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Renal and Bone Toxicity with the Use of Tenofovir: Understanding at the End

José Luis Casado

Department of Infectious Diseases, Ramón y Cajal Hospital, Madrid, Spain

Abstract

The use of tenofovir disoproxil fumarate has been associated with side effects on renal function and bone mineral density, but whether this toxicity is of clinical relevance in the middle or long term is highly debated. Current knowledge supports that the use of and time on tenofovir disoproxil fumarate, modulated by other factors such as age, baseline renal function, or classical risk factors, could led to progressive wasting in the urine of low molecular weight proteins, phosphate, uric acid, or glucose. This "partial" Fanconi syndrome seems to be slowly progressive, with increases in the proportion of patients and in the severity of different tubular abnormalities with the long term use of tenofovir disoproxil fumarate. Although progression to chronic kidney disease is relatively rare in patients on tenofovir disoproxil fumarate, in part attributed to the capacity of kidneys to compensate for loss of functioning nephrons, the severity of tubular dysfunction is associated with greater kidney function decline. In large cohorts, the use of tenofovir disoproxil fumarate is one of the main risk factors associated to chronic kidney disease. In addition, hyperphosphaturia secondary to tubular dysfunction could alter the interplay between bone, kidney, and regulatory hormones, leading to progressive bone loss in a similar manner, but in a lesser extent, to hypophosphatemic osteomalacia observed in the Fanconi syndrome. This component of osteomalacia secondary to altered phosphate metabolism explains the partial improvement observed with vitamin D supplementation, the association with altered bone-specific alkaline phosphatase, and the rapid benefit in terms of bone mineral density after tenofovir disoproxil fumarate discontinuation. **(AIDS Rev. 2016;18:59-68)**

Corresponding author: José Luis Casado, jose.casado@salud.madrid.org

Key words

Tenofovir disoproxil fumarate. Renal toxicity. Tubular dysfunction. Bone mineral density. Comorbidities.

Introduction

The widespread use of HAART has greatly reduced morbidity and mortality in HIV-infected patients, increasing life expectancy and quality of life[1]. On the other hand, different comorbidities, including metabolic, cardiovascular, bone, and renal disease, have been shown to appear earlier and to be more severe in HIV-infected patients in comparison with non HIV-infected persons[2] in relation with the persistence of inflammation, immune activation, and the possible toxicity of antiretroviral drugs[3].

Among these drugs, tenofovir disoproxil fumarate (TDF), a prodrug of tenofovir (TFV), is a widely prescribed antiretroviral drug that combines potency, convenient dosing, and a favorable safety and tolerability profile. Since its approval in 2001, it has been widely recommended and used extensively as the preferred backbone of HIV combination therapy[4,5].

Correspondence to:
José Luis Casado
Department of Infectious Diseases
Hospital Ramón y Cajal 28034 Madrid, Spain
E-mail: jose.casado@salud.madrid.org

However, while TDF therapy is generally well tolerated, with low rates of drug discontinuation, it has been associated with effects on renal function and bone mineral density (BMD).

TDF has been shown to have a modest effect on decreasing estimated glomerular filtration rate (eGFR) in clinical trials, but significantly greater in clinical cohorts[6-8]. The cause and clinical importance of this renal alteration has largely remained debated. Nowadays, it is accepted that TDF causes proximal renal tubular toxicity[9]; since despite TFV is a poor substrate and inhibitor of the mitochondrial DNA polymerase, *in vitro* and animal studies support the notion that high intracellular drug concentrations may induce a functionally relevant depletion of mitochondrial DNA in the proximal tubule cells[9,10]. As result, since energy derived is dependent on the mitochondria of the tubule, tubular alteration or dysfunction is observed, with an impaired reabsorption of low weight proteins, amino acids, glucose, uric acid, bicarbonate, and phosphate followed by spillage of these substances into the urine. Indeed, the most severe manifestation of proximal tubular alteration is the Fanconi syndrome, a rare disorder consisting of loss of amino acids, glucose, phosphate, and uric acid in urine, together with polyuria, dehydration, hypokalemia, hypophosphatemia, metabolic acidosis, and rickets in children and osteomalacia in adults.

However, to date data about the incidence, prevalence, clinical significance, and evolution of tubular abnormalities, or their correlation with kidney function decline, are controversial. Full-blown Fanconi syndrome is rare[11], and there are scarce data about the influence of other factors such as hepatitis C virus (HCV) coinfection, diabetes mellitus (DM), or hypertension on tubular parameters, or the number of tubular abnormalities of clinical significance in terms of renal deterioration. In fact, several studies showed a normal renal function in presence of tubular alterations[12,13], and therefore, whether TDF is nephrotoxic in the middle or long term is highly debated; some clinicians do not consider tubular alteration of clinical importance if renal function remains close to normal. Some experts even suggest that this subclinical tubular dysfunction could not be related to eGFR decline[14].

At the same time, changes in BMD have been observed after the initiation of HAART, being more pronounced with exposure to TDF than other antiretroviral agents in treatment-naive and treatment-experienced patients[15]. For some authors, TDF could affect bone health by inhibiting osteoblast genes, as shown in *in vitro* studies[16], or in the context of immune restoration; in both cases this is an effect that should be limited in time and therefore of low clinical importance. However, data in pre-exposure prophylaxis, in an otherwise healthy population, have shown a significant BMD decline associated with TDF use with a return to normal after TDF discontinuation[17], and discontinuing TDF is associated with improvements in BMD[18]. Unfortunately, to date it remains unclear whether tubular dysfunction is associated with altered BMD. Therefore, the role of TDF, and especially the mechanisms involved in bone evolution, continues to be a matter of research and discussion.

Renal toxicity with tenofovir disoproxil fumarate

Tenofovir is renally eliminated by the combined action of passive glomerular filtration and active tubular secretion in the proximal tubule. Tubular secretion is mediated by uptake from plasma by the organic anion transporters (OAT) 1 and 3, and efflux in the apical membrane by the multidrug resistance-related protein (MRP) 4 (and less MRP2 or MRP7) (Fig. 1). Tubular dysfunction is thought to result from TDF accumulation into proximal tubular cells. Intracellular accumulation of TFV and toxicity has been demonstrated by experiments showing that overexpression of OAT1 and OAT3 increases cytotoxicity, while co-transfection of MRP4 causes an incremental decrease in the effects[19-21]. As first conclusion, every factor increasing plasma levels of TFV (with a subsequent rise in OAT uptake), or that makes the renal secretion of this drug difficult by inhibition of MRP4, could led to greater intracellular accumulation of the drug and could increase the rate of TFV-associated toxicity (Fig. 2). Thus, plasma drug levels of TDF have been linked to a higher risk of toxicity[22-24], and recently, tubular dysfunction was found to be associated with reduced urinary output of TFV[25]. Indeed, TDF plasma levels were related with eGFR decreases in studies of pre-exposure prophylaxis[26]. Among the factors which could alter TFV intracellular levels by inhibiting MRP4 protein, it is necessary to mention the use of non-steroidal anti-inflammatory drugs (NSAID), such as diclofenac or ibuprofen[27], or the concomitant use of boosted protease inhibitors[28,29]. Moreover, other drug interactions and underlying genetic polymorphisms might help explain why TDF accumulates more in tubule cells in some patients.

Thus, the accumulation of TFV in the proximal tubule cells and the effect on mitochondrial function explains the tubular toxicity of this drug. It has been demonstrated

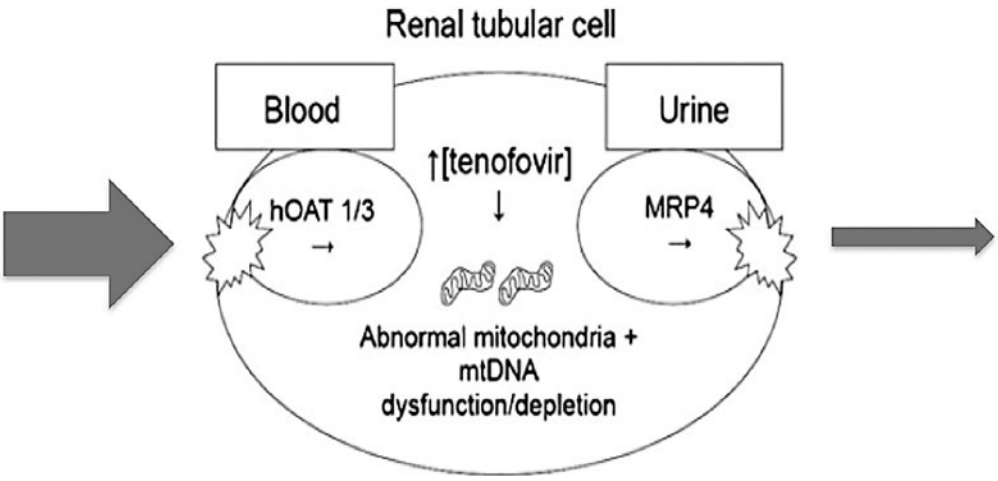

Figure 1. *Pathogenic mechanism explaining mitochondrial toxicity and tubular dysfunction in patients receiving tenofovir disoproxil fumarate. MRP4: multidrug resistance-related protein 4; hOAT: human organic anion transporter.*

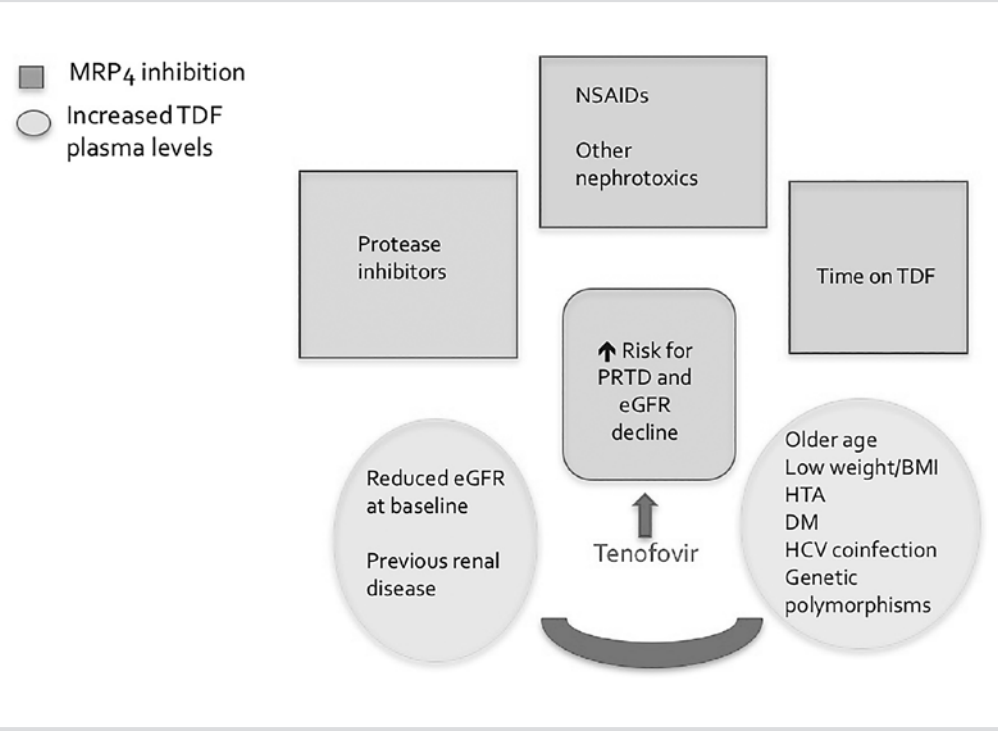

Figure 2. *Risk factors involved in tenofovir disoproxil fumarate toxicity according to the responsible mechanism, increased plasma tenofovir disoproxil fumarate levels vs. inhibition of transporter multidrug resistance-related protein 4. MRP4: multidrug resistance-related protein 4; TDF: tenofovir disoproxil fumarate; NSAID: non-steroidal anti-inflammatory drug; PRTD: proximal tubular renal dysfunction; eGFR: estimated glomerular filtration rate; BMI: body mass index; HTA: hypertension arterial; DM: diabetes mellitus.*

that the proximal tubule is intrinsically vulnerable to mitochondrial alteration, secondary to TFV, even after only five weeks, showing an increased number and irregular shape of mitochondria parallel to a decrease in mitochondrial DNA[30,31].

Tubular "dysfunction"

Tubular dysfunction or proximal tubular renal dysfunction (PRTD) has been defined as the presence of two or three or more tubular abnormalities, part of alterations observed during Fanconi syndrome (also called "partial" Fanconi syndrome), as a result of mitochondrial or cellular toxicity. Thus, impaired reabsorption is observed of low weight molecular proteins, amino acids, glucose, uric acid, bicarbonate, and phosphate followed by spillage of these substances into the urine.

However, as expected, the rate and presentation of tubular involvement varies in relation with the definition used, the number of tubular abnormalities, the risk factors, the use of different biomarkers or tubular proteins in the evaluation, such as beta-2-microglobulin (B2M) or retinol-binding protein (RBP), which could be more sensitive, or to the time on TDF before being evaluated. Indeed, there is no clear definition of what is called tubular "dysfunction", a cautious term to reflect our lack of knowledge about its clinical significance. Up to now there are no clear concepts in the order of appearance of tubular abnormalities or the contribution of the different parameters to a correct definition of tubular dysfunction. Moreover, other clinical conditions, such as diabetes or HCV coinfection, could contribute to the prevalence of PRTD by increasing proteinuria or other tubular abnormalities or by producing latent tubular damage.

With these considerations, it is not rare that the prevalence of PRTD ranges between 7 and 75%. Dauchy, et al. described PRTD (considering 2 out of 5 tubular alterations, including B2M) in 22 out of 256 patients (8.5%) after a median exposure to TDF of 16.3 months[13], while Gatanaga, et al. described a prevalence of tubular damage, defined only by increased urinary B2M level, in 30 out of 70 patients on TDF (43%) after a mean of 13 months[32]. Ezinga, et al.[33] described one or more tubular abnormalities in 63% of 161 patients, with 11% fulfilling the definition of PRTD (two or more tubular parameters) after a mean of 46 months on TDF. Also, Labarga, et al.[12] described a prevalence of tubular dysfunction (two or more, including B2M) of 22% in 153 patients receiving TDF for a median time of 36 months. In a cohort including 200 patients, our group found an overall prevalence of tubular dysfunction of 32% after a median time of five years on TDF, considering two or more abnormalities but not including B2M[34]. However, it ranges from 14% for first-line TDF-treated patients, without other classical risk factors, after three years of TDF exposure, to 46% of patients with concomitant HCV coinfection, hypertension, and/or DM in the same time of exposure. Taken together, these data confirm that tubular dysfunction is a complex interplay of use of TDF and different risk factors such as baseline renal function, age, HIV itself, HCV coinfection, hypertension, DM, and genetic susceptibility. Also, time on TDF was found in most of studies to be an independent factor, suggesting that PRTD should be included in the toxicity of TDF in the mid term, even in the absence of risk factors.

Among the different tubular abnormalities, proteinuria and phosphaturia are the most frequently observed. Proximal tubule is the part of the body that reabsorbs almost 85% of filtered phosphate. Previous *in vitro* studies have suggested that within the proximal tubule, phosphate transport from the ultrafiltrate across the proximal tubule epithelium is energy dependent, particularly sensitive to mitochondrial toxicity[35]. Thus, a reduced tubular reabsorption of phosphate (100-[urine phosphate × serum creatinine]/[urine creatinine × plasma phosphate] ×100) is observed in around 30-50% of patients receiving TDF after a median of five years. However, it is important to consider that phosphaturia is part of the kidney/bone axis, and is regulated by different hormones or substances such as 25- and 1,25-hydroxyvitamin D, parathyroid hormone (PTH), and fibroblast growth factor-23. Indeed, although it is more frequent than with other antiretroviral regimens, sustained hypophosphatemia is not usual in patients receiving TDF[36]. In any case, we observed a clear association between phosphaturia and eGFR decline, and a close and significant correlation with phosphatemia[34] (Fig. 3).

Also, significant proteinuria is found in almost half of patients receiving TDF. We consider proteinuria when the urinary protein to creatinine ratio is above 100 mg/gr of creatinine, a lower limit than that usually considered as pathologic (150-200 mg/g), but similar to the reference range for adults (115 mg/g) and to that described when dipstick is used as screening (2+, ≥ 100 mg/g)[7]. Indeed, proteinuria of tubular origin is mainly composed of low-molecular-weight proteins, such as B2M, RBP, cystatin C, or N-acetyl-glucosamine, and a large amount of proteins in urine is not expected in case of tubular dysfunction[37]. Moreover, micro- or macro-albuminuria

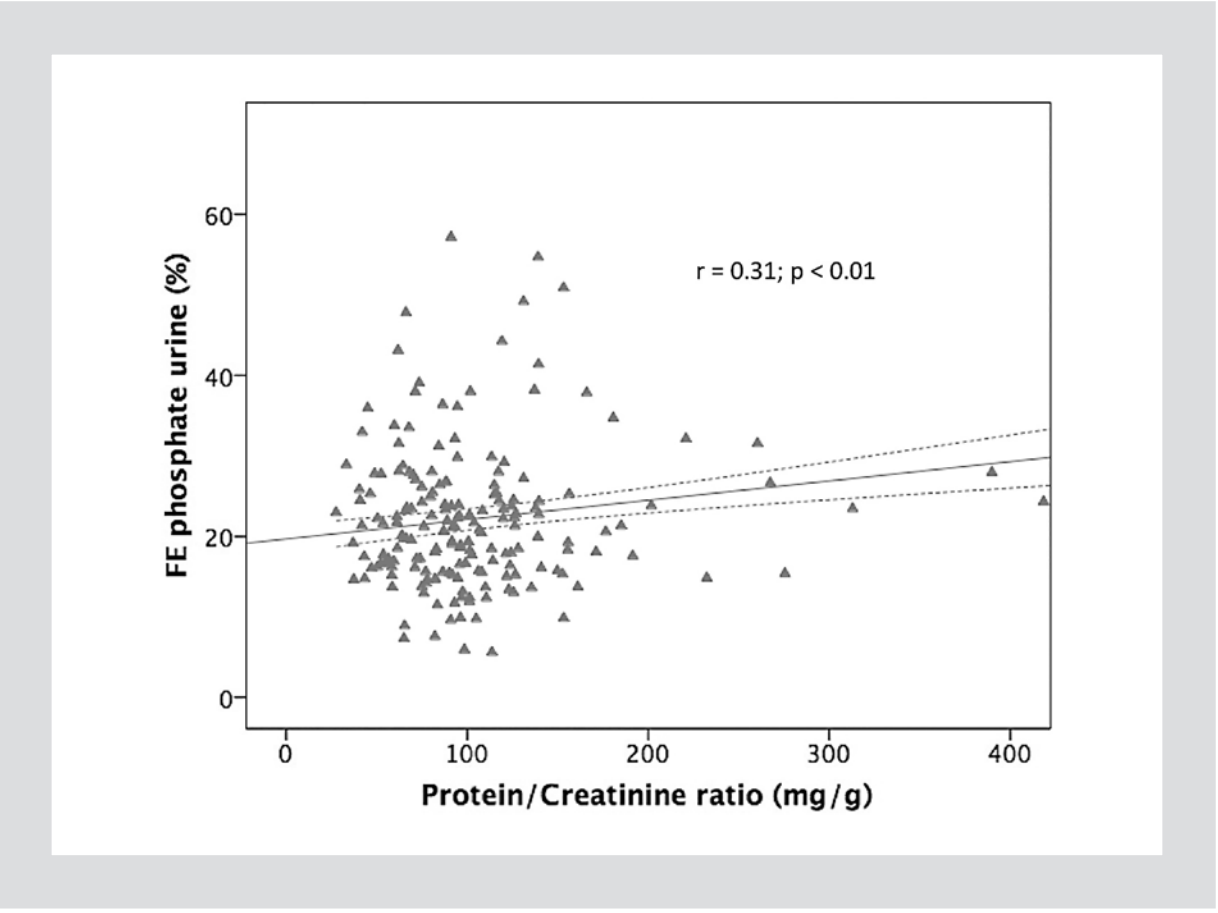

Figure 3. *Correlation between proteinuria and phosphaturia (fractional excretion of phosphate) in a cohort of 200 patients receiving tenofovir disoproxil fumarate. FE: fractional excretion.*

is rare and it is not useful as a marker of tubular involvement. A previous study found an albumin to protein ratio < 0.4 as highly suggestive of tubular toxicity[38], but we found that this ratio was usually < 0.2. In a cohort of 200 patients, only 14% had an amount of total proteins > 150 mg/gr of creatinine in urine, despite that nearly half of them had other tubular abnormalities.

Other tubular abnormalities are less frequent. Glycosuria in the presence of normoglycemia has been described in 5-15% of cases. Plasma glucose is freely filtered at the glomerulus, but in normal situations almost all of it is reabsorbed in the proximal tubule, and the ability of the proximal tubule to reabsorb glucose amplifies as the filtered load is increased by either an elevation in plasma glucose or an increase in glomerular filtration rate[39]. Again, there are controversial data about the best threshold value for considering significant glycosuria. Several authors consider 300 mg/dl, a figure rarely observed in the clinic. We choose 100 mg/dl, the limit of our laboratory in non-pregnant patients, since confirmed glycosuria is exceptional in non-diabetic patients. Finally, uricosuria is a clear marker of tubular involvement, and although most studies have been performed in patients with defects in the metabolism of uric acid or with gout, the kidney usually regulates circulating uric acid levels by reabsorbing about 90% of filtered urate[33,40].

There is a significant relationship between the different tubular parameters confirming the tubular origin of these alterations (Fig. 3).

Renal function decline

As mentioned before, a meta-analysis concluded that TDF-treated patients experienced a significant but small loss of kidney function during the course of treatment[6], but randomized studies do not include a full evaluation of tubular parameters, with the exception of proteinuria, usually as total protein. Moreover, clinical trials select patients without preexisting kidney function alteration and with less risk factors. On the other hand, the use of TDF was an independent factor for chronic

kidney disease (CKD) in large cohorts. In the D:A:D study, including 22,603 patients with baseline eGFR > 90 ml/min/1.73 m^2, TFV exposure was associated with a yearly 18% increased risk of developing CKD[8], and a recent risk score includes the use of TDF as an independent risk factor[41].

Thus, mounting evidence supports that tubular dysfunction could precede the decline in GFR. We found a relationship between the number of tubular abnormalities and kidney function decline since TDF initiation[34], and the WIHS cohort described a strong and independent association of the high tertiles of biomarkers of tubular damage with a faster rate of annual kidney function decline among HIV-infected women[42]. These data are in accordance with the independent association between TDF and increased risk of proteinuria, rapid decline in kidney function, and CKD[7]. Indeed, increased proteinuria is a known cause of kidney function decline, and hypothetically, the low-grade proteinuria (tubular) observed with TDF could explain the slow decrease of eGFR in the absence of other classical factors.

It is important to consider that kidney damage must occur to a significant extent before function becomes altered, due to the ability of the remaining nephrons to undergo hypertrophy and functionally compensate for those that are lost[43,44]. In case of original tubular alteration, renal function progressively deteriorates as a consequence of dysfunctional processes of tubular reabsorption and secretion, activation of tubular cells with recruitment of inflammatory mediators, progressive tubule loss and tissue scarring, and eventual damage of other renal structures[45].

In case series of HIV-infected persons with potential TDF-related nephrotoxicity, ultrastructural evaluations have documented acute tubular injury and necrosis with varying degrees of chronic tubulointerstitial scarring, which may account for a different evolution in case of TDF interruption[46].

These data suggest that the risk of CKD during TDF is increased, but in the short term is influenced by the interplay between time on TDF, intensity of exposure, severity of tubular alterations, and probably individual factors. Notably, it has been previously demonstrated that the extent of GFR decline correlates with previous tubular proteinuria[47], and tubular biomarkers can anticipate eGFR decrease in other nephropathies[48], and recently it has been demonstrated in HIV patients[49,50], and therefore the severity of tubulointerstitial involvement is a key factor in the progression of CKD, regardless of etiology[51,52].

Thus, eGFR consequences may only become evident after years of TDF therapy, with more intense tubular involvement, a time probably longer in those who have normal kidney function or less risks factor at TDF initiation.

Bone toxicity with tenofovir disoproxil fumarate

HIV-infected patients show an increased prevalence of osteopenia and osteoporosis of multifactorial origin, including a role for HIV infection, inflammation, or immune activation[53]. Surprisingly, however, initiation of HAART has been associated with a reduction in BMD[54], attributed to inflammation associated with T-cell and/or immune reconstitution, beginning as early as two weeks and plateauing between 12 and 24 weeks post HAART initiation.

In any case, initiation of TDF-containing antiretroviral therapy leads to a larger reduction in BMD than regimens not containing TDF, as confirmed by small or no changes in BMD in studies of dual therapies without TDF[55]. In a recent longitudinal study of patients receiving the same regimen, we found a lineal correlation between time on therapy and lower BMD, a similar finding to the continuation of bone decline previously described in the long-term evaluation of the ACTG 5224s study. In addition, the use of TDF has been associated with greater increases in markers of bone turnover[56]. Furthermore, in HIV-negative patients, pre-exposure prophylaxis studies found that initiation of TDF is also associated with mild but significant bone loss in otherwise healthy persons[17]. To highlight the importance of this association, a large observational study from 1988 to 2009 found that cumulative TDF exposure was associated with an increased rate of fractures after adjusting for classical factors of BMD deterioration[57], and recently an expert panel recommended to avoid or to discontinue TDF in those patients with high risk of fracture or with osteoporosis[58].

Although *in vitro* studies suggest that TDF may alter gene expression in both osteoblasts and osteoclasts, phosphaturia as part of renal tubular dysfunction should be the putative mechanism associated with BMD decrease in a similar manner, but to a lesser extent, to that observed in tumor-induced osteomalacia or in Fanconi syndrome[59,60]. Moreover, animal toxicology studies have shown that high-dose TDF produces an osteomalacia-like condition in the setting of normal renal function with subsequent fractures and bone deformities. There have been several case reports and case series demonstrating the appearance of hypophosphatemic

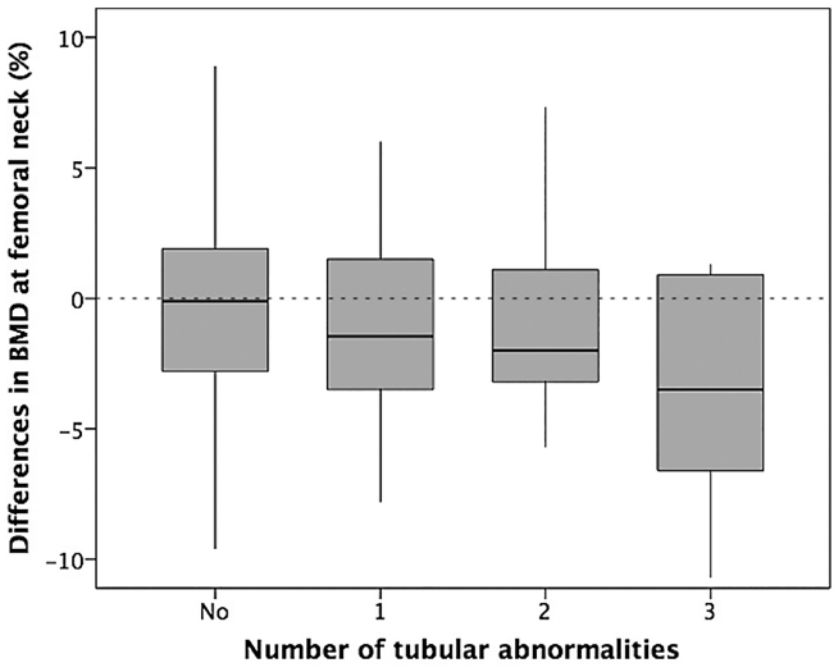

Figure 4. *Changes in bone mineral density at the femoral neck according to the number of tubular renal abnormalities in 90 patients with two sequential dual energy X-ray absorptiometry scans* (adapted with permission from Casado, et al.[65]). *BMD: bone mineral density.*

osteomalacia in patients receiving TDF[61]. Osteomalacia associated with Fanconi syndrome has been well established, although it is usually seen in the setting of hypophosphatemia, low to normal 1,25-dihydroxyvitamin D, renal insufficiency, and chronic acidosis due to bicarbonate wasting. In case of tubular dysfunction, chronic phosphaturia is closely correlated with hypophosphatemia, and therefore, these patients could present low levels of phosphate in the body in spite of normal plasma levels[62]. Cumulative data suggest that TDF initially causes elevated levels of parathyroid hormone (PTH), leading to increased levels of 1,25 vitamin D as compensatory mechanism in patients with adequate levels of 25 vitamin D[63,64], with partial recovery of serum hypophosphatemia. However, prolonged and progressive phosphaturia, secondary to tubular disease, could alter the equilibrium between bone, kidney, phosphate, PTH, and 1,25 vitamin D, leading to bone loss. Indeed, maintenance of serum phosphate within a relatively narrow range is crucial for several important cellular processes, and it depends on a complex interplay between intestinal absorption of phosphate, bone resorption, shifts between intracellular and intravascular compartments, and renal excretion, influenced by levels of vitamin D, PTH, or other molecules such as phosphatins[35]. Bone plays a major role in phosphate homeostasis as the hydroxyapatite matrix serves as the critical pool of phosphate, and serum phosphate levels are mostly determined by the rate of renal excretion[35].

We recently demonstrated that hyperphosphaturia was an independent factor for BMD decline in a median of around 3.5 years, after adjusting for age, sex, and body mass index[65]. The component of osteomalacia secondary to phosphate metabolism alteration explains the partial improvement observed with vitamin D supplementation[66], the association with altered bone-specific alkaline phosphatase[67], and the rapid benefit in terms of BMD after TDF discontinuation, suggesting a return to normal that permits a mineralization of osteoid matrix[68]. Recently, studies have found an association between tubular dysfunction and BMD reduction, supporting this link between renal alteration and bone involvement[69] and suggesting that the presence of tubular dysfunction indicates bone loss (Fig. 4).

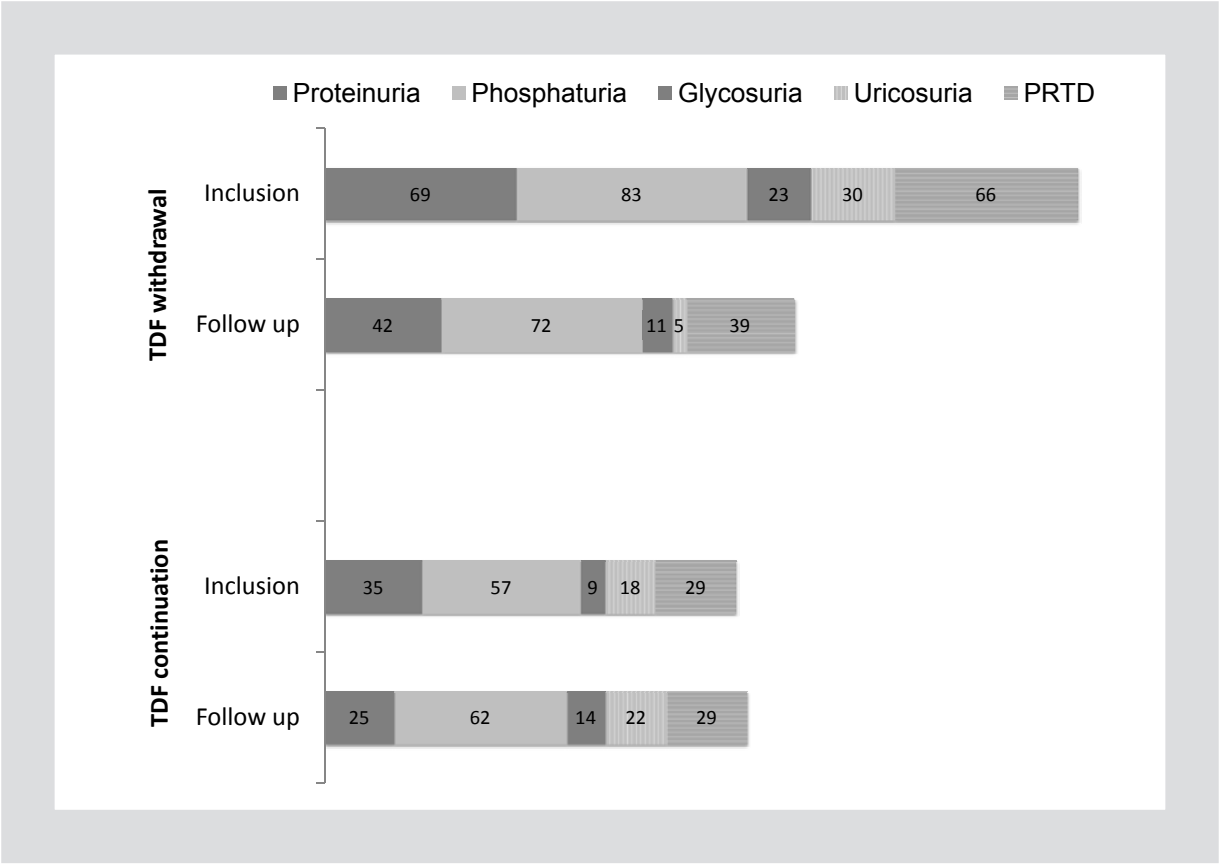

Figure 5. *Changes in the rate of tubular dysfunction and in different tubular parameters after 1 year of TDF withdrawal or continuation* (adapted with permission from Casado, et al.[71]). PRTD: proximal tubular renal dysfunction; TDF: tenofovir disoproxil fumarate.

Outcome: Tenofovir disoproxil fumarate discontinuation or change to tenofovir alafenamide?

Partial eGFR improvement and persistent damage has been reported after TDF discontinuation, with around one third of patients remaining below eGFR values at baseline[70], associated to more time on TDF or the presence of other risk factors. Thus, some of the adverse renal effects may be reversible if TDF is withdrawn early, but the optimal time to detect TDF kidney irreversibility remains unclear. In our patients discontinuing TDF, the prevalence of PRTD decreased by 50% and tubular abnormalities improved by 40-83% in around one year of follow-up[71] (Fig. 5), with the persistence associated again with time on TDF and, as expected, with tubular dysfunction severity.

Tenofovir alafenamide (TAF) is novel prodrug that is associated with TFV plasma concentrations corresponding to 10% of those observed with TDF intake. In phase III studies, TAF lead to smaller changes in eGFR, less proteinuria and albuminuria, smaller decreases in BMD in naive patients, and increased BMD in treatment-experienced patients switching from a TDF-containing regimen. Furthermore, TAF was found to have less decrease in mean BMD than TDF at 48 weeks, mimicking the data obtained after initiation of antiretroviral therapy, including non TDF-containing regimens. This finding was also corroborated in patients with renal impairment switching from TDF to TAF, with significant increases in BMD at the spine and hip after 48 weeks[72].

Despite these data, TAF has not been compared with other therapies not using TDF, even nucleoside analogue-sparing regimens, neither with non TDF regimens in patients with severe tubular dysfunction, with glycosuria or uricosuria, or in cases of osteoporosis. Therefore, we need more data before the indication of this molecule in high-risk patients or those severely affected.

Conclusions

Current knowledge supports that the use of and time on TDF, modulated by other factors such as age, baseline renal function, or classical risk factors (hypertension,

DM, HCV coinfection), leads to the progressive wasting in the urine of substances that are normally reabsorbed by the proximal tubule, such as low-molecular-weight proteins, phosphate, or glucose. This "partial" Fanconi syndrome seems to be slowly progressive, with an increase in the proportion of patients and in the degree of the different tubular abnormalities with the use of TDF. Although progression to CKD is relatively rare, in part attributed to the capacity of the kidneys to compensate for loss of functioning nephrons, the tubular dysfunction severity is associated with greater kidney function decline, and in large cohorts the use of TDF is one of the main risk factors associated to CKD. In addition, tubular alteration of phosphate metabolism could alter the interplay between bone, kidney, and regulatory hormones, leading to progressive loss of bone in a similar manner to hypophosphatemic osteomalacia observed in Fanconi syndrome, at least in part. Also, serum phosphate concentrations may not reliably reflect total body phosphate depletion, nor even tubular phosphate reabsorption. Thus, cross-sectional serum phosphate measurements, and usual cutoffs for phosphaturia, may be of limited use in identifying patients at greatest risk of bone loss, and longitudinal evaluation is necessary. As recommendations, vitamin D supplementation should be used with TDF, but in case of advanced bone disease or in presence of other risk factors for bone deterioration, TDF should be discontinued. Although data are not conclusive, it is cautious to not use bisphosphonates in patients receiving TDF.

As patients require lifelong antiretroviral therapy, and in view of the increasing complexity of HIV therapeutic management with advancing age and a higher incidence of comorbidities, it is imperative for clinicians to consider the importance of TDF-associated toxicities. Both renal and bone toxicity can result in significant morbidity, limiting the expectations for patients. Since most patients could improve at least in part in case of TDF discontinuation (and some patients with change to TAF), its prompt recognition can result in improved outcome for patients.

Declaration of interest

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References

1. Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord; Lewden C, Bouteloup V, De Wit S, et al. All-cause mortality in treated HIV-infected adults with CD4 >/=500/mm^3 compared with the general population: evidence from a large European observational cohort collaboration. Int J Epidemiol. 2012;41:433-45.
2. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. Clin Infect Dis. 2011;53:1120-6.
3. Deeks S. HIV infection, inflammation, immunosenescence, and aging. Annu Rev Med. 2011;62:141-55.
4. Expert Panel of GESIDA and the National AIDS Plan; Berenguer J, Polo R, Aldeguer JL, et al. Executive summary of the GESIDA/National AIDS Plan Consensus Document on antiretroviral therapy in adults infected by the HIV (updated January 2015). Enferm Infecc Microbiol Clin. 2015;33:544-56.
5. Soriano V. Update of the DHHS antiretroviral treatment guidelines. AIDS Rev. 2014;16:117-8.
6. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. Clin Infect Dis. 2010;51:496-505.
7. Scherzer R, Estrella M, Li Y, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. AIDS. 2012;26:867-75.
8. Ryom L, Mocroft A, Kirk O, et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. J Infect Dis. 2013;207:1359-69.
9. Ramamoorthy H, Abraham P, Isaac B. Mitochondrial dysfunction and electron transport chain complex defect in a rat model of tenofovir disoproxil fumarate nephrotoxicity. J Biochem Mol Toxicol. 2014;28:246-55.
10. Kohler JJ, Hosseini SH, Hoying-Brandt A, et al. Tenofovir renal toxicity targets mitochondria of renal proximal tubules. Lab Invest. 2009;89:513-9.
11. Gupta SK. Tenofovir-associated Fanconi syndrome: review of the FDA adverse event reporting system. AIDS Patient Care STDS. 2008;22:99-103.
12. Labarga P, Barreiro P, Martin-Carbonero L, et al. Kidney tubular abnormalities in the absence of impaired glomerular function in HIV patients treated with tenofovir. AIDS. 2009;23:689-96.
13. Dauchy F, Lawson-Ayayi S, de La Faille R, et al. Increased risk of abnormal proximal renal tubular function with HIV infection and antiretroviral therapy. Kidney Int. 2011;80:302-9.
14. Vrouenraets S, Fux C, Wit F, et al. Persistent decline in estimated but not measured glomerular filtration rate on tenofovir may reflect tubular rather than glomerular toxicity. AIDS. 2011;25:2149-55.
15. McComsey G, Kitch D, Daar E, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: Aids Clinical Trials Group A5224s, a substudy of ACTG A5202. J Infect Dis. 2011;203:1791-801.
16. Grigsby I, Pham L, Mansky L, Gopalakrishnan R, Carlson A, Mansky K. Tenofovir treatment of primary osteoblasts alters gene expression profiles: implications for bone mineral density loss. Biochem Biophys Res Commun. 2010;394:48-53.
17. Liu A, Vittinghoff E, Sellmeyer D, et al. Bone mineral density in HIV-negative men participating in a tenofovir pre-exposure prophylaxis randomized clinical trial in San Francisco. PLoS One. 2011;6:e23688.
18. Negredo E, Domingo P, Perez-Alvarez N, et al. Improvement in bone mineral density after switching from tenofovir to abacavir in HIV-1-infected patients with low bone mineral density: two-centre randomized pilot study (OsteoTDF study). J Antimicrob Chemother. 2014;69:3368-71.
19. Stray K, Bam R, Birkus G, et al. Evaluation of the effect of cobicistat on the in vitro renal transport and cytotoxicity potential of tenofovir. Antimicrob Agents Chemother. 2013;57:4982-9.
20. Kohler JJ, Hosseini SH, Green E, et al. Tenofovir renal proximal tubular toxicity is regulated by OAT1 and MRP4 transporters. Lab Invest. 2011;91:852-8.
21. Ray AS, Cihlar T, Robinson KL, et al. Mechanism of active renal tubular efflux of tenofovir. Antimicrob Agents Chemother. 2006;50:3297-304.
22. Rodriguez-Novoa S, Labarga P, Soriano V, et al. Predictors of kidney tubular dysfunction in HIV-infected patients treated with tenofovir: a pharmacogenetic study. Clin Infect Dis. 2009;48:e108-16.
23. Baxi S, Greenblatt R, Bacchetti P, et al. Common clinical conditions - age, low BMI, ritonavir use, mild renal impairment - affect tenofovir pharmacokinetics in a large cohort of HIV-infected women. AIDS. 2014;28:59-66.
24. Gervasoni C, Meraviglia P, Landonio S, et al. Low body weight in females is a risk factor for increased tenofovir exposure and drug-related adverse events. PLoS One. 2013;8:e80242.
25. Calcagno A, Cusato J, Marinaro L, et al. Tenofovir clearance is reduced in HIV-positive patients with subclinical tubular impairment. AIDS. 2016;30:915-20.
26. Mugwanya K, Wyatt C, Celum C, et al. Changes in glomerular kidney function among HIV-1-uninfected men and women receiving emtricitabine-tenofovir disoproxil fumarate preexposure prophylaxis: a randomized clinical trial. JAMA Intern Med. 2015;175:246-54.
27. Bickel M, Khaykin P, Stephan C, et al. Acute kidney injury caused by tenofovir disoproxil fumarate and diclofenac co-administration. HIV Med. 2013;14:633-8.
28. Kiser J, Carten ML, Aquilante C, et al. The effect of lopinavir/ritonavir on the renal clearance of tenofovir in HIV-infected patients. Clin Pharmacol Ther. 2008;83:265-72.

29. Calcagno A, Gonzalez de Requena D, Simiele M, et al. Tenofovir plasma concentrations according to companion drugs: a cross-sectional study of HIV-positive patients with normal renal function. Antimicrob Agents Chemother. 2013;57:1840-3.
30. Kohler J, Hosseini S. Subcellular renal proximal tubular mitochondrial toxicity with tenofovir treatment. Methods Mol Biol. 2011;755:267-77.
31. Abraham P, Ramamoorthy H, Isaac B. Depletion of the cellular antioxidant system contributes to tenofovir disoproxil fumarate - induced mitochondrial damage and increased oxido-nitrosative stress in the kidney. J Biomed Sci. 2013;20:61.
32. Gatanaga H, Tachikawa N, Kikuchi Y, et al. Urinary beta2-microglobulin as a possible sensitive marker for renal injury caused by tenofovir disoproxil fumarate. AIDS Res Hum Retroviruses. 2006;22:744-8.
33. Ezinga M, Wetzels J, Bosch M, van der Ven A, Burger D. Long-term treatment with tenofovir: prevalence of kidney tubular dysfunction and its association with tenofovir plasma concentration. Antivir Ther. 2014;19:765-71.
34. Casado JL, Banon S, Santiuste C, et al. Prevalence and significance of proximal renal tubular abnormalities in HIV-infected patients receiving tenofovir. AIDS. 2016;30:231-9.
35. Blaine J, Chonchol M, Levi M. Renal control of calcium, phosphate, and magnesium homeostasis. Clin J Am Soc Nephrol. 2015;10:1257-72.
36. Day S, Leake Date H, Bannister A, Hankins M, Fisher M. Serum hypophosphatemia in tenofovir disoproxil fumarate recipients is multifactorial in origin, questioning the utility of its monitoring in clinical practice. J Acquir Immune Defic Syndr. 2005;38:301-4.
37. del Palacio M, Romero S, Casado JL. The use of biomarkers for assessing HAART-associated renal toxicity in HIV-infected patients. Curr HIV Res. 2012;10:521-31.
38. Samarawickrama A, Cai M, Smith E, et al. Simultaneous measurement of urinary albumin and total protein may facilitate decision-making in HIV-infected patients with proteinuria. HIV Med. 2012;13:526-32.
39. Mather A, Pollock C. Glucose handling by the kidney. Kidney Int Suppl. 2011:S1-6.
40. Bobulescu I, Moe O. Renal transport of uric acid: evolving concepts and uncertainties. Adv Chronic Kidney Dis. 2012;19:358-71.
41. Scherzer R, Gandhi M, Estrella MM, et al. A chronic kidney disease risk score to determine tenofovir safety in a prospective cohort of HIV-positive male veterans. AIDS. 2014;28:1289-95.
42. Oboho I, Abraham A, Benning L, et al. Tenofovir use and urinary biomarkers among HIV-infected women in the Women's Interagency HIV Study (WIHS). J Acquir Immune Defic Syndr. 2013;62:388-95.
43. Lubowitz H, Purkerson M, Sugita M, Bricker N. GFR per nephron and per kidney in chronically diseased (pyelonephritic) kidney of the rat. Am J Physiol. 1969;217:853-7.
44. Brenner B. Nephron adaptation to renal injury or ablation. Am J Physiol. 1985;249:F324-37.
45. Lopez-Novoa J, Rodriguez-Pena A, Ortiz A, Martinez-Salgado C, Lopez Hernandez F. Etiopathology of chronic tubular, glomerular and renovascular nephropathies: clinical implications. J Transl Med. 2011;9:13.
46. Zaidan M, Lescure FX, Brocheriou I, et al. Tubulointerstitial nephropathies in HIV-infected patients over the past 15 years: a clinico-pathological study. Clin J Am Soc Nephrol. 2013;8:930-8.
47. Bazzi C, Petrini C, Rizza V, Arrigo G, Beltrame A, D'Amico G. Characterization of proteinuria in primary glomerulonephritides. SDS-PAGE patterns: clinical significance and prognostic value of low molecular weight ("tubular") proteins. Am J Kidney Dis. 1997;29:27-35.
48. Reichert L, Koene R, Wetzels J. Urinary excretion of beta 2-microglobulin predicts renal outcome in patients with idiopathic membranous nephropathy. J Am Soc Nephrol. 1995;6:1666-9.
49. Nishijima T, Kurosawa T, Tanaka N, et al. Urinary beta2 microglobulin can predict TDF-related renal dysfunction in HIV-1-infected patients who initiate TDF-containing antiretroviral therapy. AIDS. 2016 [Epub ahead of print].
50. Jotwani V, Scherzer R, Estrella M, et al. Cumulative tenofovir disoproxil fumarate exposure is associated with biomarkers of tubular injury and fibrosis in HIV-infected men. J Acquir Immune Defic Syndr. 2016 [Epub ahead of print].
51. Hodgkins K, Schnaper H. Tubulointerstitial injury and the progression of chronic kidney disease. Pediatr Nephrol. 2012;27:901-9.
52. Tramonti G, Kanwar Y. Review and discussion of tubular biomarkers in the diagnosis and management of diabetic nephropathy. Endocrine. 2013;43:494-503.
53. Brown T. HIV: an underrecognized secondary cause of osteoporosis? J Bone Miner Res. 2013;28:1256-8.
54. Brown T, McComsey G, King M, Qaqish R, Bernstein B, da Silva B. Loss of bone mineral density after antiretroviral therapy initiation, independent of antiretroviral regimen. J Acquir Immune Defic Syndr. 2009;51:554-61.
55. Bernardino JI, Mocroft A, Mallon P, et al. Bone mineral density and inflammatory and bone biomarkers after darunavir-ritonavir combined with either raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults with HIV-1: a substudy of the NEAT001/ANRS143 randomised trial. Lancet HIV. 2015;2:e464-73.
56. Tebas P, Kumar P, Hicks C, et al. Greater change in bone turnover markers for efavirenz/emtricitabine/tenofovir disoproxil fumarate versus dolutegravir + abacavir/lamivudine in antiretroviral therapy-naive adults over 144 weeks. AIDS. 2015;29:2459-64.
57. Bedimo R, Maalouf N, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. AIDS. 2012;26:825-31.
58. Brown T, Hoy J, Borderi M, et al. Recommendations for evaluation and management of bone disease in HIV. Clin Infect Dis. 2015;60:1242-51.
59. Hautmann A, Schroeder J, Wild P, et al. Tumor-induced osteomalacia: increased level of FGF-23 in a patient with a phosphaturic mesenchymal tumor at the tibia expressing periostin. Case Rep Endocrinol. 2014;2014: 729387.
60. Lucey J, Hsu P, Ziegler J. Tenofovir-related Fanconi's syndrome and osteomalacia in a teenager with HIV. BMJ Case Rep. 2013;2013.
61. Mateo L, Holgado S, Marinoso ML, et al. Hypophosphatemic osteomalacia induced by tenofovir in HIV-infected patients. Clin Rheumatol. 2016;35:1271-9.
62. Bagnis C, Karie S, Deray G, Essig M. Hypophosphataemia: an easy strategy for diagnosis and treatment in HIV patients. Antivir Ther. 2009; 14:481-8.
63. Masia M, Padilla S, Robledano C, Lopez N, Ramos JM, Gutierrez F. Early changes in parathyroid hormone concentrations in HIV-infected patients initiating antiretroviral therapy with tenofovir. AIDS Res Hum Retroviruses. 2012;28:242-6.
64. Childs K, Fishman S, Constable C, et al. Inadequate vitamin D exacerbates parathyroid hormone elevations in tenofovir users. AIDS Res Hum Retroviruses. 2010;26:855-9.
65. Casado JL, Santiuste C, Vazquez M, et al. Bone mineral density decline according to renal tubular dysfunction and phosphaturia in tenofovir-exposed HIV-infected patients. AIDS. 2016 [Epub ahead of print].
66. Overton E, Chan E, Brown T, et al. Vitamin D and calcium attenuate bone loss with antiretroviral therapy initiation: A randomized trial. Ann Intern Med. 2015;162:815-24.
67. Fux C, Rauch A, Simcock M, et al. Tenofovir use is associated with an increase in serum alkaline phosphatase in the Swiss HIV Cohort Study. Antivir Ther. 2008;13:1077-82.
68. Bhambri R, Naik V, Malhotra N, et al. Changes in bone mineral density following treatment of osteomalacia. J Clin Densitom. 2006;9:120-7.
69. Hamzah L, Samarawickrama A, Campbell L, et al. Effects of renal tubular dysfunction on bone in tenofovir-exposed HIV-positive patients. AIDS. 2015;29:1785-92.
70. Jose S, Hamzah L, Campbell L, et al. Incomplete reversibility of estimated glomerular filtration rate decline following tenofovir disoproxil fumarate exposure. J Infect Dis. 2014;210:363-73.
71. Casado JL, Del Rey J, Banon S, et al. Changes in kidney function and in the rate of tubular dysfunction after tenofovir withdrawal or continuation in HIV-infected patients. J Acquir Immune Defic Syndr. 2016 [Epub ahead of print].
72. Ray A, Fordyce M, Hitchcock M. Tenofovir alafenamide: A novel prodrug of tenofovir for the treatment of HIV. Antiviral Res. 2016;125:63-70.