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Differential Skeletal Impact of Tenofovir Disoproxil Fumarate in Young versus Old HIV-Infected Adults

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Abstract

Background—Lower peak bone mass in early adulthood predicts subsequent fragility fractures. Antiretroviral toxicity could contribute to young HIV-infected individuals not achieving adequate peak bone mass.

Objective—To determine if tenofovir disoproxil fumarate's (TDF) effect on bone mineral density (BMD) differs by age.

Methods—We examined BMD data at the lumbar spine and hip from ACTG A5224s and ASSERT, randomized treatment-naïve studies comparing TDF/emtricitabine versus abacavir/lamivudine (with efavirenz or atazanavir/ritonavir). In this post-hoc analysis, we defined the TDF effect as the difference between mean 48-week BMD percent changes for lumbar spine and hip in individuals randomized to TDF versus abacavir. We used multivariable linear regression to compare the TDF effect in individuals younger and older than 30 years. If TDF effect by age did not differ significantly between studies, we pooled study populations. Otherwise, analyses were conducted separately within each study population.

Results—Among 652 subjects, 21% were below age 30 years. The relationship between age and TDF effect significantly differed between A5224s and ASSERT ($p=0.008$ for lumbar spine; $p=0.007$ for hip). In A5224s, there was more bone loss with TDF at lumbar spine and hip in subjects under 30 years old versus in older subjects (-4.5% versus -1.4% ; $p=0.045$; -4.3% versus -1.6% ; $p=0.026$, respectively). There was no significant evidence for this age-associated TDF effect in ASSERT.

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Adherence to ethics and reporting requirements: Approval was obtained from each participating sites' institutional review board in both A5224s and ASSERT. All participants provided written informed consent prior to study entry.

Conclusions—There was heterogeneity in the observed effect of TDF on bone density in young adults compared to older adults, suggesting that further investigation is required to understand the impact of age on BMD decline with TDF.

Keywords

Anti-HIV Agents; administration & dosage; adverse effects; HIV Infections; drug therapy/virology; Bone Density

Introduction

Low bone mineral density (BMD) occurs in 40-90% of HIV-infected individuals,¹ leading to an increased fracture risk compared to uninfected individuals.²⁻⁵ The etiology of bone fragility in HIV-infected persons is multifactorial with contributions from HIV infection and associated immunosuppression, antiretroviral therapy (ART), and high rates of osteoporosis risk factors including low body mass index (BMI), smoking, hepatitis C, and hypogonadism.⁶⁻⁸

While osteoporosis is generally considered a condition of the aged, a lower peak bone mass in the young is a major determinant of subsequent osteoporosis and fracture in older adults.⁹ For example, a 10% higher peak bone mass in young women is associated with an estimated 50% reduction in fracture risk after menopause.¹⁰ Peak bone mass is achieved during the second to fourth decades of life, with some variation by skeletal site, gender, and measurement technique.¹¹⁻¹³ Bone mass reaches its peak at the hip at approximately age 20 years,¹² at the spine at approximately aged 30 years,¹² and for the total body in the mid-to-late twenties.¹¹ Previous studies suggest that young HIV-infected adults fail to reach peak bone mass.^{14,15}

BMD decreases by 2-6% during the first 48-96 weeks of ART¹⁶⁻²² and appears to stabilize subsequently.²³ Tenofovir disoproxil fumarate (TDF) exposure led to a 1-2% greater BMD loss versus other nucleoside reverse transcriptase inhibitor (NRTI) comparators in randomized trials of HIV-infected persons initiating ART.¹⁶ However, there are limited data on the skeletal effects of TDF in the young, especially after ART initiation. In young adults who may not have not achieved their peak bone mass and have high rates of bone turnover,²⁴ ART initiation with TDF could lead to a greater decrease in BMD compared to in older adults who generally have stable BMD and lower bone turnover. Here, we examine the relationship between TDF use and BMD change in young adults (<30 years) versus in older adults, utilizing data from two large randomized treatment-naïve ART initiation studies.

Methods

Parent Studies

We analyzed participant-level data from two large randomized treatment-naïve ART initiation studies in which individuals were randomized to TDF versus abacavir (ABC) and serial site-specific dual x-ray absorptiometry (DXA) was performed.

AIDS Clinical Trials Group (ACTG) A5202 substudy A5224s randomized individuals from the U.S. and Puerto Rico aged 16 years to blinded TDF/emtricitabine (FTC) or ABC/lamivudine (3TC) combined with open-label ritonavir-boosted atazanavir (ATV/r) or efavirenz (EFV).¹⁹ Participants in A5224s had DXA of the lumbar spine and hip performed at baseline and at weeks 24 and 48 and then every 48 weeks until 96 weeks after the last participant enrolled in A5202. All DXAs were read centrally (Tufts University; Boston, MA) by blinded personnel.

ASSERT was a multi-center European study that randomized individuals 18 years and older to open-label TDF/FTC versus ABC/3TC combined with EFV.²⁵ Participants in ASSERT had DXA of the lumbar spine and hip performed at baseline, and at weeks 24, 48 and 96²² that were read centrally (CCBR-Synarc; Hamburg, Germany) by blinded personnel.

Statistics

Baseline characteristics were compared between the two studies, using Fisher's exact tests and Kruskal-Wallis tests, as appropriate.

We defined the TDF effect as the difference between the mean BMD percent change in individuals randomized to TDF versus ABC. We focused on the change in BMD at 48 weeks, as this is the timepoint at which BMD loss is maximal during ART initiation studies.²⁶

To assess if the TDF effect differed by age group we used multivariable linear regression to compare the TDF effect at 48 weeks after ART initiation in individuals younger versus older than 30 years. Subsequently, we adjusted for the following variables: sex, race, BMI, hepatitis C antibody positivity, current smoking status (available in all ASSERT participants and in only a subset of A5224s participants), baseline CD4 count, baseline HIV-1 RNA level, and randomization to ATV/r (versus EFV). If the TDF effect by age group did not differ significantly between studies, the two study populations were to be pooled for analysis. Otherwise, all analyses were conducted within each study population separately. The previously published primary analysis of A5224s was performed based on intention-to-treat principles according to randomized treatment assignment.¹⁹ However, to match the analysis of ASSERT, subjects who modified the NRTI component of their regimen prior to their week 48 DXA (n=27) were not included in the present analysis.

All analysis testing was two-sided with a type I error of 5%; thus p-values of <0.05 were considered statistically significant with no adjustment for multiple comparisons.

Ethics

Approval was obtained from each participating sites' institutional review board in both A5224s and ASSERT. All participants provided written informed consent prior to study entry.

Results

Baseline Characteristics

Table 1 displays the baseline characteristics by parent study (269 participants in A5224s and 383 in ASSERT) of the included participants. Twenty-one percent of participants (22% in A5224s and 20% in ASSERT) were below age 30; the median age was 38 years with 83% male. Participants enrolled in A5224s were more likely to be black (35% versus 14%; $p<0.001$), have a higher BMI (mean 24.9 versus 23.6 kg/m²; $p=0.004$), and have a lower baseline HIV-1 RNA level (mean 4.6 log₁₀ copies/mL versus 5.0 log₁₀ copies/mL; $p<0.001$) than those enrolled in ASSERT.

BMD Changes by Study and Age

For the overall study population, the mean BMD percent change (standard deviation) at the lumbar spine and total hip at 48 week was -2.4% (3.8) and -2.9% (3.0), respectively. Individuals enrolled in A5224s had a greater loss of BMD at the lumbar spine (-2.8% versus -2.1%) and total hip (-3.2% versus -2.7%) than those enrolled in ASSERT.

TDF effect

In unadjusted analyses, the relationship between age and TDF effect at 48 weeks at both the lumbar spine and total hip significantly differed in A5224s versus ASSERT ($p=0.008$ and $p=0.007$, respectively), precluding the pooling of data from the two studies. In ACTG A5224s, there was a more negative TDF effect (i.e., more bone loss with TDF) at the lumbar spine at 48 weeks in participants under 30 years old versus in older study participants (-4.5% versus -1.4%; $p=0.045$; Table 2). Similarly, there was more bone loss at the hip with TDF in A5224s in participants under 30 years old versus in older participants (-4.3% versus -1.6%; $p=0.026$). However, in ASSERT, there was no significant relationship between participant age and TDF effect at either the lumbar spine or hip ($p=0.12$ and 0.19 , respectively).

In multivariate analyses adjusting for potential confounders, there remained a significant difference in the relationship between age and the TDF effect at 48 weeks at both the lumbar spine and total hip in A5224s versus in ASSERT (Table 3; $p=0.015$ and $p=0.016$, respectively), precluding the pooling of data from the two studies. Multivariable adjustment did not appreciably change the observed age-related TDF effects seen in A5224s and ASSERT. In A5224s, younger study participants had a more negative TDF effect than those older than 30 years at both the lumbar spine and the total hip but these differences did not reach statistical significance in the multivariable analysis (Table 3). There were no significant relationships between participant age and the TDF effect at the lumbar spine or hip in ASSERT.

Discussion

Few studies have investigated the effect of TDF on bone in young adults, a population where TDF could have a more deleterious effect given high rates of bone turnover. In our analysis of two large treatment-initiation trials, we found suggestive evidence in A5224s,

but not in ASSERT, that TDF may have a more negative effect on BMD change in young adults compared to in older adults.

The reason for the differing effect of TDF on bone loss in young versus older adults in A5224s versus ASSERT is unclear. We controlled for many differences in study populations and antiretroviral treatment in the studies in our adjusted analyses, but a significant interaction between study and the TDF effect in the young and old remained. Given that the primary aim of our study was to investigate the TDF effect on bone loss in young versus older adults, we did not control for baseline BMD in our multivariate analysis, as baseline BMD is highly correlated with age. However, in neither A5224s nor ASSERT was baseline BMD associated with percent BMD decline.^{19,22}

TDF was recently FDA-approved for use in children two years and older.²⁷ Most studies on the effect of TDF on bone in children and adolescents report significant bone loss with ART initiation in these groups. Under normal circumstances, BMD increases rapidly in adolescents. Gilead Study 321 randomized 87 treatment-experienced HIV-1 infected adolescents to TDF or placebo in combination with other antiretroviral agents for 48 weeks.²⁸ The mean rate of bone gain was less in the TDF-treated group compared to in the placebo group. Six TDF-treated adolescents and one placebo-treated adolescent had significant (>4%) lumbar spine BMD loss at 48 weeks.²⁸ In another study, 6 of 15 ART-experienced HIV-infected children (mean age of 12 years) who switched to a TDF-containing regimen had a >6% drop in BMD over 48 weeks of therapy, 4 of whom experienced improvements after TDF discontinuation.²⁹ In this study, individuals with the greatest bone loss were younger than those who had stable bone density during the study period. In contrast, BMD did not decrease in 21 perinatally-infected children who remained on a stable TDF-containing regimen over 5 years, despite high bone turnover markers.³⁰ The reason for the discrepancies in these studies is unclear, but other studies have shown that after an initial decline in BMD after TDF initiation, BMD subsequently stabilizes.^{16,23}

Notwithstanding the effect of specific antiretrovirals, young HIV-infected individuals, both adolescents and young adults, are known to have lower BMD and higher rates of osteopenia compared to uninfected controls.^{14,15,31} One study of HIV-infected adults has linked TDF use with an increased risk of fracture.³² Given that young individuals are expected to be on ART for an extended period of time, understanding the bone toxicities of ART becomes increasingly important.

There are several limitations to our study that deserve highlighting. The BMD changes found at one year in our study were relatively modest and of unclear clinical significance. However, it has been noted that fracture incidence is highest in the first two years after ART initiation compared to in subsequent years.³³ Given the difference in TDF effect by age group in A5224s versus ASSERT that precluded the pooling of the two study populations, our study had diminished power to evaluate the TDF effect by age group, and our stratified multivariable analyses were severely limited in this regard. Differences in third drug (i.e. ATV/r or EFV in A5224s versus EFV in ASSERT) or differences in study populations may have accounted for the difference in the TDF effect by age group between the two studies but this difference persisted despite our controlling for these factors in adjusted

multivariable analyses. We did not have complete data on covariates such as tobacco or alcohol use, dietary or physical activity measures, testosterone or vitamin D levels, or use of relevant concomitant medications (e.g., calcium, vitamin D, bisphosphonates, etc.) that are known to affect BMD and unmeasured factors such as these could have accounted for the difference in the TDF effect by age group between the two studies. Additionally, since this was a post-hoc analysis with multiple comparisons, marginally significant associations should be interpreted cautiously.

Conclusions

In ASSERT and A5224s, there was heterogeneity in the observed effect of TDF on bone mineral density in young adults compared to in older adults, suggesting that further investigation is required to understand the impact of age on BMD decline with TDF.

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Table 1
Baseline Characteristics by Parent Study

Characteristic	All Subjects (n=652)	A5224s (n=269)	ASSERT (n=383)	p-value
Age (yrs)				0.94
18-29	21% (135/652)	22% (59/269)	20% (76/383)	
30-39	39% (254/652)	33% (89/269)	43% (165/383)	
40-49	29% (189/652)	32% (85/269)	27% (104/383)	
50-59	9% (59/652)	12% (31/269)	7% (28/383)	
60	2% (15/652)	2% (5/269)	3% (10/383)	
Sex				0.25
Male	83% (541/652)	85% (229/269)	81% (312/383)	
Female	17% (111/652)	15% (40/269)	19% (71/383)	
Race				<0.001
Asian	2% (11/652)	1% (4/269)	2% (7/383)	
Black	23% (147/652)	35% (93/269)	14% (54/383)	
White	71% (462/652)	59% (160/269)	79% (302/383)	
Other	5% (32/652)	4% (12/269)	5% (20/383)	
Mean BMI - kg/m ² (s.d.)	24.5 (4.3)	25.5 (4.7)	23.8 (3.8)	0.004
HCV Positive	9% (58/648)	9% (23/265)	9% (35/383)	0.61
Current Smoker	39% (237/601)	43% (94/218)	37% (143/383)	0.88
Mean Baseline CD4 - cells/ μ L (s.d.)	233 (135)	236 (165)	231 (109)	0.98
Mean Baseline HIV RNA - log ₁₀ copies/mL (s.d.)	4.9 (0.7)	4.6 (0.7)	5.0 (0.7)	<0.001
Mean Baseline Lumbar BMD - g/cm ² (s.d.)	1.10 (0.17)	1.13 (0.19)	1.08 (0.16)	<0.001
Mean Baseline Total Hip BMD - g/cm ² (s.d.)	1.01 (0.15)	1.04 (0.16)	1.00 (0.13)	<0.001

Table 2

Unadjusted Analysis of the TDF Effect (i.e., Difference between Mean BMD Percent Change in Individuals on TDF versus ABC) by Age During ACTG A5224s and ASSERT 48 Weeks after ART Initiation^{*}

Study	Site	Age <30 years	Age ≥ 30 years	p-value
ACTG A5224s	Lumbar Spine	-4.5% (n=39) (95% CI: -7.1%, -1.9%)	-1.4% (n=145) (95% CI: -2.8%, -0.1%)	0.045
	Total Hip	-4.3% (n=38) (95% CI: -6.3%, -2.2%)	-1.6% (n=143) (95% CI: -2.7%, -0.5%)	0.026
ASSERT	Lumbar Spine	+0.3% (n=50) (95% CI: -1.5, 2.2)	-1.3% (n=216) (95% CI: -2.2%, -0.4%)	0.12
	Total Hip	-0.9% (n=49) (95% CI: -2.3%, 0.5%)	-1.9% (n=210) (95% CI: -2.6%, -1.2%)	0.19

* A5224s and ASSERT study data not pooled as the relationship between age and TDF effect at both the lumbar spine and total hip significantly differed between A5224s and ASSERT (p=0.008 and p=0.007, respectively).

Table 3

Adjusted Analysis of the TDF Effect (i.e., Difference between Mean Percentage BMD Change in Individuals on TDF versus ABC) by Age During ACTG A5224s and ASSERT 48 Weeks after ART Initiation *

Study	Site	Age <30 years	Age ≥ 30	p-value
ACTG A5224s	Lumbar Spine	-3.9% (n=39) (95% CI: -6.4%, -1.4%)	-1.6% (n=145) (95% CI: -2.9%, -0.4%)	0.11
	Total Hip	-3.9% (n=38) (95% CI: -5.9%, -1.8%)	-1.7% (n=143) (95% CI: -2.8%, -0.7%)	0.068
ASSERT	Lumbar Spine	+0.5% (n=50) (95% CI: -1.3, 2.4)	-1.3% (n=216) (95% CI: -2.2%, -0.4%)	0.12
	Total Hip	-0.7% (n=49) (95% CI: -2.0%, 0.7%)	-1.8% (n=210) (95% CI: -2.4%, -1.1%)	0.14

* A5224s and ASSERT study data not pooled as the relationship between age and TDF effect at both the lumbar spine and total hip significantly differed between A5224s and ASSERT (p=0.015 and p=0.016, respectively); models adjusted for sex, race, BMI, Hepatitis C antibody positivity, current smoking status, baseline CD4 count, baseline HIV-1 RNA level, and randomization to ATV/r (versus EFV).