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Tenofovir and Bone Health

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Abstract

Purpose of review—With continued improvements to the antiviral efficacy and tolerability of antiretroviral therapy (ART), long term safety of ART has become paramount. Low bone mineral density and fragility fractures are more common in HIV-infected individuals than in the general population. The aims of this review are to describe potential mechanisms underlying the adverse effects of tenofovir on bone, clinical studies of tenofovir disoproxil fumarate (TDF) and bone, and more recent bone data on tenofovir alafenamide (TAF).

Recent finding—Several studies have demonstrated an approximately 1–3% greater bone mineral density loss with TDF compared with other agents. Recent studies with TAF have shown improved bone (and renal) safety with similar virologic efficacy when compared to TDF.

Summary—Given these findings, TDF-containing regimens may be gradually replaced with non-TDF containing regimens for the treatment of HIV infection, especially in those at higher risk for fragility fracture.

Keywords

Anti-HIV agents/adverse effects; Bone Density/drug effects; tenofovir disoproxil; GS-7340; tenofovir alafenamide

Introduction

Low bone mineral density (BMD), consistent with a diagnosis of osteopenia or osteoporosis, occurs in 40–90% of HIV-infected individuals (1). A meta-analysis reported a 60% increased fracture risk in HIV-infected individuals when compared to uninfected individuals (2). Fragility fractures are expected to become more common as the age of HIV-infected individuals continues to increase.

The etiology of low BMD in HIV infection is multifactorial (3, 4), but antiretroviral toxicity, in particular from tenofovir disoproxil fumarate (TDF), contributes significantly. More rarely, TDF use can lead to osteomalacia. With the availability of several well-tolerated and

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potent antiretroviral regimens, understanding and reducing long-term toxicities of antiretroviral agents has become increasingly important in optimizing the care of HIV-infected individuals.

The aim of this review is to describe the mechanisms underlying the adverse effects of tenofovir (TFV) on bone, clinical studies evaluating TDF's effect on bone, and more recent bone data with tenofovir alafenamide (TAF).

Potential Mechanisms of Tenofovir Toxicity in Bone

While reductions in BMD occur at antiretroviral therapy (ART) initiation irrespective of regimen, the magnitude of reductions are greater with TDF-containing regimens, suggesting that TDF has an effect on bone independent of host, viral and immunologic factors. Whether this negative effect on bone is direct (drug effect on osteoclasts and/or osteoblasts) and/or indirect (drug effect on the proximal renal tubule and/or vitamin D metabolism) is not entirely clear.

Direct Effect of TDF on Bone

Data implicating TDF exposure with bone pathology are limited. *In vitro* studies have demonstrated altered expression of genes involved in cell signaling, energy and amino acid metabolism in osteoclasts and osteoblasts exposed to physiological doses of TFV (5, 6). TFV exposure resulted in abnormal calcium deposition in a study utilizing a sarcoma cell line (7). The generalizability and applicability of these findings to HIV-infected individuals are unknown but warrant further research.

Indirect Effects of TDF on Bone via Renal/Endocrine Systems

TFV is eliminated by glomerular filtration and active proximal tubule secretion. Animal studies have demonstrated mitochondrial dysfunction and tubular toxicity after TFV exposure, albeit at supra-therapeutic TFV levels (8, 9).

Severe proximal tubulopathy, Fanconi's Syndrome, was first reported in temporal association with TDF in 2002 (10) but is rare. In its most severe form, it is characterized by bicarbonate and phosphate wasting leading to osteomalacia and bone pain. Cross-sectional studies have reported the prevalence of TDF-associated tubulopathy, as defined by the presence of at least two relevant laboratory criteria, at 17–22% (11), but post-marketing surveillance reported severe renal impairment and tubulopathy in association TDF use was uncommon with rates of <0.6% and 0.1%, respectively (12).

Sub-clinical tubulopathy may be a key factor in TDF-driven reductions in BMD. Retinol-binding protein (RBP) and β2-microglobulin are markers of proximal tubule dysfunction that have been shown to be more frequently elevated in those on TDF-containing ART in cross-sectional and prospective studies (13, 14). While the long-term consequences of sub-clinical tubulopathy are unknown, an elevated RBP/creatinine ratio has been independently associated with lower lumbar spine BMD in those on TDF-containing ART in one recent study (15).

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While the hypothesis of TDF-driven sub-clinical tubulopathy leading to bone pathology is compelling, there are data gaps. Most importantly, the renal hypothesis does not explain the characteristic dynamics of BMD change observed with TDF use. Once tubular dysfunction develops on TDF it generally persists, but BMD loss with TDF-containing regimens is greatest during the first year of ART with subsequent stabilization. Long term TDF does not seem to drive continued BMD loss (16–18).

Perhaps compounding the effect of proximal tubulopathy on bone metabolism, TDF may affect vitamin D metabolism directly driving a state of sustained hyperparathyroidism and increased bone turnover. Parathyroid hormone (PTH) levels become elevated early after initiation of TDF (19). Increases in PTH levels are greater in those with vitamin D deficiency (19, 20) but also occur in those with adequate (25-hydroxy) vitamin D levels (21). In subjects on stable TDF-containing ART, higher plasma TDF levels have been associated with higher levels of vitamin D binding receptor leading to lower free (biologically active) 1,25-hydroxy-vitamin D. This novel finding of “functional” vitamin D deficiency may drive secondary hyperparathyroidism in those on TDF-containing ART (22). Furthermore, there may be a therapeutic role for vitamin D3 supplementation at initiation of TDF-containing ART; supplementation with vitamin D3 attenuates increases in PTH (21) and reductions in BMD (23).

Tenofovir Disoproxil Fumarate: Clinical Data

TDF was FDA-approved in 2001. The principal advantage of TDF over older nucleos(t)ide reverse transcriptor inhibitors (NRTIs) such as stavudine and zidovudine was reduced mitochondrial toxicity, resulting in lower rates of lipoatrophy and peripheral neuropathy. However, the bone toxicity seen with TDF was apparent in early clinical studies of TDF (24).

TDF and Bone Mineral Density: Treatment-naive Studies

Table 1 displays randomized studies in treatment-naive individuals that have compared BMD changes with TDF-containing vs. non-TDF-containing regimens (24–33). The results of the various studies that have compared TDF to non-TDF-non-TAF comparators have been generally consistent despite that the studies assessed BMD changes at various time points between 48 and 144 weeks after ART initiation. Summarizing across studies, TDF-containing regimens lead to an approximately 1–3% greater BMD loss compared to non-TDF containing regimens. The magnitude of TDF’s negative effect on BMD is similar to what has been reported with emtricitabine (FTC)/TDF in HIV-uninfected individuals in pre-exposure prophylaxis studies (34, 35).

Increased bone turnover marker levels have been noted soon after the initiation of TDF-containing ART (29), translating into increased BMD loss by 24 weeks (25). Individuals on TDF-containing ART have been shown to have increased bone turnover marker levels compared to those individuals on non-TDF-containing ART through at least 144 weeks after ART initiation (34). However, as mentioned above, studies with extended follow-up in individuals on TDF-containing regimens do not appear to show additional BMD loss with TDF, outside the 1–3% BMD loss that occurs early after ART initiation (16–18).

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TDF and Bone Mineral Density: Switch Studies

Table 2 displays switch studies that evaluated BMD change after switches from TDF to non-TDF containing regimens (37–39). Prior to the recently reported TAF switch study (40; described in a subsequent section in this review), the studies were small. The OsteoTDF Study enrolled 54 participants on a TDF-containing regimen and randomized participants to continuation of their TDF-containing regimen versus a switch from TDF to abacavir with continuation of the rest of the background regimen (37). At 48 weeks, BMD change at both the lumbar spine and hip was numerically greater in those randomized to the switch arm versus continuation of the original TDF-containing regimen, but the differences were not significant. The TROP Study was a single-arm study in which 37 virologically suppressed individuals on an antiretroviral regimen containing a protease inhibitor and TDF had the TDF component of their regimen switched to raltegravir (38). Forty-eight weeks after the switch, individuals had a significant increase in BMD from baseline of 3.0% and 2.5% at the lumbar spine and hip, respectively. Finally, the MIDAS Study randomized 64 individuals on efavirenz/emtricitabine/TDF to continued therapy versus a switch to darunavir/ritonavir monotherapy (39). At 48 weeks, individuals randomized to darunavir/ritonavir had a statistically significant improvement in BMD at both the lumbar spine and femoral neck compared to those individuals maintained on their baseline TDF-containing therapy (Lumbar spine change: 0.0% vs. +2.6%; $p<0.001$; Femoral neck change: 0.0% vs. +2.9%, $p<0.001$), suggesting that the BMD decrease with TDF initiation may be largely reversible.

TDF and Fractures

Several studies have evaluated the contribution of TDF to fracture risk in HIV-infected individuals. Using the United States Veteran's Affairs database, Bedimo and colleagues found that TDF use was associated with a 12% increased risk of fragility fracture in the ART era (41). However, there have been three studies that showed no significant increase in fracture risk associated with TDF use. In a case-control study using administrative claims' data from the United States, Mundy and colleagues found a protective effect of ART (vs. no ART) on all-cause fracture (42). In this study, TDF-containing ART had a similarly protective effect on all-cause fracture as ART that did not contain TDF. Evaluating data from the Women's Interagency Health Study, Sharma and colleagues found no association between TDF use and increased all-cause fracture (43). Yong and colleagues performed a case-control study using data from a clinic in Australia and found no association between TDF use and fragility fracture risk (44). It should be noted, however, that the latter two studies were small with wide confidence intervals that could not exclude a clinically meaningful effect of TDF on fracture risk.

TDF and Osteomalacia

As described above, some degree of proximal tubular dysfunction appears relatively frequently in individuals on TDF-containing regimens. More complete proximal tubular dysfunction with glucosuria, hyperaminoaciduria, and abnormal fractional excretion of phosphate, uric acid, and β2-microglobulin is uncommon (45) and does not commonly lead to a reduction in creatinine clearance (46). Similarly, classical Fanconi's Syndrome, as

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characterized by osteomalacia and altered proximal tubular function, is uncommon with TDF.

Osteomalacia occurs when hypophosphatemia leads to altered mineralization in regenerating bone. There are numerous case reports describing TDF-associated Fanconi's Syndrome and osteomalacia (47–50). Many of the affected individuals were also receiving ritonavir-boosted protease inhibitors, which raise TDF levels. Patients with osteomalacia typically present with severe bone pain, often around the pelvic girdle. Whole-body bone scintigraphy (or "bone scan") shows increased activity around multiple joints with multiple hot spots, suggesting pseudo-fractures. Osteomalacia has been reported to improve after discontinuation of TDF (51).

Tenofovir Alafenamide: Clinical data

TAF is an alanine ester prodrug of TFV that is characterized by reduced systemic levels of TFV, improved lympho-reticular cell permeability, and greater intracellular accumulation of active drug TFV-diphosphate (TDF-pp) (52). Compared to TDF, plasma TFV levels after oral administration of TAF are 90% lower, while intracellular concentrations of TFV are up to 20-fold higher (53). Taken together, these characteristics suggested that TAF, as a component of ART, might offer potent HIV viral suppression and reduced toxicity due to lower systemic exposure of TFV. To date, there have been five published clinical trials comparing TAF-containing vs. TDF-containing regimens, four treatment-naive studies (Table 1) and one switch study (Table 2). TAF has been licensed to the global patent pool to allow for generic manufacturing (54), but at this point it is not being produced by generic manufacturers and is not routinely available in resource-limited settings.

TAF and Bone Mineral Density: Treatment-naive Studies

In general, data from clinical studies demonstrate non-inferior virologic and superior bone (and renal) outcomes with TAF vs. TDF-containing regimens. A phase II, placebo-controlled study randomized 171 participants to elvitegravir (EVG)/cobicistat (COBI)/FTC/TAF versus EVG/COBI/FTC/TDF (31). Participants were mostly young, male and Caucasian. Smaller reductions in BMD were seen in those randomized to TAF at both the lumbar spine (−1.0% vs −3.4%, $p < 0.001$) and the hip (−0.6% vs. −2.4%, $p < 0.001$) at 48 weeks. The TAF arm (vs. the TDF arm) was also associated with significantly smaller increases in markers of bone turnover.

Two phase III, placebo-controlled studies with TAF enrolled larger and more diverse study populations, including greater numbers of women and non-Caucasians, and reported very similar BMD findings at the spine and hip as the earlier Phase II study (Table 1) (32). Finally, the fourth published clinical trial compared FTC/TAF vs. FTC/TDF, both combined with cobicistat-boosted darunavir (DRV/COBI) (33). Again, smaller reductions in BMD were observed at both the lumbar spine (−1.6% vs −3.6%, $p=0.003$) and hip (−0.8% vs −3.8%, $p<0.001$) in those randomized to the TAF arm.

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TAF and Bone Mineral Density: Switch Studies from TDF to TAF

A large open-label study (n=1443) randomized participants on a variety of TDF-containing regimens to switch to EVG/COBI/FTC/TAF or to remain on their baseline TDF-containing regimen (40). Participants in this study were slightly older compared to those enrolled in the naive studies. There was a significantly greater percent BMD change in those randomized to EVG/COBI/FTC/TAF compared to those continuing on their baseline regimen at both the lumbar spine (+1.6% vs. −0.4%, $p<0.001$) and the hip (+1.5% vs. −0.3%, $p<0.001$).

Conclusion

TDF has been one of the most commonly used NRTI for many years given its virologic efficacy and generally benign side effect profile. However, the reduction of BMD associated with TDF is a limitation. The mechanistic basis for TDF's effect on bone has not been fully determined, whether it be due to direct bone toxicity or secondary to TDF's effect on the proximal tubule or PTH/vitamin D metabolism. TDF use results in a 1–3% increased BMD loss compared to other NRTIs during the first year of ART. One study showed an association between TDF use and fragility fractures. Several switch studies have demonstrated that the BMD loss associated with TDF is largely reversible.

TAF appears to be an improvement over TDF in terms of bone safety, while not compromising antiviral efficacy. However, long term data, including on fracture, are lacking. There is no clear consensus on which individuals on TDF-containing ART should be switched to a more "bone-friendly" regimen. Guidelines suggest that TDF should be avoided in those at higher risk for fracture (i.e., those with a previous fragility fracture, osteoporosis, or osteopenia and an elevated FRAX score) (55). In other HIV-infected individuals without this increased risk including in children and adolescents who have not obtained peak bone mass, clinical practice is evolving. Given the promising results from treatment-naive and switch studies, many clinicians will likely replace TDF-containing regimens with non-TDF containing regimens over time, potentially reducing long-term ART-associated bone toxicity.

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Conflicts of interest

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Key Points

- Tenofovir disoproxil fumarate (TDF) use leads to a 1–3% greater bone mineral density loss compared to other NRTIs during the first year of ART
- In one study, TDF use was associated with increased fracture risk
- The mechanism of the increased BMD loss with TDF may be due to a direct effect on bone, proximal tubule dysfunction, and/or altered vitamin D metabolism
- Based on data from switch studies, the bone loss associated with TDF initiation appears largely reversible
- Tenofovir alafenamide appears to have limited, if any, bone toxicity and non-TDF containing regimens may supplant TDF-containing regimens over time

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Table 1

Randomized Treatment Initiation Studies Comparing Bone Mineral Density Changes with Tenofovir Disoproxil Fumarate (TDF)-containing Regimens versus Non-TDF Containing Comparator Regimens[†]

Study(number randomized)	Regimens	Time Point for BMD Changes	BMD Change in TDF arm	BMD Change in Comparator Arm	*P*-value
Studies with non-tenofovir alafenamide-containing comparator arm					
Gilead 903 (n=602)[24]	EFV/TDF/FTC vs EFV/d4T/3TC	Week 144	LS: −2.2% TH: −2.8%	LS: −1.0% TH: −2.4%	0.001 0.06
ACTG A5202 Substudy A5224s (n=269)[25]	ATV/r vs. EFV + TDF/FTC vs ABC/3TC	Week 96	LS: −3.3% TH: −4.0%	LS: −1.3% TH: −2.6%	0.004 0.024
ASSERT (n=385)[26]	EFV/TDF/FTC vs EFV/ABC/3TC	Week 48	LS: −2.4% TH: −3.6%	LS: −1.6% TH: −1.9%	0.036 <0.001
NEAT Substudy (n=146)[27]	DRV/r/FTC/TDF vs DRV/r/RAL	Week 48	LS: −2.5% TH: −3.3%	LS: −1.0% TH: −0.7%	0.046 <0.001
PROGRESS (n=209)[28]	LPV/r/FTC/TDF vs LPV/r/RAL	Week 96	Total: −2.5%	Total: +0.7%	<0.001
RADAR (n=85)[29]	DRV/r/FTC/TDF vs DRV/r/RAL	Week 48	Total: −7.0 g/cm2	Total: +9.2 g/cm2	0.002
ACTG A5303 (n=262)[30]	DRV/r/FTC/TDF vs DRV/r/FTC/MVC	Week 48	LS: −2.4% TH: −2.4%	LS: −0.9% TH: −2.4%	
Studies with tenofovir alafenamide-containing comparator arm					
GS-292-0102 (n=171)[31]	EVG/COBI/FTC/TDF vs EVG/COBI/FTC/TAF	Week 48	LS: −3.4% TH: −2.4%	LS: −1.0% TH: −0.6%	<0.001 <0.001
GS-US-292-0104 & GS-US-292-0111 (n=1744)[32]	EVG/COBI/FTC/TDF vs EVG/COBI/FTC/TAF	Week 48	LS: −2.9% TH: −3.0%	LS: −1.3% TH: −0.7%	<0.001 <0.001
GS-US-299-0102 (n=153)[33]	DRV/COBI/FTC/TDF vs DRV/COBI/FTC/TAF	Week 48	LS: −3.6% TH: −3.8%	LS:−1.6% TH: −0.8	0.003 <0.001

[†]ABC, abacavir; ATV, atazanavir; BMD, bone mineral density; d4T, stavudine; COBI, cobicistat; DRV, darunavir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; 3TC, lamivudine; LPV, lopinavir; LS, lumbar spine; MVC, Maraviroc; r, low-dose ritonavir (i.e., ritonavir boosting); RAL, raltegravir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TH, total hip.

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Table 2

Selected Switch Studies Evaluating Bone Mineral Density Changes After Switch from Tenofovir Disoproxil Fumarate-containing regimens[†]

Study (number randomized)	Baseline Regimen	Regimens	Time point for BMD Changes Endpoint	BMD Change in TDF Arm	BMD in Comparator Arm	*P*-value
Studies with non-tenofovir alafenamide-containing comparator arm						
OsteoTDF (n=54) [37]	Any TDF-containing regimen	Continue TDF-containing regimen vs. continue regimen except with TDF to ABC switch	Week 48	LS: −1.2% TH: +0.7%	LS: −0.7% TH: +2.1%	0.31 0.23
TROP (n=37)[38]	Any regimen containing PI/r + TDF	Single-arm switch of TDF to RAL with continuation of other components of regimen	Week 48	N.A.	LS: *+3.0 %* TH: *+2.5%*	<0.001 <0.001
MIDAS (n=64)[39]	EFV/FTC/TDF	Continue EFV/FTC/TDF vs switch to DRV/r	Week 48	LS:0.0% Femoral neck: 0.0%	LS: +2.6% Femoral neck: +2.9%	<0.05 <0.05
Study with tenofovir alafenamide-containing comparator arm						
GS-US-292-0109 (n=1443)[40]	TDF/FTC + either ATV/COBI, ATV/r, EFV,orEVG/COBI	Continue baseline regimen vs E/C/F/TAF	Week 48	LS: −0.4% TH: −0.3%	LS: 1.6% TH: 1.5%	<0.001 <0.001

[†]ABC, abacavir; ATV, atazanavir; BMD, bone mineral density; COBI, cobicistat; DRV, darunavir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; LS, lumbar spine; PI/r, ritonavir-boosted protease inhibitor; r, low-dose ritonavir (i.e., ritonavir boosting); RAL, raltegravir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TH, total hip.