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Tenofovir disoproxil fumarate as pre-exposure prophylaxis for HIV prevention in women with osteoporosis: A case report and review of the literature

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Abstract

Pre-exposure prophylaxis (PrEP), using tenofovir disoproxil fumarate (TDF), can effectively prevent HIV acquisition. However, TDF can cause changes in bone mineral density (BMD). There is little information on the use of PrEP among patients with bone disease. We present a case report of a female with pre-existing osteoporosis who was prescribed PrEP. Over the course of nine months of consistent PrEP use, verified by dried blood spot testing, we report a lack of BMD changes on serial dual-emission x-ray absorptiometry scans in this patient. This case can inform PrEP care for patients with pre-existing bone disease.

Keywords

osteoporosis; PrEP; pre-exposure prophylaxis; bone mineral density

Introduction

Pre-exposure prophylaxis (PrEP), containing tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC), is highly effective in preventing HIV in men and women [1,2]. One concern that has been raised about TDF as PrEP is potential decreased bone mineral density (BMD). Among HIV-infected persons, initiation of antiretroviral therapy (ART) is associated with a 2–6% loss of BMD; this loss is significantly greater in patients taking TDF-based therapy when compared to tenofovir alafenamide or abacavir [3–5]. Use of FTC/TDF as PrEP also results in declines in BMD with reversal upon discontinuation of PrEP [1,6–12]. Among 1579 patients who were taking FTC/TDF in the Partners PrEP Study, only nine (<1%) experienced a bone fracture (P=0.66) [2]. A placebo-controlled trial among 498 participants revealed hip (-0.61%, P=0.001) and spine (-0.91%, P=0.001) BMD decline on serial dual-emission x-ray absorptiometry (DEXA) scans at six months in those taking FTC/TDF compared to those not [9]. These BMD changes were correlated with increases in

detectable intracellular tenofovir and reversible upon discontinuing FTC/TDF; there were no differences in fractures among participants in both study arms during the two-year follow up period [9].

The impact of PrEP on HIV-uninfected persons with pre-existing osteoporosis is unknown. Bone disease and history of pathological bone fracture were exclusion criteria in the major randomized control trials [1,2,13]. It is estimated that 200 million people worldwide have osteoporosis, and related fractures, with rates highest in North America and lowest in Africa [14,15]. The Centers for Disease Control and Prevention guidelines have not recommended DEXA scans as part of routine PrEP care [7]. However, no data exists about PrEP use in those with a known clinical history of osteoporosis, and there are no guidelines for prescribing PrEP for patients with a diagnosis of osteoporosis. We present a case of a female with treated osteoporosis prescribed FTC/TDF as PrEP and describe lack of BMD changes on serial DEXA scans, suggesting that PrEP may be safely used in some patients with osteoporosis.

Case Report

A 56 year-old White female presented to discuss TDF/FTC as PrEP for HIV prevention (Figure 1). Her husband had been newly diagnosed with HIV one-month prior, had an elevated HIV viral load, and was not on ART treatment at the time of her visit. She desired to continue to have condomless penile-vaginal sex with her husband. The patient had a past medical history of hypothyroidism, osteoporosis, asthma, hyperglycemia, and hypercholesterolemia. She had a history of five bone fractures (finger, bilateral shoulders, toe, foot) since age 20, all attributed to trauma (i.e. sports injuries or falls). Her most recent fracture two years ago was of the greater tuberosity of the left shoulder after a fall down several stairs. Her osteoporosis was diagnosed six years prior to presentation by both clinical history and BMD studies. She reported a family history of osteoporosis in her biological mother and maternal grandmother. She had been taking alendronate (Fosamax, 70 mg, once weekly), calcium calcium-vitamin D (600 mg/400 units, twice daily) and vitamin D (2000 units, once daily) for four years. Other medications included a fluticasone-vilanterol inhaler, levothyroxine, atorvastatin, and montelukast. Three years prior to presentation, her quantitative computed tomography scan demonstrated a lumbar BMD of 88.7 mm/cc (T-score = -2.56) which was consistent with a scan three years prior to that. According to the thresholds put forth by the World Health Organization, these results were consistent with osteoporosis [16]. Three years prior to presentation, she also had a vitamin D level of 22.1 ng/mL, which was low.

At the time of her initial PrEP visit, she had no specific complaints. On physical examination, the patient had a height of 5 feet 10 inches, weighed 225 pounds, and had a body mass index of 32.28 kg/m². Her physical exam was otherwise unremarkable. Laboratory results were essentially unremarkable, with negative testing for HIV-1, syphilis, urine gonorrhea and chlamydia, and normal baseline creatinine 0.76 mg/dL (estimated glomerular filtration rates 88 mL/min/1.73m²), calcium 9.1 mg/dL, thyroid-stimulating hormone 3.940 uIU/mL, and hemoglobin A1C 5.7%. After an extensive discussion of the

risks and benefits of PrEP including the further risk of decreases in BMD, the patient decided to initiate PrEP.

The patient followed-up at one month and reported 100% adherence to the medication. Dried blood spot (DBS) levels for tenofovir diphosphate (TFV-DP) were 1690 fmol per punch. Levels above 1250 fmol per punch indicate the use of FTC/TDF at seven pills per week [17]. She had resumed condomless vaginal sex 20 days post-PrEP initiation with her husband, who had initiated ART and reported a viral load <20 copies/mL. DEXA results during that visit revealed a lumbar spine BMD of 0.936 gm/cm² (T-score = -1.0), left hip BMD of 0.818 gm/cm² (T-score = -1.0), and femoral neck BMD of 0.671 gm/cm² (T-score = -1.6 gm/cm²). These results were consistent with low bone mass, osteopenia, and pose a moderate increase in risk for fracture [16].

The patient followed up three months later (four months after initiation) and reported 100% adherence to PrEP, confirmed by DBS TFV-DP of 2344 fmol per punch. Her husband had been undetectable for three months. She continued to have condomless vaginal sex with her husband. She had no changes in her medications nor any medical events to report. She remained HIV negative on 4th generation testing. Her other laboratories were unremarkable. She had a vitamin D level of borderline low (36 ng/mL) and her calcium was normal (8.8 mg/dL). The patient was counseled extensively about the risks and benefits of PrEP use, including the low risk of transmission when an HIV-infected partner is undetectable. The patient expressed a desire to continue PrEP citing that she would feel better knowing there was more protection in place with the use of PrEP.

The patient followed up four months later (eight months since PrEP initiation). Her husband continued to be undetectable and she remained HIV-negative. We obtained a DEXA scan at nine months post PrEP initiation, which showed no significant changes from the prior scan eight months before. At this time, BMD of the lumbar spine, femoral neck, and left hip were stable at 0.936 gm/cm² (T-score = -1.0), 0.671 gm/cm² (T-score = -1.6 gm/cm²), and 0.813 gm/cm² (T-score = -1.1), respectively. She was referred to an endocrine specialist who confirmed stable bone disease, recommended she stay on her current therapy, and advised fall prevention measures and healthy exercise patterns for bone disease.

The patient continued to take PrEP at one year with no change in her clinical symptoms. Her PrEP physician had extensive discussions on the very low risk of HIV transmission in her case during the last two clinic visits. The patient displayed adequate comprehension of her risk and requested continued PrEP services. Her physician plans to continue discussions regarding future PrEP use at each visit.

Discussion

This case report supplements the current literature on FTC/TDF as PrEP in women. When using FTC/TDF as PrEP in individuals with known osteoporosis, in light of no formal guidance, we suggest continuous BMD monitoring and evaluation of the need for PrEP at follow-up clinic visits. In our case, a patient with a history of osteoporosis on FTC/TDF as PrEP had no change in her existing bone disease despite electing to continue on the

medication. The frequency of which to obtain BMD measurements in PrEP patients with osteoporosis is unknown.

The impact of oral daily FTC/TDF as PrEP on BMD has been extensively studied in those without pre-existing bone disease [2,8–12]. These reports focus largely on young men and African females. Mirembe et al. reported small but reversible BMD loss among a cohort of 518 HIV-uninfected females taking oral TDF or FTC/TDF in Zimbabwe and Uganda. Among women with tenofovir detection in plasma samples, BMD in the lumbar spine had a mean percent change of –1.4% ($P=0.002$) and –0.9% in the total hip ($P=0.018$) from baseline to week 48. After discontinuation of the study drug, DEXA scans were repeated within three months and then 48 weeks after. BMD increased significantly among the active arm compared to the placebo arm, showing 0.9% increase at the lumbar spine ($P=0.007$) and 0.7% at the total hip ($P=0.003$). Overall mean BMD levels at 48 weeks after stopping treatment were at least as high as mean BMD levels at baseline for both the lumbar spine and total hip among all study participants [11]. A BMD sub-study of a large clinical trial on PrEP efficacy found that females in the FTC/TDF group had significant differences in BMD T-scores and Z-scores at the forearm, hip, and lumbar spine. However when analyzing the clinical adverse events across the entire study cohort, bone fractures did not differ significantly across study arms ($P=0.69$) [18]. Similarly, the Partners PrEP randomized placebo-controlled trial among heterosexual men and women found that there was no significant difference in bone fracture events across study groups [19].

Clinical trials have shown smaller reductions in BMD with co-administration of anti-resorptive therapy, such as zoledronate, and calcium and vitamin D supplementation in HIV-infected patients who were starting antiretroviral therapy [20,21]. In this case, the patient had been compliant with her anti-resorptive therapy and vitamin D and calcium supplementation, which may have ameliorated any negative impacts of FTC/TDF on her BMD. The latter emphasizes the need to concurrently optimize treatment for osteoporosis when individuals with a prior history of osteoporosis are taking PrEP [16,22]. We underscore providing other evidence-based measures to minimize morbidity in patients with osteoporosis, such as exercise, smoking cessation, and counseling on fall prevention, are extremely important [23]. This is a single case report and the outcome in this case may not be generalizable to all patients with pre-existing bone disease who may be taking FTC/TDF as PrEP.

As PrEP roll out occurs worldwide, more persons with histories of bone disease may require PrEP for protection against HIV acquisition. In guidelines, TDF is the only approved PrEP regimen, but other forms of PrEP are being developed which may have less effect on BMD [7,24]. However, in resource-limited settings, TDF may continue to be the drug of choice given its expected availability as a generic in late 2017. Further investigation on this topic is warranted to inform population-level PrEP implementation.

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Figure 1.

Pre-exposure prophylaxis for HIV use and bone mineral density measurements for a female with history of osteoporosis

Abbreviations: QCT: quantitative computed tomography; PrEP: pre-exposure prophylaxis; DEXA: dual energy X-ray absorptiometry; DBS: dried blood spot; TFV-DP: tenofovir-diphosphate