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Antiretroviral drugs and the kidney: Further precisions

To the Editor: We read with interest the excellent article of Daugas et al [1] on HAART-related nephropathies and we would like to clarify several points.

There has been no case report of Fanconi syndrome (FS) related to reverse transcriptase inhibitors (RTIs) except one induced by didanosine [2]. Actually, the suspected case of nevirapine-induced FS was largely related to lactic acidosis rather than renal tubular acidosis, considering the anion gap that was increased [3].

It is speculative to incriminate enfuvirtide as a potential cause of membranoproliferative glomerulonephritis (MPGN). Indeed, the diagnosis of MPGN was made on a renal biopsy performed after 57 days of enfuvirtide therapy together with tenofovir, lamivudine, lopinavir-ritonavir, amprenavir, and efavirenz, and in a patient with a history of diabetes and seasonal allergies. Furthermore, in this patient, renal abnormalities (proteinuria and hematuria) were already present before enfuvirtide was started [4].

Finally, the entire chapter on nucleotide reverse transcriptase inhibitors (NtRTIs) is confusing with regard to adefovir potential renal toxicity. Effectively, it is crucial to specify that at its normal dosage of 10 mg daily for the treatment of (hepatitis B virus) HBV infection, adefovir is not nephrotoxic [5]. Furthermore, cidofovir at 3 mg/kg for BK virus infection has also been reported not to be nephrotoxic [6].

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Hypotonic fluids should not be used in volume-depleted children

To the Editor: Dr. Friedman recommends that dehydrated children requiring intravenous therapy should receive hypotonic fluids with a sodium concentration of 3 mEq per 100 ml, after initially receiving bolus therapy with isotonic fluid [1]. A recent report revealed that many children treated in this fashion developed acute hyponatremia [2]. Dr. Friedman is also incorrect when stating that most cases of hospital-acquired hyponatremia resulted when "maintenance therapy was applied erroneously." By Dr. Friedman's own calculations, 0.45% sodium chloride would be used for the treatment of dehydration according to the deficit therapy approach. Dr. Friedman offers no data to support the safety of using hypotonic fluid in volume-depleted children. It makes no physiologic sense to administer hypotonic fluids to patients with a hemodynamic stimulus for vasopressin production.

The recommendations of using 3 mEq of sodium chloride per 100 mL of parenteral fluids are based on the sodium content of human and cow milk [3]. This is far less than the sodium content in the standard American diet and has no applicability to the hospitalized child who may have impaired free water excretion. The safety of this approach has never been demonstrated in the hospitalized children. What we do know is that there have been numerous deaths resulting from hypotonic fluid administration, prompting us to recommend the use of 0.9% sodium chloride in parenteral fluid as prophylaxis against hospital-acquired hyponatremia [4]. Dr. Friedman is critical of our recommendations, stating that "high volumes" of fluid could result in fluid overload. We have never

recommended high volumes of fluid administration, and have recommended fluid restriction for diseases where fluid overload could develop.

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Active vitamin D agents and refractory hyperparathyroidism in dialysis patients

To the Editor: In the March 2005 issue of *Kidney International*, Nakanishi et al [1] presented a very interesting study showing that only serum levels of fibroblast growth factor-23 (FGF-23) were significantly related to the prognosis of parathyroid function in dialysis patients. The factors they included in their stepwise regression analysis were serum FGF-23, calcium, phosphate, intact PTH, intact osteocalcin, bone-specific alkaline phosphatase levels, age, and dialysis vintage [1]. They did not include treatment with active vitamin D agents, even though the pretreatment serum FGF-23 levels were significantly higher in those patients (47 out of 103) who were receiving vitamin D. A very recent paper by Foley et al [2] showed that parathyroidectomy was associated, among other factors, also with the previous use of IV vitamin D (hazards ratio 2.44, $P < 0.0001$). Furthermore, we showed that nodular hyperplasia of parathyroid glands was significantly associated with IV calcitriol pulse therapy (CPT) in hemodialysis patients [3]. The simplest explanation for the paradoxic association between this histologic pattern and IV CPT could be that CPT is often attempted as a "final" nonsurgical strategy when parathyroidectomy is being considered [2]. On the contrary, we hypothesized that, paradoxically, long-term IV CPT might be among the factors determining nodular hyperplasia: in fact, a disturbed and/or decreased action of long-term IV CPT at the level of the parathyroid cell might cause progression into the cell cycle and a disinhibition of *c-myc* expression, leading to a more aggressive nodular type proliferation of parathyroid glands [4]. Therefore, we kindly ask Nakanishi et al to reanalyze their data, including vitamin D treatment in their stepwise regression analysis.

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Reply from the Authors

Thank you for your interest in our recent paper [1]. We agree with you that the cumulative dosage of active vitamin D therapy may correlate with the severity of secondary hyperparathyroidism. However, we believe that the more intensive vitamin D therapy should be the consequence, but not the cause, of the nodular transformation of parathyroid cells, since such cells displayed less sensitivity to vitamin D [2].

We have reported that the use of active vitamin D agents may be related to the increased serum FGF-23 levels in dialysis patients [1, 3, 4]. Therefore, we needed to avoid applying FGF-23 and active vitamin D therapy together as independent variables when performing a stepwise regression analysis. Although it may be possible to perform a stepwise analysis applying active vitamin D therapy instead of FGF-23, it must be "active vitamin D therapy throughout the observation period," but not "active vitamin D therapy at the beginning of the observation period."

Furthermore, the physicians in charge changed treatment strategy depending upon the plasma intact PTH levels in our study. Accordingly, "active vitamin D therapy throughout the observation period" was obviously a