMD in HIV-infected children but not with improvement in BMD over time (37).

B. Weight-bearing exercise
It is not clear if moderate exercise during growth leads to improved BMD. Several studies in school children in which exercises are incorporated into the physical education program for 20–30 minutes three times weekly have shown variable degrees of improvement in BMD and thickening of cortices. However, it is not clear if the modest improvements in bone mass and structure continue beyond two years or are maintained after these exercise programs are stopped (50-56).

The positive impact of calcium and vitamin D on bone is enhanced by physical activity. During adolescence, about 25 to 30% of the adult bone mass is gained (2). Physical activity during this period can have significant impact on bone health. Some of this impact on bone may be influenced by the changing hormonal milieu of the early adolescent (54). Physical activity has been directly correlated with bone density. For example, in studies of tennis and racquet ball players, the dominant arm had a higher bone mineral content when compared to the non-dominant arm. It has been additionally shown that these changes were most significant when the exercise was begun at an early age (57;58). Thus, as part of this study, the use of exercise to enhance bone density gains through alendronate administration will be required.

Although studies have shown the importance of weight-bearing and impact sports on bone mineral density (BMD) gains, few data are available from randomized controlled trials to make specific recommendations concerning the type of exercise in which a child or adolescent must engage which has the most beneficial skeletal effects. Thus, this study does not require one specific exercise regimen, but rather a generalized approach to exercise. To impact on bone health, children and adolescents should engage in at least 60 minutes of exercise per day. There are two approaches to exercise that can be beneficial and will be required to monitor as part of this study. First, are those exercises associated with weight-bearing together with short impact exercises such as basketball, gymnastics, and jumping.

The types of exercises that have the most significant skeletal impact on those bones are directly involved in weight-bearing or impact activity. Performance enhancing exercises that improve strength can also be quite helpful. Examples of these, in addition to those mentioned above, include hopping, skipping, volleyball, bicycle riding, and soccer. These exercises both improve cardiovascular performance as well as provide sufficient weight bearing and impact to enhance bone mineral density. It should be noted that exercises, such as swimming, that do not involve weight-bearing or impact do not promote bone health and are not recommended as part of the exercise plan for subjects enrolled into this study.
The Surgeon General’s Report (59) on bone health includes the following exercises as examples of exercises that enhance bone health and will be acceptable for exercise recommended for subjects enrolled into this study:

- Running
- Jumping
- Hopping
- Skipping
- Jumping rope
- Dancing
- Climbing stairs
- Jogging
- Aerobic dancing
- Hiking
- Inline skating; ice skating
- Tennis, racquet ball, handball and other racquet sports
- Team sports such as soccer, volleyball, basketball, field hockey, softball and baseball

Subjects enrolled in this study will be asked to engage in weight-bearing exercises for 60 minutes per day. A list of these activities will be provided and reviewed with each participant. A validated tool will also be administered to each subject at each study visit in an attempt to quantitate their physical activity throughout the trial.

C. Bisphosphonates

Adult Indications:

Oral bisphosphonates, including alendronate and risendronate, are approved for the prevention and treatment of osteoporosis in adults. They are also approved for treatment of glucocorticoid-induce osteoporosis and Paget’s disease of bone in adult men and women. These agents are chemically absorbed into bone, decreasing osteoclast number and activity and thereby decreasing bone resorption.

Postmenopausal women with lumbar spine BMD at least 2 standard deviations below the premenopausal mean treated with alendronate 10 mg once daily for two or three years (depending on study) experienced significant increases in BMD in the spine, other sites and total BMD (60). Increases in BMD were evident as early as three months and continued throughout the three years of treatment. Significant reduction in vertebral
fractures was also documented. Following discontinuation of alendronate, there were no further increases in bone mass and the rates of bone loss were similar to those of the placebo groups, suggesting that continued treatment may be required to maintain the beneficial effect of the drug.

Men and women (age range, 17-83 years) receiving systemic steroids were treated with 5-10 mg daily alendronate in two, one-year, placebo-controlled studies. After one year, significant increases in spinal BMD (and BMD at other sites) were seen. After two years of treatment, spine BMD increased by 3.7% and 5.0% relative to placebo with 5 and 10 mg daily doses, respectively. A significant reduction in vertebral fractures was documented at the end of two years of treatment. Significant increases in BMD (relative to placebo) were also observed at the femoral neck, trochanter, and total body.  (package insert)

Pediatric Experience:

Alendronate is not currently indicated for use in children.

Osteogenesis Imperfecta (OI): The greatest experience in treating children with OI with bisphosphonates has been with intravenous pamidronate, but there are limited data from studies of oral alendronate in this pediatric population.

As reported in the product information for alendronate (published study not found), the efficacy and safety of alendronate were examined in a randomized, double-blind, placebo controlled two-year study of 139 pediatric patients, aged 4-18 years, with severe osteogenesis imperfecta. 109 patients were randomized to 5 mg alendronate daily (weight <40 kg) or 10 mg alendronate daily (weight ≥40 kg) and 30 patients to placebo. The mean baseline lumbar spine BMD Z-score of the patients was -4.5. The mean change in lumbar spine BMD Z-score from baseline to month 24 was 1.3 in the alendronate-treated patients and 0.1 in the placebo-treated patients. Alendronate treatment did not reduce the risk of fracture. Sixteen percent of the alendronate group with confirmed fracture by Month 12 of the study had delayed fracture healing (callus remodeling) or fracture non-union when assessed radiographically at Month 24 compared with 9% of the placebo-treated patients. In alendronate-treated patients, bone histomorphometry data obtained at Month 24 demonstrated decreased bone turnover and delayed mineralization time; however, there were no mineralization defects (60).

In a clinical trial, eighteen children with OI > 3 years old were stratified by bone age, pubertal stage, and type of OI and then randomized to
receive oral alendronate (1 mg/kg/day) or intravenous pamidronate (3 mg/kg/4 months) for a period of 2 years. Total body and lumbar spine BMD increased, turnover markers decreased, and linear growth increased equivalently with oral and intravenous therapy. Fracture incidence showed a trend to decrease in both groups. Acute phase reaction was noted in some pamidronate patients; no adverse effects were reported in the children receiving alendronate (61).

Thirty children with OI, from 4-16 years old, were treated with daily alendronate (5 mg for 4-10 yrs old; 10 mg if >10 yrs old) for three years. After one year of treatment, areal and volumetric vertebral BMD z-score by DXA significantly increased, fracture frequency decreased, chronic pain measures improved and mobility increased relative to baseline. No adverse events were reported. While benefits persisted in the subsequent 2 years of treatment, there did not appear to be additional improvements beyond the first year of treatment (62).

Three children (3–7 years old) were treated with oral alendronate (0.3–0.56 mg/kg per day orally) for 2 years. Bone mineral density by DXA improved significantly from baseline after two years of treatment, increasing by 48-107% in the lumbar spine and by 24%-51% in forearm bones. The z-score of lumbar spine DXA values increased from -5.26 to -3.1. There was no documented reduction in fractures in the three patients. No side effects were reported (63).

Malignancy:

Ten children, 3-15 years old, on maintenance chemotherapy for ALL or NHL were treated with daily calcium and weekly oral alendronate for six months for steroid-induced osteopenia (64). Entry Z-scores DXA for this group were -4.7 to +0.01 (mean (-1.92) for WB BMC and -2.66 to -0.31 (mean (-1.28) for LS BMD. Gain in Z score was observed in 7/9 evaluable patients demonstrated mean increases in Z-scores for whole body BMC of 0.49 and for lumbar spine BMD of 0.51. The treatment was well tolerated. In addition, there was improvement in measures of motor function and gains in measures of health-related quality of life. In a subsequent study, fifteen 2-18 year old children undergoing maintenance therapy for ALL who had LS BMD Z-score <-1.0 were treated with weekly alendronate for 6-24 months (65) and demonstrated a median gain in LS DXA BMD with improvement in 14 of the fifteen patients. In addition, there was no short-term toxicity and no adverse effect on height velocity over the subsequent 2 years.

Glucocorticoid-treated children:
Twenty-two children with prednisone-dependent chronic illness were randomized to receive either once-weekly oral placebo or alendronate (1-2 mg/kg body weight) for one year. **Baseline LS BMD Z-score was -4.2 to +1.4 with a median of -0.65.** Alendronate treatment was well tolerated, suppressed bone resorption (measured by urine N-telopeptide excretion) and increased DXA lumbar spine volumetric BMD z-score compared to baseline. There was no effect on bone growth (66).

Sixteen deflazacort-treated boys with Duchennes muscular dystrophy (DMD) who had DXA spine and/or total body BMD z scores < -1.00 site (BMD) were treated for 2 years with alendronate 0.08mg/kg/day (rounded to either 2.5 or 5.0mg/d) together with 750mg/d of supplemental calcium and 1000IU/d of vitamin D. At 2 years, mean BMD z scores were unchanged overall but improvement in total body and spine z scores was observed in those at younger ages. No adverse events were reported (67).

**Children with BMD and history of fracture:**

46 children (boys and girls), mean age of 12 years old, who had documented fracture, absence of deficiencies of vitamin D or growth hormone, and a DXA lumbar spinal z-score < -1.0 were assigned to treatment with alendronate for 2 years followed by observation without alendronate for an additional year. Children over 30kg received 10mg daily or 70 mg weekly, while smaller children received 5 mg daily or 35 mg weekly. All children also received vitamin D and calcium supplementation. BMD z-score improved to normal at the end of 2 years of treatment, and the Z-scores remained normal at the assessment one year after the end of alendronate treatment. Somatic growth was normal, urinary N-telopeptide/creatinine ratio was reduced, and age-adjusted alkaline phophatase was unaffected (Langman C, reported at PAS 2007, manuscript in preparation).

**Other Disorders with Low BMD in Children:**

Thirty-eight children with low bone mass (DXA vertebral BMD z-score < -1.5) secondary to diffuse connective tissue diseases were treated with alendronate for one year and were compared to 38 untreated children with similar but less severe same primary disorders. Spinal BMD increased by a mean of 14.9% compared to baseline in the treated patients (reaching normal in 13 patients), but increased only 2.6% compared to baseline in the control group (15 had a decrease). No new fractures were observed after alendronate therapy was initiated. One patient had esophageal erosions (68).
Unal and colleagues treated 22 4-19 year-old children who had spinal BMD DXA z-score <-2.0 with oral alendronate for a period of 6-36 months (69). These children had various underlying disorders, including connective tissue disorder (11), epilepsy (5), immobilization (3), OI (1), Fanconi aplastic anemia (1), leukemia in remission (1) and thirteen children had received systemic steroids for at least 2 months. Children weighing over 30kg received 10 mg oral alendronate daily while smaller children received 5 mg daily. After an average of 14 months of treatment, BMD z-score was significantly improved and alkaline phosphatase was significantly lower. Patients taking steroids had significant improvement in average BMD z-score but the magnitude of this increase was less than that seen in children not taking steroids. Sclerotic bands were detected in the knee metaphyses of most children, especially those who were prepubertal. There were no other adverse effects reported. The authors report a decrease in fractures during treatment compared to the pretreatment period, but few details are provided (69).

D. Treatment of low BMD in HIV infected Adults

There have been limited studies examining interventions that could mitigate bone mineral loss in HIV infection. Effective HAART (without TDF) is associated with improved BMD. Jacobsen et al. (37) found that multivitamin use was strongly and independently associated with higher BMD in HIV infected children. Very limited data exist for of raloxifene, testosterone and growth hormone-releasing hormone in HIV infected adults. Oral bisphosphonates, including alendronate and risendronate, which are approved for the prevention and treatment of osteoporosis in adults, have generated the greatest interest.

Mondy et al. conducted a 48-week prospective, randomized, open label study to evaluate the effects of alendronate, vitamin D, and calcium supplementation on bone mineral density (BMD) in patients with HIV infection (70). Thirty-one HIV-infected subjects (mean age 44 years, mostly male) with lumbar spine BMD t-scores less than -1.0 on antiretroviral therapy for a minimum of 6 months were randomized to receive (n = 15) or not to receive (n = 16) 70 mg of alendronate weekly for 48 weeks. All subjects received calcium (1000 mg daily as calcium carbonate) and vitamin D supplementation (400 IU daily). The study was powered to detect 3% changes in BMD in the lumbar spine within treatment arms at 48 weeks. Patients were mostly male, suppressed and without severe immunosuppression. Alendronate in combination with vitamin D and calcium increased lumbar spine BMD by 5.2% (95% confidence interval [CI]: 1.3–6.4) at 48 weeks compared with an increase
of 1.3% (95% CI: 22.4 to 4.0) in subjects receiving vitamin D and calcium alone. There were no serious adverse events (70).

A5163 was a prospective, randomized, placebo-controlled multicenter trial to evaluate the effectiveness of calcium and vitamin D supplementation with or without once-weekly alendronate (70 mg) in improving bone mineral density in HIV-infected individuals (median age, 48 years) with lumbar spine t-scores ≤ −1.5. The study was powered to detect differences of 3.5% between arms and to evaluate moderate effects of gender in the response to therapy. All DXA scans were analyzed centrally, blinded by arm. Compared with calcium/vitamin D, alendronate + calcium/vitamin D resulted in improvements in lumbar spine (3.38% vs 1.10%, \( p = 0.03 \)), total hip (3.95% vs 1.31%, \( p = 0.004 \)), and trochanter (4.52% vs 0.72%, \( p = 0.03 \)), but not femoral neck (2.21% vs 1.24%, \( p = 0.35 \)). There was at least a trend toward increase in the bone mineral density values in calcium/vitamin D at lumbar spine, total hip and femoral neck, with \( p = 0.08, 0.03, \) and 0.07 respectively, compared to baseline. Black race was associated with a smaller change from baseline in bone mineral density of lumbar spine with alendronate. There were no apparent gender differences in the responses to therapy. Alendronate was well tolerated, without significant adverse events. The results demonstrate that once-weekly alendronate is safe and efficacious in the treatment of decreased bone mineral density in HIV-infected patients. Vitamin D and calcium alone is associated with modest improvements in bone mineral density (71).

Guaraldi et al. randomized 41 HIV infected adults (mean age, 43-45 years) on stable HAART with osteopenia (t-score <−1.0) to alendronate or no-alendronate for one year. All patients received vitamin D and calcium (72). The primary endpoint of the study was the change in bone metabolism evaluated by N-telopeptide of type 1 collagen and bone-specific alkaline phosphatase; the secondary endpoint was BMD variation. The alendronate-treatment group showed a significant decrease in serum N-telopeptides, consistent with a reduction in bone resorption. There was a small but significantly better improvement from baseline in femoral neck BMD in the alendronate group (72).

E. Treatment of low BMD in HIV infected children

There have not been any studies of alendronate in HIV infected children and youth. The only reported use of alendronate in pediatric HIV infection is a single case report (73). In this report, a 6-year old perinatally infected ARV-naïve girl with severe malnutrition including low vitamin D3 (8.1 pg/mL), CD4 625/15% and pretreatment viral load of 78,000 cpm was found to have multiple old and extant fractures, including
collapsed vertebrae, and marked loss of BMD by plain film and DXA. Two weeks after initiation of HAART (zidovudine, lamivudine, nelfinavir), antibiotic prophylaxis, vitamin D, calcium and general nutrition, she was treated with alendronate (10mg daily). By 6 months, her viral load was undetectable, CD4 had increased to 1074/22%, her body weight was improved and DXA demonstrated a 72% increase in bone mass from baseline. Through 15 month of alendronate treatment, no adverse events were reported.

The expected lack of interactions with antiretroviral drugs makes alendronate an appealing agent for use in HIV infection.

F. Safety concerns and Adverse Events associated with bisphosphonates:

Contraindications in package labeling:
- Inability to stand or sit upright for at least 30 minutes
- Patients at increased risk of aspiration should not receive alendronate oral solution.
- Hypersensitivity to any component of the product
- Hypocalcemia
- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia

Esophageal and Gastrointestinal Adverse Events (60):

Alendronate may cause local irritation of the upper gastrointestinal mucosa, including esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation. Presenting symptoms may include dysphagia, odynophagia, retrosternal pain or new or worsening heartburn. The risk of severe esophageal problems can be decreased if the patient avoids lying down for at least 30 minutes after an alendronate dose. The package insert advises CAUTION when giving alendronate to patients with active upper gastrointestinal problems (such as dysphagia, esophageal diseases, gastritis, duodenitis, or ulcers). The package insert indicates there have also been post-marketing reports of gastric and duodenal ulcers, though these events were not increased in controlled clinical trials. Children with severe OI who took alendronate for up to 24 months had similar adverse events rates as adult osteoporosis patients with the exception of a higher rate of vomiting: 29% alendronate versus 10% placebo (60).

Reduction in serum calcium and phosphate: In adult studies, reductions from baseline in serum calcium (2%) and phosphate (4-6%) after one month of alendronate treatment were evident. Longer treatment did not
result in further decreases in serum calcium, and serum phosphate normalized by year three (60).

Musculoskeletal Pain (60)
In post marketing experience, but not in clinical studies, severe and occasionally incapacitating bone, joint, and/or muscle pain has been infrequently reported in patients taking other bisphosphonates, with onset from days to months after starting the drug. Most patients had relief of symptoms after stopping but some had recurrence of symptoms when rechallenged with alendronate.

Pregnancy Category C: (60)
Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. At higher doses (10mg/kg/day), increased sites of incomplete fetal ossification were observed. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/m^2). Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (3.9 times a 40 mg human daily dose based on surface area, mg/m^2) resulting in delays and failures of delivery. Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Enteral calcium supplementation did not decrease the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery, while IV calcium supplementation prevented maternal but not fetal deaths (60).

There are no studies in pregnant women. The drug labeling cautions that alendronate should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus (60).

Alendronate is not classified as a teratogen. Each year Merck reports to FDA a summary of all pregnancy events that are reported to Merck in an NDA update document. Merck monitors reports (to Merck) of all pregnancy events in studies and in marketed use and thus far have not detected any reproductive toxicity signal.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. The terminal half-life in
humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. It is estimated that after 10 years of oral treatment with alendronate (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract (60). Seven children with severe osteoporosis who were treated with pamidronate for 4-10 years beginning at 10-14 years of age were documented to have detectable urine pamidronate for up to 8 years after cessation of treatment, leading to concerns about potential fetal exposure in women who become pregnant well after treatment with bisphosphonates (74). Some adult studies have included measurement of urine alendronate, but there are no standardized assays to measure alendronate in urine or interpret the finding of detectable alendronate in urine (75). However, given the concern in youth of reproductive potential about persistent systemic alendronate after drug administration has been discontinued, use of investigational assays to detect alendronate in urine at various time points after alendronate discontinuation may help estimate the duration of alendronate persistence.

There are very limited data on and absence of systematic study of fetal risk in humans, but there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied (60). Published human data about pregnancy outcome in women who received bisphosphonate therapy prior to pregnancy are extremely limited (76-80). In sum, these reports comprised data from 44 women taking bisphosphonates (including 34 taking alendronate) during or shortly before pregnancy. The higher rates of spontaneous abortion and of low birthweight in alendronate-exposed pregnancies compared to historical controls (77) were attributed to the effects of maternal illnesses (e.g., autoimmune diseases) contributing to bone disease for which the mother was receiving alendronate; there was no evidence of increase in birth defects or infant bone toxicity in this small number of cases.

Merck has had women of reproductive age in glucocorticoid-osteoporosis alendronate studies. And in those studies an inclusion criterion was that women (and partners) need to use double-barrier contraceptive methods and the entrants state that they are planning to avoid pregnancy. Patients who become pregnant were required to stop study drug (60).

Hypersensitivity reactions including urticaria and rarely angioedema have been reported in post-marketing surveillance. Transient symptoms of
myalgia, malaise, asthenia and rarely, fever have been reported with FOSAMAX, typically in association with initiation of treatment. In a pharmacokinetic study, 6 of 24 pediatric OI patients who received a single oral dose of FOSAMAX 35 or 70 mg developed fever, flu-like symptoms, and/or mild lymphocytopenia within 24 to 48 hours after administration. These events, lasting no more than 2 to 3 days and responding to acetaminophen, are consistent with an acute-phase response that has been reported in patients receiving bisphosphonates (60).

Arrhythmia
After an increase in atrial fibrillation was noted in a study of yearly intravenous zoledronic acid for postmenopausal osteoporosis (81), review of a previous alendronate trial in postmenopausal women also revealed a non-significant trend for an increase in atrial fibrillation with alendronate (82). In both cases, the absolute increase in atrial fibrillation risk was small and the events occurred weeks (81) to years (82) after treatment.

Delayed fracture healing
Sixteen percent of the pediatric OI patients assigned to study treatment with alendronate (60) who sustained a radiologically-confirmed fracture by Month 12 of the study had delayed fracture healing (callus remodeling) or fracture non-union when assessed radiographically at Month 24 compared with 9% of the placebo-treated patients. Among children with OI with 197 fractures and 200 surgical osteotomies, pamidronate therapy was associated with delayed healing of osteotomies but not with fracture healing, when age, mobility and other factors were accounted for (83). In a smaller study of OI children who underwent osteotomy an average of 2 months after initiation of bisphosphonate (oral alendronate or intravenous pamidronate) therapy, there was not evidence of delayed healing (84).

Atypical hip fractures
Atypical hip fractures, including low-energy proximal femur or femoral shaft fractures, have been reported in patients using alendronate for several years. In a case-control study, a significantly higher proportion of patients who presented with such subtrochanteric/femoral shaft fractures were receiving long-term bisphosphonates (mostly alendronate, on average for 7 years) than intertrochanteric/femoral neck fractures (85). These atypical femoral fractures occurred in elderly (average, 81 years old) postmenopausal, white (98%) women. This pattern of fracture has not been reported in children or young adults using alendronate (personal communication: Arthur Santora, Merck, 1/29/2010).
Jaw Osteonecrosis: Recent reports of jaw osteonecrosis (JON) have raised concerns about this potential serious adverse effect of bisphosphonate therapy (86). In this condition, areas of jaw bone that become exposed or necrotic, usually after dentoalveolar surgery or mild trauma, but occasionally spontaneously. From 2003-2006, 25 cases of JON have been reported in adults taking alendronate (in some cases, as well as other bisphosphonates), generally for treatment of myeloma or malignancy. Incidence appears to rise when treatment extends beyond 12 months. The greatest number of cases and greatest risk are associated with high-dose, parenteral bisphosphonates for long periods in cancer patients. Estimated incidence of JON over 36 months of treatment was 10% for zoledronate and 4% for pamidronate. The estimated incidence among those using alendronate, on the other hand, was 0.7 per 100,000 person-years. Based on post-marketing reports, as of January 15, 2009, Merck estimates the worldwide, cumulative reporting rate of osteonecrosis of the jaw to range between 1.6/100,000 patient-treatment-years and 3.84/100,000 patient-treatment-years, regardless of causality (87). Cases of alendronate-related JON have not been reported in children under 18 years old, but use in this age group is limited. Recommendations by Woo et al. (88) for patients beginning bisphosphonate therapy are shown in Table 1 below.

Table 1: Management Recommendations

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Treatment Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: patients about to begin aminobiphosphonate</td>
<td>Treat active oral infections, eliminate sites at high risk for infection (partially impacted wisdom teeth, nonrestorable teeth, or teeth with substantial periodontal bone loss)</td>
</tr>
<tr>
<td>therapy</td>
<td>Encourage routine dental care</td>
</tr>
<tr>
<td></td>
<td>Perform biannual oral examination and dental cleaning</td>
</tr>
<tr>
<td></td>
<td>Minimize periodontal inflammation</td>
</tr>
<tr>
<td></td>
<td>Provide routine restorative care of carious teeth</td>
</tr>
<tr>
<td></td>
<td>Provide endodontic therapy of nonsalvageable teeth</td>
</tr>
</tbody>
</table>

An IND is anticipated for this study of alendronate, both because of targeted age range and because of underlying HIV infection.

Issues Affecting Dosing or Eligibility for Bisphosphonates:
Alendronate is not metabolized in animals or humans (60). Therefore, drug and food interactions will be only related to effect on absorption or elimination, not on metabolism. Bioavailability was reduced by food, coffee, orange juice and likely calcium supplements and antacids; however, it was increased by ranitidine. Patients are advised to take alendronate 30 minutes before and at least 2 hours after food; they should wait at least 30 minutes after alendronate before taking other medications, including vitamin and mineral supplements (60).

Alendronate is not recommended for patients with renal insufficiency (creatinine clearance <35 mL/min) (60).

Drug Interactions
Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H2-antagonists is unknown (60).

Calcium Supplements/Antacids
It is likely that calcium supplements and antacids will interfere with absorption of alendronate. Therefore, patients must wait at least one-half hour after taking alendronate before taking any other oral medications.

Aspirin
In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving concomitant therapy with aspirin-containing products.

1.2 Rationale
HIV-infected youth are at increased risk of low bone mineral density due to HIV infection, its treatment, co-morbid conditions and other factors. Progressive bone mineral loss at an age when bones are usually at the peak of growth and mineral deposition may put them at increased risk of fractures in the short and long term.

Subjects in this study will be assessed for vitamin D status, supplemented appropriately with vitamin D and with calcium, and educated about food choices that are rich in vitamin D and calcium. In addition, subjects will be counseled in the importance and type of weight-bearing exercise that may improve bone health, and they will be asked to perform weight-bearing exercises every day. Thus, all subjects will have optimized nutritional and exercise approaches to improve low BMD throughout the study. The principal goal of the study is to determine if the addition of oral alendronate to this optimal background management of low BMD will result in substantial improvements in BMD.
Oral alendronate has been proven effective in reversing DXA-documented, low BMD and in reducing fractures in adults. Limited data suggest it is similarly safe and effective in children with low BMD or otherwise at increased risk of fracture. Previous pediatric studies of alendronate have used history of fractures, low BMD as defined by low DXA Z-score (range of eligibility criterion from cited studies: Z-score <-2.0, <-1.5 or <-1.0), or conditions associated with increased risk of fracture (regardless of BMD Z-scores) as study entry criteria. BMD improvement begins within 48 weeks of therapy in adult studies. This trial will aim to determine the safety and efficacy of 48-96 weeks of alendronate therapy in HIV-infected youth with low BMD by DXA. Because a vertebral compression fracture is diagnostic of osteoporosis but may falsely elevate LS DXA BMD reading, subjects with a history (in the prior 12 months) of a vertebral compression (atraumatic) fracture would also be eligible, regardless of their LS DXA BMD result.

This study will be an important opportunity to characterize underlying mechanisms associated with low BMD in HIV-infected youth who have multiple risk factors. The finding of disturbance in normal OPG/RANKL control of bone turnover (bone turnover measured by osteocalcin, alkaline phosphatase, and urine markers) may be different by degree of virologic control of HIV infection, different by degree of inflammation (as measured by cytokines), and may be different for those on TDF- and non-TDF-containing regimens. Furthermore, serial assessments of bone turnover in relation to alendronate treatment and to DXA measured changes in BMD will be potentially important in understanding different types or degrees of BMD response to alendronate treatment.

Because alendronate can persist in bones and persist in its effects beyond the duration of treatment, the study will be designed to have comparison periods of placebo and active alendronate treatment, and there will be an additional assessment 48 weeks after all subjects have completed study treatment.

Because the subjects eligible for this study must have a standardized LS BMD at least 1.5 standard deviations below average (a level associated with increased fracture risk in healthy children and consistent with DXA low BMD criteria used in other pediatric alendronate studies) and/or have suffered an atraumatic fracture, there is a compelling rationale to give these subjects access, in the systematic and scientific context of an investigational study, to a drug like alendronate, that has a proven track record of improving BMD in several adult populations (including HIV-infected adults) and in limited studies of children with other conditions associated with low BMD or bone fragility. We believe that the strong prospect for direct benefit in these subjects with established low BMD justifies (a) a study design that provides access to active drug for all subjects during the course of the study and (b) theoretical concerns about use of this
antiresorptive agent in youth whose bones are potentially immature and incompletely grown. In addition, the importance of treating existing bone problems in all affected youth justifies including female youth in this study despite the theoretical concerns (based on some animal data) about the potential negative effects (abnormal bone development or fetal loss) of alendronate if unintended pregnancy occurs during (animal data) or after (completely theoretical; no animal or human data) alendronate treatment. Further reassurance for including females includes: the lack of evidence of these reproductive concerns in the limited human data available; the requirement by the protocol to avoid pregnancy and use two forms of contraception throughout the study which will be stressed in the informed consent process and systematically reinforced at each study visit; and the inclusion in the study design of at least 48 weeks after cessation of active alendronate therapy during which pregnancy avoidance is still required, beyond the requirements of the package labeling (no minimum time between drug cessation and conception), other FDA-monitored studies (no minimum time between drug cessation and conception), and clinical practice by many experts (6 month deferral of conception, based on normalization of bone turnover markers suggestive of persistent bisphosphonate effect by that time).

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.11 To estimate and compare changes from pre-treatment levels in BMD of the lumbar spine after 24 and 48 weeks of alendronate treatment versus placebo.

2.12 To assess the safety of 48 weeks of alendronate use as measured by the incidence of new ≥ Grade 3 hematology or chemistry laboratory values, signs or symptoms, or new cases of jaw osteonecrosis (JON), atrial fibrillation or non-healing fractures.

2.2 Secondary Objectives

2.21 To estimate and compare changes from pre-treatment levels in whole body BMD after 24 and 48 weeks of alendronate treatment versus placebo.

2.22 To estimate and compare changes from pre-treatment levels in whole body and lumbar spine BMD after 96 weeks of alendronate treatment versus 48 weeks of alendronate followed by 48 weeks of placebo.

2.23 To assess the safety of 96 weeks of alendronate use as measured by the incidence of new ≥ Grade 3 hematology or chemistry laboratory values,
signs or symptoms, or new cases of jaw osteonecrosis (JON), atrial fibrillation or non-healing fractures.

2.24 To assess the effect of other known bone mineral determinants (age, gender, race/ethnicity, steroid use, Depo-Provera, tenofovir, pubertal stage, bone age, vitamin D status) and inflammatory cytokine levels on changes in BMD after 24 and 48 weeks of alendronate treatment.

2.25 To assess changes in BMD over a 48 and 96-week period after completion of 48 weeks of alendronate therapy

2.26 To characterize the alterations in pre-treatment bone marker turnover, RANKL/OPG ratio, central fat content (by whole body DXA) at baseline compared to levels after 48 weeks of alendronate therapy and determine if the changes in these outcomes correlate with changes in BMD.

2.27 To evaluate the effect of alendronate therapy on changes in HIV status (as measured by changes in viral load, CD4% and CDC disease category) and determine if the changes in these outcomes correlate with changes in BMD.

2.28 To estimate the duration of detectable urinary alendronate in adolescent subjects who have completed 48 and 96 weeks of alendronate therapy.

3.0 STUDY DESIGN

3.1 Overview

The study population consists of HIV-infected boys and girls, ≥11 to < 25 years old, on no antiretroviral or on stable antiretrovirals, with (1) DXA lumbar spine BMD z-score < -1.5 OR (2) history of fragility fracture (in the prior 12 months). This is a pilot study to assess the effect of 48 weeks of alendronate therapy on BMD in HIV-infected youth with low BMD.

Fifty-one (51) subjects will be randomized equally to one of three treatment groups: Group 1a will receive alendronate for 96 weeks; Group 1b will receive alendronate for 48 weeks followed by alendronate placebo for 48 weeks; Group 2 will receive alendronate placebo for 48 weeks followed by alendronate for 48 weeks. All three Groups will be followed off study treatment for an additional 48 weeks when they will continue to receive Vitamin D/Calcium and conform to the recommended exercise regimen.

Since alendronate is expected to persist in subjects even after discontinuing the drug, the effects of alendronate on some of the outcomes may persist after
subjects are taken off active treatment. This design will allow estimation of changes in BMD after one and two years of active treatment, but the primary treatment comparisons will focus on treatment differences in the first Step.

All DXA scans performed for screening and during the study will be interpreted by the site’s institution; these local readings will be used for confirmation of eligibility and clinical monitoring. In addition, all DXA performed for screening (with the exception of DXA performed for clinical care prior to the study) and during the study will be transmitted for centralized readings by a single reviewer; these centralized readings will be used for study end points and analyses.

As optimized background treatment for low BMD, all subjects will receive vitamin D/calcium supplementation, instruction to perform daily weight-bearing exercise*, and nutritional counseling about foods rich in vitamin D and calcium throughout the initial 96-week, alendronate/placebo period of the study.

* Subjects who are unable to perform weight-bearing exercises are still eligible to participate in the study.

3.2 Screening

A separate screening visit will be required for this study. Entry should take place no more than 4 weeks from screening. Up to 12 weeks is allowed for screening DXA and dental results. Sites must have the results of the following tests from screening before being able to proceed to entry: LS DXA, chemistry laboratory results, hematology results, negative pregnancy test for females of reproductive potential, 25-OH-vitamin D (total), intact PTH (with accompanying calcium measurement), dental exam and dental panoramic radiograph. For subjects who are consented and found to be ineligible (i.e. screening failure) after undergoing study-directed LS DXA, dental evaluation and/or 25-OH vitamin D/ intact PTH laboratory evaluations, sites must complete a Screening Failure case report form (CRF) as well as the results/tracking forms for all of the previously specified evaluations using their Screening Number, which will collect data regarding reasons for subject ineligibility.

Screening DXA [See Table 2]:
It is expected that many subjects will have results of a LS DXA scan obtained through clinical care (i.e., pre-study LS DXA) as part of the basis for qualifying for this study.

- If a qualifying pre-study LS DXA (i.e., LS DXA z-score < -1.5) was performed within 12 months prior to entry, that result may be used as the basis for DXA eligibility criterion and as the screening LS DXA. In this case, a study LS DXA together with a whole body (including head)
DXA will be performed at entry, and no DXA is required at the screening visit, provided that the entry DXA is performed within 12 months of the pre-study DXA. In this case, the pre-study LS DXA can be on any DXA model.

- If entry does not occur until ≥12 months from the pre-study DXA, then a screening LS-DXA should be obtained to confirm eligibility. In this case, the screening DXA must be performed on one of the DXA models outlined in the SIP in Section 4.5. The screening visit LS DXA z-score must be < -1.5 in order for the patient to be eligible; the exception to this rule is that a patient with a history in the prior 12 months of atraumatic fracture will be eligible to continue, regardless of LS DXA z-score. The screening LS DXA will also be used as the entry LS DXA as long as study drug is initiated within 12 weeks of the screening DXA; however, a whole-body (including head) DXA will be required at study entry in all cases. If more than 12 weeks elapse between screening and entry, then the patient will need a repeat LS DXA and an initial whole-body (including head) DXA at entry in order to continue in the study.

- The subject’s entry visit LS DXA z-score must be confirmed as <-1.5 before study drug can be initiated. The subject will be ineligible to continue in the study (and will be replaced by another subject) if the entry LS DXA z-score is ≥1.5; the exception to this rule is that a patient with a history in the prior 12 months of atraumatic fracture will be eligible to continue, regardless of LS DXA z-score, since DXA z-scores often underestimate degree of low BMD in these patients at high risk of additional fractures.
Table 2: Qualifying Screening DXA

<table>
<thead>
<tr>
<th>Pre-study/Qualifying DXA (i.e., Clinical Care)</th>
<th>Interval between Pre-study/Qualifying DXA to Study Entry</th>
<th>Screening Visit</th>
<th>Interval to Entry</th>
<th>Entry Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS DXA (any model) z-score &lt; -1.5</td>
<td>&lt;12 months</td>
<td>No DXA required</td>
<td>&lt;12 months from Pre-study/qualifying DXA to Entry</td>
<td>LS DXA** (must have z-score &lt; -1.5) &amp; Whole-body (including head) DXA**</td>
</tr>
<tr>
<td>LS DXA (any model) z-score ≥-1.5</td>
<td>≥12 months</td>
<td>LS DXA** (must have z-score &lt; -1.5)</td>
<td>&lt;12 weeks (ideally &lt;4 weeks)</td>
<td>Whole-body (including head) DXA** only</td>
</tr>
<tr>
<td>NONE*</td>
<td></td>
<td>At least 2 of protocol-specified low BMD risk factors required: LS DXA** (must have z-score &lt; -1.5)</td>
<td>&lt;12 weeks (ideally &lt;4 weeks)</td>
<td>Whole-body (including head) DXA** only</td>
</tr>
</tbody>
</table>

*Not eligible for study unless Protocol Team activates plan for study-funded initial DXA to improve accrual

** These DXA must be performed using one of the DXA models outlined in the SIP in Section 4.5.

NOTE: For subjects with atraumatic fractures (defined as a fracture that occurs as a result of a fall from standing height or less), in the prior 12 months follow guidelines in this table for the timing and scanner model of DXAs, BUT ANY BMD z-score is considered eligible (See Section 4.15).

If study accrual is inadequate (See Section 8.511) and the Protocol Team announces that study funds will be made available to pay for screening LS DXA in subjects who have never had a DXA in the past, the sites will be limited to the number of study-funded initial DXAs they can perform (number to be determined by Protocol Team based on accrual need) and will be limited to otherwise eligible patients who have (a) history of atraumatic fracture ≥12 months before entry, (b) history of at least two fractures of any kind that have occurred on at least two different days, (c) highly limited ambulation or non-ambulatory [e.g., daily wheelchair use or daily leg-brace use for ambulation], or (d) have at least TWO of the following risk factors for low BMD: BMI<10%ile, persistent cigarette smoking, Depo-Provera use for >12 months, Tanner I/II in a girl >13 or a boy >14 years old, more than 8 weeks of systemic steroid use (any dose) in the past 6 months. In such cases, a screening LS DXA z-score < -1.5 will meet...
the DXA eligibility criterion. These screening DXA must be performed on one of the DXA models outlined in the SIP in Section 4.5. It is estimated that approximately 25% of these study-funded screening DXAs will meet this criterion. Subjects will need to sign consent before undergoing a study-funded initial LS DXA. The LS DXA will not need to be repeated at entry if entry and study medication initiation occur within 12 weeks of the screening LS DXA; however, whole-body (including head) DXA will still need to be performed at entry.

Each subject will be in the study for 144 weeks from the time of study entry.

Subjects will be unblinded after follow-up is complete on all enrolled subjects and the clinical and laboratory databases have been reviewed and finalized for analysis. Once this date has been determined by the Protocol Team, unblinding lists for each site will be distributed as outlined in the IMPAACT Unblinding SOP (SDM-4001-01), which can be downloaded from the IMPAACT website:

http://www.impaactgroup.org/files/sops/SDM-4001-01.doc

Refer to Appendix I for specific study requirements.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Step 1 Inclusion Criteria

4.11 Age ≥11 to < 25 years of age, at entry.

4.12 Documentation of HIV-1 infection defined as positive results from two samples collected at different time points. The same method may be used at both time points. All samples tested must be whole blood, serum or plasma.

Subjects < 18 months of age

The first test may be any of the following:

- One HIV DNA PCR
- One HIV RNA PCR (quantitative >5,000 copies/mL or qualitative)
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid

If the first test is positive, a second sample should be collected and tested in an NIH-approved laboratory participating in an appropriate external quality assurance program using any of the tests listed above (except for qualitative RNA assays).
Subjects > 18 months of age

The first test may be any of the following:

- Two rapid antibody tests from different manufacturers or based on different principles and epitopes
- One rapid antibody test AND one [enzyme immunoassay (EIA) OR Western blot (WB) OR immunofluorescence OR chemiluminescence]
- One EIA AND one [WB OR immunofluorescence OR chemiluminescence]
- One HIV DNA PCR
- One HIV RNA PCR (quantitative >5,000 copies/mL or qualitative)
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid

If the first test(s) is positive, a second sample collected and tested in an NIH-approved laboratory participating in an appropriate external quality assurance program using any of the tests listed above (except for qualitative RNA assays).

4.13 HIV-infection acquired before puberty.

4.14 For subjects receiving antiretroviral therapy, they must be prescribed the same antiretroviral agents for at least 12 weeks prior to study entry and have a viral load <10,000 copies/mL. N.B.: Fluctuating ARV adherence difficulties are not an exclusion. Changes in formulation (e.g. liquid or pill) and switches between individual component and co-formulated ARVs are not exclusions, provided there is no change in the individual ARVs included in the regimen. Substitution of a single ARV in the past 12 weeks for toxicity/intolerance or for greater dosing convenience will be permitted with the permission of the Protocol Team.

For subjects who are NOT receiving antiretroviral therapy, they must have not been prescribed antiretroviral therapy for at least 12 weeks before study entry, and they must have no absolute indication for therapy (Subjects not receiving antiretroviral therapy must have VL <50,000 copies/mL, CD4 >20%, CD4 >350 and be CDC Classification N, A, or B).

4.15 A lumbar spine (LS) DXA BMD z-score < -1.5 OR history within the prior 12 months of fragility fracture (regardless of DXA result),
which is defined as a fracture that occurs as a result of a fall from standing height or less within the timeframe specified in Section 3.2.

4.16 Availability for routine dental exam and care every 6 months.

4.17 Demonstrated ability and willingness to swallow study medications.

4.18 Female subjects of reproductive potential (having reached menses, or not having reached menopause or not having undergone hysterectomy, bilateral oophorectomy, or tubal ligation) must have a negative pregnancy test at screening and within 48 hours prior to study entry.

4.19 Female subjects of reproductive potential (having reached menses, or not having reached menopause or not having undergone hysterectomy, bilateral oophorectomy, or tubal ligation) who engage in sexual activity that could lead to pregnancy must agree to avoid pregnancy during the entire 144 week trial and to consistently and appropriately use at least two of the following contraception methods: condoms, diaphragm or cervical cap with spermicide, IUD, hormonal-based contraception. A list of acceptable methods can be found at the FDA Birth Control Guide (http://www.fda.gov/fdac/features/1997/babyguide.pdf).

Note: “Female subjects of reproductive potential” is defined as girls who have reached menarche or women who have not been post-menopausal for at least 24 consecutive months (e.g. who have had menses within the preceding 24 months), or have not undergone a sterilization procedure (hysterectomy, bilateral oophorectomy or salpingotomy). If the female subject is not of reproductive potential, she is eligible without requiring contraception.

4.110 Parent or legal guardian able and willing to provide signed informed consent for children who can not provide consent for themselves.

4.2 **Step 2 Inclusion Criteria**

4.21 Completion of Step 1.

4.3 **Step 1 Exclusion Criteria**

4.31 Weight > 300 lbs [Exceeds weight limit of DXA scanners].
4.32 Depo-Provera taken by female subjects for less than one full year during the year prior to study entry.

Note:
- Female subjects who are on Depo-Provera at study entry should have been receiving Depo-Provera continuously for at least one year prior to study entry.
- Female subjects who are not on Depo-Provera at study entry should not have received any Depo-Provera during the year prior to study entry.
- Female subjects who have never received Depo-Provera or who only received Depo-Provera more than 12 months prior to study entry are eligible.

4.33 Anticonvulsant therapy.

4.34 Proven growth hormone (GH) deficiency.

4.35 Use of GH in the 12 months prior to entry (past use allowed).

4.36 Primary hyperparathyroidism.

4.37 Hypoparathyroidism.

4.38 Renal failure (CrCl <35mL/min).

4.39 Cushing syndrome.

4.310 Active dental infection.

4.311 Dental or periodontal disease that is expected to require more than basic restorative care (formally confirmed by a dentist at study screening visit).

4.312 Pregnancy or lactation.

4.313 Esophageal or gastric ulcer, chronic NSAID use, aspirin use.

4.314 Change in antiretroviral regimen within 12 weeks of study entry.
N.B.: Fluctuating ARV adherence difficulties are not an exclusion. Changes in formulation (e.g. liquid or pill) and switches between individual component and co-formulated ARVs are not exclusions, provided there is no change in the individual ARVs included in the regimen. Substitution of a single ARV in the past 12 weeks for
toxicity/intolerance or for greater dosing convenience will be permitted with the permission of the Protocol Team.

4.315 Tenofovir disoproxil fumarate (TDF) taken by subjects for less than one full year during the year prior to study entry.

Note:
- Subjects who are on TDF at study entry should have been receiving TDF continuously for at least one year prior to study entry.
- Subjects who are not on TDF at study entry should not have received any TDF during the year prior to study entry.
- Subjects who have never received TDF or who only received TDF more than 12 months prior to study entry are eligible.

4.316 Hemoglobin < 10 g/dL.

4.317 Any past pharmacologic treatment (except vitamin D and/or calcium supplementation) for low bone density.

4.318 Inability to stand or sit upright for at least 30 minutes.

4.319 Hypersensitivity to any component of alendronate.

4.320 Hypocalcemia (less than the lower limit of normal established by the local laboratory in which it is performed).

4.321 Known abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia.

4.322 25-OH vitamin D <10 ng/mL in combination with elevated intact PTH above the ULN for the local laboratory in which it is performed.

4.4 Concomitant Medications Guidelines

4.41 Disallowed Medications
- Aminoglycosides
- Anticonvulsants
- Chronic aspirin therapy (occasional use allowed; please consult the P1076 team [actg.teamp1076@fstrf.org] for guidance)
- Chronic non-steroidal anti-inflammatory drug, such as ibuprofen and naproxen (occasional use allowed; please consult the P1076 team [actg.teamp1076@fstrf.org] for guidance)
4.5 Enrollment Procedures

Prior to implementation of this study, each site must have the protocol document and the consent form approved by the local Institutional Review Board (IRB)/Ethics Committee (EC). A Site Implementation Plan (SIP) is required from each site participating in the study. The SIP will collect data concerning availability of Hologic DXA scanner (QDR4500A, QDR4500W or Delphi A models preferred; other Hologic models will require Protocol Team approval) and the software used for the DXA scanner (e.g., Discovery, Apex), access to a dentist who can perform oral exams and panoramic radiographs (preferably, electronically-transmissible), and the site’s ability to follow and collect data on subjects who become pregnant while on study. The site must have capability for local interpretation of study DXA scans (since local DXA reading is required in addition to central readings for study DXA scans). The plan must be submitted to the Protocol Team for review and approval before protocol registration can occur. Each site must complete the protocol registration process through the DAIDS Regulatory Compliance Center (RCC) Protocol Registration Office and receive DAIDS notification of approval to begin enrollment before subjects can be enrolled in this study.

Subjects meeting the study eligibility criteria will be enrolled through the Data Management Center (DMC) registration screens. Written informed consent for study participation must be obtained before any study related procedures are performed. All subjects who sign the consent for P1076 must be registered for P1076 using the DMC Screening Program at the time consent is signed. Subjects who meet the eligibility criteria may proceed to randomize to P1076 at the entry visit. All subjects who fail screening after completing study-directed LS DXA, dental evaluations and/or 25-OH vitamin D/intact PTH laboratory evaluations will complete the Screening Failure CRF as well as the results/tracking forms for all of the previously specified evaluations using their Screening Number, which will collect data regarding reasons for subject ineligibility. Subjects registered to Step 1 will be randomly assigned to Groups 1a, 1b or Group 2. Registration to Step 2 will take place at the 48 week visit through the Data Management Center (DMC) registration screens in order to help ensure that the pharmacy has crossed subjects over to the next assigned treatment (i.e. alendronate -> alendronate, alendronate-> placebo, or placebo-> alendronate).

4.6 Co-enrollment Procedures

1. Co-enrollment in observational trials and non-antiretroviral treatment trials is permitted.
2. Co-enrollment in P1074: “A Prospective Surveillance Study of Long-term Outcomes in HIV-Infected Infants, Children and Adolescents” is encouraged and must be offered to each subject in P1076 as a means to provide additional, longer-term follow-up.

3. Subjects in this protocol should be on a stable ARV regimen in order to avoid resulting changes in virologic suppression that may confound interpretation of study drug effect on BMD. Thus, co-enrollment in ARV treatment trials is discouraged but may be permitted with approval from the Protocol Team.

4. Co-enrollment in ATN 061: “Preservation and Expansion of T-cell Subsets Following HAART De-intensification to Atazanavir/ritonavir (ATV/r) in Adolescents and Young Adults with CD4 + T Cells > 350 cells/mm³ Initiating HAART” is NOT permitted.

5. All other co-enrollments in protocols require the assent of the protocol chairs of the main protocol and the co-enrollment protocols.

5.0 STUDY TREATMENT

Study treatment is defined as alendronate or placebo plus calcium carbonate/vitamin D plus minerals. For Step 1, the first dose of alendronate/placebo must be taken within 7 days of randomization or of entry DXA result availability, whichever occurs later. For Step 2, the first dose of alendronate/placebo must be taken within 7 days of registration. Discontinuation of alendronate/placebo is considered discontinuation of study treatment. Subjects are randomized at Step 1 to Group 1a, 1b or Group 2.

5.1 Drug Regimens, Administration and Duration

5.11 Group 1a

- **STEP 1: Day 1 until Week 48 study visit**
  
  Alendronate 70 mg if > 30 kg or 35 mg if ≤ 30 kg p.o. once weekly
  Calcium carbonate 600 mg/vitamin D 400 IU + minerals tablet one daily p.o. for subjects with 25-OH-vitamin D levels ≥20 ng/mL: one tablet p.o. twice daily in divided doses for subjects with 25-OH-vitamin D levels: <20 ng/mL

- **STEP 2: Week 48 study visit until Week 96 study visit**
  
  Alendronate 70 mg if > 30 kg or 35 mg if ≤ 30 kg p.o. once weekly. Calcium carbonate 600 mg/vitamin D 400 IU + minerals tablet one daily p.o. for subjects with 25-OH-vitamin D levels ≥20 ng/mL: one tablet p.o. twice daily in divided doses for subjects with 25-OH-vitamin D levels: <20 ng/mL
Week 96 study visit until Week 144
Calcium carbonate 600 mg/vitamin D 400 IU + minerals tablet one daily p.o. for subjects with 25-OH-vitamin D levels ≥20 ng/mL: one tablet p.o. twice daily in divided doses for subjects with 25-OH-vitamin D levels: <20 ng/mL

5.12 Group 1b
• STEP 1: Day 1 until Week 48 study visit
  Alendronate 70 mg if > 30 kg or 35 mg if ≤ 30 kg p.o. once weekly Calcium carbonate 600 mg/vitamin D 400 IU + minerals tablet one daily p.o. for subjects with 25-OH-vitamin D levels ≥20 ng/mL: one tablet p.o. twice daily in divided doses for subjects with 25-OH-vitamin D levels: <20 ng/mL

• STEP 2: Week 48 study visit until Week 96 study visit
  Placebo for alendronate 70-mg tablet if >30kg or Placebo for alendronate 35-mg tablet if ≤ 30 kg p.o. once weekly. Calcium carbonate 600 mg/vitamin D 400 IU + minerals tablet one daily p.o. for subjects with 25-OH-vitamin D levels ≥20 ng/mL: one tablet p.o. twice daily in divided doses for subjects with 25-OH-vitamin D levels: <20 ng/mL

Week 96 study visit until Week 144
Calcium carbonate 600 mg/vitamin D 400 IU + minerals tablet one daily p.o. for subjects with 25-OH-vitamin D levels ≥20 ng/mL: one tablet p.o. twice daily in divided doses for subjects with 25-OH-vitamin D levels: <20 ng/mL

5.13 Group 2
• STEP 1: Day 1 until Week 48 study visit
  Placebo for alendronate 70-mg tablet if >30kg or Placebo for alendronate 35-mg tablet if ≤ 30 kg p.o. once weekly. Calcium carbonate 600 mg/vitamin D 400 IU + minerals tablet one daily p.o. for subjects with 25-OH-vitamin D levels ≥20 ng/mL: one tablet p.o. twice daily in divided doses for subjects with 25-OH-vitamin D levels: <20 ng/mL

• STEP 2: Week 48 study visit until Week 96 study visit
Alendronate 70 mg if > 30 kg or 35 mg if ≤ 30 kg p.o. once weekly
Calcium carbonate 600 mg/vitamin D 400 IU + minerals tablet one
daily p.o. for subjects with 25-OH-vitamin D levels ≥ 20 ng/mL:
one tablet p.o. twice daily in divided doses for subjects with 25-
OH-vitamin D levels: < 20 ng/mL

Week 96 study visit until Week 144
Calcium carbonate 600 mg/vitamin D 400 IU + minerals tablet one
daily p.o. for subjects with 25-OH-vitamin D levels ≥ 20 ng/mL:
one tablet p.o. twice daily in divided doses for subjects with 25-
OH-vitamin D levels: < 20 ng/mL

5.14 Alendronate Administration

Alendronate/placebo will be administered as one tablet by mouth one time
per week. Subjects should choose the day of the week that best fits their
schedule. Every week, subjects will take one alendronate/placebo tablet on
their chosen day. For Step 1, the first dose of alendronate/placebo must be
taken within 7 days of randomization or of entry DXA result availability,
whichever occurs later. For Step 2, the first dose of alendronate/placebo
must be taken within 7 days of registration. Subject must not take
alendronate/placebo at bedtime or before getting up for the day.

After getting up for the day, and at least 30 minutes before the first food,
beverage, or other medication, subjects should swallow
alendronate/placebo with a full glass (6 to 8 ounces) of plain water (not
mineral water, not coffee or tea, not juice) on an empty stomach.
Alendronate/placebo should be taken in the morning at least 30 minutes
before any food, beverage, or other medicines, since consumption of these
during this interval will decrease the amount of alendronate absorbed by
the body. Waiting longer than 30 minutes will allow more of the drug to
be absorbed, thereby increasing its effectiveness. Medicines such as
antacids, calcium, and vitamin supplements (including the study-supplied
calcium/vitamin D supplement) will also decrease the absorption of
alendronate and must not be taken until at least 30 minutes after
alendronate/placebo.

Subjects must remain fully upright (sitting, standing or walking) for at
least 30 minutes after taking alendronate/placebo. Subjects must not lie
down until after their first food of the day. Remaining fully upright will
help alendronate reach the stomach faster and will also help prevent
irritation to the esophagus.
Subjects who miss a dose may take one alendronate/placebo tablet on the morning after remembering, provided that it is at least 3 days from the next scheduled dose. Subjects should return to their original schedule as quickly as possible. If more than 3 days pass following a missed dose, subjects should skip that dose altogether and return to their original schedule. Alternatively, subjects may choose to establish a new schedule following a missed dose.

5.15 Calcium/Vitamin D Administration

Calcium carbonate/vitamin D+ minerals will be administered as one combination tablet by mouth, one or two times per day, depending on 25-OH-vitamin D levels [see Sections 5.11, 5.12, and 5.13]. For Step 1 and Step 2, the first dose of calcium/vitamin D must be taken within 72 hours after randomization. The calcium/vitamin D should be taken at mealtime and should be taken with a full glass of water or juice. Calcium/vitamin D supplements should be taken at least 30 minutes after study alendronate/placebo.

5.2 Drug Formulation

Alendronate: 70-mg tablets and matching placebo and 35-mg tablets and matching placebo. Store in pharmacy in a well-closed container at room temperature, 15°-30°C (59°-86°F).

At the time of Version 2.0, Calcium carbonate 600-mg/vitamin D 400-IU+ minerals chewable tablets (Caltrate®) are being provided. Other calcium/vitamin D formulations that appear equivalent in dosing of calcium and vitamin D may be permitted upon review and approval by the P1076 protocol team. Store in pharmacy at 15°-30°C (59°-86°F). Do not expose to excessive heat or moisture.

5.3 Drug Supply, Distribution and Pharmacy

Alendronate 70-mg tablets, 35-mg tablets and placebo for alendronate 70-mg and placebo for alendronate 35-mg will be supplied by Merck & Co, Inc.

Calcium carbonate 600-mg/vitamin D 400-IU+ minerals tablets will be purchased by the IMPAACT.

Alendronate, matching placebos and calcium carbonate/vitamin D+ minerals tablets will be available through the NIAID Clinical Research Products Management Center. The IMPAACT pharmacist can obtain the study products for this protocol by following the instructions in the manual, Pharmacy
Guidelines and Instructions for DAIDS Clinical Trials Networks, in the section Study Product Management Responsibilities.

Sufficient supplies of study drugs should be dispensed at each clinic visit to last until the next scheduled clinic visit. Alendronate/placebo will not be supplied after the end of the 96 week treatment period. Calcium carbonate/vitamin D will not be supplied after the end of the 144 week treatment period.

5.31 Study Product Accountability

The IMPAACT pharmacist is required to maintain complete records of all study products received from the NIAID Clinical Research Products Management Center and subsequently dispensed. All unused study products must be returned to the NIAID Clinical Research Products Management Center after the study is completed or terminated. The procedures to be followed are provided in the manual, Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks, in the section Study Product Management Responsibilities.

5.4 Replacement of Subjects

Subjects will be replaced if they do not receive alendronate/placebo drug.

In the event of replacement, the subject is considered off-study and requires no further follow-up.

6.0 SUBJECT MANAGEMENT

6.1 Exercise Regimen

Subjects will be asked to perform 60 minutes of weight-bearing exercise each day. Neuromuscular problems, other disability, and degree of fitness may impact on the ability of an individual subject to achieve full adherence to the exercise regimen. A standardized questionnaire will be used to systematically collect information from participants about their weight-bearing exercise.

The subject instruction sheet will include the following instructions for subjects about the exercise regimen:

Try to do weight-bearing exercise every day for 60 minutes

- Weight-bearing exercise helps strengthen your bones.
Examples of weight-bearing exercises include: Running, Jumping, Hopping, Skipping, Jumping rope, Dancing, Climbing stairs, Jogging, Aerobic dancing, Hiking, Inline skating, ice skating, tennis, racquet ball, handball and other racquet sports

Team sports such as soccer, volleyball, basketball, field hockey, softball and baseball are also good weight-bearing exercises.

6.2 Consistency of TDF and Depo-Provera Use

The greatest effect on BMD occurs in the months following initiation or discontinuation of TDF or Depo-Provera, and then the effects on BMD generally level off. As a result, subjects are only eligible for entry onto the study if they have had stable TDF and Depo-Provera use status. Once on study, it is also important for subjects to maintain the same TDF status and Depo-Provera status as existed at entry. However, it is also recognized that circumstances for subjects may arise over the course of this 144 week study that would make change in TDF or Depo-Provera use in the best clinical interest of the patient. Thus, subjects will not be required to come off study or off study drug on the basis of a change in TDF or Depo-Provera use during the study, but providers and subjects should make every effort to avoid change in TDF or Depo-Provera during the study.

- Every effort should be made to avoid initiation or discontinuation of Depo-Provera while on study.
- Every effort should be made to avoid initiation or discontinuation of TDF while on study.

6.3 Toxicity Management

In addition to toxicity monitoring at the major study visits at 24, 48, 72 and 96 weeks (±2 weeks) and a final visit at week 144 (±8 weeks), subjects will have an additional toxicity/adherence monitoring study visit at 12 ± 2 weeks after each of the major study visits: i.e., weeks 12, 36, 60, and 84. Furthermore, screening for toxicity (and assessment of adherence) will take place by phone at weeks 1, 4, 49, and 52 (±3 days) and 4 weeks (±2 weeks) after each of the major study visits: i.e., weeks 28, 76, and 100.

A standardized questionnaire will be used at each phone contact and clinic visit to assess for signs and symptoms related to targeted adverse events:
• Pain or difficulty with swallowing
• Midline chest pain or burning
• Palpitations, or feeling like heart not beating normally
• Fainting or nearly fainting, without any other explanation
• Heartburn
• Tooth or jaw pain
• Muscle or joint swelling or pain
• Bone fracture or injury
• Concern about pregnancy
• Hospitalization

A positive response to telephone-administered questions about signs and symptoms related to targeted adverse events will require a follow-up study visit as soon as possible and within 72 hours. See Appendix I-B for additional details. The exception to this time requirement would be if the patient were hospitalized outside the site’s institution; in this case, the site would be asked to obtain information by phone from the medical team caring for the patient in the hospital.

All toxicities will be graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004, must be used and is available on the RCC web site (http://rcc.tech-res.com/safetyandpharmacovigilance/).

Management of adverse experiences will be according to the best clinical practice and the judgment of the site investigator. Alternate explanations for clinical and laboratory abnormalities must be sought. Laboratory reference ranges will be the institutional values. However, if a site does not have an age-specific normal range/value for a particular laboratory analyte, the site should use the latest edition of the Harriet Lane Handbook for normal ranges/values and document this for monitoring (89). Abnormal clinical and laboratory findings should be followed until resolution to < Grade 2.

The toxicity management guidelines are for events for which a relationship to study drugs cannot be excluded. Most clinical or laboratory adverse events (AEs) that are definitely unrelated to study drug(s) will not result in study drug interruption. However, life-threatening clinical or laboratory adverse events (AEs) that are definitely unrelated to study drug(s) will require consultation of the Protocol Team to determine if study drug should be temporarily or permanently discontinued.
Toxicity management will be as outlined below, except for pregnancy, tooth or jaw pain, atrial fibrillation, musculoskeletal pain, or non-healing fracture (see 6.31).

Grade 1 Toxicity:
Continue study drugs.

Grade 2 Toxicity:
Continue study drugs.

Grade 3 Toxicity:
Study drugs can be continued at the discretion of the site investigator/clinician for clinical events, or while awaiting a repeat assessment/confirmation of an abnormal laboratory test as soon as possible (at most within 1 week). If repeat assessment confirms Grade 3 toxicity, hold study drug (alendronate or placebo) and follow abnormal laboratory values weekly. If toxicity resolves to < Grade 2 within 21 days, study drug can be restarted. If Grade 3 toxicity persists for >21 days, or recurs to > Grade 3 after reintroduction of study drugs, all study drugs must be permanently discontinued.

Grade 4 Non-Life-Threatening Toxicity:
All study drugs should be held. For abnormal laboratory test, repeat assessment/confirmation should be done as soon as possible (at most within 1 week). If repeat assessment confirms Grade 4 toxicity, all study drugs should be permanently discontinued. If repeat assessment shows a Grade 3 toxicity, continue to hold all study drugs and follow abnormal laboratory values weekly. If toxicity resolves to < Grade 2 within 21 days, all study drugs can be restarted. If > Grade 3 toxicity recurs after reintroduction of study drugs, all study drugs must be permanently discontinued.

Grade 4 Life-Threatening Toxicity:
All study drugs should be permanently discontinued.

Subjects discontinuing study treatment will not be unblinded to their treatment unless the information is critical for making immediate therapeutic decisions for the subject (e.g. if withholding the treatment information would put the subject at risk of serious adverse events or death). If a subject does need to be unblinded, then the site should notify the study Chairs and Medical Officers and with their approval, submit a request to the Data Management Center using the Unblinding Request Program on the DMC Web site, as outlined in the IMPAACT Unblinding SOP (SDM-4001-01), which can be downloaded from the IMPAACT website:
6.31 Special Toxicity Management Guidelines

6.311 Tooth or Jaw Pain

Any episode of tooth or jaw pain or abnormality on dental exam will be fully evaluated for possible jaw osteonecrosis by dentist at study site. Evaluation will include, but not be limited to, dental exam, and panoramic radiographs. If tooth or jaw pain is reported, the Protocol Team [actg.teamp1076@fstrf.org] should be notified within 48 hours and the study medication will be discontinued immediately, pending results of dental evaluation. Dental evaluation should take place as soon as possible and no later than one week after the problem is reported. If JON is confirmed or considered probable by dental evaluation, alendronate will be permanently discontinued, and the event will be reviewed by the Core Protocol Team (including Protocol Dentist) within 72 hours according to protocol-defined reporting requirements. [see Section 7.0]

6.312 Atrial fibrillation (AFib)

Any episode of AFib (whether suspected or confirmed) will be fully evaluated at the clinical study site. Evaluation will include, but not be limited to, an electrocardiogram, interpreted by the site cardiologist and the site cardiologist report transmitted to the Protocol Team actg.teamp1076@fstrf.org. Once AFib is suspected, the Protocol Team will be notified within 48 hours and the study medication will be discontinued immediately, pending results of the cardiac evaluation. If AFib is confirmed or considered probable after full evaluation, alendronate will be permanently discontinued, and the event will be reviewed by the Core Protocol Team within 72 hours according to protocol-defined reporting requirements. [see Section 7.0]

6.313 Non-healing fracture (NHFx)

Any episode of NHFx (whether suspected or confirmed) will be fully evaluated at the clinical study site. Evaluation will include, but not be limited to, a plain radiograph of the affected site, interpreted by the site radiologist and
transmitted to the Protocol Team
actg.teamp1076@fstrf.org. The results of the evaluation, including the report of the radiograph interpretation, will be transmitted to the Protocol Team. Once NHFx is suspected, the Protocol Team will be notified within 48 hours and the study medication will be discontinued immediately, pending results of the radiologic evaluation. If NHFx is confirmed or considered probable after full evaluation, alendronate will be permanently discontinued, and the event will be reviewed by the Core Protocol Team (including Protocol Radiologist) within 72 hours according to protocol-defined reporting requirements. [see Section 7.0]

6.314 Musculoskeletal Swelling or Pain

Any episode of bone joint or muscle swelling or pain for which no other cause is clearly identified will be fully evaluated at the clinical study site.

For Grade 1 symptoms, continue study drugs.

For Grade 2 symptoms, for which no other cause is apparent, study drugs can be continued. Patient should be reevaluated within 21 days; if symptoms persist at grade 2, study drugs should be temporary held until symptoms resolve to grade ≤ 1. Study drugs can then be restarted at the discretion of the clinician and upon consultation with the study team. If symptoms recur to grade ≥ 2, study drugs should be permanently discontinued.

For Grade 3 symptoms for which no other cause is apparent, study drugs can be continued. Patient should be reevaluated within 7 days; if symptoms persist at grade 3, drugs should be discontinued. If symptoms resolve to grade ≤ 1 within 12 days, drug can be restarted under close observation at the discretion of the clinician and upon consultation with the study team; if symptoms recur to grade ≥ 2 after restarting study drug, they should be permanently discontinued.

For Grade 4 symptoms, study drug should be held. If no other cause is identified by the site, study drugs should be permanently held. If a cause is identified by the site and
symptoms resolve to grade ≤ 1 within 21 days holding study drugs and, study drugs can be restarted at the discretion of the clinician and upon consultation with the study team. If symptoms recur to grade ≥ 2, study drugs should be permanently discontinued.

6.315 Pregnancy Loss (Miscarriage, Spontaneous Abortion)

Any episode of loss of a confirmed pregnancy must be reported to DAIDS and the P1076 Protocol Team [actg.teamp1076@fstrf.org] as an Expedited Adverse Event. The event will be reviewed by the Core Protocol Team within 72 hours according to the protocol-defined reporting requirements. [See Section 7.0]

6.4 Subject Management

6.41 Pregnancy

Any episode of pregnancy (whether suspected or known) must be confirmed within 72 hours with an FDA-cleared serum or urine pregnancy test performed at a CLIA-licensed local laboratory. Once pregnancy is suspected, the P1076 Protocol Team [actg.teamp1076@fstrf.org] must be notified within 48 hours and the study medication will be discontinued immediately, pending results of confirmatory pregnancy test. Subject may immediately restart study medication once pregnancy has been ruled out. If pregnancy is confirmed, alendronate will be permanently discontinued, and the event will be reviewed by the Core Protocol Team within 72 hours according to protocol-defined reporting requirements. [See Section 7.0] Information about pregnancy outcome will be collected. Sites will be strongly encouraged to report pregnancy occurrence and outcome directly to Merck & Co., Inc. for inclusion in their alendronate pregnancy registry.

6.42 Management of Vitamin D levels and supplementation through Week 96

6.421 For subjects who initially are prescribed ONE vitamin D/Calcium supplement daily (with screening 25-OH vitamin D ≥20 ng/mL):

- If 25-OH vitamin D falls below 10 ng/mL AND intact PTH is above the ULN for the local laboratory in which
it is performed, see 6.5 for Temporary discontinuation of study treatment.

- If 25-OH vitamin D falls below 20 ng/mL (but intact PTH remains within normal limits for the local laboratory in which it is performed), subject should be prescribed one vitamin D/calcium supplement TWICE daily.
- If 25-OH vitamin D rises above 30 ng/mL but remains <180 ng/mL, subject should continue to take ONE vitamin D/Calcium supplement daily.
- For 25-OH vitamin D ≥180 ng/mL, See Section 6.423 (Vitamin D toxicity)

6.422 For subjects who initially are prescribed one vitamin D/Calcium supplements TWICE daily (with screening 25-OH vitamin D <20 ng/mL):

- If 25-OH vitamin D falls below 10 ng/mL AND intact PTH is above the ULN for the local laboratory in which it is performed, see 6.3 for Temporary discontinuation of study treatment.
- If 25-OH vitamin D rises above 20 ng/mL but remains <180 ng/mL, subject should continue to take TWO vitamin D/Calcium supplement daily.
- For 25-OH vitamin D ≥180 ng/mL, See Section 6.423 (Vitamin D toxicity).

6.423 Potential vitamin D toxicity: 25-OH vitamin D ≥180 ng/mL

The level of 25-OH vitamin D that is considered toxic in humans has not been established (90). Hypercalcemia, the main clinical criterion for and main concern with vitamin D toxicity, occurs when free 1,25-dihydroxyvitamin D becomes elevated, which, in turn, occurs as 25-OH vitamin D concentrations begin to exceed 240 ng/mL. The average 25-OH vitamin D in confirmed cases of vitamin D toxicity is 214 ng/mL. Thus, 25-OH vitamin D will be maintained <180 ng/mL to add an extra measure of safety. Given that clinical trial evidence shows that a prolonged daily intake of 10,000 IU of vitamin D is likely to pose no risk of vitamin D toxicity in the general population, excessive levels of 25-OH vitamin D are not anticipated in this trial (in which maximum vitamin D supplementation is 800 IU daily), and, if excessive levels
do occur, careful investigation for additional sources and/or incorrect dosing of vitamin D is warranted.

For subjects who have 25-OH vitamin D ≥180 ng/mL:

- vitamin D/calcium supplementation should be immediately discontinued.
- 25-OH vitamin D should be repeated at the local laboratory; blood for 1,25-(OH)2-vitamin D and calcium levels should also be sent to the local laboratory.
- Clinical or research staff should confirm ALL current medications and dosages, including study medication and study vitamin D/calcium. It is important to ask about and record all vitamin, mineral, natural and other supplements, and determine the vitamin D content of these supplements, if possible.
- If blood calcium and/or 1,25-(OH)2-vitamin D are elevated above the local laboratory ULN, then the subject should discontinue all ingested sources of supplemental (i.e., non-dietary) vitamin D. Referral to an endocrinologist should be considered if no obvious source of excessive vitamin D intake can be identified. Subject may remain on study drug (alendronate/placebo), unless the site investigator believes it is in the best interest of the subject to discontinue study treatment, in which case, the subject should be followed on study but off study drug through week 144.
- If blood calcium and 1,25-(OH)2-vitamin D are within the local laboratory normal limits, then the subject should discontinue all ingested sources of supplemental (i.e., non-dietary) vitamin D, including discontinuing the study-supplied vitamin D/calcium supplementation. The subject should continue study treatment (alendronate/placebo) and will have 25-OH vitamin D measured again at the next routine study time point.

6.5 Criteria for Treatment Discontinuation

Following are criteria for temporary deferral of study treatment:

25-OH vitamin D <10 ng/mL in combination with an intact PTH above the ULN for the local laboratory in which it is performed: subject must stop study drug (alendronate/placebo) temporarily. If site treats subject for vitamin D
deficiency with resulting normalization of intact PTH and 25-OH vitamin D ≥10 ng/mL within 8 weeks of study drug cessation, then subject may resume study treatment. More than 8 weeks of study drug deferral will result in permanent study drug discontinuation, but patient will be followed off treatment but on study through week 144.

Following are criteria for permanent study treatment discontinuation. Note that subjects who discontinue treatment will still be followed for safety outcomes.

- Treatment with disallowed medications
- Drug toxicity that requires permanent study drug discontinuation as defined in Section 6.3
- Nonadherence to study medication or study medication administration instructions
- Confirmed pregnancy [N.B.: All DXA, dental radiographs and bone ages will be deferred or omitted while the subject is pregnant.]
- Exceeding a Lumbar Spine BMD z-score of +1.0 during the study unless subject qualified for study entry on basis of recent fragility fracture.
- 25-OHvitaminD<10 ng/mL in combination with elevated intact PTH persisting for more than 8 weeks after study drug deferral.

Subjects who meet criteria for permanent drug discontinuation (other than pregnancy) will still be followed for all efficacy and safety outcomes, and will be asked to follow the evaluations scheduled for visits at weeks 24, 48, 72, 96 and 144. Subjects who discontinue treatment because of pregnancy will follow all study monitoring procedures with the exception of DXA, dental radiographs, and bone ages during the pregnancy; these radiologic studies may be resumed when the subject is no longer pregnant.

6.6 Criteria for Discontinuation of Subject from Study

- Entry lumbar spine DXA z-score higher than -1.5 (unless subject has history of fragility fracture within the prior 12 months). In this case, the subject is replaced with a new subject.
- The subject or legal guardian refuses further treatment and/or follow-up evaluations.
- The investigator determines that further participation would be detrimental to the subject’s health or well-being.
- The subject fails to comply with the study requirements so as to cause harm to him/herself or seriously interfere with the validity of the study results.
7.0 EXPEDITED ADVERSE EVENT REPORTING

7.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RCC website at http://rcc.tech-res.com/safetyandpharmacovigilance/.

The DAERS internet-based reporting system must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov or from within the DAERS application itself.

Sites where DAERS has not been implemented will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RCC website: http://rcc.tech-res.com/safetyandpharmacovigilance/. For questions about EAE reporting, please contact the RCC (RCCSafetyOffice@tech-res.com).

7.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, regardless of relationship to the study agents. In addition, for the purpose of this protocol fetal losses will be considered SAEs.
- The study agents for which expedited reporting are required are: alendronate/placebo.

7.3 Grading Severity of Events

DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004, Clarification August 2009, must be used and is available on the RCC web site (http://rcc.tech-res.com/safetyandpharmacovigilance/).

Additional grading instructions:
- Use DAIDS table grading for cardiac arrhythmia for grading of atrial fibrillation events.
- Use DAIDS table grading for Dysphagia-Odynophagia for grading of esophagitis.
• Use DAIDS table grading for arthralgia, arthritis and/or myalgia, as appropriate, for grading of musculoskeletal events.
• Use DAIDS table grading for osteonecrosis for grading of JON.
• For non-healing fracture, no grading; indicate as present or absent.

7.4 **Expedited AE Reporting Period**

• The expedited AE reporting period for this study is the entire study duration for an individual subject (from study enrollment until study completion or discontinuation of the subject from study participation for any reason).

• After the protocol-defined AE reporting period, unless otherwise noted, only SUSARs as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8.0 **STATISTICAL CONSIDERATIONS**

8.1 **General Design Issues**

This is a randomized, blinded, placebo-controlled study designed to compare changes in BMD occurring over 48 and 96 weeks of alendronate therapy compared to changes on no therapy (placebo). Primary analyses will use percent change in lumbar spine BMD. However interpretation of within-subject changes in BMD is complicated by the fact that BMD is dependent on gender, age, race/ethnicity, pubertal stage, body size and many other factors. The NICHD-sponsored Bone Mineral Density in Childhood Study has established age, race and gender specific reference curves for DXAs measured on children and adolescents using specific Hologic and Delphi A models that will allow calculation of z-scores for the P1076 study population. These will help with interpretation of the percent changes. An additional complication is that the effects of alendronate on some of the outcomes may persist after subjects are taken off active treatment. This means that primary treatment comparisons will focus on treatment differences in the first Step.

With the small sample size and many potential confounders, this should be considered a pilot study with analyses that are largely exploratory and hypothesis-generating in nature.

8.2 **Outcome Measures**
All outcomes will be assessed at baseline, weeks 24, 48, 72, 96 and 144 weeks.

Primary outcomes:

- BMD of the lumbar spine as measured by Hologic bone densitometers
- New ≥ grade 3 signs, symptoms or laboratory abnormalities or new cases of jaw osteonecrosis, atrial fibrillation or non-healing fractures occurring on study treatment.

Secondary outcomes:

- Whole-body BMD by DXA scan as measured by Hologic bone densitometers
- Central body fat measurement (from whole body DXA)
- Bone formation serum markers: osteocalcin and bone-specific AlkPhos
- Bone resorption markers: urine deoxypyridioline, urine N-terminal and serum C-terminal telopeptides, urine phosphate, urine creatinine (to calculate urine NTX/creatinine ratio)
- Bone age
- 25-OH Vitamin D (vitamin D store)
- 25-OHD3 (indicates both endogenous production and supplementation.)
- 25-OHD2 (an indicator of exogenous sources such as diet or supplementation)
- 1,25-(OH)2-Vitamin D
- Intact PTH
- Proinflammatory cytokines (IL-1B, NF-alpha, IL-6), RANKL, OPG
- Dental assessments, including panoramic radiographs
- HIV quantitative RNA PCR (viral load)
- CD4 count and percent
- Urine alendronate detection/quantitation

8.3 Randomization

Fifty-one subjects will be randomized equally into three Groups:

- Group 1a will receive alendronate for 96 weeks
- Group 1b will receive alendronate for 48 weeks followed by 48 weeks on placebo
- Group 2 will receive placebo for 48 weeks followed by 48 weeks on alendronate.

All three Groups will be followed off treatment for an additional 48 weeks.

To ensure adequate balance in enrollment by gender, no more than 70% of the subjects can be one gender within each Group.

8.4 Sample Size and Accrual

8.41 Changes from pre-treatment levels to 48 weeks in LS BMD

Previous studies assessing the efficacy of alendronate in adults have used percent change in LS BMD as the primary outcome measure. In adolescents however, increases in BMD would be expected due to growth, so it will be necessary to compare changes in LS BMD over 48 weeks observed on alendronate with changes occurring on placebo. The variation between DXAs performed at the same point in time within an individual is only 0.5-1% for spinal and total body DXAs.

In adults, the standard deviation of the percent change from baseline in LS BMD to values after 12 months on alendronate was estimated to be about 4% (ACTG 5163). Variation in changes over time in adolescents may be larger than in adults. Standard deviations reported for percent annual changes in LS BMD in children included in the Cochrane review (2008) ranged from 3% to 9.8%. Secondary analyses will consider changes in LS BMD z-scores. Using data from the NICHD Bone Mineral Density in Childhood Study, the standard deviations of one year changes in LS BMD z-scores ranged from 0.22 (16 year old males, n=39) to 0.43 (9 year old females, n=65).

In surveys sent to IMPAACT sites, a feasible upper limit on accrual to this study is 51 subjects, of whom we estimate about 45 would be evaluable. Subjects who do not start study treatment (alendronate/placebo) will be replaced. Using this sample size and focusing on Step 1 when there will be 30 evaluable subjects on alendronate and 15 on placebo, Table 3 shows detectable (with 80% power and alpha=0.05) within and between (comparing changes over 48 weeks between those on alendronate in the first Step to those on placebo in the first Step) treatment 48 week changes in LS BMD, with a range of standard deviations. For example using the 4% standard deviation in percent change from A5163, there would be
80% power to detect within subject percent changes on alendronate of 2.1% and differences in percent changes over 48 weeks between the alendronate and placebo groups of 3.6%.

Table 3: Difference detectable with 80% power (alpha=0.05)

<table>
<thead>
<tr>
<th>Change metric</th>
<th>Standard deviation</th>
<th>Within Placebo (n=15)</th>
<th>Within Alendronate (n=30)</th>
<th>Between Treatment (n=15 vs. n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% change in LS BMD</td>
<td>3%</td>
<td>2.2%</td>
<td>1.6%</td>
<td>2.7%</td>
</tr>
<tr>
<td></td>
<td>4%</td>
<td>2.9%</td>
<td>2.1%</td>
<td>3.6%</td>
</tr>
<tr>
<td></td>
<td>9.8%</td>
<td>7.1%</td>
<td>5.1%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Change in z-score</td>
<td>0.22</td>
<td>0.16</td>
<td>0.12</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>0.43</td>
<td>0.32</td>
<td>0.22</td>
<td>0.39</td>
</tr>
</tbody>
</table>

8.42 Safety

A second primary objective is to assess the safety of 48 and 96 weeks of alendronate treatment as measured by the percent of subjects who develop new ≥ grade 3 laboratory values, signs, symptoms, or new cases of JON, atrial fibrillation or non-healing fractures. All 51 subjects will be included in safety analyses. Proportions of subjects developing these events over 48 weeks on placebo (n=17) and on alendronate (n=34) will be estimated and compared in Step 1 and will also be estimated over one year on alendronate by combining events in all Groups while on active treatment (n=51), since in which Step subjects receive active treatment should not influence the safety assessments. The design will also allow estimation of proportions of subjects developing events in a second year of treatment (n=17) in Group 1a.

For estimation of the proportion of subjects developing new events, with 17 subjects, the width of a 95% confidence interval (CI) could be as wide as +/-25%, with 34 subjects the CI could be as wide as +/-18%, and with 51 subjects, the width of a 95% CI could be as wide as +/-15%.

8.5 Monitoring

This study will be monitored by a Study Monitoring Committee (SMC) who will review recent screening failures, safety, accrual and protocol feasibility. The SMC members will be independent of the study and have no financial or
perceived conflict of interest. The Chair of the SMC will have primary responsibility for reporting the Committee’s comments to the IMPAACT Leadership and to the P1076 team. Formal reviews may take place via teleconference call. Details on the contents of routine monitoring reports and analyses presented to the SMC will be described in a separate protocol monitoring plan which will be prepared before the study opens to accrual.

8.51 Routine Monitoring

Team calls will be held monthly, with the frequency increasing if deemed necessary by the Study Chairs and Medical Officers, to review accrual, loss-to-follow-up, study conduct and to review all new adverse events. In addition, a Core Team comprised of the Study Chairs, Medical Officers (MOs), Statisticians, Data Manager, and Clinical Trials Specialist (CTS) will be responsible for reviewing adverse events (confirmed JON, atrial fibrillation or non-healing fracture) that require review within 72 hours. Relationship of new adverse events to study treatment will be assigned and recorded in the database. It is the responsibility of the Study Chair, Medical Officers and Protocol Team to interpret toxicity data and make any decisions needed to protect subjects from undue risk. If at any time the Protocol Team determines there are any treatment-related events that may compromise subject safety, the study may be suspended pending a thorough investigation.

The following specific occurrences will trigger a safety review by the Protocol Team and SMC:

- more than 20% of subjects (or more than four if less than 20 have been enrolled) have experienced ≥ grade 3 possibly/probably treatment-related events, or

- there is a possibly/probably treatment-related life-threatening event or death, or

- there is a possibly/probably treatment-related diagnoses of a targeted adverse event (confirmed JON, atrial fibrillation or non-healing fracture).

If any of these events occur, accrual will be temporarily suspended and the relevant safety data presented to the SMC. The SMC will make recommendations for continuation or suspension of the study.

8.511 Accrual
Accrual should be complete by 72 weeks after the tenth site has been registered to the protocol. If accrual seems slower than expected, or if fewer than 24 subjects have been enrolled by 48 weeks after the tenth site has registered, the P1076 Protocol Team will assess barriers to accrual and present plans to improve recruitment to the Complications SC and the IMPAACT Scientific Oversight Committee (SOC). This will include a determination of whether to activate the plan for study funded screening DXAs as described in the Study Design section (Section 3.0).

8.52 Interim Analyses

The study will be formally reviewed by the SMC for safety, accrual, and feasibility (i) after 25 subjects have been followed at least 24 weeks (if the accrual rate is high) or (ii) 9 months after the first subject has enrolled (if accrual is slow), whichever occurs first. This will allow an early review for safety to be completed before the first subject reaches their transition to Step 2. If the early review is triggered by (ii), then the second review will be done after 25 subjects have been followed at least 24 weeks and at least 6 months after the first review, to allow sufficient time between reviews. Otherwise reviews will take place at yearly intervals after the first review. The SMC will operate according to the procedures determined by the network.

Table 4 shows, for a range of true underlying rates of ≥ grade 3 treatment-related adverse events (AE), the probability of observing at least one event for various sample sizes. For example at the first interim analysis, assuming it is triggered when half the subjects have been followed at least 24 weeks, there will be approximately 8 subjects on placebo and 17 on alendronate. The probability of observing at least one treatment-related adverse event in the subjects on alendronate would be 16% if the true underlying rate of adverse events was 1% and 83% if the true underlying rate was 10%. By the end of 48 weeks when there will be 17 subjects on placebo and 34 on alendronate, the probability of observing at least one treatment-related adverse event on alendronate would have risen to 29% if the underlying rate was 1% and to 97% if the underlying rate was at least 10%.

Table 4: Probability of observing at least one treatment-related AE for various underlying true rates
As illustrated in Table 4, at the time of the first interim analysis there will be a low probability of observing serious but rare treatment-related events. In addition, the precision with which the adverse event rate will be estimated will be poor (the width of a 95% confidence interval could be as wide as +/- 34% in the placebo group and as wide as +/- 25% in the subjects on alendronate) and there will be low power to detect differences in rates of adverse events between the alendronate and placebo groups (<80% power unless the true difference between the alendronate and placebo groups is greater than 64%). Taking these issues into account and after considering the specific types of toxicities and their clinical importance, if the lower limit of a 95% confidence interval for the difference in proportions of possibly/probably treatment-related ≥ grade 3 adverse events including diagnoses of the targeted diagnoses of JON, atrial fibrillation, or non-healing fracture between the alendronate and placebo groups is >0%, then the SMC should consider whether the study should continue.

8.6 Analyses

Primary objectives:

1. To estimate and compare changes from pre-treatment levels in lumbar spine BMD after 24 and 48 weeks of alendronate treatment versus placebo

Percent changes from entry to weeks 24 and 48 (Step 1) in all Groups, and week 48 to weeks 72 and 96 (first 48 weeks of Step 2 in Group 2) will be estimated. However, because the effects of alendronate may remain after subjects are taken off treatment, unbiased comparisons between alendronate and placebo can only be done using data collected during Step 1. Depending on the distribution of the outcomes, two-sample Wilcoxon or t-tests will be used to test whether percent changes to weeks 24 and 48 in LS BMD in Step 1 differ between the alendronate (Groups 1a and 1b combined) and placebo groups.
Analyses using similar methods will also be done using z-scores calculated from the NICHD Bone Mineral Density in Childhood Study normative population [currently for girls up to 16 years old and boys up to 17 years old], which are adjusted for age, gender and race/ethnicity. By the time data are available for analysis, it is expected that normative data from the ongoing NICHD Bone Mineral Density in Childhood Study will be available through 20 years of age for girls and boys (personal communication, Dr Karen Winer, NICHD).

2. To assess the safety of 48 weeks of alendronate use

All subjects who receive at least one dose of study treatment will be included in safety analyses. Safety and tolerability will be assessed by summarizing (frequencies, percents and 95% confidence intervals) all new ≥ grade 3 hematology and chemistry laboratory results, signs and symptoms, new cases of jaw osteonecrosis, atrial fibrillation or non-healing fractures occurring after the start of study treatment by placebo (Group 2) and alendronate (Groups 1a and 1b) use during Step 1, and by each Group separately in Step 2. In addition, proportions of subjects with new events after starting alendronate will be summarized for all 51 subjects (combining Groups 1a and 1b on Step 1 with Group 2 during the first 48 weeks on Step 2).

Time to first new event will be estimated using Kaplan-Meier curves and compared by treatment using log-rank tests during each Step, censoring at the end of each Step. These analyses will be repeated combining data on alendronate from Groups 1a and 1b on Step 1 and Group 2 during the first 48 weeks on Step 2 (n=51).

All analyses will be repeated using only those events judged by the Team to be possibly/probably related to study treatment.

Secondary objectives:

1. To estimate and compare changes from pre-treatment levels in whole body BMD after 24 and 48 weeks of alendronate treatment versus placebo. This will be addressed using the same methods as described for Primary Objective 1.

2. To estimate and compare changes from pre-treatment levels in whole body and lumbar spine BMD after 96 weeks of alendronate treatment versus 48 weeks of alendronate followed by 48 weeks of placebo.
Percent changes from entry to week 96 in Group 1a will be estimated and compared to percent changes from entry to week 96 in Group 1b. Similar summaries and comparisons will be done on changes in z-scores. Analyses adjusted for confounders will also be performed. These comparisons will allow assessment of benefit of two years versus one year of alendronate use.

3. To assess the safety of 96 weeks of alendronate use as measured by the incidence of new ≥ Grade 3 hematology or chemistry laboratory values, signs or symptoms, or new cases of jaw osteonecrosis (JON), atrial fibrillation or non-healing fractures.

Analyses will be similar to those outlined for Primary Objective 2, focusing on events occurring during the first 48 weeks of Step 2 in Group 1a.

4. To assess the effect of other known bone mineral determinants (age, gender, race/ethnicity, steroid use, Depo-Provera, tenofovir, pubertal stage, bone age, vitamin D status) and inflammatory cytokine levels on changes in BMD after 24 and 48 weeks of alendronate treatment.

Potential confounders of the outcomes should in theory be balanced across Groups due to randomization. Stepwise regression will be used to screen out non-confounders of the treatment comparisons and to identify factors that are correlated with changes in lumbar spine and whole body BMD.

5. To assess changes in BMD over a 48 and 96 week period following 48 or 96 weeks of alendronate therapy.

Absolute and percent changes in LS BMD and changes in z-scores will be estimated for each Step separately by treatment received. Depending on the distribution of the outcomes, parametric or non-parametric tests will be used to do within Group comparisons of changes observed after one or two years of alendronate use compared to changes on alendronate, unadjusted for other factors. Analyses will be repeated using multiple linear regression models adjusted for other important covariates.

6. To characterize the alterations in pre-treatment bone marker turnover, cytokine levels, RANKL/OPG ratio, central fat content (by whole body DXA) at baseline compared to levels after 48 or 96 weeks of alendronate therapy and determine if the changes in these outcomes correlate with changes in BMD.
Changes in each outcome will be estimated for each time period separately by treatment received. Analyses on changes will be conducted as described for the first primary objective. In addition, to determine if the changes in these outcomes correlate with changes in BMD, multiple regression models will be fit using change in BMD during Step 1 as the outcome variable and change in each measure of interest as a predictor, adjusted for other important covariates. These models will be fit using data from Step 1 and where possible, also including data from the first 48 weeks of Step 2.

7. To evaluate the effect of alendronate therapy on changes in HIV status (as measured by changes in viral load, CD4% and CDC disease category) and determine if the changes in these outcomes correlate with changes in BMD.

This will be analyzed using the same methods as for secondary objective 6 for viral load and CD4%. Summaries of numbers of subjects progressing by CDC disease category during the study will be generated for each Group and each treatment period of interest separately.

8. To estimate the duration of detectable urinary alendronate in subjects who have completed 48 and 96 weeks of alendronate therapy.

The percent of subjects in each Group with detectable alendronate in urine will be summarized 12, 24 and 96 (Group 1b only) weeks after stopping alendronate.

9.0 HUMAN SUBJECTS

HIV-infected youth are at increased risk of low bone mineral density due to HIV infection, its treatment, co-morbid conditions and other factors. Progressive bone mineral loss at an age when bones are usually at the peak of growth and mineral deposition may put them at increased risk of fractures in the short and long term.

Subjects in this study will be assessed for vitamin D status, supplemented appropriately with vitamin D and with calcium, and educated about food choices that are rich in vitamin D and calcium. In addition, subjects will be counseled in the importance and type of weight-bearing exercise that may improve bone health, and they will be asked to perform weight-bearing exercises every day. Thus, all subjects will have optimized nutritional and exercise approaches to improve low BMD throughout the study. The principal goal of the study is to determine if the addition of oral alendronate to this optimal background management of low BMD will result in substantial improvements in BMD.
Because the subjects eligible for this study must have a standardized LS BMD at least 1.5 standard deviations below average (consistent with abnormally low BMD) and/or have suffered an atraumatic fracture, there is a compelling rationale to give these subjects access, in the systematic and scientific context of an investigational study, to a drug like alendronate, that has a proven track record of improving BMD in several adult populations (including HIV-infected adults) and in limited studies of children with other conditions associated with low BMD or bone fragility. We believe that the strong prospect for direct benefit in these subjects with established low BMD justifies (a) a study design that provides access to active drug for all subjects during the course of the study and (b) theoretical concerns about use of this antiresorptive agent in youth whose bones are potentially immature and incompletely grown. In addition, the importance of treating existing bone problems in all affected youth justifies including female youth in this study despite the theoretical concerns (based on some animal data) about the potential negative effects (abnormal bone development or fetal loss) of alendronate if unintended pregnancy occurs during (animal data) or after (completely theoretical; no animal or human data) alendronate treatment. Further reassurance for including females includes: the lack of evidence of these reproductive concerns in the limited human data available; the requirement by the protocol to avoid pregnancy and use two forms of contraception throughout the study which will be stressed in the informed consent process and systematically reinforced at each study visit; and the inclusion in the study design of at least 48 weeks after cessation of active alendronate therapy during which pregnancy avoidance is still required, beyond the requirements of the package labeling (no minimum time between drug cessation and conception) , other FDA-monitored studies (no minimum time between drug cessation and conception), and clinical practice by many experts (6 month deferral of conception, based on normalization of bone turnover markers suggestive of persistent bisphosphonate effect by that time).

9.1 Institutional Review Board and Informed Consent

This protocol, the informed consent document (Appendix V), and any subsequent modifications must be reviewed and approved by the IRB or EC responsible for oversight of the study. Written informed consent must be obtained from the subject (or parents or legal guardians of subjects who cannot consent for themselves, such as those below the legal age). The subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks of the study. An assent form has been drafted (Appendix VI) to encourage an in-depth assent process for study subjects, and a test of understanding (Appendix VII) will be used to check that subjects comprehend the basic information. The informed consent will describe the purpose of the study, the procedures to be followed, and the
risks and benefits of participation. A copy of the consent form will be given to the subject (or parent or legal guardian).

Each site which receives US HHS funding and follows the United States Code of Federal Regulations Title 45—Public Welfare, Part 46—Protection of Human Subjects (also known as the Common Rule) should have on record at the site a plan that detects and addresses any change in guardianship occurring in pediatric subjects and determines when a study subject must have a consent process which involves a legally authorized representative (LAR) other than a family member with guardianship. The plan will include how the site determines when a LAR is initially or no longer needed and how frequently the LAR re-signs the consent. The plan should follow all national, local and state guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.

9.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain subject confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, parent or guardian, except as necessary for monitoring by the FDA, Merck & Co., Inc. (the pharmaceutical sponsor), the Office for Human Research Protections (OHRP), the NIH, the local IRB or Ethics Committee.

9.21 Confidential Testing Results for Adolescents

This protocol is focused on youth who will span the ages when a parent/guardian will usually be granting permission for their participation (11-17 years old) through older ages when the youth will usually consent for themselves (18-24 years old). Questions and testing related to pregnancy, sexual activity, smoking and alcohol use are included in the protocol. These elements are important aspects of maximizing subject safety (contraception, pregnancy) and for understanding contributors to low BMD (smoking, alcohol, certain contraceptives). Adolescents are entitled to confidential testing and care for reproductive health and substance abuse in many jurisdictions, and, in general, access to confidential care is thought to improve the ability for adolescents to access this care. As a result, information collected in this study (including for screening for this study) related to pregnancy, sexual activity, smoking and alcohol will not be shared with parents (or other adults
consenting for youth’s participation) without permission of the youth, and study staff will ensure that the subject is referred to his or her medical provider for appropriate counseling and management if problems in these areas are identified. However, since local guidelines, practice and regulations may vary, instructions to sites appear in the sample informed consent to emphasize that sites may have to adapt this approach, e.g., “[Sites should modify the preceding language about confidentiality of pregnancy test results to conform to their local practice, regulations and IRB requirements.]”

9.3 Study Discontinuation

The study may be discontinued at any time by the NIAID, the FDA, the IRB or EC, Merck & Co., Inc. (the pharmaceutical sponsor), OHRP, IMPAACT Network, or other governmental agencies as part of their duties to ensure that research subjects are protected.

10.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by IMPAACT policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical sponsors prior to submission.

11.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other bloodborne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention.

All infectious specimens will be sent using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN3373, Biological Substance, Category B, and Packing Instruction 650. Refer to individual carrier guidelines (e.g., Federal Express or Airborne) as well as specific requirements of the host country for specific instructions required for ground transportation within that country.
12.0 REFERENCES


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## APPENDIX I-A: SCHEDULE OF EVALUATIONS

<table>
<thead>
<tr>
<th>EVENT</th>
<th>SCREENING</th>
<th>ENTRY</th>
<th>STEP 1</th>
<th>STEP 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL EVALUATIONS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History (including targeted symptoms and events)</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exam</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanner Stage Assessment</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DXA Scan (limb)</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DXA Scan (whole body including head)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiograph (bone age)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dietary Intake Questionnaire</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking History</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental Assessment and Oral Health History (performed by a dentist)</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental Panoramic Radiograph</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherence Questionnaire</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Activity Assessment</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject Contact</td>
<td>X X</td>
<td>X</td>
<td>X X</td>
<td>X X</td>
</tr>
<tr>
<td>Participant Instruction Sheet</td>
<td>X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
</tr>
<tr>
<td>Dispense alendronate/placebo</td>
<td>X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
</tr>
<tr>
<td>Dispense VitD/Ca</td>
<td>X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
</tr>
<tr>
<td>Pill Count (alendronate/placebo &amp; VitD/Ca)</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
</tr>
<tr>
<td>LABORATORY EVALUATIONS</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hematology</td>
<td>3 ml</td>
<td>3 ml</td>
<td>3 ml</td>
<td>3 ml</td>
</tr>
<tr>
<td>Chemistry</td>
<td>3 ml</td>
<td>3 ml</td>
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<td>3 ml</td>
</tr>
<tr>
<td>Urine Pregnancy test</td>
<td>3 ml</td>
<td>3 ml</td>
<td>3 ml</td>
<td>3 ml</td>
</tr>
<tr>
<td>Urine for Storage (bone marker and/or alendronate)</td>
<td>5 ml</td>
<td>5 ml</td>
<td>5 ml</td>
<td>5 ml</td>
</tr>
<tr>
<td>Blood for 25-OHvitD, intact PTH</td>
<td>3 ml</td>
<td>3 ml</td>
<td>3 ml</td>
<td>3 ml</td>
</tr>
<tr>
<td>Blood for Serum Storage (endorcrine/vitamin/bone markers/inflammatory cytokines)</td>
<td>17 ml</td>
<td>17 ml</td>
<td>17 ml</td>
<td>17 ml</td>
</tr>
<tr>
<td>Virology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA</td>
<td>3 ml</td>
<td>3 ml</td>
<td>3 ml</td>
<td>3 ml</td>
</tr>
<tr>
<td>Immunology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte subsets</td>
<td>3 ml</td>
<td>3 ml</td>
<td>3 ml</td>
<td>3 ml</td>
</tr>
<tr>
<td>TOTAL BLOOD VOLUMES</td>
<td>15 ml</td>
<td>29 ml</td>
<td>32 ml</td>
<td>32 ml</td>
</tr>
</tbody>
</table>
APPENDIX I-A (Cont.)

1. Screening evaluations should be performed within 4 weeks of Entry. Up to 12 weeks is permitted for screening DXA and dental results. Screening elements may be performed on different days as long as DXA and dental assessments take place no more than 12 weeks before entry and all other screening tests take place no more than 4 weeks before entry. All subjects who sign the consent for P1076 must be registered for P1076 using the DMC Screening Program at the time consent is signed. Subjects who meet the eligibility criteria may proceed to randomize to P1076 at the entry visit. All subjects who fail screening after completing study-directed LS DXA, dental evaluations and/or 25-OH vitamin D/ intact PTH laboratory evaluations will complete the Screening Failure form as well as the results/tracking forms for all of the previously specified evaluations using their Screening Number.

2. Sites must have the results of the following tests from screening before proceeding to entry: LS DXA, chemistry laboratory results, hematology results, negative pregnancy test for females of reproductive potential, 25-OH-vitamin D (total), intact PTH (with accompanying serum calcium), dental exam and dental panoramic radiograph.

3. Evaluations performed within window are acceptable.

4. A complete (5-year) history is required at Screening; a targeted history is sufficient at subsequent visits. For non-reproductive age subjects enrolled in the study, onset of menarche and/or sexual activity will be assessed by history.

5. The demographic evaluation can be performed either at screening or entry.

6. Physical exam should include height, weight, and vital signs. Height and weight each need to be confirmed with a second measurement; a third measurement will be required if the discrepancy between the first two measurements is greater than the allowed tolerance (specified on the Vital Signs CRF).

7. Testicular volume is required until the participant’s Tanner Stage reaches ‘5’.

8. LS DXA scans obtained for screening do not need to be submitted to the central DXA readers at Tufts University unless that same screening LS DXA is also being used as the entry LS DXA. All study DXA scans require local reading, including generation of Z-scores, even though study scans (with exception of screening LS DXA not also used as entry LS DXA scans) will also be read and interpreted by the central DXA reading group at Tufts University.

9. LS DXA not required at screening visit if qualifying pre-study LS DXA performed <12 months from entry; in this case entry LS DXA must be confirmed by local reading as z-score <1.5 before initiating study drug.

10. LS DXA not required at entry if qualifying pre-study LS DXA performed >12 months from entry and screening LS DXA <12 weeks from entry visit.

11. ALL subjects require a bone age radiograph at Entry and at Week 144 (or at time of early discontinuation). However, interval bone age radiographs may be omitted for subjects who have reached the limit of maturity standards for bone ages on their last bone age, i.e., female subjects who reach bone age of 18 years and male subjects who reach bone age of 19 years.

12. Information about tobacco and non-tobacco smoking will be collected.

13. The optional Dentist Brochure (Appendix IV) can be completed at any study dental visit to relay dental related study findings to the subject’s primary dentist.

14. Dental assessment at entry can be omitted if entry <12 weeks from the screening dental assessment.

15. IMPAACT P1076 Adolescent Adherence Questionnaire

16. Subject contact via telephone should take place to screen for adverse events, assess adherence (to study medications, ARVs, and exercise instructions), and to reinforce study instructions. If potential adverse events are detected during these telephone contacts then the subject will be required to have an additional clinic visit and evaluations within the specified timeframe noted in Appendix I-B.


18. For Step 1, the first dose of alendronate/placebo must be taken within 7 days of randomization or of entry DXA result availability, whichever occurs later. Entry LS DXA results should be available no more than 7 days after the entry DXA scan is performed. For Step 2, the first dose of alendronate/placebo must be taken within 7 days of registration.

19. Hematology should include CBC with differential and platelet count. (Tests are performed in real-time at the clinic’s local CLIA-licensed laboratory.)

20. Chemistries should include AST, ALT, alkaline phosphatase, total bilirubin, BUN, electrolytes, albumin, glucose, creatinine, calcium, phosphorous, and total amylase. (Tests are performed in real-time at the clinic’s local CLIA-licensed laboratory.)
APPENDIX I-A (Cont.)

21. May be either urine or HCG blood test. Must be performed on all female subjects of reproductive potential (having reached menses, not having reached menopause, or not having undergone hysterectomy, bilateral oophorectomy, or tubal ligation) within 48 hours prior to enrollment and at each visit indicated in the Table (weeks 24, 48, 72, 96, 144, and early discontinuation). If no pregnancy test was required at entry, pregnancy testing at subsequent visits should be performed if change in reproductive potential status during the course of the study occurs, and subject should be offered contraception as defined in Section 4.19. (Tests are performed in real-time at the clinic’s local facility.)

22. Urine storage (bone marker/alendronate) – Should be collected from second morning void. Note: Subjects are permitted to bring refrigerated urine from home, if the clinic visit occurs later in the day. Collect, process, and ship to NIAID or NICHD Central Specimen Repository on a monthly basis. (Specimen aliquots are prepared according to instructions provided in the Laboratory Processing Chart. Tests are performed in batch at designated P1076 central laboratories.)

23. Blood for 25-OH-Vitamin D and for intact PTH (with accompanying serum calcium) must be sent to the clinic’s local CLIA-licensed laboratory. Refer to Section 6.422 for criteria describing enrollment requirements and on study toxicity management.

24. Blood for Serum Storage—Collect, process and ship to NIAID or NICHD Central Specimen Repository on a monthly basis. (Specimen aliquots are prepared according to instructions provided in the Laboratory Processing Chart. Tests are performed in batch at designated P1076 central laboratories.)

25. HIV RNA and lymphocyte subset (CD3/CD4/CD8) results can be abstracted from studies sent as part of clinical care as near to the date of the study visit as available but within 2 weeks (±2 weeks) of the study visit. These particular tests need not necessarily be performed as distinct protocol laboratory tests if already performed as part of clinical care. CD4 percentage and CD4 absolute count are required; CD3 and CD8 values should be recorded if available.

26. Subjects who want to prematurely discontinue participation in the study entirely will be asked to have one set of off-study evaluations, as listed in this column. Subjects who prematurely discontinue study treatment will continue to be followed at scheduled major study visits (Week 24, 48, 72, 96 and 144 week visits) and undergo all study procedures and tests listed for those visits. Dispensing and pill count of discontinued study drug will not be performed. Evaluations involving radiation will not be performed during pregnancy, as outlined in Section 6.5.

For insufficient blood draws, priorities are as follows:
1. Local safety related tests (Hematology/Chemistry/Vitamin D/Intact PTH)
2. Serum/Plasma storage for storage for future batch testing of Vitamin D/endocrine/bone marker/inflammatory markers
3. HIV-1 RNA
4. Lymphocyte subsets
APPENDIX I-B

SCHEDULE OF EVALUATIONS
FOR SUBJECTS WHO HAVE A POSITIVE RESULT FROM SUBJECT CONTACT EVALUATION

A positive response to any of the following items on the standardized questionnaire (used at each phone contact and clinic visit to assess for signs and symptoms related to targeted adverse events) as well as to abnormal dental exam will require additional evaluation:

- Pain or difficulty with swallowing
- Midline chest pain or burning
- Palpitations, or feeling like heart not beating normally
- Fainting or nearly fainting, without any other explanation
- Heartburn
- Tooth or jaw pain
- Muscle or joint swelling or pain
- Bone fracture or injury
- Concern about pregnancy
- Hospitalization

Please see Sections 6 and 7 for details of toxicity management and reporting requirements, respectively. Required evaluation of each positive screen above is summarized in the table below:

<table>
<thead>
<tr>
<th>Positive Screen</th>
<th>Evaluation</th>
<th>Time Frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain or difficulty swallowing</td>
<td>By clinical provider: history, physical and additional evaluations as needed to assess for potential causes. Ensure that patient has been taking study drug with 6-8 ounces of water and has been staying upright at least 30 minutes after study drug.</td>
<td>Visit ≤72 hours</td>
</tr>
<tr>
<td>Midline chest pain or burning or Heartburn</td>
<td>By clinical provider: history, physical and additional evaluations as needed to assess for potential causes. Ensure that patient has been taking study drug with copious water and has been staying upright at least 30 minutes after study drug.</td>
<td>Visit ≤72 hours</td>
</tr>
<tr>
<td>Palpitations, or feeling like heart not beating normally; Fainting or nearly fainting, without any other explanation</td>
<td>By clinical provider: history, physical exam, EKG (interpreted by local cardiologist) and additional evaluations as needed. Evaluation by cardiologist if EKG abnormal or other aspects of evaluation concerning for potential arrhythmia.</td>
<td>Visit ≤72 hours</td>
</tr>
<tr>
<td>Tooth or jaw pain</td>
<td>By dentist: Evaluation will include, but not be limited to, dental exam, and panoramic and bitewing radiographs.</td>
<td>Visit ≤72 hours</td>
</tr>
<tr>
<td>Muscle or joint swelling or pain</td>
<td>By clinical provider: history, physical and additional evaluations as needed to assess for potential causes.</td>
<td>Visit ≤72 hours</td>
</tr>
<tr>
<td>Bone fracture or injury</td>
<td>By clinical provider: history, physical and additional evaluations as needed to assess for potential causes. Radiography and Orthopedic evaluation should be performed for any case in which fracture or bone injury is suspected after provider’s clinical evaluation.</td>
<td>Visit ≤72 hours</td>
</tr>
<tr>
<td>Concern about pregnancy</td>
<td>By clinical provider: urine or serum pregnancy test. If negative, review study requirement for contraception and assess subject’s willingness to adhere to this requirement.</td>
<td>Visit &lt;24 hours</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>By clinical provider or clinical/research staff: Obtain information about reasons for hospitalization and ask about occurrence of targeted signs/symptoms above.</td>
<td>Obtain information &lt;48 hours.</td>
</tr>
</tbody>
</table>
APPENDIX II
INFORMATION REGARDING RADIATION EXPOSURE

Each spinal DXA will entail an exposure of \( \leq 5 \) mrem; each whole body DXA will entail an exposure of \( \leq 5 \)mrem. Thus, each scheduled DXA (spine+whole body) in this study will result in exposure \( \leq 10 \)mrem. Over the course of the study, each subject will have 6 whole body DXA studies and 6-7 LS DXA studies (7th LS DXA only in cases when prolonged interval between screening and entry required screening LS DXA + entry LS SXA), resulting in a total exposure over the course of 144 weeks of \( \leq 60-65 \) mrem.

Each bone age radiograph will result in an exposure of 5 mrem. Over the course of the study, each subject will have up to 6 bone age radiographs for a maximum total exposure of 30 mrem.

Each dental panoramic radiograph results in an exposure of 1.3 mrem for digital and 2.6 mrem for traditional radiographs. In most cases, sites are expected to obtain digital panoramic radiographs. Over the course of the study, 2 dental panoramic radiographs will be performed resulting in a maximum exposure (assuming non-digital for highest possible estimate) of 5.2mrem.

Thus, over the course of the study, the maximum, cumulative radiation exposure related to protocol tests will be 65mrem (DXA) + 30mrem (bone ages) + 5.2mrem (dental radiographs)= 100.2 mrem over the course of this 3 year (144 week) study. This is equivalent to approximately 4 chest radiographs per year over the 3 year study or 12 chest radiographs over the entire course of the study.

The maximum radiation doses allowed in human research subjects vary by IRB. The guidelines below are based on the Food and Drug Administration's allowable dose limits for radioactive drugs used in research.

Title 21 CFR (Code of Federal Regulations) Part 361.1 (b)(3) “Limit on radiation dose” states:

"The amount of radioactive material to be administered shall be such that the subject receives the smallest radiation dose with which it is practical to perform the study without jeopardizing the benefits to be obtained from the study.

(i) Under no circumstances may the radiation dose to an adult research subject from a single study or cumulatively from a number of studies conducted within 1 year be generally recognized as safe if such doses exceed the following:

<table>
<thead>
<tr>
<th>Organ Type</th>
<th>Single Dose Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole body, active blood-forming organs, lens of the eye, and gonads:</td>
<td>3 Rems (3,000 mRems)</td>
</tr>
<tr>
<td>Annual and total dose commitment</td>
<td>5 Rems (5,000 mRems)</td>
</tr>
<tr>
<td>Other organs:</td>
<td></td>
</tr>
<tr>
<td>Single dose</td>
<td>5 Rems (5,000 mRems)</td>
</tr>
<tr>
<td>Annual and total dose commitment</td>
<td>15 Rems (15,000 mRems)</td>
</tr>
</tbody>
</table>
APPENDIX II (Cont.)

(ii) For a research subject under 18 years of age at his last birthday, the radiation dose shall not exceed 10 percent of that set forth in paragraph (b)(3)(i) of this section.

(iii) All radioactive material included in the drug either as essential material or as a significant contaminant or impurity shall be included when determining the total doses and dose commitments. Radiation doses from x-ray procedures that are part of the research study (i.e. would not have occurred but for the study) shall also be included. The possibility of followup studies shall be considered for inclusion in the dose calculations.
APPENDIX III
DXA IN MEASURING BONE DENSITY

Detailed protocols will be provided to each participating site regarding DXA scanner operations and QA, patient instructions and procedures for DXA, and instructions for collecting and submitting DXA data.

Please note:
1. LS DXA scans obtained for screening do not need to be submitted to the central DXA readers at Tufts University unless that same screening LS DXA is also being used as the entry LS DXA.
2. All study DXA scans require local reading, including generation of Z-scores, even though study scans (with exception of screening LS DXA not also used as entry LS DXA scans) will also be read and interpreted by the central DXA reading group at Tufts University.

Questions related to performing DXAs, calibrations, and transmitting results should be directed to:

Roger A. Fielding
Director of Body Composition Analysis Center
Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University
711 Washington Avenue, 13th Floor
Boston, MA 02111
Phone: (617) 556-3016
Fax: (617) 556-3083
Email: roger.fielding@tufts.edu

Andrea Desilets
Sr. Research Coordinator
Friedman School of Nutrition Science and Policy
BCAC 150 Harrison Avenue Jaharis Bldg, Room #212
Boston, MA 02111
Phone: (617) 636-3497
Fax: (617) 636-3662
Email: andrea.desilets@tufts.edu

Justin Wheeler, Scan Technician
Friedman School of Nutrition Science and Policy Body Composition Analysis Center
150 Harrison Avenue Jaharis Bldg, Room #211
Boston, MA 02111
Tel: (617) 636-3745
Fax: (617) 636-3662
Email: justin.wheeler@tufts.edu
APPENDIX IV
DENTIST BROCHURE

This individual is a subject in the following study: P1076, “Impact of Oral Alendronate Therapy on Bone Mineral Density in HIV-Infected Children and Adolescents with Low Bone Mineral Density” Version 2.0, dated March 31, 2010

This study is being done to find out if alendronate, plus calcium and vitamin D, is safe and effective for treating low bone density in children and youth infected with HIV. It is clear that older adults with low bone density have a higher risk of spinal fracture or other broken bone. Many experts believe that children and youth with low bone density are also at risk of a spinal fracture or other broken bone over time, but they are not as certain. Doctors are not sure about the best way to treat children and youth with low bone density. There are some things that can keep or make bones stronger, like getting enough vitamin D, calcium, and exercise and not smoking cigarettes. There are also drugs, like Alendronate, that work by stopping bones from losing the minerals that make them strong. Alendronate (brand name Fosamax®) is a drug approved by the Food and Drug Administration (FDA) to treat and prevent low bone density and prevent broken bones in adults. Alendronate is not approved for the treatment of low bone density related to HIV infection or its treatment. Alendronate is not approved for use in patients under 18 years old. It is not known if alendronate will have the same safety and benefit in bones of children and youth, since their bones are still developing and growing. This study is being done to see if alendronate can safely improve bone density more than vitamin D, calcium and exercise alone in children and youth with HIV infection who already have low bone density.

The purpose of this document is to provide information specific to the oral examination of this subject by study dental investigators.

1. Exclusive of the initial and end study dental examination, a dental examination may happen for various reasons:
   • Complaint related to pain or infection
   • Concerns other than pain or infection e.g. bite problem
   • Traumatic injury
   • Occlusion concerns evaluation
   • Routine recall or prevention visit with primary care dentist (not study doctor)

2. The study protocol dentist should discuss the concerns for adverse affect of osteonecrosis of the jaws at the initial visit. Recommend the protocol include an appropriate brochure that is included for all initial study dental examinations. Subject should receive a standardized document for future dental visits and self assessment strategies. A standardized protocol letter should also be given to the patient for their private provider with an outcomes checklist specific to the subject at the end study dental visit.
APPENDIX IV

P1076, “Impact of Oral Alendronate Therapy on Bone Mineral Density in HIV-Infected Children and Adolescents with Low Bone Mineral Density”

**Dental Visit Summary**

<table>
<thead>
<tr>
<th>Concerns observed</th>
<th>Patient has discomfort/pain</th>
<th>Gingival inflammation</th>
<th>Gingival recession</th>
<th>Gingival hypertrophy</th>
<th>Demineralizations</th>
<th>Cavitation</th>
<th>Trauma</th>
<th>Dental erosion/abrasion</th>
<th>Periodontium</th>
<th>Mobile teeth</th>
<th>Malodor</th>
<th>Occlusion: crowding, crossbite etc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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Evidence of osteonecrosis: _Yes_  _No_

- **Clinical**
  
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- **Radiographic**
  
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**Comments**

Dear doctor, If you have questions please contact the dentist below who provided this examination

Dentist: _______________________________ Phone: ____________

Email: _______________________________

Thank you.
INTRODUCTION

You are/your child is being asked to take part in this research study because you are/your child is infected with HIV and you have/your child has low bone density or you/your child may have low bone density. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be/want your child to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part or agree to allow your child to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

This study is being done to find out if alendronate, plus calcium and vitamin D, is safe and effective for treating low bone density in children and youth infected with HIV. It is clear that older adults with low bone density have a higher risk of spinal fracture or other broken bone. Many experts believe that children and youth with low bone density are also at risk of a spinal fracture or other broken bone over time, but they are not as certain. Doctors are not sure about the best way to treat children and youth with low bone density. There are some things that can keep or make bones stronger, like getting enough vitamin D, calcium, and exercise and not smoking cigarettes. There are also drugs, like alendronate, that work by stopping bones from losing the minerals that make them strong.
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Alendronate (brand name Fosamax®) is a drug approved by the Food and Drug Administration (FDA) to treat and prevent low bone density and prevent broken bones in adults. Alendronate is not approved for the treatment of low bone density related to HIV infection or its treatment. Alendronate is not approved for use in patients under 18 years old. It is not known if alendronate will have the same safety and benefit in bones of children and youth, since their bones are still developing and growing. This study is being done to see if alendronate can safely improve bone density more than vitamin D, calcium and exercise alone in children and youth with HIV infection who already have low bone density.

In addition, some urine samples will be tested for the presence of alendronate to help doctors understand how long after treatment the drug is still present in a person's body.

WHAT DO I/DOES MY CHILD HAVE TO DO IF I AM/HE/SHE IS IN THIS STUDY?

DXA (dual energy x-ray absorptiometry) Screening
After you have read and signed this consent form, you/your child will come to the clinic for a DXA screening visit that may last about 1 hour. DXA is a special type of x-ray used to evaluate the density of the bones. If you/your child had a recent DXA scan of the spine you/your child may not need a DXA screening visit.

At this DXA screening visit you/your child will have the following done:

- For the scan, you/your child will lie still on a table for up to 15 minutes while a scanning machine passes over your/your child’s body. You will receive the results of this exam as soon as they are available or at your/your child’s next study visit.

Screening

If the spine DXA scan shows that you/your child have/has low bone density, you/your child will come to the clinic for a screening visit to make sure that you/your child meet(s) the requirements for joining this study. This visit may last about 1 hour.

At this screening visit, you/your child will have the following done:

- You will be asked questions about your/your child’s medications and medical history.
- You/your child will have a complete physical exam.
- **You/your child will fill out a form about how much you/your child smoke(s). This form will take about 15 minutes to complete.**
APPENDIX V

- You/your child will have about 3 teaspoons of blood drawn:
  - for routine blood tests,
  - to measure your/your child’s HIV viral load (how much HIV is in your/your child’s blood) and CD4 count (a test that shows how strong your/your child’s immune system is)
  - to measure parathyroid hormone and vitamin D levels. Parathyroid hormone is produced by a gland in your/your child’s body and helps your/your child’s body control and use calcium.

If you/your child can become pregnant, you/your child will provide a urine sample for a pregnancy test. The test must show that you/your child are/is not pregnant in order for you/your child to participate in this study.

As part of screening, you/your child will need to have a dental exam by a dentist. This exam may take place on the same day as the other screening tests or on a different day. The dentist will also perform a panoramic X-ray of your/your child’s teeth and jaw. A panoramic X-ray is a special dental X-ray that includes all of the teeth and the jaw in a single X-ray.

You/your child will be given the results of the pregnancy test, dental exam, panoramic x-ray, routine tests, vitamin D level, parathyroid hormone level, HIV viral load, and CD4 cell counts as soon as they become available or at your/your child’s next study visit. The results of these tests will determine if you/your child are/is eligible to enter study. Even if you/your child are/is not eligible to enter the study, the results of the screening tests will be used by the protocol team in their research on bone density in HIV-infected youth.

Entry

This visit may last about 2 hours.

Beginning at entry and at all on-study visits, study staff will provide you/your child with a study participant instruction sheet. This sheet will give you/your child information about how to take your/their medications and vitamins, and about exercising.

At this visit you/your child will have the following done:
- You will be asked questions about changes (including missed doses) in your/your child’s medications and in your/your child’s health since your/their last visit.
- You/your child will have a physical exam.
- You/your child will have about 3 teaspoons of blood drawn for routine blood tests, and to measure your/your child’s HIV viral load (how much HIV is in your/your
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child’s blood) and CD4 count (a test that shows how strong your/your child’s immune system is)

- If you/your child are/is female, you/your child will be asked about your/her menstrual periods.
- You/your child will fill out forms about how physically active you/your child have/has been, and about how much you/your child smoke(s) and drink(s) alcohol. These forms will take about 15 minutes to complete.
- You will fill out a form about the foods you/your child eat. This form may take about 30 minutes to complete.
- You/your child will have a DXA scan of your/their whole body. You/your child may also need a spine DXA scan, if you/your child did not have a screening DXA scan of your spine.
- You/your child will have an X-ray of your/their hand, called a bone age.
- You/your child will have an additional 3 teaspoons of blood drawn and provide a urine sample for bone tests (to show if you/your child are/is gaining or losing bone), hormones that affect bone, inflammation, and immunologic function (ways that the body fights infection). Some of the blood and urine will be stored until these tests are done on them at the end of the study.
- If you/your child can become pregnant, you/your child will provide a urine sample for a pregnancy test.

You/your child will be given the results of the pregnancy test, DXA scans, hand X-ray and routine tests as soon as they are available or at your/your child’s next study visit.

Study drugs:
Everyone will receive calcium and vitamin D, combined into a single pill. If your/your child’s vitamin D level is low, then you/your child will need to take the pill twice a day. Otherwise, you/your child will take it once each day.

You/your child will be randomized (assigned by chance, as if by the toss of a coin) to receive either alendronate or a placebo first (a placebo is a tablet that looks like the active drug, but has no active drug in it. It is like a sugar pill.). You are/your child is twice as likely to receive alendronate first. You have/your child has a 1 in 3 chance of receiving placebo first. Neither you nor your/your child’s doctor will know whether you/your child are/is receiving alendronate or a placebo.

You/your child will be randomized (assigned by chance) to one of three of the following groups:
- Group 1a- Alendronate for 96 weeks
- Group 1b- Alendronate for 48 weeks + Placebo for 48 weeks
- Group 2- Placebo for 48 weeks + Alendronate for 48 weeks
All study participants will be followed off alendronate for an additional 48 week period, making a total study length of 144 weeks.

You/your child should take a dose of alendronate (or placebo) once a week on the same day of each week. Each dose should be taken in the morning before you/your child have/has had anything to eat or drink. Each dose must be taken with at least 6-8 ounces of water. After you/your child take(s) each dose, you/your child must not eat for at least 30 minutes. You/your child should remain sitting or standing for at least 30 minutes after each dose. You/your child must wait at least 30 minutes before taking your/their calcium/vitamin D pill, your/their HIV medicines or any medicines on the day you/your child take(s) your/their alendronate.

On-Study Visits
You/your child will return to the clinic 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, and 144 weeks after you/your child enter(s) the study. These visits may last about 2 hours. In addition, you will be contacted by telephone 1, 4, and 49 weeks after you/your child enter(s) the study and 4 weeks after each of the study visits at weeks 24, 48, 72, and 96. Based on your/your child’s responses to the questions during the telephone interview, you/your child may have an additional clinic visit and evaluations. Evaluations during the study visits or telephone calls may include:

- questions about your/your child’s medications (including missed doses) and medical history
- a physical exam
- a dental exam by a dentist, and panoramic X-ray of your/your child’s teeth and jaw
- a pregnancy test, if you/your child can become pregnant

At your/your child’s study visits at weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, and 144, you/your child will be asked questions about changes in your/your child’s medications and health since your/your child’s last visit. You/your child will have a physical exam. At weeks 24, 48, 72, 96, and 144, you/your child will have about 6 teaspoons of blood drawn. The blood will be used for routine tests at all of these visits, and vitamin D levels and parathyroid hormone level will be done at all visits EXCEPT the week 144 visit. At weeks 0, 24, 48, 60, 72, 96, 120, and 144, you/your child will also be asked to provide a urine sample for bone tests. If you/your child can become pregnant, you/your child will have a pregnancy test at weeks 24, 48, 72, 96, and 144. Most visits will last about 1 hour. You will be given the results of the pregnancy test and routine tests as soon as they are available or at your/your child’s next study visit. Some of the blood and urine will be stored for tests that will be done on them at the end of the study. These tests will include bone tests (to show if you/your child are/is gaining or losing bone), hormones that affect bone, inflammation, immunologic function (ways that
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the body fights infections), and urine levels of the study drug. After all of the planned testing has been completed, any remaining samples of blood or urine will be destroyed.

At Weeks 24, 48, 72, 96 and 144, you/your child will have a spine and whole body DXA scan, and an X-ray of the hand. The DXA scan may take about 1 hour. You/your child will complete a form about how physically active you/your child have/has been. You/your child will fill out a form about how much you/your child smoke(s) and drinks alcohol. These forms will take about 15 minutes to complete. If you/your child are/is female, you/your child will be asked about your/their menstrual periods. You will be given the results of the DXA scans and hand X-ray as soon as they are available or at your/your child’s next study visit.

If You/Your Child Stop(s) the Study Drugs Early
If you/your child stop(s) taking the study drugs before the end of the study, you/your child will also be asked to return for only the Week 24, 48, 72, 96 and 144 week visits. At these visit you will be asked questions about changes in your/your child medications and health since your last visit. You/your child will have a physical exam. At this visit, you /your child will have about 6 teaspoons of blood drawn. The blood will be used for routine tests and bone tests (to show if you/your child are/is gaining or losing bone). Some of the blood will be stored for other tests, including measurements of bone hormones, inflammation, and immunologic function (ways that the body fights infections), to be done at the end of the study. You/your child will have a DXA scan and complete the food form. You/your child will complete a form about how physically active you/your child have/has been. You/your child will fill out a form about how much you/your child smoke(s) and drinks alcohol. These forms will take about 15 minutes to complete. If you/your child are/is female, you/your child will be asked about your/their menstrual periods.

You/your child will be given the results of the pregnancy test and routine tests as soon as they are available or at your/your child’s next study visit.

If You/Your Child Stop(s) the Study Early
If you/your child stop(s) the study before you/your child have/has completed all of the study visits, you/your child will be asked to return to the clinic for a final visit that may include most of the procedures described in the On-Study Visits section and may last about 2 hours.

OTHER INFORMATION

Information provided throughout this study about smoking and alcohol use and sexual activity will not be shared with parents or caretakers of adolescent participants. [Sites should modify the language about confidentiality of smoking, alcohol
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use and sexual activity to conform to their local practice, regulations and IRB requirements.

The information collected in this study may be used for other IMPAACT-approved HIV-related research.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 51 children and adolescents will take part in this study.

HOW LONG WILL I/MY CHILD BE IN THIS STUDY?

You/your child will be in this study for about 144 weeks.

WHY WOULD THE DOCTOR TAKE ME/MY CHILD OFF THIS STUDY EARLY?

The study doctor may need to take you/your child the study early without your permission if:

- The study is cancelled.
- An IMPAACT Study Monitoring Committee (SMC) recommends that the study be stopped early (The SMC is a group of experts who monitor the study.)
- You are/your child is not able to attend the study visits as required by the study

During the study:
If you/your child must permanently stop taking study-provided alendronate before your/your child’s study participation is over, the study staff will discuss other options that may be of benefit to you/your child. The study doctor may ask you/your child to continue to be part of the study and return for some study visits and procedures.

After the study:
After you/your child have/has completed your/their study participation, the study will not be able to continue to provide you/your child with the alendronate or calcium/vitamin D you/your child received on the study. If continuing to take these or similar (drugs/agents) would be of benefit to you/your child, the study staff will discuss how you/your child may be able to obtain them.

The study doctor may also need to take you/your child off the study drug(s) without your permission if:
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• Continuing the study drug(s) may be harmful to you/your child
• You/your child need(s) a treatment that you/your child may not take while on the study
• You are/your child is not able to take the study drug(s) as required by the study
• You/your child become(s) pregnant.

If you/your child must stop taking the study drug(s) before the study is over, the study doctor may ask you/your child to continue to be part of the study and return for some study visits and procedures.

WHAT ARE THE RISKS OF THE STUDY?

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known possible relationship. If you have questions concerning other study drug side effects, please ask the medical staff at your site.

For your safety, it is important that you tell the study doctor or nurse about all medications you are taking before you start the study and about any new medications that you may begin taking while on the study. In addition, it is important that you tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Risks of Study Drug, Alendronate:

• irritation or inflammation (swelling) of the lining of the esophagus and the stomach; erosions or ulcers of the mouth, esophagus, stomach, and duodenum (first part of the small intestines) In some cases, these conditions may lead to severe complications and require hospitalization. Such complications are: blood loss, narrowing of the esophagus, and tears in the esophagus/stomach/duodenum
• abdominal pain/bloating
• nausea/vomiting
• heartburn/acid reflux
• constipation
• diarrhea
• flatulence (gas)
• bone and muscle pain
• headache
• altered taste
• rash (may be related to exposure to the sun)
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- allergic reaction (swelling of the face, lips, tongue, throat)
- inflammation of the eye (uveitis)
- slow healing of broken bones
- abnormal heart beat
- low calcium levels in the blood
- low phosphate levels in the blood
- jaw osteonecrosis is a problem of poor healing or delayed healing of the jaw bone, usually after a dental procedure, such as having a tooth pulled. It has been seen rarely in adults taking alendronate. You will have an evaluation by a dentist before starting this study to make sure that you do not have serious dental problems that may put you at higher risk of jaw osteonecrosis. If you have serious dental problems, you cannot participate in the study. You will also be evaluated by a dentist throughout the study to look for signs of this condition. If serious dental problems occur during the study, you will be assessed by a dentist who will make recommendations for treatment.

Alendronate protects older women from having fractures. But when older women treated with alendronate have a fracture the location may be in a specific part of their thigh bone.

Risks of Study Drug, Calcium/Vitamin D

Calcium
- constipation
- flatulence (gas)
- increased acid in the stomach
- increased risk of kidney stones

Vitamin D
- high calcium levels in the blood (muscle weakness, headache, indifference, loss of appetite, nausea/vomiting, bone pain, calcium deposits in the tissues of the body, kidney disease, high blood pressure, and irregular heart beats)
- allergic reactions

Risk of Radiation from the DXA Scans, hand X-rays, and panoramic dental X-rays: The DXA scans and the x-rays involve a small amount of radiation. The amount of radiation received during each DXA scan is small, like that of getting a routine chest x-ray. The amount of radiation received during each hand X-ray is small, slightly less than that of getting a routine chest x-ray. The amount of radiation received during each panoramic dental X-ray is small, less than half the amount of getting a routine chest x-ray. Over the course of the entire study, including screening and 144 weeks on study, there is a maximum of 7 spine DXA, 6 whole-body DXA, 6 hand X-rays, and 2
panoramic dental X-rays as part of the study. All of these tests together are about equivalent to 4 chest X-rays each year for 3 years or 12 chest X-rays over the course of screening and 144 weeks of the study. To put it another way, the background radiation that every person absorbs from natural sources in daily life in ONE year is about three times greater than the total radiation from all of the tests a participant would receive in all three years of this study.

Risks of Blood Draws:
There is risk of some discomfort, bruising, or bleeding at the site where the blood is drawn. Occasionally, there is swelling in the area where the needle enters the body and a small risk of fainting and/or infection.

Other Risks
You/your child may feel uncomfortable or embarrassed by some parts of your/your child’s physical exam and with some of the questions related to smoking, alcohol use, and sexual activity.

ARE THERE RISKS RELATED TO PREGNANCY?

It is not known whether the drug in this study, alendronate, harms unborn babies. Studies in animals suggest that alendronate can cause miscarriage. There was no increase in birth defects in these animal studies. There was no increase in birth defects in infants of about 30 women who became pregnant while taking alendronate. The bones of a fetus/newborn grow rapidly and the drug alendronate has a very low, but possible risk to growing bone. For adult women who use this drug, it is recommended to avoid pregnancy while taking alendronate and to stop alendronate immediately if pregnancy occurs. However, alendronate can remain in bones for a long time, even after a person stops taking it. It is not known how long it remains in the bones, but it may persist for several years, even as long as 10 years. Additionally, alendronate that has been absorbed into the bone can come back out of the bone and into the blood at low levels. It is not known if alendronate coming back out of bones after the end of treatment poses any risk to a fetus when a woman becomes pregnant after stopping alendronate treatment. There is no formal recommendation by the FDA to avoid pregnancy for a specific amount of time after a woman has stopped taking the drug. Many doctors in practice recommend avoiding pregnancy for a period of 6 months after a woman stops taking alendronate. In this study, as an extra precaution, if you are female, you will be asked to avoid pregnancy for the entire duration of the study, including at least 48 weeks after you have stopped taking alendronate.

If you/your child are/is having sex that could lead to pregnancy, you/your child must agree not to become pregnant. If you/your child can become pregnant, you/your child
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must use at least two methods of reliable birth control that you discuss with the study staff throughout the whole study.

If you/your child can become pregnant, you/your child must have a pregnancy test before you/your child take the study drugs. The test must show that you/your child are/is not pregnant in order for you/your child to join the study. If you/your child think(s) you/they may be pregnant at any time during the study, tell your study staff right away. If you/your child are/is pregnant, you/your child must stop taking the study drugs right away. If you/your child are/is pregnant, you/your child will be asked to share information about the pregnancy and the outcome of the pregnancy. If you/your child have/has not had a study visit in the past month, you/your child will return to the clinic for an additional visit.

Pregnancy test results will be shared confidentially with participants, even if a parent or other adult is consenting for the child’s participation in the study. If the pregnancy test is positive, the study staff will refer pregnant participants to their primary provider for counseling about pregnancy and pregnancy care. [Sites should modify the preceding language about confidentiality of pregnancy test results to conform to their local practice, regulations and IRB requirements.]

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you/your child take(s) part in this study, there may be a direct benefit to you/your child, but no guarantee can be made.

It is clear that older adults with low bone density have a higher risk of spinal fracture or other broken bones. Many experts believe that children and youth with low bone density are also at risk of a spinal fracture or other broken bone over time, but they are not as certain. You/your child will benefit from the vitamin D, calcium and exercise recommendations provided in this study, as doctors know that these all help bone health in children. Studies have shown that alendronate improves low bone density in adults with HIV infection and in children with other medical problems. For this reason, it is anticipated that the alendronate you/your child receives in this study will improve your/his/her low bone density. Improving low bone density may also decrease your/your child’s risk of broken bones in the future. However, it is also possible that you/your child may not have an improvement in bone density or a reduction in future broken bones from the alendronate provided in this study.

Information learned from this study may also help others who have HIV.

WHAT OTHER CHOICES DO I/DOES MY CHILD HAVE BESIDES THIS STUDY?
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Instead of being in this study you have the choice of:

- treatment with prescription drugs (including alendronate) available to you/your child
- treatment with experimental drugs, if you/your child qualify(ies)
- no treatment

Things that can help your bone health even if you are/your child is not in this study include getting enough vitamin D, calcium and exercise. Please talk to your doctor about these and other choices available to you/your child. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the NIH. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal FDA.

People who may review your records include the U.S. FDA, the site institutional review board (IRB) (insert name of site IRB) or Ethics Committee, the National Institutes of Health, the Office for Human Research Protections (OHRP), study staff, study monitors, drug companies supporting the study (Merck & Co., Inc.), and their designees.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you or your participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

(The researchers should include language such as the following if they intend to make voluntary disclosure about things such as child abuse). The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following circumstances. (The researchers should state here the conditions under which voluntary disclosure will be made.)

WHAT ARE THE COSTS TO ME?
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Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you/your child is/are taking part in a research study.

WHAT HAPPENS IF I AM/MY CHILD IS INJURED?

If you/your child is/are injured as a result of being in this study, you/your child will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY/MY CHILD’S RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to take part/not to allow your child to take part in this study or leave this study/take your child out of the study at any time. You/your child will be treated the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your/your child’s health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:
- name of the investigator or other study staff
- telephone number of above

For questions about your/your child’s rights as a research subject, contact:
- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above
SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

Participant’s Name (print)  Participant’s Signature and Date

Participant’s Legal Guardian (print)  Legal Guardian’s Signature and Date
(As appropriate)

Study Staff Conducting Consent Discussion (print)  Study Staff Signature and Date

Witness’ Name (print)  Witness’s Signature and Date
P1076 SAMPLE ASSENT FORM

Protocol Title: IMPAACT P1076 - Impact of Oral Alendronate Therapy on Bone Mineral Density in HIV-Infected Children and Adolescents with Low Bone Mineral Density

Application No.:

Sponsor: NIH

Principal Investigator:

Date:

We want to tell you about a research study we are doing. A research study is a way to learn information about something. We are asking you to participate in this study because your bones are weak. We would like to find out more about treating adolescents with weak bones (or bones with low density). Weak bones may be more likely to break. We know that vitamin D, calcium and exercise can all help build healthy bones. We are not sure if adolescents with weak bones need other treatments besides vitamin D, calcium and exercise to make them stronger. Alendronate is a drug that can help make bones stronger in some people. But we do not know if alendronate works on weak bones in the same way in adolescents with HIV infection as in adults and children with other medical conditions. The purpose of this study is to see if alendronate works in a safe way to make bones stronger in adolescents with weak bones and HIV infection.

If you agree to join this study, you will be asked to take study drugs

- Everyone will receive calcium and vitamin D, combined into a single pill.
- You will be randomized to take alendronate or placebo (a tablet that looks like the real drug, but has no active drug in it, like a sugar pill) once a week, on the same day of each week, for the first 96 weeks (2 years) of the study. Randomized means that you are assigned by chance, as if by the toss of a coin.
- Everyone in the study will be assigned to take at least 48 weeks of alendronate during the first 96 weeks (2 years) of the study.
- Your doctors and nurses, and the people who work with you on this study will not know if you are getting active medication or placebo during the study.

If you agree to join this study, you will be asked to

- Come to 14 visits. Each visit will last about 2 hours. The study will last 144 weeks, or about 3 years.
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- DXA scan. DXA stands for dual energy x-ray absorptiometry scan. DXA is a special type of x-ray used to measure how strong or dense bones are.
- You will be asked questions about your medications and medical history and have a complete physical examination at each visit.
- You will have up to 6 teaspoons of blood drawn at each visit.
- You will be given the results of common blood tests, X-rays and DXA results as soon as they become available or at your next study visit.
- **Information you provide in this study about sexual activity, smoking, and alcohol use will not be shared with your parents or caretakers without your permission.**

If you are a girl who can become pregnant, then here is some additional information that you need to know:
- You will be asked about your menstrual periods at study visits.
- You will be asked for a urine sample at the beginning of the study and at each study visit to make sure that you are not pregnant. You cannot join this study if you are pregnant.
- You will be asked to make sure that you do not become pregnant during the study. This may mean that you do not have sex during the study. If you do have sex, it will mean that you use 2 forms of birth control, including a condom. You will be asked to contact the study team right away if you think you might be pregnant, so that a pregnancy test can be arranged.
- If you are already in the study and you become pregnant, then you will stop taking alendronate and you will not have any of the X-ray tests. But you will be asked to complete the remaining study visits.
- **Information you provide in this study about sexual activity and pregnancy test results will not be shared with your parents or caretakers without your permission.** [Sites should modify the preceding language about confidentiality of pregnancy test results and sexual activity information to conform to their local practice, regulations and IRB requirements.]

What are the risks if you agree to be in this study?
- There could be some risk related to pregnancy. It is not known if an unborn baby could be harmed by the mother taking alendronate during pregnancy. Alendronate can also stay in your bones and in your system time after you stop taking it. We don’t know how long it can stay in your system but it may last for months or years. We believe that it goes down to very low levels within a few months of stopping and there’s a chance it could still be hanging around for some years after the study is over. We don’t think that there is harm when a woman becomes pregnant after she stops taking alendronate but we can’t be sure. Many doctors recommend waiting for 6 months after stopping alendronate before getting
pregnant. In this study, we will be asking you to wait at least 12 months, to be even more careful.

- The drugs used in this study may have side effects that we want you to know about
  - Alendronate can have these side effects
    - Irritation of your stomach or esophagus (the way that food passes from your mouth to your stomach). It can feel like burning in your chest or stomach, heartburn or upset stomach.
    - Nausea and vomiting
    - Constipation or diarrhea
    - Passing gas
    - Pain in your muscles or bones
    - Headache
    - Change in how things taste
    - Rash, especially after going out in the sun
    - Allergic reaction (swelling of the face, lips, tongue, throat)
    - Inflammation of the eye (uveitis)
    - Slow healing of broken bones
    - Abnormal heart beat
    - low calcium levels in the blood
    - low phosphate levels in the blood
    - jaw osteonecrosis is a problem of poor healing or delayed healing of the jaw bone, usually after a dental procedure, such as having a tooth pulled. It has been seen rarely in adults taking alendronate. You will have an evaluation by a dentist before starting this study to make sure that you do not have serious dental problems that may put you at higher risk of jaw osteonecrosis. If you have serious dental problems, you cannot participate in the study. You will also be evaluated by a dentist throughout the study to look for signs of this condition. If serious dental problems occur during the study, you will be assessed by a dentist who will make recommendations for treatment.
  - Calcium/Vitamin D tablets can have these side effects:
    - Heartburn or upset stomach.
    - Constipation
    - Passing gas
    - Allergic reaction (swelling of the face, lips, tongue, throat)
    - Problems if the calcium level in your blood gets too high, like feeling weak, losing your appetite, vomiting, bone pain, kidney problems, high blood pressure, and irregular heart beats
APPENDIX VI

- As part of this study, you will be exposed to a small amount of radiation from the DXA Scans, hand X-rays, and panoramic dental X-rays: If you add up all of the DXA and X-rays for the whole study, the total radiation is about the same as the amount of radiation that an average person absorbs naturally from the environment in ONE year.

- You will have blood drawn as part of this study:
  - When you have blood drawn, it can sometimes cause discomfort, bruising, swelling or bleeding at the site where the blood is drawn.
  - Sometimes people faint when they have their blood drawn.
  - Occasionally, you can get an infection where you have blood drawn.

- We do not know if you will be helped by being in this study:
  - Exercise, vitamin D and calcium should all be good for your bones.
  - We believe that alendronate might make your bones stronger but we can’t be sure.
  - We also may learn something that will help other children with HIV infection and weak bones some day.

You do not have to join this study. It is up to you. You can say okay now, and you can change your mind later. All you have to do is tell us. No one will be upset if you change your mind, and you will continue to receive medical care as you did before.

Before you say yes to being in this study, we will answer any questions you have. If you want to be in this study, please sign your name. You will get a copy of this form to keep for yourself.

__________________________________________  _________________________________________
Sign your name here                        Date
APPENDIX VII

P1076 SUBJECT CHECK FOR UNDERSTANDING

Say whether you think each of the following statements about being in this study in TRUE or FALSE. Then, we can discuss the answers together.

1. The main goal this study is to find out more about treating adolescents with HIV infection who have weak bones.

2. You are REQUIRED to participate in this study.

3. There are NO risks to taking part in this study.

4. The study treatment will DEFINITELY make your bones stronger.

5. Alendronate can stay in your body for months or years after you stop taking it.

6. You can’t be pregnant when you join this study, but it’s OK to get pregnant while you are in the study.

7. We know FOR SURE that if a pregnant woman takes alendronate, it will harm her unborn baby.
APPENDIX VII

Answers with Discussion points:

1. True. The purpose of this study is to see if alendronate works in a safe way to make bones stronger in adolescents with weak bones and HIV infection.

2. False. You do not have to join this study. It is up to you. You can say okay now, and you can change your mind later. All you have to do is tell us. No one will be upset if you change your mind, and you will continue to receive medical care as you did before.

3. False. The drugs used in this study may have side effects. Alendronate can have side effects like irritation of your stomach or esophagus. Calcium/Vitamin D tablets can have side effects like heartburn or upset stomach. You will be exposed to a small amount of radiation from the DXA Scans, hand X-rays, and panoramic dental X-rays. You can have bleeding or pain when you have blood drawn.

4. False. We do not know if you will be helped by being in this study. Exercise, vitamin D and calcium should all be good for your bones. We believe that alendronate might make your bones stronger but we can’t be sure.

5. True. Alendronate can also stay in your bones and in your system after you stop taking it. We don’t know how long it can stay in your system but it may last for months or years. We believe that it goes down to very low levels within a few months of stopping and there’s a chance it could still be hanging around for some years after the study is over.

6. False. It is true that you cannot join this study if you are pregnant. You will also be asked to make sure that you do not become pregnant during the study. This may mean that you do not have sex during the study. If you do have sex, it will mean that you use 2 forms of birth control, including a condom. You will be asked to contact the study team right away if you think you might be pregnant, so that a pregnancy test can be arranged.

7. False. There could be some risk related to pregnancy, but it is not known if an unborn baby could be harmed by the mother taking alendronate during pregnancy. We don’t think that there is harm when a woman becomes pregnant after she stops taking alendronate but we can’t be sure. Many doctors recommend waiting for 6 months after stopping alendronate before getting pregnant. In this study, we will be asking you to wait at least 12 months, to be even more careful.