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Journal

AIDS Research and Human Retroviruses, 35(8)

ISSN

0889-2229

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Publication Date

2019-08-01

DOI

10.1089/aid.2018.0270

Peer reviewed

AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 35, Number 8, 2019

DOI: 10.1089/aid.2018.0270

Tenofovir Has Minimal Effect on Biomarkers of Bone Health in Youth with HIV Receiving Initial Antiretroviral Therapy

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Abstract

Both HIV infection and tenofovir disoproxil fumarate (TDF) treatment adversely impact bone metabolism and may lead to osteopenia, which has critical implications for youth with HIV (YWH). This study evaluates changes in the biomarkers of bone metabolism and inflammation among YWH receiving initial treatment with TDF- and non-TDF-containing antiretroviral therapies (ARTs). YWH [$n=23$, median age 21 years (range 18–24), 87% male, 61% African American] were assessed for inflammatory and bone metabolism biomarkers at enrollment, after 48 weeks of TDF-containing ART, and 96 weeks of ART without TDF with continued viral suppression. Spearman's rank correlation evaluated biomarker associations. Bone alkaline phosphatase, parathyroid hormone, and osteopontin increased after TDF treatment. All fell after TDF was discontinued. Levels of RANKL and osteoprotegerin did not change throughout the study. There was little correlation between biomarkers of bone metabolism and either macrophage or lymphocyte activation at any time point. Our results establish baseline associations between bone metabolism and immune biomarkers for this population, and find that before CD4 T cell decline chronic inflammation does not perturb biomarkers of bone metabolism among YWH. The adverse effects of TDF on bone health may be marginal for YWH at the early stages of disease.

Keywords: bone metabolism, tenofovir disoproxil fumarate (TDF), youth with HIV (YWH), biomarker, macrophage activation, lymphocyte activation

Introduction

HIV infection and its treatment with antiretroviral therapy (ART) adversely affect bone metabolism and leads to low bone mineral density (BMD). Increased fracture rates have been reported in chronically infected adults as they age.[1–3] While the low BMD is a known comorbidity among aging HIV-infected individuals, characterization of its progression and potential impact on youth with HIV (YWH) has not been fully evaluated.

There is growing recognition that low BMD affects perinatally infected YWH who have received ART over many years as well as behaviorally infected YWH.[4–6] Furthermore, studies show that rate of low bone mass in HIV-infected males is greater than that in females in both the adult population and perinatally infected children, and effect is more pronounced as Tanner stage increases.[4,7,8] The impact of HIV infection on BMD is particularly relevant among this population because 85%–90% of bone mass is attained during childhood through adolescence.[9–11] Impaired bone formation during this critical period may compromise bone mass and increase fracture risk later in life. Twenty-one percent of newly diagnosed HIV infections in the United States occur among youth aged 13–24, making it important for clinicians to understand the effects of HIV infection and treatment on bone metabolism in YWH.[12,13]

Proposed mechanisms for HIV-associated osteopenia include direct effect of the virus, ART, and chronic inflammation.[14]

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HIV exerts both direct and indirect effects on bone metabolism.[14] Studies of ART-naïve HIV-infected individuals showed that longer duration of infection and greater levels of viremia are both associated with lower BMD, suggesting that both viral and inflammatory factors affect bone mass.[15,16] In addition, ART independently affects bone mass in HIV-infected individuals. In a meta-analysis of adult studies, HIV-infected individuals receiving multiple classes of ART had 2.5-fold increased odds of having low BMD compared with ART-naïve HIV-infected individuals.[17–19]

YWH are commonly treated with tenofovir disoproxil fumarate (TDF)-containing ART regimens, which are associated with 1%–3% more bone loss compared with treatment with other nucleotide reverse transcriptase inhibitors.[20–23] Reversible TDF-associated bone loss has also been observed in healthy HIV-uninfected individuals taking TDF for pre-exposure prophylaxis (PrEP), further supporting the adverse effects of TDF on bone metabolism.[24–26] Tenofovir accumulation (active metabolite of TDF) in the proximal renal tubular cells causes renal tubular dysfunction with subsequent phosphate wasting and leads to bone loss. Severe cases progress to a Fanconi-like syndrome with hyperphosphaturia, hyperaminoaciduria, and glucosuria, which results in osteopenia and osteomalacia.[27–29] Even mild TDF-associated renal tubular dysfunction is associated with reduction in BMD.[30,31]

While there have been no reports of osteoporosis or fractures in YWH, bone densitometry measured by dual-energy X-ray absorptiometry (DXA) has shown lower Z-scores and a lower annual BMD accrual compared with age- and gender-matched uninfected youth.[4,32–35] However, DXA has been an insensitive tool in detecting loss of or impaired bone mass accrual among recently infected YWH.[5] There is a need to identify surrogate biomarkers of BMD loss in YWH and determine the relative contribution of ART, viral replication, and inflammation to long-term bone dysmetabolism.

In this study, we analyzed plasma bone metabolism biomarkers as surrogates for early changes in bone health, and correlated them with inflammatory biomarkers before and after treatment with a TDF-containing ART regimen. Using these results, the effects of HIV infection, ART regimen with and without TDF, and immune activation on bone metabolism in YWH were evaluated.

Materials and Methods

Study design

Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) protocol 061 was a randomized study of adolescents and young adults, aged 18–24 years, with confirmed HIV-1 infection acquired during adolescence. Enrollment came from 23 clinical sites within the ATN and U.S. sites in the International Maternal, Pediatric and Adolescent AIDS Clinical Trials Group (IMPAACT). Entry criteria included YWH with confirmed HIV-1 infection after the age of 9 years, no prior ART, and CD4 T cell count >350 cells/μL.[36] Subjects who were pregnant or had AIDS defining illnesses were excluded.

Participants randomized to the experimental arm were started on ART consisting of tenofovir/emtricitabine (TDF/FTC) along with ritonavir-boosted atazanavir (ATV/r), and were eligible to deintensify treatment to ATV/r as sole therapy at 52 weeks if HIV RNA was maintained <100 copies/mL between 24 and 48 weeks. ATV/r was continued for the next 2 years if HIV levels remained <400 copies/mL and CD4 T cell levels were stable. Participants who displayed viral levels ≥400 copies/mL during deintensification were required to have a viral load repeated within 6 weeks, and if it remained ≥400 copies/mL, then they reached a study endpoint.

The Institutional Review Boards at each participating site approved the protocol, posted on ClinicalTrial.gov (Identifier NCT00491556). A Data Safety and Monitoring Board appointed by the Eunice Kennedy Shriver National Institute of Child Health and Human Development reviewed the results of the study semiannually. The last subject completed the study in 2013.

To examine the effect of HIV replication and TDF on biomarkers of immune activation and bone metabolism, we performed a secondary analysis of 23 participants who completed the study with durable viral suppression from week 24 to 152 and had plasma samples available. A schema of the study is shown in Supplementary Figure S1.

Study monitoring

Analyses for T cell subsets and plasma viral load were performed at 12-week intervals throughout the study. Flow cytometry of lymphocyte subsets included percentages and absolute numbers of CD3, CD4, CD8, CD19, CD56/CD16, and CD45 (BD TruCount™ BD Bioscience, San Jose, CA). The UltraSensitive Roche Amplicor HIV-1 Monitor Test, v2.0 (Roche Diagnostics USA, Indianapolis, IN) was used to assess plasma viral load.

Bone metabolism and inflammation biomarkers

Plasma biomarkers were measured at entry, 48, and 152 weeks using samples collected in acid citrate dextran and stored in cryovials at −80°C. Plasma bone metabolism biomarkers alkaline phosphatase (Alk Phos), phosphorus (Phos), calcium, osteopontin (OPN) as well as inflammatory markers sCD14, sCD163, sCD27, interferon gamma (IFNγ), tumor necrosis factor alpha (TNFα), and IL-10 were measured through commercially available enzyme-linked immunosorbent assay kits as previously described.[36,37]

Bone alkaline phosphatase (BAP), osteocalcin (OC), osteoprotegerin (OPG), parathyroid hormone (PTH), RANKL, and 25-(OH)D were measured using previously frozen cryopreserved plasma samples that were thawed to room temperature. BAP samples were analyzed at Quest Diagnostics (Baltimore, MD), and OC, OPG, PTH, and RANKL samples were analyzed at Duke University Medical Center Human Vaccine Institute Core Facility utilizing EDM Millipore Milliplex panel with a detection range of 146–600,000 pg/mL for OC, 7–30,000 pg/mL for OPG, 5–20,000 pg/mL for PTH, and 4.88–20,000 pg/mL for RANKL. 25-(OH)D samples were measured at Duke University Medical Center Clinical Immunology Laboratory using the LIAISON® Analyzer (DiaSorin, Saluggia, Italy) through chemiluminescence method. Samples below the level of detection were recoded to the lowest detectable value for each biomarker.

Statistical analysis

All data were summarized using descriptive statistics. HIV viral load, absolute CD4 T cell counts, inflammatory biomarkers, and bone metabolism biomarkers were evaluated for each subject using the Wilcoxon signed-rank test at 0 and

48 weeks, 48 and 152 weeks, and 0 and 152 weeks. Then, Spearman's rank correlation was used to determine if associations were present between bone metabolism biomarkers and inflammatory markers, CD4 count, and viral load at each time point. All analyses were two sided, with a p-value of .05 considered statistically significant, and were performed with Python™ and Graphpad Prism software.

Results

Study cohort

At entry, median age of the study cohort was 21 years, with a median body mass index of 24, and all were Tanner stage V (Table 1). Participants were 87% ($n=20$) male and 61% ($n=14$) African American. Pretherapy median viral load was 13,132 copies/mL with all subjects achieving undetectable viral load (<100 copies/mL) by 24 weeks on treatment, and remaining <400 copies/mL to end of study (EOS) ($p<.001$, Wilcoxon signed-rank test). Absolute median CD4 T cell count increased from 520 cells/μL at entry to 850 cells/μL by week 48 ($p<.001$, Wilcoxon signed-rank test), and remained elevated at 959 cells/μL at EOS. Subjects were generally vitamin D insufficient with median 25-(OH)D level of 19.6 ng/mL (interquartile range 13.9, 24.8) at study entry.

Changes in bone and inflammatory biomarkers after initiation of ATV/r/TDF/FTC

To determine how viral suppression by ATV/r TDF/FTC influences bone metabolism and inflammation among YWH, biomarkers were measured before and after 48 weeks of therapy (Figs. 1 and 2).

Serum total alkaline phosphatase and BAP both increased significantly during initial treatment [median alkaline phosphatase 72 U/L at entry to 88 U/L at 48 weeks ($p<.0001$), median BAP 11.5 U/L at entry to 15.3 U/L at 48 weeks ($p=.0002$)] (Fig. 1a, b). 25-(OH)D and OPN followed similar trends as 25-(OH)D levels increased on ATV/r/TDF/FTC with median 25-(OH)D 19.6 ng/mL at entry rising to 26 ng/mL at 48 weeks ($p=.0035$) and OPN increasing from a median level of 53.4 to 62.4 ng/mL at 48 weeks ($p=.023$) (Fig. 1c, d). PTH and OC levels also trended upward during the first 48 weeks on treatment (Fig. 1e, f). Median PTH levels rose from 29.2 to 39.4 pg/mL ($p=.07$), while OC increased from 25,490 pg/mL at entry to 37,514 pg/mL at week 48 ($p=.18$). Levels of phosphorus, calcium, OPG, and RANKL did not change after initiation of therapy (Fig. 1g–j).

As expected, initial therapy with viral suppression impacted biomarkers of inflammation and immune activation (Fig. 2). The levels of sCD163 and TNFα decreased significantly between entry and week 48 on treatment with median sCD163 levels falling from 575 ng/mL at entry to 453 ng/mL at 48 weeks ($p<.0001$) (Fig. 2b). Similarly, median TNFα levels fell from 9.4 to 5.2 pg/mL ($p=.0015$) (Fig. 2e). Median levels of sCD14, IFNγ, sCD27, and IL-10 did not change significantly between 0 and 48 weeks.

Table 1. Demographics of the Study Population

	Median (IQR), n *(%)*
N	23
Age in years[a]	21 (19, 22)
Gender,[b] *n* (%)	
Male	20 (87)
Female	3 (13)
Race,[b] *n* (%)	
African American	14 (61)
White	4 (17)
Asian/Pacific Islander	1 (4)
Native American/Alaskan	1 (4)
Other/mixed	3 (13)
BMI (kg/m^2)[a]	24 (21, 30)
Viral load (copies/mL)[a]	
Entry (week 0)	13,132 (5513, 24,602)
Week 48	<50
EOS (week 152)	<50
Absolute CD4 count (cells/μL)[a]	
Entry (week 0)	520 (452, 730)
Week 48	850 (670, 906)
EOS (week 152)	959 (812, 1134)

[a]Median (IQR).
[b]*n* (%).
BMI, body mass index; EOS, end of study; IQR, interquartile range.

Changes in bone and inflammatory biomarkers after discontinuation of TDF/FTC in viral-suppressed YWH

To determine if discontinuation of TDF/FTC altered bone and inflammatory biomarkers among YWH, biomarker levels were compared between 48 weeks of treatment with ATV/r/TDF/FTC and EOS when TDF/FTC was discontinued and ATV/r monotherapy continued for an additional 96 weeks.

Both alkaline phosphatase and BAP decreased significantly over this time, approaching pretreatment levels at EOS [median alkaline phosphatase at EOS 75 U/L (week 48–EOS $p=.0001$) and BAP at 11.1 mcg/L (week 48–EOS $p<.0001$)] (Fig. 1a, b). Similarly, vitamin D and OPN levels also declined to a median of 19.8 ng/mL ($p=.0021$) and 43.7 ng/mL ($p=.0001$), respectively, with OPN level lower than that at pretherapy (Fig. 1c, d). PTH decreased significantly from 48 weeks to EOS to 37.4 pg/mL ($p=.0054$) (Fig. 1e) as did OC levels from median of 37,514 pg/mL at 48 weeks to 21,738 pg/mL at EOS ($p=.011$) (Fig. 1f). Phosphorus levels decreased significantly from 48 weeks to EOS to a median of 3.4 mg/mL at EOS ($p=.023$) (Fig. 1g). Levels of calcium, OPG, and RANKL did not change significantly from 48 weeks to EOS (Fig. 1h–j).

In contrast to biomarkers of bone metabolism, inflammatory biomarkers showed little change between 48 weeks and EOS (Fig. 2). Soluble CD163 levels remained similar, whereas TNFα levels declined further to a median of 4.2 pg/mL ($p<.0001$) by EOS (Fig. 2b, e). IFNγ levels decreased significantly between week 48 and EOS from a median of 14.25 pg/mL at 48 weeks to 1.44 pg/mL at EOS ($p=.0001$) (Fig. 2c).

Associations between markers of bone metabolism and markers of inflammation

To determine associations between inflammatory and bone biomarkers with and without TDF-containing ART, correlations at entry, 48 weeks, and EOS were examined as shown in Figure 3. As expected, BAP significantly correlated with

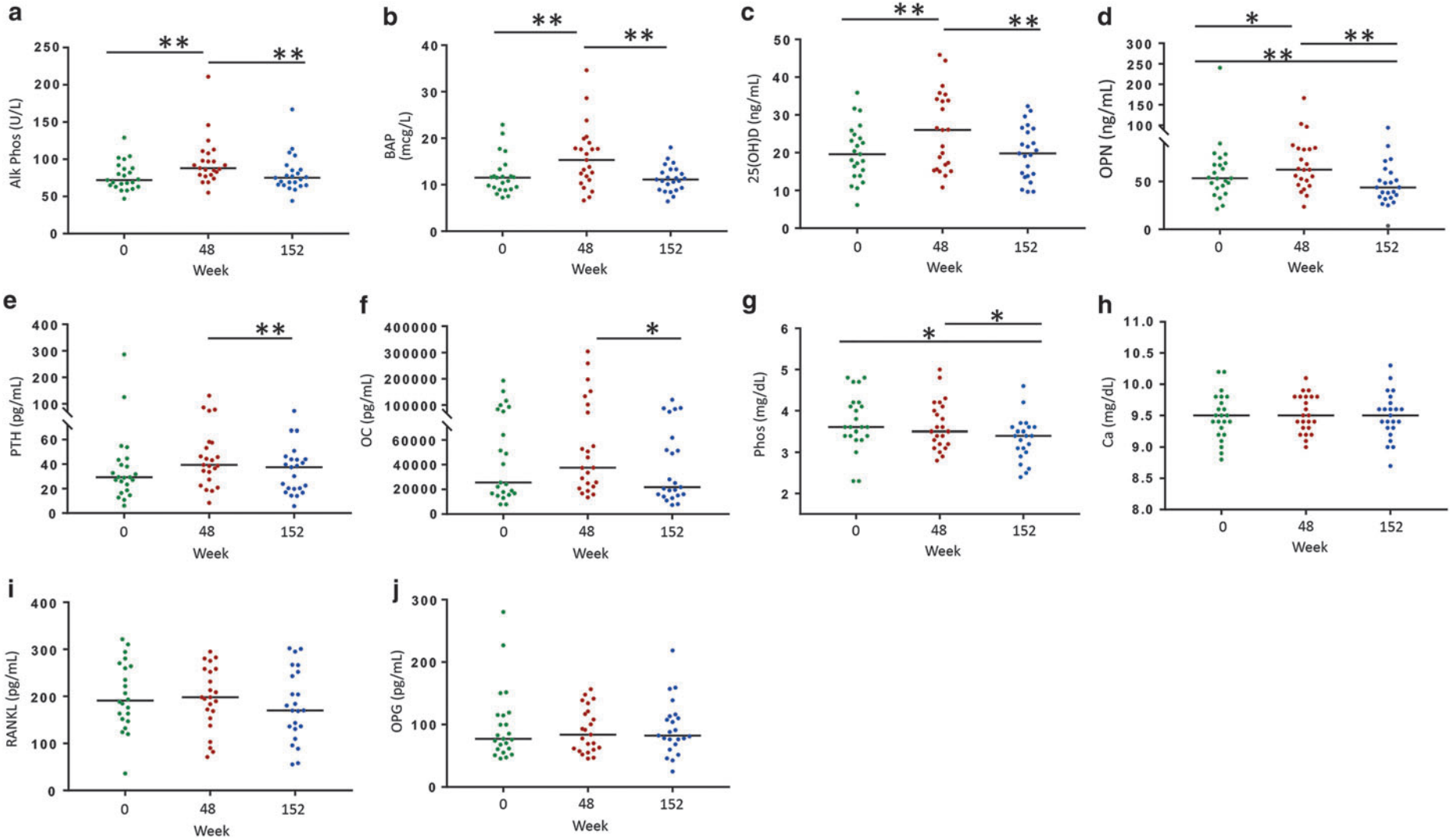

FIG. 1. Changes in biomarkers of bone metabolism. Biomarkers **(a–j)** are shown on the *X* axis for individual participants for week 0 (pretherapy, *green circles*), week 48 (TDF-containing ART, *red circles*), and week 152 (ATV/r monotherapy, *blue circles*). *Y* axis shows individual biomarkers. Median and *p*-values are shown in the graph as difference between 0–48 weeks, 48–152 weeks, and 0–152 weeks. Comparisons were tested by the Wilcoxon signed-rank test $*p < .05$, $**p < .01$. ART, antiretroviral therapy; ATV/r, ritonavir-boosted atazanavir; TDF, tenofovir disoproxil fumarate.

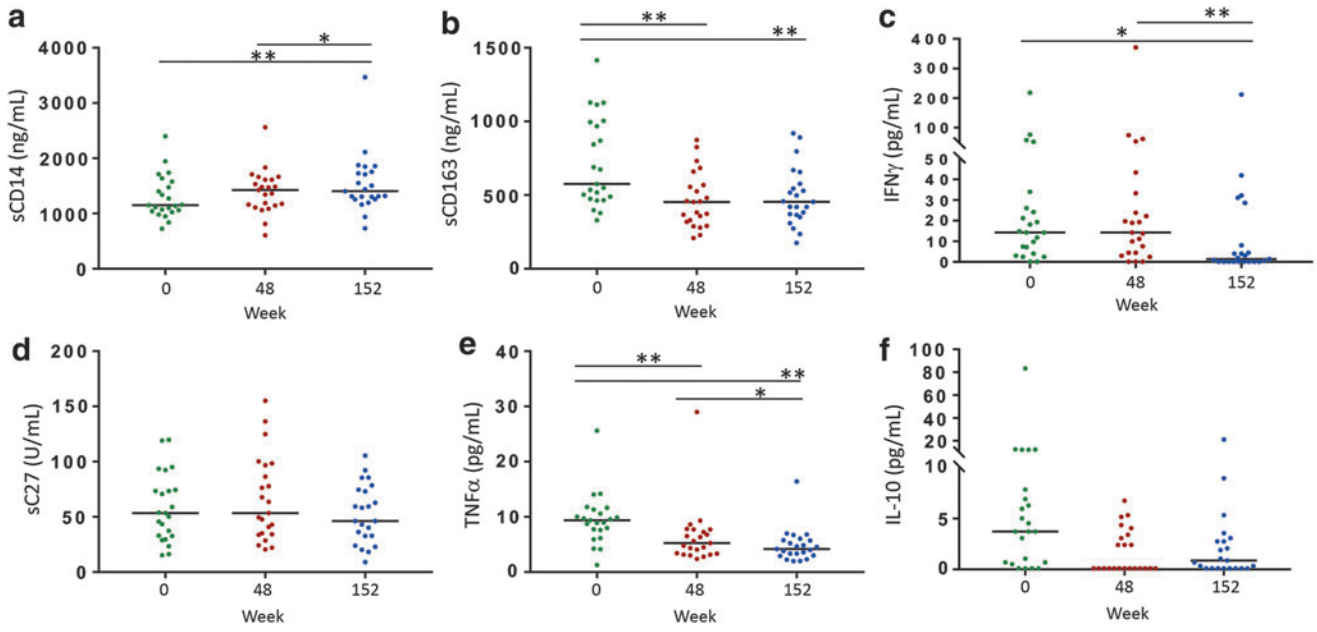

FIG. 2. Changes in inflammatory biomarkers. Biomarkers (**a–f**) are shown on the *X* axis for individual participants for week 0 (pretherapy, *green circles*), week 48 (TDF-containing ART, *red circles*), and week 152 (ATV/r monotherapy, *blue circles*). *Y* axis shows individual biomarkers. Median and *p*-values are shown in the graph as difference between 0–48 weeks, 48–152 weeks, and 0–152 weeks. Comparisons were tested by the Wilcoxon signed-rank test $*p < .05$, $**p < .01$.

alkaline phosphatase independent of viral replication or type of therapy ($\rho = 0.645 \sim 0.727$, $p \leq .001$). Similarly, PTH positively correlated with OPG at all three time points ($\rho = 0.436 \sim 0.596$, $p \leq .038$). RANKL, which induces osteoclast differentiation and bone resorption, correlated with pretherapy sCD27 ($\rho = 0.572$, $p = .005$), a biomarker of lymphocyte activation, as well as with pretherapy CD4 T cell counts ($\rho = 0.558$, $p = .007$). High pretherapy viral load was associated with higher PTH levels at entry ($\rho = 0.503$, $p = .014$). Before therapy and at 48 weeks, OPN positively correlated with BAP ($\rho = 0.584$ at entry and 0.496 at 48 weeks, $p \leq .016$), but this association was not evident at EOS. OPN displayed a negative correlation with TNF at 48 weeks ($\rho = -0.462$, $p = .026$). Vitamin D levels positively correlated with OPN at entry ($\rho = 0.433$, $p = .044$) and with sCD163 at 48 weeks ($\rho = 0.511$, $p = .015$).

Although urinary values were not available to calculate renal clearance, serum phosphorus and calcium levels were associated with certain bone and inflammatory biomarkers. Serum phosphorus level correlated with sCD27 ($\rho = 0.489$, $p = .021$) and RANKL ($\rho = 0.518$, $p = .014$) at pretherapy, and with sCD27 ($\rho = 0.489$, $p = .021$), TNFα ($\rho = 0.470$, $p = .024$), and sCD14 ($\rho = 0.505$, $p = .014$) at 48 weeks. Calcium levels negatively correlated with CD4 count at EOS ($\rho = -0.433$, $p = .044$).

Discussion

Standard of care for the initiation of ART for HIV-infected individuals has changed rapidly since the START (Strategic Timing of AntiRetroviral Treatment) trial showed that early initiation of ART benefits all HIV-infected individuals regardless of CD4 T cell counts.[38] YWH now initiate ART well before CD4 T cell decline, increasing the potential for adverse long- and short-term impacts on bone metabolism. Assessing changes in bone metabolism is challenging, as youth undergo constant bone modeling and accrual.[9–11] For youth in the early phases of chronic diseases, few studies examine bone metabolism using biomarkers as a measurement of bone turnover. In

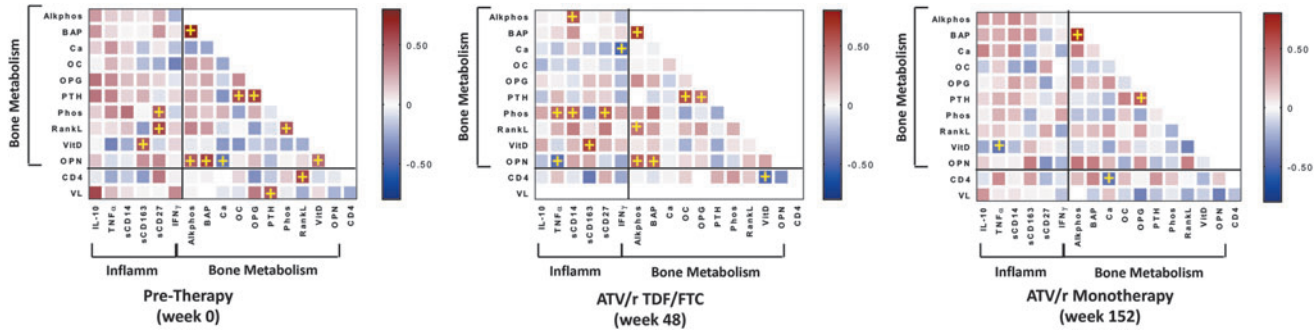

FIG. 3. Correlation among biomarkers. Heat map shows relative *rho* values between markers of bone metabolism and inflammation at 0, 48, and 152 weeks on study. (+) denotes a $p < .05$.

YWH with CD4 T cell counts >350, we hypothesized that the immune reconstitution associated with early therapy would perturb biomarkers of bone turnover. We assessed the bone–immune interface by examining the relationship between markers of bone turnover and inflammation in YWH.[37,39]

Changes in bone metabolism biomarkers correlated with TDF use. Both BAP and alkaline phosphatase increased with initiation of TDF and decreased when TDF was discontinued. This reflects evidence that TDF increases bone turnover and impairs bone mineralization, presumably due to enhanced phosphaturia.[27–30]

OPN, an early T lymphocyte activation phosphoprotein that initiates osteoclast-driven bone resorption,[40] increased in our cohort while on TDF and fell below pretherapy levels after TDF was discontinued. Increased levels of OPN on TDF with concomitant impairment of bone mineralization again reflect a mechanism in which TDF impairs bone mass accrual. OC is an osteoblast-specific protein that incorporates into the extracellular matrix during bone formation, and generally increases when bone turnover is high.[40,41] In our cohort, OC trended upward in subjects on TDF and fell significantly when TDF was discontinued. This finding further supports reported associations between TDF and increased bone turnover.[27–30] PTH levels in our cohort followed the same pattern, possibly due to increased production of vitamin D-binding protein accompanied by a reduction in free 1, 25-OH(2)D.[42,43]

A known mechanism by which TDF acts on bone loss is renal phosphate wasting.[27–30] In our cohort on TDF, serum phosphorus levels trended downward, then decreased significantly further when TDF was discontinued. However, these results are difficult to interpret because urinary phosphate levels were not available to calculate phosphate clearance.

The majority of ART-associated bone loss occurs during the first 2 years of treatment, and then subsequently stabilizes.[44,45] Among HIV-infected adults with low CD4 T cells, the initiation of therapy results in significant bone loss, in part due to T cell immune reconstitution.[46] Similar findings have been validated in murine models.[47] The proposed mechanism is an increased ratio of T cell-derived RANKL relative to B cell-derived OPG.[48,49]

In our cohort with normal CD4 T cell counts before therapy, levels of RANKL and OPG remained stable through the EOS. However, before ART, there was a correlation between sCD27, a measure of lymphocyte activation, and RANKL. This validates the association between lymphocyte activation and increased bone resorption during active viral replication. Taken together, our data indicate that bone metabolism biomarkers are not highly perturbed in YWH, likely due to their intact immune system at the time of ART initiation.

The relationship between immunity and bone metabolism is extensively investigated across diseases, particularly in autoimmune disorders.[50] Associations between HIV and bone loss parallel similar observations in rheumatoid arthritis.[50] HIV infection perturbs the immunology of bone metabolism through inflammatory pathways involving lymphocytes and macrophages.[37,51]

Soluble CD14 and soluble CD163, biomarkers of macrophage activation, remain elevated despite long-term control of viral replication in HIV-infected individuals.[36,37] M2 macrophages preferentially express CD163. Upon macrophage activation, TNFα-converting enzyme (TACE/ADAM17) cleaves CD163, which allows for its measurement in plasma.[52,53] In our study, viral control on ART during weeks 48 through 152 was associated with a decrease in sCD163. On entry and at 48 weeks, sCD163 levels also positively correlated with vitamin D levels. During HIV infection, persistent microbial translocation through the gut activates macrophages through a different pathway in which LPS binds to TLR4 and raises sCD14 levels.[54,55] In a cross-sectional analysis of YWH by Adolescent Trials Network, higher sCD14 levels correlated with lower bone mass.[56] This suggests that the latter macrophage activation pathway contributes to bone loss. While sCD14 levels remained elevated throughout our study, they were positively correlated only with phosphorus level.

Another mechanism thought to contribute to bone loss in autoimmunity and HIV infection is RANKL activity amplification by TNFα, which promotes osteoclast differentiation.[39,50] However, TNFα levels negatively correlated with OPN in our study. Although IFNγ directly inhibits osteoclast differentiation, its effect on bone mass is unclear.[47,57,58] Within our cohort, there was no clear association between IFNγ and bone biomarkers. Our study does not identify clear relationships between immune and bone biomarkers, but the results do not exclude the hypothesis that chronic inflammation perturbs these biomarkers over time.

A limitation in our study design is the use of surrogate biomarkers of bone metabolism, which does not directly measure bone mass using the DXA. However, based on previous studies in this age group, DXA scans are unlikely to detect significant changes in youth at early stages of HIV infection. Our study's small sample size weakens the conclusion for a lack of a significant effect by TDF or HIV infection on BMD among YWH. In addition, urinary samples were unavailable to evaluate for urine phosphorus and calcium excretion, which would directly assess renal phosphorus wasting.

Another limitation of our study is the less number of HIV-infected females enrolled, reflecting the HIV epidemic in the United States. As a result, our findings may not be directly applicable to young females with HIV. However, low BMD affects HIV-infected males more than females.[4,7,8] Our results indicate that TDF effect on bone health may be reversible and minimal for both male and female YWH, as these biomarkers do not vary substantially between genders in this age and Tanner stage.[59] Finally, the presence of 25-(OH)D deficiency at baseline, although mild, and subsequent changes in 25-(OH)D levels during the study that may have occurred due to unrelated factors could have influenced bone biomarkers.[60]

Among YWH with viral suppression on and off TDF-containing ART, bone biomarker changes showed that TDF independently increased bone turnover. This is consistent with prior studies across the age spectrum. Many of the perturbed biomarkers identified in our study returned to pretherapy levels when TDF was discontinued. This coincides with observations of uninfected individuals taking TDF for PrEP for whom TDF-associated bone loss was also reversible.[24–26] A recent study observed bone biomarker changes in YWH recently treated with TDF, which did not associate with a reduction in bone mass.[61] As such, the negative effect of TDF on bone health may be minimal for YWH at the early stages of disease. Longitudinal follow-up is needed to evaluate the long-term effects of TDF in this population.

This study examines biomarkers of bone metabolism and inflammation in youth who have normal CD4 T cell counts and are initiating ART at early stages of HIV infection. Bone

biomarkers may be useful in monitoring bone health, especially when changes in bone mass cannot be detected through imaging or clinical signs. The most applicable clinical biomarker to monitor bone health in YWH would include BAP measured in concert with serum phosphorus, as significant elevation in these levels could suggest development of osteomalacia on TDF.

The strength of the study design resides in the longitudinal assessment of biomarkers over 3 years of viral suppression. There are no similar studies on bone metabolism in YWH receiving initial ART. HIV is a chronic inflammatory disease that requires continuous assessments due to its known long-term complications. As the bone health will impact HIV-infected individuals across their life span, long-term monitoring will be an important component of clinical care. BAP levels remain relatively consistent in sexually mature males throughout life and in sexually mature females until menopause.[62] Longitudinal assessments of bone biomarkers such as BAP are necessary to characterize the utility of these biomarkers in detecting early changes in BMD and to identify interventions that will maintain BMD in this population.

While we did not identify a clear relationship between inflammatory and bone biomarkers, this study provides important baseline information for overall bone health in YWH receiving initial ART that can be applied to long-term monitoring.

Acknowledgments

This work was supported by the Adolescent Trials Network for HIV/AIDS Interventions (ATN) from the National Institutes of Health [U01 HD 040533 and U01 HD 040474] through the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development with supplemental funding from the National Institutes on Drug Abuse and Mental Health. The study was coendorsed by the IMPAACT. Support for the IMPAACT was provided by the National Institute of Allergy and Infectious Diseases (NIAID), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Institute of Mental Health (NIMH) [U01 A1068632]. The study was scientifically reviewed by the ATN's Therapeutic Leadership Group. Network, scientific, and logistical support was provided by the ATN Coordinating Center, at The University of Alabama at Birmingham. Dr. Sleasman was also supported by 1U01-DA044571-02, and Dr. Wilson was supported by T32 AI-007062-35. This publication resulted in part from research supported by the Duke University Center for AIDS Research (CFAR), an NIH-funded program (5P30 AI064518).

The following ATN sites participated in this study: University of South Florida, Tampa (Emmanuel, Lujan-Zilberman, Julian), Children's Hospital of Los Angeles (Belzer, Flores, Tucker), University of Southern California at Los Angeles (Kovacs, Homans, Lozano), Children's National Medical Center (D'Angelo, Hagler, Trexler), Children's Hospital of Philadelphia (Douglas, Tanney, DiBenedetto), John H. Stroger Jr. Hospital of Cook County, and the Ruth M. Rothstein CORE Center (Martinez, Bojan, Jackson), University of Puerto Rico (Febo, Ayala-Flores, Fuentes-Gomez), Montefiore Medical Center (Futterman, Enriquez-Bruce, Campos), Mount Sinai Medical Center (Steever, Geiger), University of California-San Francisco (Moscicki, Auerswald, Irish), Tulane University Health Sciences Center (Abdalian, Kozina, Baker), University of Maryland (Peralta, Gorle), University of Miami School of Medicine (Friedman, Maturo, Major-Wilson), Children's Diagnostic and Treatment Center (Puga, Leonard, Inman), St. Jude's Children's Research Hospital (Flynn, Dillard), and Children's Memorial (Garofalo, Brennan, Flanagan).

The following IMPAACT sites participated in this study: Children's Hospital of Michigan–Wayne State (Moore, Rongkavilit, Hancock), Duke University Medical Center Pediatric CRS (Cunningham, Wilson), Johns Hopkins University (Agwu, Chang, Noletto), New Jersey Medical School CTU/CRS (Dieudonne, Bettica, Monti), St. Jude/Memphis CTU/CRS (Flynn, Dillard, McKinley), University of Colorado School of Medicine/The Children's Hospital (Reirden, Kahn, Witte), University of Southern California Medical Center (Homans, Lozano), and Howard University Hospital (Rana, Deressa). Four of the ATN and IMPAACT sites utilized their General Clinical Research Center (GCRC)/Pediatric Clinical Research Center (PCRC) for the study. The centers were supported by grants from the General Clinical Research Center Program of the National Center for Research Resources (NCRR), National Institutes of Health, Department of Health and Human Services as follows: Children's National Medical Center, M01RR020359; Howard University Hospital, MO1-RR010284; University of California at San Francisco, UL1 RR024131; and University of Colorado School of Medicine/Children's Hospital, UL1 RR025780. The University of Pennsylvania/Children's Hospital of Philadelphia utilized its Institutional Clinical and Translational Science Award Research Center (CTRC), supported by grant UL1 RR024134 from NCRR. The Tulane University Health Sciences Center utilized its Clinical and Translational Research Center (CTRC) for the study, which was supported in whole or in part by funds provided through the Louisiana Board of Regents RC/EEP (RC/EEP - 06).

We thank Ruth Gakpo and Daniel Levine for their assistance with data analysis.

Author Disclosure Statement

No competing financial interests exist.

Supplementary Material

Supplementary Figure S1

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