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ORIGINAL RESEARCH ARTICLE

Long-term Renal Effects of Tenofovir-Disoproxil-Fumarate in Vertically HIV-Infected Children, Adolescents, and Young Adults: A 132-Month Follow-Up Study

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Abstract

Background and Objectives The introduction of highly active anti-retroviral therapy has led to a significant decline in morbidity and mortality. Although several studies in adult populations have shown that tenofovir-disoproxil-fumarate (TDF) use is associated with a significant loss of renal function, there is still uncertainty on the long-term TDF safety profile in pediatric HIV populations, mostly in vertically HIV-infected patients. The aim of this study was to evaluate the long-term TDF renal safety profile, during a ten-year follow up.

Methods Twenty-six vertically HIV-infected patients were evaluated for a total of 132 months of follow up, monitoring anthropometric parameters, renal function, viral load and CD4+ count. Generalized estimating equations were used to evaluate the changes in anthropometric and laboratory variables. Multivariable fractional polynomials were used to test for the existence of non-linear relationships of outcomes with time and other continuous covariates. In all patients, weight, height and body mass index increased linearly with time. CD4+ count and glomerular filtration rate decreased linearly with time ($p < 0.01$).

Results No significant increase of serum creatinine was registered. An inverse linear relationship between time and plasma phosphate was found. Hypophosphatemia was detected in 17 patients, mostly mild. In 14 out of 17 we also genotyped single nucleotide polymorphisms rs717620 mapping in *ABCC2*, a gene encoding for a renal transporter.

Conclusions Our study demonstrates the relative safety of prolonged use of TDF in vertically HIV-infected children and young adults. The most relevant alteration that emerged was hypophosphatemia, appearing after 72 months of TDF therapy, mostly mild and without clinical significance.

Key Points

TDF, hypophosphatemia, HIV, children, adolescents, kidney.

1 Introduction

The introduction of highly active antiretroviral therapy (HAART) has changed the prognosis and the natural history of HIV infection in adult and pediatric patients, leading to a significant decline in morbidity and mortality. The HAART led to the improvement of long-term survival, but a continuous follow up is necessary to evaluate the side effects of the prolonged use of antiretrovirals [1, 2]. Tenofovir-disoproxil-fumarate (TDF), the first nucleotidic inhibitor of HIV reverse transcription, became available in 2001 for adult therapy. In March 2010, the US Food and Drug Administration (FDA) approved TDF for use in

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adolescents aged 12–17 years and, in January 2012, this approval was extended to children aged 2 to less than 12 years. Since then, it has been extensively used worldwide and is now a recommended first-line drug in HIV-infected adolescents and young adults, due to the simple once-daily dosing in fixed-dose combinations (FDC) [3–5]. Several studies have been performed studying the effect of TDF on renal toxicity in pediatric HIV populations, but there is still uncertainty on the long-term safety profile in pediatric patients, mostly in vertically HIV-infected children and adolescents, in whom therapy is started early and, as a consequence, exposure to potential nephrotoxic drugs [6–14]. Genetic risk factors were reported to be associated with TDF-induced nephrotoxicity. In particular rs717620 (−24C>T) SNP in "ATP-binding cassette, sub-family C, member 2 (*ABCC2*)" gene was associated to kidney tubular dysfunction since individuals with this condition were significantly higher in CC genotype than in CT/TT carriers. The aim of this study was to evaluate the long-term renal safety profile, during a ten-year follow up on the use of TDF in vertically HIV-infected children, adolescents, and young adults.

2 Subjects and Methods

2.1 Study Design

This study is the continuation of the previous 60-month follow-up study [2]: a total of 26 vertically HIV-infected patients were evaluated every 6 months (for others 72 months), for a total of 132 months of follow up. Three patients were lost after 114, 66, and 72 months of follow up. All patients were administered HAART with emtricitabine (FTC), lamivudine and protease inhibitor. At enrollment all patients underwent changes in ongoing HAART, replacing the FTC with efavirenz and protease inhibitor with TDF. All patients maintained lamivudine for the duration of the study and took efavirenz once daily in doses tailored according to weight. The dose of TDF, which is also administered once daily, has been calculated on the basis of the body surface area (BSA): 150 mg for BSA including between 0.5 to 0.84 m^2, 225 mg for BSA between 0.85–1.29 m^2 and 300 mg for BSA >1.30 m^2. In all patients, comorbidities such as diabetes or co-infections and the use of nephrotoxic drugs were excluded. In addition, rs717620 (−24C>T) *ABCC2* polymorphism was analyzed in patients with more significant hypophosphatemia.

2.2 Anthropometric Assessment

Weight was measured to the nearest 0.1 kg using a beam scale (Seca GmbH & Co. KG, Hamburg, Germany) and height was measured to the nearest 0.1 cm using a wall-mounted stadiometer (Holtain Ltd, Crosswell, UK). Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Renal function was assessed every 6 months in all patients.

2.3 Assessment of Renal Function

The estimated glomerular filtration rate (eGFR) was estimated using Schwartz's redux equation in subjects aged <18 years and using the Modification of Diet in Renal Disease (MDRD) equation in subjects aged ≥18 years. Renal failure was defined by eGFR <60 mL/min [15, 16]. Increases in serum creatinine have been defined as grade 1 (≥0.5–2.0 mg/dL vs. baseline), grade 2 (2.1–3.0 mg/dL vs. baseline) or grade 3 (3.1–6.0 mg/dL) vs baseline [17]. Proteinuria was defined by urine protein/urine creatinine ratio >0.2 [18]. Hypophosphatemia was divided in grades according to Division of Acquired Immune Deficiency (DAIDS) scale. For patients under 14 years old: "mild" for values ranging 3.0 to 3.5 mg/dL, "moderate" for values ranging from 2.5 to 2.9 mg/dL, "severe" for values from 1.5 to 2.5 mg/dL and "potentially life-threatening" for values <1.5 mg/dL. For patients older than 14 years: "mild" for values ranging 2.5 to 3.0 mg/dL, "moderate" for values ranging from 2.4 to 2.0 mg/dL, "severe" for values from 1.9 to 1.0 mg/dL and "potentially life-threatening" for values <1.0 mg/dL.

2.4 Statistical Analysis

Continuous variables are reported as means and standard deviations. Generalized estimating equations (GEE) were used to evaluate the changes in weight (continuous, kg), height (continuous, cm), BMI (continuous, kg/m^2), CD4+ cells (continuous, count), GFR (continuous, $mL/min/m^2$) and serum phosphate (continuous, mg/dL) during the study. GEE provide a population-average or marginal model, i.e. they quantify how much the average response would change across the population for every one-unit increase in a predictor and are robust to data missing at random (MAR) [19]. In addition to time (continuous, 12 equally spaced intervals of 6 months), age at baseline (continuous, years) and sex (categorical, 0 = female; 1 = male) were used as covariates. The within-subject correlation matrix of GEE was set as exchangeable and robust 95 % confidence intervals (CI) were calculated. Multivariable fractional polynomials were used to test for the existence of non-linear relationships of outcomes with time and other continuous covariates [20]. All relationships of outcomes with time were linear and were modelled as such. Statistical significance was set to a p value <0.05 and all tests were two-tailed. Statistical analysis was performed using Stata 13.1 (Stata Corp, College Station, TX, USA).

2.5 Genetic analysis

Genotyping of rs717620 in *ABCC2* gene was carried out by Real-Time PCR, using LightSNiP (TIB Molbiol) on LightCycler 480 (Roche). DNA extraction and genotyping were performed after obtaining approval by the Ethics Committee of Luigi Sacco Hospital and an informed consent and assent were obtained as appropriate.

3 Results

We performed a long-term follow up of the 26 HIV-infected children (13 girls and 13 boys) whom we had studied from 0 to 60 months after starting a TDF-containing HAART. The present follow up was performed every 6 months from 66 to 132 months. One patient was lost to follow up at 72 months, one at 84 months and one at 120 months. Missing data for the variables of interest varied from 1 to 22 %, were mostly intermittent and, after inspection of clinical charts, were assumed to be MAR and handled by GEE [2, 17]. The mean age of the children at the start of the study, i.e. at the 66th month of follow up after starting a TDF-containing HAART, was 17.3 years (range 10.5 to 23.0 years).

At all times of the study, patients were in good physical condition, with no presence of acute illness, and maintained viral load undetectable for the whole follow up.

Table 1 reports the measurements of the patients during the study.

In all patients, weight, height and BMI increased linearly with time ($p < 0.01$). Median increase of weight was from 52.5 to 60 kg, median increase of height was from 157 to 167 cm, and median increase of BMI was from 20 to 21.3 kg/m^2. CD4+ count decreased linearly with time ($p < 0.01$) but this change was far from being clinically relevant. GFR decreased linearly with time ($p < 0.01$) but again this change was not clinically relevant. More interestingly, there was an inverse linear relationship between time and plasma phosphate (Fig. 1).

Table 2 reports the GEE models used to evaluate the changes in anthropometry, immunological function and renal function, and Fig. 1 plots the changes estimated by these models.

One patient (ID21), developed transient renal failure from the 72nd to the 78th month of the study, with a pathologic eGFR ranging from 48.8 to 57 ml/min and a pathologic proteinuria defined by the urinary creatinine/urine protein ratio of 0.2 in two time-points. No significant increase of serum creatinine was found during the follow up. Twenty-four-hour urine analysis was performed and proteinuria was <4 mg/m^2/h. Creatinine and GFR values gradually returned to normal range after the 78th month and TDF therapy was continued. The patient showed good clinical condition and no other alteration. Proteinuria was detected in another three patients. ID14 showed proteinuria on one occasion, at the 66th month, but it later normalized without treatment. ID17 showed pathologic values of proteinuria at all time-points, reaching the value of 0.22 at the 66th month and the highest value 0.57 at the 126th month of follow up. The patient, a female, did not showed any increase in serum creatinine from baseline to the end of the study nor a pathologic eGFR, but showed low concentrations of serum phosphate at two time-points (see below). ID18 showed pathologic proteinuria on three occasions, at the 84th, 90th, 96th month, that subsequently normalized without therapy. TDF was not discontinued after the first occasion of pathological values. Since values normalized in the following controls of these patients, TDF was not replaced with another drug.

Hypophosphatemia was detected in 17 (65 %) of 26 patients, for a total of 40 episodes (15 %) over 270 detections, mostly mild (89 %) and moderate (11 %). No severe or life-threatening hypophosphatemia was detected.

ID1 showed progressive and constant decrease of serum phosphate from the 96th month of follow up until to the value of 2.2 mg/dL at the end of the study.

ID2 showed mild hypophosphatemia (nadir 3.0 mg/dL) in 3/12 time-points.

ID3 showed mild hypophosphatemia in 1/12 time-point (nadir: 3.0 mg/dL).

ID4 showed mild hypophosphatemia in 2/12 time-points, reaching the nadir of 2.5 mg/dL.

ID6 showed from the 90th month a constant decrease in phosphate levels up to the value of 3.0 mg/dL (mild hypophosphatemia) at the 132nd month.

ID10 experienced hypophosphatemia at eight time-points, mainly mild and moderate in two (nadir 2.0 mg/dL).

ID11 showed normal phosphate values (range 3.3–4.2) for most time-points, and at the end of the study (132nd month) the value of phosphate decreased to 2.9 mg/dL (mild hypophosphatemia).

ID12 showed the value of 3.0 mg/dL (mild hypophosphatemia) at the 72nd month. No values have been collected after.

ID13 showed mild hypophosphatemia (2.9 mg/dL) at the 66th month and a constant and progressive decrease in serum phosphate values from 96th month of the follow up to 126th month reaching the nadir of 2.8 mg/dL.

ID15 showed a mild hypophosphatemia at the 78th month (2.7 mg/dL), and 3 mg/dL (cut-off value) in 2/12 time-points.

ID16 showed mild hypophosphatemia at the 66th and 102nd, respectively, 2.9 mg/dL and 2.8 mg/dL, and a cut-off value (3.0 mg/dL) at 84th month.

Table 1 Measurements of the children at the follow-up visits

	60 months	66 months	72 months	78 months	84 months	90 months	96 months	102 months	108 months	114 months	120 months	126 months	132 months
Age (years)	17.3	17.8	18.4	18.8	19.3	19.8	20.3	20.8	21.3	21.8	22.2	22.7	23.2
	3.9	3.9	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.1	4.1	4.1
Weight (kg)	54.6	55.7	54.7	56.4	56.8	57.4	58.8	60.0	60.3	59.3	59.0	59.7	59.7
	12.7	12.0	10.7	11.1	9.9	10.0	10.3	10.7	10.1	9.2	8.7	9.4	10.0
Height (cm)	1.63	1.64	1.65	1.66	1.66	1.67	1.67	1.68	1.68	1.67	1.67	1.68	1.68
	0.11	0.10	0.09	0.09	0.09	0.08	0.08	0.08	0.08	0.08	0.07	0.08	0.08
BMI (kg/m^2)	20.2	20.5	20.1	20.4	20.4	20.5	20.9	21.2	21.2	21.0	21.1	21.1	21.1
	2.4	2.4	2.3	2.4	2.1	2.2	2.3	2.3	2.3	2.0	2.1	2.0	2.0
CD4+ (count)	796	806	845	874	800	730	756	715	703	756	749	723	690
	278	251	279	331	346	219	294	211	209	217	252	254	257
CD4 cells (%)	36	37	37	38	39	39	38	39	39	40	39	37	37
	6	7	6	6	6	8	6	7	7	6	7	10	9
Creatinine (mg/dl)	0.7	0.7	0.7	0.7	0.7	0.8	0.8	0.7	0.8	0.8	0.8	0.8	0.8
	0.2	0.2	0.2	0.2	0.1	0.2	0.2	0.2	0.2	0.1	0.2	0.2	0.2
GFR (ml/ min/m^2)	105	108	110	114	107	105	106	108	107	100	104	101	98
	18	20	23	25	19	20	21	23	22	18	23	21	21
Serum phosphate (mg/dl)	4.0	4.1	3.8	3.9	3.9	3.8	3.9	3.7	3.6	3.6	3.4	3.3	3.2
	0.8	0.8	0.7	0.7	0.6	0.6	0.5	0.7	0.5	0.5	0.5	0.6	0.5

Values are means and standard deviations

mo Month, *BMI* body mass index, *GFR* glomerular filtration rate

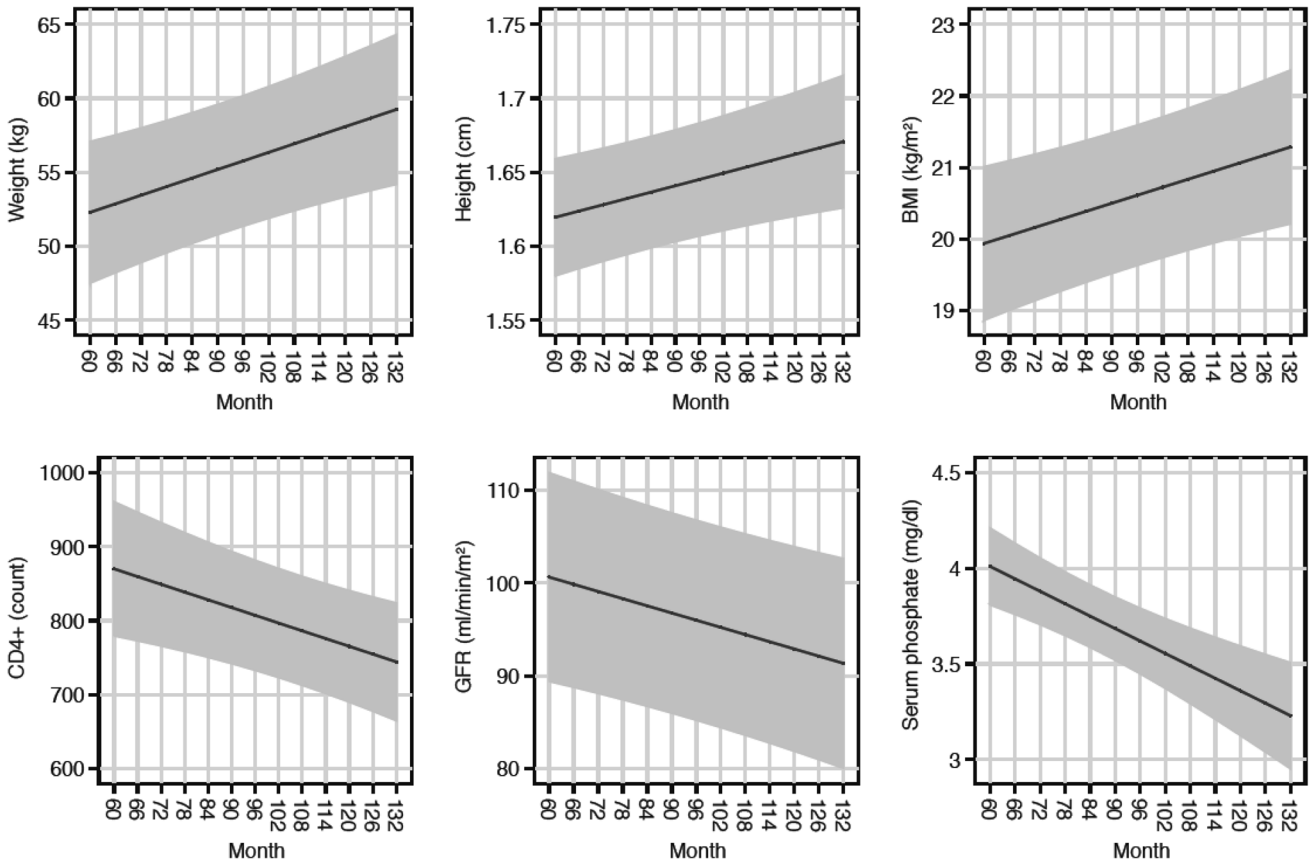

Fig. 1 Partial residuals of time (see Table 2 for the corresponding GEE models). *Gray bands* are 95 % pointwise confidence intervals

ID17 showed one value at the cut-off for hypophosphatemia at 102nd month and mild hypophosphatemia (2.9 mg/dL) at 120th month.

ID18 showed constant decrease of phosphate levels from the 84th month up to the nadir of 2.9 mg/dL (mild hypophosphatemia) at the 132nd month.

ID21 showed 3.0 mg/dL (cut-off for mild hypophosphatemia) at 90th month and 2.9 mg/dL at 132nd month.

ID24 showed a slow and irregular decline from 84th month, reaching the values of 2.5 and 2.7 mg/dL at the 126th and 132nd month of the follow up, respectively.

ID25 experienced mild and moderate hypophosphatemia at the 66th and from the 96th month, reaching the nadir of 2.4 mg/dL at the 120th month (moderate hypophosphatemia).

ID26 showed at only one time-point (108th month) mild hypophosphatemia (3.0 mg/dL).

Figure 2 shows time trend of serum phosphate of 14 patients with more significant hypophosphatemia. In addition, the analysis of the rs717620 (−24C>T) SNP in ABCC2 in these patients has led to the identification of nine homozygous CC (ID1, ID2, ID3, ID10, ID11, ID15, ID16, ID17, ID24), four heterozygous CT (ID4, ID18, ID21, ID25), and 1 homozygous CT (ID13).

4 Discussion

We performed a long-term follow up from 60 to 132 months in 26 HIV-infected children, adolescents and young adults. The eGFR values decreased in all patients without a clinical relevance. The more frequent and significant alteration was hypophosphatemia, detected in 12 out of 26 patients (46 %): it was mainly mild and without clinical relevance. No patients showed severe or life-threatening hypophosphatemia. Pathologic values of proteinuria of ID17 could be explained in part by the low BMI, considered as an independent risk factor for tenofovir-associated renal dysfunction [21, 22]. Several studies in adult populations have showed that TDF use is associated with a statistically significant loss of renal function [20, 23, 24] and several cases of complete or partial TDF-induced Fanconi syndrome are reported in the FDA adverse effects registry [25]. In other adult studies, the risk of chronic kidney failure was demonstrated to be not significantly increased when compared to control [26, 27].

Furthermore, TDF has been demonstrated to be a predisposing factor of TDF-induced nephrotoxicity, as well as elevated serum creatinine at baseline, concomitant nephrotoxic medications, low body weight, advanced age,

Table 2 Changes of anthropometry, immunological function and renal function during the study

	(1) Weight (kg)	(2) Height (cm)	(3) BMI (kg/m2)	(4) CD4+ (count)	(5) GFR (ml/min/m2)	(6) Serum phosphate (mg/dl)
Time[a]	0.097** [0.035, 0.158]	0.001** [0.000, 0.001]	0.019** [0.007, 0.031]	−1.746** [−2.907, −0.586]	−0.129** [−0.221, −0.037]	−0.011*** [−0.016, −0.006]
Age[b]	0.961* [0.163, 1.758]	0.007* [0.000, 0.014]	0.167 [−0.000, 0.335]	12.740 [−3.360, 28.841]	−0.232 [−2.579, 2.115]	−0.080*** [−0.109, −0.051]
Male	5.199 [−3.110, 13.508]	0.044 [−0.019, 0.107]	0.423 [−1.159, 2.004]	−81.933 [−183.476, 19.611]	19.917 [−5.365, 45.200]	0.129 [−0.105, 0.363]
Constant	55.699*** [51.295, 60.103]	1.645*** [1.607, 1.683]	20.599*** [19.620, 21.578]	808.645*** [734.106, 883.184]	96.071*** [85.303, 106.839]	3.634*** [3.464, 3.803]
Observations	310	310	310	311	304	281

Robust 95 % confidence intervals in brackets

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

[a] Centered on mean (95 months)

[b] Centered on mean (12 years)

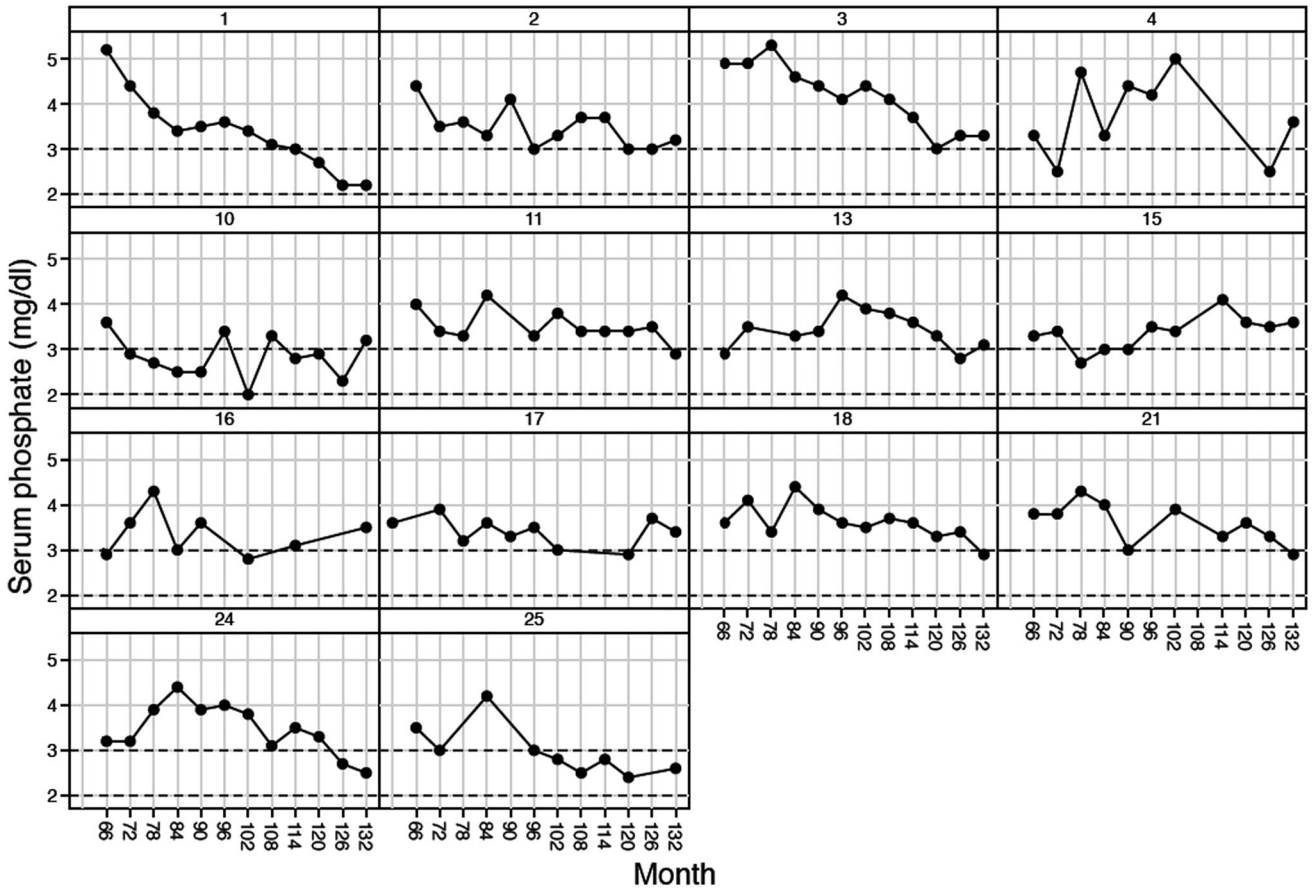

Fig. 2 Time trend of serum phosphate of patients with more significant hypophosphatemia. *Graphs* by ID

duration of treatment and lower CD4 count [6, 28]. A meta-analysis of 17 studies demonstrates that TDF use is associated with a small but statistically significant loss of renal function [29]. In a retrospective analysis, TDF-containing regimens in children showed a 2.2 per 100 child-years of incidence of renal adverse events, and 3.7 % of serious nephrotoxicity [6].

Data from the Pediatric AIDS Clinical Trials Group 219/219C showed that 22 % of 2102 children in the cohort had a persistent renal abnormality: in patients who received

TDF, the risk was higher when compared with those who had no exposure to nephrotoxic medication [8].

Reversible TDF-associated hypophosphatemia occurs with an incidence of 4.5–10 %, usually asymptomatic [6–8], even if proximal renal tubulopathy is also documented with a lower incidence [12, 13, 30, 31]. However, studies that report the renal safety associated with TDF use in children are based on a limited follow-up period and no data are available on populations of only vertically HIV-infected patients [8, 10–13, 31–33].

The *ABCC2* gene, encoding for the multidrug-resistance protein 2 (MRP2), a protein located at the luminal surface of kidney tubular cells, is implicated in tenofovir efflux into the glomerular filtrate through an active mechanism. Although the mechanism by which MRP2 influences the risk of kidney tubular dysfunction is not well understood, genetic variations in *ABCC2* gene could interfere with the efflux of drugs at the luminal membrane, resulting in its intracellular accumulation and renal toxicity. The homozygosity for the C allele at position −24 of the *ABCC2* gene is known to be strongly associated with phosphorus wasting and kidney dysfunction [30, 34–37].

5 Conclusion

Our study demonstrates the relative safety of prolonged use of TDF in vertically HIV-infected children and young adults. The most relevant alteration that emerged was hypophosphatemia, the prevalence of which, in our study, was higher than previously reported in literature. However, this side effect was isolated, without clinical significance and mostly mild or moderate, since no severe or life-threatening hypophosphatemia was registered. Based upon our experience, we suggest that a 24-h urine analysis, frequent anthropometric and renal assessment be performed before considering TDF discontinuation, since in many cases kidney alterations are mild and reversible.

However, more studies are necessary to evaluate the presence of other side effects, e.g. in bone metabolism, correlated to TDF long-term therapy in pediatric population.

Moreover, genetic analysis of functional variants in *ABCC2* gene and other genes known to be involved in kidney transporting of antiretroviral drugs may help to identify patients at greater risk of developing tenofovir-associated hypophosphatemia, in order to ensure a close monitoring of renal function.

Conflict of interest The authors have indicated that they have no other conflicts of interest regarding the content of this article. No funding has been used in this study.

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