

Arnaiz de las Revillas F¹, Marcote Ibáñez C¹, González-Lamuño D², García Unzueta M³, Lino Montenegro E⁴, Riancho JA¹

1 Servicio Medicina Interna - Hospital Universitario Marqués de Valdecilla - Universidad de Cantabria - IDIVAL - Santander (España)

2 Servicio de Pediatría - Hospital Universitario Marqués de Valdecilla - Universidad de Cantabria - IDIVAL - Santander (España)

3 Servicio de Análisis Clínicos - Hospital Universitario Marqués de Valdecilla - Universidad de Cantabria - IDIVAL - Santander (España)

4 Gerencia de Atención Primaria - Servicio Cántabro de Salud - Santander (España)

General and bone pain syndrome in a patient treated with tenofovir

Correspondence: Francisco Arnaiz de las Revillas - Hospital Universitario Marqués de Valdecilla - Servicio de Medicina Interna - Avda. Valdecilla, s/n - 39008 Santander (Spain)
e-mail: farnaiz@humv.es

Date of receipt: 03/09/2015

Date of acceptance: 07/10/2015

Summary

Tenofovir (TDF), is the only nucleotide analogue reverse transcriptase inhibitor for treating human immunodeficiency virus (HIV). Occasionally, it may cause acute renal failure and Fanconi syndrome.

We report the case of a 64-year-old male diagnosed with HIV infection 22 years previous and treated with tenofovir. In outpatient follow-up, the patient complained of progressive fatigue and diffuse aching bones. In several check-ups, increased alkaline phosphatase and parathyroid hormone (PTH) were observed. Over the past month, his condition worsened and he was admitted to hospital. Analytical data included marked glycosuria, hypophosphatemia, hyperphosphaturia and hypouricemia. All changes were resolved when TDF was discontinued. This illustrates the importance of clinical evaluations that include possible TDF-induced proximal tubulopathy in patients with general bone pain syndrome or mineral metabolism disturbances.

Key words: *general syndrome, tenofovir, osteomalacia, Fanconi syndrome.*

Introduction

Tenofovir (TDF), is the only inhibitor of nucleotide analogue reverse transcriptase for treatment of human immunodeficiency virus (HIV) infection. It is sometimes associated with renal impairment, including tubular dysfunction and Fanconi syndrome^{1,2}. This syndrome involves a defect in the transport of amino acids, glucose, phosphate, uric acid, potassium, bicarbonate and protein at proximal tubule level³.

Case report

We report the case of a 64-year-old man diagnosed with HIV infection 22 years previous, taking didanosine, tenofovir and lopinavir/ritonavir. In outpatient revisions over the past two years, the patient complained of diffuse bone pain and fatigue. Several analyses detected elevated total and bone alkaline phosphatase (AP) and the parathyroid hormone (PTH). The 25-hydroxyvitamin D (25-HCC), total and ionized calcium and other routine biochemical parameters in serum and elementary and sediment in urine were normal (Table 1). Plain radiography of the spinal column showed degenerative signs and CT scan was normal.

During the last month, his condition worsened, with increased fatigue, loss of strength, difficulty walking and a loss of 7 kg so he was admitted to hospital. Physical examination was unremarkable except for predominantly proximal muscle weakness. The analytical data highlighted mild hyperglycemia (154 mg/dl), marked glycosuria (4+), hypophosphatemia, unusually high phosphaturia, hypouricemia (2 mg/dl), mild metabolic acidosis (bicarbonate 19 mmol/l) and (945 mg/24h). Furthermore, there was moderate aminoaciduria with increased glycine (x2), valine (x2), serine (x4) and threonine (x4) values. FGF23 serum levels were 6 pg/ml. Other parameters shown in Table 1.

From these results, incomplete Fanconi syndrome was diagnosed with probable severe hypophosphatemia and osteomalacia linked to TDF. The drug was discontinued and treatment commenced with raltegravir and darunavir boosted with ritonavir. Furthermore phosphorus supplements, HCC-25 and 1.25-dihydroxyvitamin D (1.25 DHCC) were administered. His condition gradually improved with this regime. Six months after the withdrawal of TDF, bone pain and muscle weakness stopped, the patient had regained baseline weight and had normalized serum laboratory abnormalities, although phosphate reabsorption remained slightly low.

Discussion

The TDF is excreted by glomerular filtration and is actively transported by cells of the proximal tubule renal¹. Although tubular disorders, including Fanconi syndrome, are a known complication of TDF treatment, acknowledged in its technical specifications and the subject of different publications^{4,5}, it is not often accompanied by clinical

demonstrations^{1,2}. Indeed, in a study of 422 patients with HIV infection, of which 381 received TDF, this drug was not found to be associated with globally altered levels of calcium, phosphorus, vitamin D or markers of bone remodeling, nor in bone mineral density (BMD)⁶. On the other hand, in a clinical trial involving 299 patients treated with TDF and followed up over 144 weeks, 10 cases of hypophosphatemia (similar to that found among stavudine frequency) were found, although none were necessary to remove the drug or developing Fanconi syndrome⁷. In that same study the authors found a slight decrease in spinal BMD, but not in the hip in those individuals treated with TDF. It has been suggested that concomitant administration of other drugs such as didanosine and lopinavir boosted with ritonavir, may increase the risk of tubulopathy^{8,9}.

Increased phosphate excretion with consequent hypophosphatemia was most relevant in this patient's evolution. The role of FGF23 in hypophosphatemia associated with PDT is controversial^{10,11}. In our patient, FGF23 levels were decreased, which runs contrary to the implication of this phosphaturic factor and is consistent with a direct effect of the drug on the renal tubules. Although a bone biopsy was not carried out to confirm the accumulation of osteoid, clinical and laboratory manifestations, including increased PTH and FA are consistent with the existence of a hypophosphatemic osteomalacia^{12,13}. The resolution after discontinuing TDF confirms the causal implication of this drug. However, this is a rare complication.

In a recent review of the literature, 53 cases of TDF-induced tubulopathy were found, of which 27 had bone changes consistent with osteomalacia. The median time from treatment initiation to the onset of renal impairment was 2.5 years¹⁴. The fact that these tubular alterations are not necessarily associated with a decreased glomerular filtration rate, next to that phosphatemia often not included in the biochemical parameters analyzed routinely, can lead to delays in diagnosis.

This case illustrates the importance of clinicians including the possibility of hypophosphatemia secondary to a proximal tubulopathy in the diagnosis of patients treated with vague TDF symptoms such as weakness or pain, which could otherwise be attributed to the underlying disease or other concomitant processes.

Competing interests: All authors declare no conflict of interest.

Bibliography

1. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis* 2010;51:496-505.
2. O'Donnell EP, Scarsi KK, Darin KM, Gerzenshtein L, Postelnick MJ. Low incidence of renal impairment observed in tenofovir-treated patients. *J Antimicrob Chemother* 2012;66:1120-6.

Table 1. Analytical parameters observed in the patient 2 years and 6 months before admission, during hospitalization and 6 months afterward

	Normal values	24 months before	6 months before	To the admitted	6 months then
Cr, mg/dl	0.7-1.2	1.2	1.0	0.8	0.9
AP, U/l	40-129	231	200	180	132
PTH, pg/ml	10-45	56	51	25	-
P, mg/dl	2.5-4.5	1.9	-	1.1	2.6
Mg, mg/dl	1.6-2.5			2.4	2.3
Tubular reabsorption of phosphate, %	80-90			40	60

Cr: creatinine; AP: alkaline phosphatase; PTH: parathormone.

- Asplin JR, Coe FL. Tubular disorders. In: Kasper D, Braunwald E, Fauci A, Hauser S, Longo D, Jameson J, editors. *Harrison's Principles of Internal Medicine*. 16th ed. New York: McGraw Hill; 2005. p. 1701.
- Hall AM, Hendry BM, Nitsch D, Connolly JO. Tenofovir-associated kidney toxicity in HIV-infected patients: a review of the evidence. *Am J Kidney Dis* 2011;57:773-80.
- Woodward CLN, Hall M, Williams IG, Madge S, Copas A, Nair D, et al. Tenofovir-associated renal and bone toxicity. *HIV Med* 2009;10:482-7.
- Samarawickrama A, Jose S, Sabin C, Walker-Bone K, Fisher M, Gilleece Y. No association between vitamin D deficiency and parathyroid hormone, bone density and bone turnover in a large cohort of HIV-infected men on tenofovir. *J Int AIDS Soc* 2014;17(4 Suppl 3):19568.
- Gallant JE, Staszewski S, Pzniak AL, De Jesus E, Suleiman JM, Miller MD, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. *JAMA* 2004;292:191-201.
- Gupta SK. Tenofovir-associated Fanconi syndrome: review of the FDA adverse event reporting system. *Aids Patient Care STDS* 2008;22:99-103.
- Goicoechea M, Liu S, Best B, Sun S, Jain S. Greater Tenofovir-Associated Renal Function Decline with Protease Inhibitor-Based versus Nonnucleoside Reverse-Transcriptase Inhibitor-Based Therapy. *J Infect Dis* 2008;197:102-8.
- Haverkort ME, Van der Spek BW, Lips P, Sliker WA, ter Heine R, Huitema AD, Bronsveld W. Tenofovir-induced Fanconi syndrome and osteomalacia in two HIV-infected patients: role of intracellular tenofovir diphosphate levels and review of the literature. *Scand J Infect Dis* 2011;43:821-6.
- Saeedi R, Jiang SY, Holmes DT, Kendler DL. Fibroblast growth factor 23 is elevated in tenofovir-related hypophosphatemia. *Calcif Tissue Int* 2014;94:665-8.
- Riancho JA. Osteomalacia y raquitismo. *Rev Esp Enf Metab Oseas* 2004;13:77-9.
- Francis RM, Selby PL. Osteomalacia. *Balliere's Clin Endocrinol Metab* 1997;11:145-63.
- Mateo L, Holgado S, Mariñoso ML, Perez-Andres R, Bonjoch A, Romeu J, Olive A. Hipophosphatemic osteomalacia induced by tenofovir in HIV infected patients. *Clin Rheumatol* 2014 May 3. [Epub ahead of print].