Case Report

Hypokalemic paralysis and proximal renal tubular acidosis secondary to tenofovir-induced Fanconi syndrome: A contributing cause of death

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ABSTRACT

Nucleotide reverse transcriptase inhibitors (NRTIs, primarily cidofovir and adefovir, less likely tenofovir) pose a well-known risk of nephrotoxicity. Acute renal failure, nephrogenic diabetes insipidus (NDI), and Fanconi syndrome (FS) are the primarily reported renal adverse effects associated with NRTIs. In this report, we describe a case of a 52-year-old female who presented to the outpatient department of a tertiary-care facility with polyuria, polydipsia, convulsions, myalgias, and hypokalemic paralysis (quadriparesis) after 10 months exposure to tenofovir disoproxil fumarate (TDF), which she was taking for HIV and Hepatitis-B virus coinfection. The patient developed hypokalemic paralysis and proximal renal tubular acidosis (pRTA) with normal anion gap hyperchloremic metabolic acidosis. On evaluation, renal tubulopathy was evident, which was resolved post-TDF discontinuation and therapeutic corrections. A diagnosis of TDF-induced FS, pRTA, and NDI were considered, as there were no clear alternative explanations. This report also highlights the characteristics of TDF-induced FS from the published case reports in the Indian context.

Key words: Fanconi syndrome, Hypokalemic paralysis, Renal tubular acidosis, Tenofovir

Tenofovir disoproxil fumarate (TDF), an oral prodrug of tenofovir, has been licensed for the long-term management of HIV and Hepatitis-B virus (HBV) infections. The drug is prescribed in combination with other antiretroviral and antiviral medications. It is generally recognized that when using nucleotide reverse transcriptase inhibitors (NRTIs, primarily cidofovir and adefovir), nephrotoxicity can occur. Tenofovir is the third member of this family and is regarded as a safer and less nephrotoxic drug for treating these infections compared to other NRTIs. The first report of TDF-induced renal adverse effects in adults dates back to 2002 [1]. The three main renal adverse effects associated with the use of TDF are acute renal failure (ARF), nephrogenic diabetic insipidus (NDI), and Fanconi syndrome (FS). There are only a few reported instances of TDF-induced FS and NDI in the Indian context [2-7], and none of them reported the adverse reaction as a contributing cause of death.

Hence, we aim to report a case of FS and NDI manifesting hypokalemic paralysis which was developed post-exposure to TDF, which ultimately complicated the whole case and contributed to the death of a patient. This article also reviews and compares clinical characteristics from recently published case reports in the Indian context.

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CASE REPORT

A 52-year-old female diagnosed with HIV (type-1) and HBV coinfection and receiving HAART (combination of dolutegravir 50 mg/d, tenofovir 300 mg/d, and lamivudine 300 mg/d; virally suppressed: <50 copies/mL) presented to a tertiary-care hospital after 10 months with complaints of acute-onset muscle weakness and myalgias for 2 weeks that initially started in her lower extremities and spread proximally to the trunk and upper extremities. She was anorexic for the past 1–2 weeks. She had an episode of convulsion lasting for 3–4 min. She also had polyuria, polydipsia, and 3–4 episodes of emesis per day for a week.

In an emergency room, her serum glucose was 104 mg/dL, serum sodium was 153 meq/L, serum potassium was 1.4 meq/L, serum calcium was 7.3 mg/dL, serum chloride was 137 meq/L, serum bicarbonate was 7.2 meq/L, and serum phosphorous was 1.3 mg/dL. Blood ammonia was 124 µmol/L. Arterial blood gas analysis recorded pH 7.0, pCO_2 25.7, pO_2 113, bicarbonate 6.8, and lactate 2.2. The patient had normal anion-gap metabolic acidosis (NAGMA, anion-gap of 10.2 meq/L) with suspected proximal

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renal tubular acidosis (pRTAtype-II), and hypoalbuminemia (2.4 g/dL). Serum osmolarity was 324 osm/kg H_2O. Her renal function was impaired (serum creatinine 2.3 mg/dL, creatinine clearance 28.2 mL/min, creatinine kinase 698 mcg/L). Urine analysis recorded pH 5.0, proteinuria 2+ (protein-creatinine ratio 6.3 mg/mg), glucosuria 3+, myoglobinuria 2+, ketone bodies 1+, hematuria 1+, spot potassium 39 meq/L, spot sodium 82 meq/L, spot chloride 95 meq/L, and spot calcium 24 mg/dL. The urine anion gap was positive (26 meq/L). The patient's HBV status on current hospitalization was inactive (viral load, <2000 IU/mL). Her 25-hydroxy Vitamin-D levels were 16 ng/mL (reference range: 30–100) and alkaline phosphatase levels were 397 IU/L (40–145); hence, osteomalacia was suspected. Thyroid function and the lipid profile were normal. In view of convulsion and quadriparesis, a magnetic resonance imaging of the brain was performed, which was found to be inconclusive of any abnormalities. Echocardiography showed prolonged QTc with mild ST-T depression, right-atrial and left-ventricular hypertrophy, degenerative valve changes, tricuspid regurgitation, and pulmonary hypertension (mild, 30 mmHg). Her chest X-ray was normal. Blood and urine cultures did not grow any pathogens. Renal ultrasound and Doppler showed hyperechogenic renal pyramids with altered vasculature, which was suggestive of nephrocalcinosis.

Based upon the investigations, renal tubulopathy secondary to TDF-induced FS leading to hypokalemic paralysis and muscle wasting was suspected. Moderate-to-severe grade renal tubulopathy was evident, as there was a presence of elevated creatinine, proteinuria, albuminuria, myoglobinuria, hyperphosphaturia, hypercalciuria, and glucosuria without hyperglycemia. The decision to withhold HAART was made. Other HIV-associated renal pathologies, such as nephrotic syndrome and focal segmental glomerulosclerosis, were also considered. However, the fact that these pathologies are usually present in uncontrolled HIV infection (>10,000 copies/mL) did not support the diagnosis of underlying renal pathology in our patient, who remained virally suppressed on HAART (<50 copies/mL).

As the CD4 cells counted at 327 cells/mL, hepato-safe HAART containing dolutegravir 50 mg/d and lamivudine 150 mg/d was initiated. TDF was discontinued. Adequate rehydration with intravenous fluids and potassium repletion were administered. Serum potassium was improved to 2.5 meq/L, and serum creatinine came down to 2.0 mg/dL (estimated glomerular filtration rate [eGFR] 30 mL/min). Sulfamethoxazole 400 mg/d and trimethoprim 80 mg/d were initiated for *pneumocystic jiroverci pneumonia* (Pneumocystis carinii pneumonia) prophylaxis. On day 6, serum potassium normalized (4.1 mg/dL), and so the sodium-potassium balance was maintained. She required a total of 80 meq of potassium chloride thrice daily (divided) to keep potassium levels above 3.0 meq/L for the first 5 days of hospitalization. Hypophosphatemia was corrected with a phosphorous supplement. On day 7, her other renal function was also improved (serum creatinine, 1.2 mg/dL; eGFR, 53.3 mL/min). The pRTA was resolved. The urine protein-creatinine ratio normalized to 2.5 mg/mg. Hypokalemic paralysis got subsided, and she regained her muscle strength (B/L, 4/5); however, her plantar reflexes were abnormal (dorsiflexion) and asymmetrical.

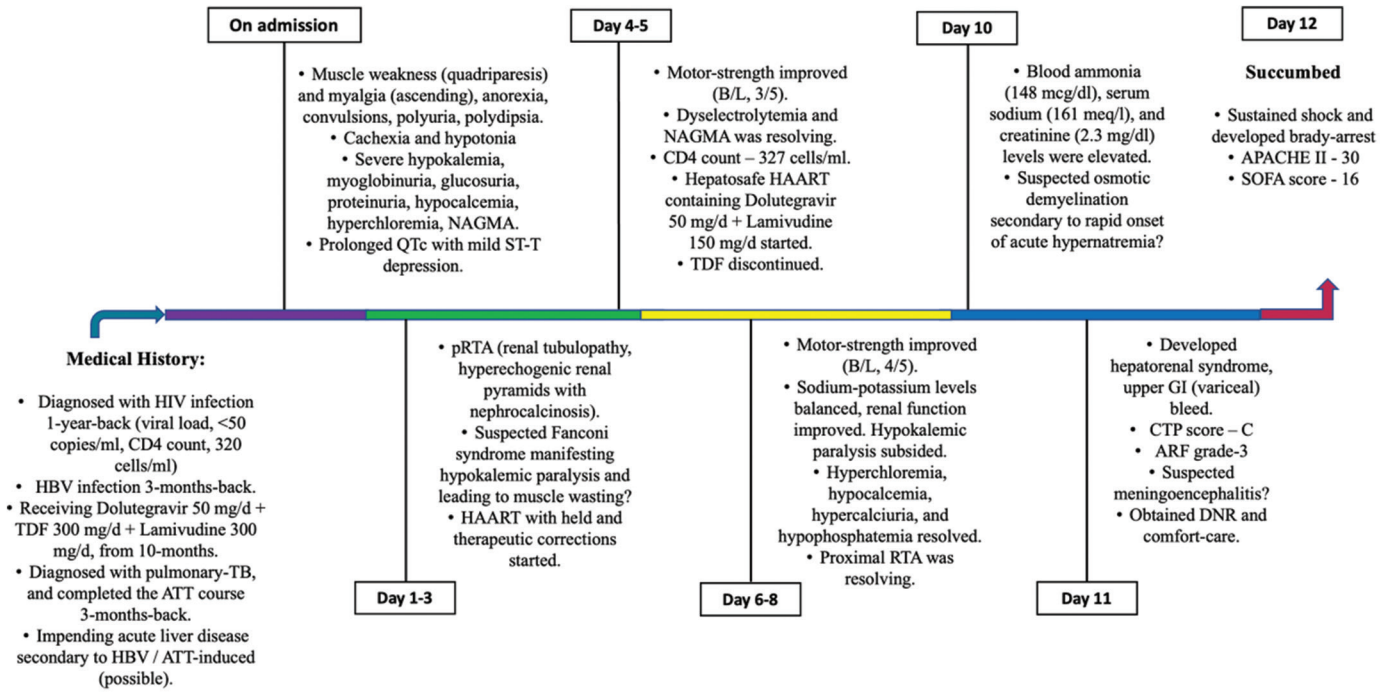

Figure 1: Representation of the medical history, laboratory tests, interventions, and outcome provided the time course of the patient. HIV: Human immunodeficiency virus, HBV: Hepatitis-B virus, TDF: Tenofovir disoproxil fumarate, ATT: Antitubercular therapy, NAGMA: Normal anion-gap metabolic acidosis, pRTA: Proximal renal tubular acidosis, HP: Hypokalemic paralysis, HAART: Highly active antiretroviral therapy, ARF: Acute renal failure, CTP: Child-Turcotte-Pugh, DNR: Do not resuscitate, APACHE: Acute physiology and chronic health evaluation, SOFA: Sequential organ failure assessment

Table 1: Characteristics of Tenofovir-induced FS from the published case reports in the Indian context [2-5] and comparison with present case

Characteristics	Reference ranges (Our hospital)	Kapadia *et al.* [2]	Venkatesan *et al.* [3]	Ramteke *et al.* [4]	Komandla *et al.* [5]	Francis *et al.* [6]	Dave *et al.* [7]	Present case
Age (y)/gender/body weight (kg)	-	43/M/NS	55/F/NS	50/M/NS	60/F/NS	56/F/NS	36/M/NS	52/F/51
HIV diagnosed at age (y)	-	41	48	47	49	48	27	51
Antiretroviral Medications (mg/d)	-	Tenofovir 300 mg + Lamivudine 300 mg + Lopinavir 500 mg	Tenofovir + Emtricitabine + Atazanavir (doses not specified)	Tenofovir based antiretroviral therapy (details not specified)	Tenofovir 300 mg + Emtricitabine 200 mg + Efavirenz 600 mg	Tenofovir + Efavirenz + Lamivudine (doses not specified)	TDF 300 mg + Lamivudine 300 mg + Dolutegravir 50 mg	TDF 300 mg + Lamivudine 300 mg + Dolutegravir 50 mg
Tenofovir exposure	-	1 year	10 months	6 months	4 years	8 years	6 months	10 months
Serum creatinine (mg/dL)	0.6 - 1.2 mg/dL	Normal	2.2	3.2	1.6	1.0	1.2	2.3
Urine analysis	-	Albuminuria 3 + , glycosuria 2 +	pH 5.5, albuminuria 2 + , glycosuria 3 +	pH 5.5, albuminuria 2 + , glycosuria 3 +	Proteinuria 2 + , glycosuria 2 + , phosphaturia, aminoaciduria, uricosuria	Glycosuria, phosphaturia, aminoaciduria, uricosuria	pH 6.0, protein 1 + , glycosuria +	pH 5.2, albuminuria 2 + , protein 2 + , glycosuria 3 +
Urine K^+ (spot sample) (mEq/L)	<20 meq/l	Not specified	32	Not specified	Not specified	Not specified	Not specified	39
Na^+ , K^+ (mEq/L)	Na^+ - 135–145 meq/l, K^+ –3.5–5.5 meq/l	Not specified	140, 1.7	140, 1.7	Not specified, 3.0	Not specified	146, 2.3	153, 1.4
Cl^- (mEq/L)	98–107 meq/l	Not specified	118	118	Not specified	Not specified	115	137
HCO^3 (mEq/L)	22–27 meq/l	Not specified	9.4	11.4	12.0	Not specified	18	7.2
Ca^{+2} (mg/dL)	8.4–10.2 mg/dL	Not specified	8.4	8.4	9.3	9.7	7.1	9.2
PO^4 (mg/dL)	2.0–4.5 mg/dL	1.7	2.2	1.6	1.6	2.2	4.6	1.3
Type of acidosis	-	Not specified	Normal anion gap metabolic acidosis	Normal anion gap metabolic acidosis	Normal anion gap metabolic acidosis	Hyperchloremic metabolic acidosis	Normal anion gap metabolic acidosis	Normal anion gap metabolic acidosis
RTA Type	-	Not specified	Not specified	Not specified	Not specified	Proximal RTA (Type II)	Distal RTA (Type I)	Proximal RTA (Type II)
TTKG	6–8	Not specified	Not specified	11.4	Not specified	Not specified	Not specified	33
Protein-creatinine ratio (mg/mg)	<0.20 mg/mg	Not specified	Not specified	2.1	Not specified	Not specified	Not specified	6.3
Hypokalemic paralysis	-	Not present	Present	Present	Not present	Not present	Present	Present
Drug de-challenged	-	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Drug re-challenged	-	No	No	No	No	No	No	No
Revised antiretroviral therapy (mg/d)	-	Abacavir 600 mg + Lamivudine 300 mg + Didanosine 400 mg	Not specified	Not specified	Not specified	Zidovudine/ Lamivudine and Efavirenz	Abacavir 600 mg + Lamivudine 300 mg	Dolutegravir 50 mg + Lamivudine 150 mg

(Contd...)

Table 1: ***(Continued)***

Characteristics	Reference ranges (Our hospital)	Kapadia *et al.* [2]	Venkatesan *et al.* [3]	Ramteke *et al.* [4]	Komandla *et al.* [5]	Francis *et al.* [6]	Dave *et al.* [7]	Present case
ADR causality (WHO/ Naranjo's assessment)	-	Probable	Not specified	Not specified	Probable	Not specified	Probable	Probable
ADR severity (Hartwig's scale)	-	Severe	Not specified	Not specified	Moderate	Not specified	Severe	Severe (Level 7)
Outcomes	-	Normalization of laboratory parameters after 5 months.	Normalization of laboratory parameters and improved muscle power.	Normalization of laboratory parameters and improved muscle power.	Normalization of laboratory parameters after 3 months.	Normalization of laboratory parameters and become symptom-free after 6 months.	Normalization of laboratory parameters and improved muscle power.	Post-TDF discontinuation - Normalization of laboratory parameters and improved muscle power. *Death on 12th day of hospitalization

HIV: Human immunodeficiency virus, HBV: Hepatitis-B virus, CLD: Chronic liver disease, PTB: Pulmonary tuberculosis, TTKG: Trans-tubular potassium gradient, RTA: Renal tubular acidosis, ADR: Adverse drug reaction, WHO: World health organization, NS: Not specified

On day 10 of admission, her blood ammonia and serum creatinine were raised to 148 mcg/dL and 2.5 mg/dL, respectively. Thereafter, she developed decompensated chronic liver disease (DCLD) manifesting hepatorenal syndrome (portal venous pressure, 15 mmHg; serum creatinine, 3.5 mg/dL; ARF, grade 3 [anuria]) and upper GI (variceal) bleed. This time her multislice computed tomography brain with resonance imaging diffusion showed bulky pons with diffuse fluid attenuated inversion recovery hyperintensities. Serum sodium was elevated (161 meq/L); hence, osmotic demyelination secondary to the rapid onset of acute hypernatremia was suspected. Considering positive Brudzinski's sign, meningoencephalitis was kept in differentials. The patient's family obtained do not resuscitate (DNR) and comfort care. She sustained bradyarrest and succumbed to shock on day 12 of hospitalization (APACHE-II score, 30; sequential organ failure assessment score, 16). Fig. 1 represents the medical history, laboratory tests, interventions, and outcome provided the time course of the patient.

DISCUSSION

This case illustrates the documented use of TDF (commonly practiced HAART and anti-HBV therapy) in a patient coinfected with HIV and HBV, leading to acquired FS (renal tubulopathy) and pRTA, which manifested as hypokalemic paralysis. Widespread proximal renal tubule dysfunction underlies FS, which results in decreased reabsorption of amino acids, glucose, urate, bicarbonate, and phosphate and increased excretion of these solutes into the urine. As observed in our patient, typical clinical presentation of FS includes polyuria, dehydration, hypokalemia, hypophosphatemia, hyperchloremic metabolic acidosis, and osteomalacia. FS can be acquired or inherited [8].

The mechanism is speculated to be TDF's interference with tubular transport, which results in drug build-up and mitochondrial toxicity in the proximal tubule. Tenofovir-related nephrotoxicity is associated with advancing age, low body weight, pre-existing renal impairment, concurrent use of nephrotoxic drugs, prolonged treatment duration, and polymorphisms in tubular transporter genes [8]. However, FS may arise in the absence of risk factors and at any point during therapy, as observed in our patient. Certain drugs have been identified to possess the potential to cause FS (acquired FS), namely ifosfamide, cisplatin, streptozocin, mercaptopurine, tetracycline, and adefovir are well reported in the literature. The primary method of excretion of tenofovir is filtration; however, an organic anion transporter-1 (OAT-1) in the proximal tubule actively transports 20–30% of the drug. The multidrug resistance protein-2 and cellular accumulation through OAT-1 are also thought to be the modes of toxicity. This ultimately results in reduced efflux into the tubular lumen, which is mediated by the protein, and inhibits mitochondrial DNA polymerase-gamma, impairing the function of proximal tubular cells [9]. Hypokalemic paralysis is the result of low potassium levels hyperpolarizing the skeletal muscles and decreasing the neuromuscular junction's sensitivity to nerve impulses.

If identified in time and TDF is discontinued, damage to the proximal tubules can be reversed promptly.

There is a scarcity of reports concerning TDF-induced FS in the Indian context [2-7]. Reviewing the same, we attempted a comparison of clinical characteristics with the present case (Table 1). The reported instances in the literature were in between the 40 and 60 year age group. Hypokalemic paralysis leading to muscle wasting was a documented complication of tenofovir therapy in three previously reported cases [3,4,7]. TDF-induced FS was observed after a median interquartile range of 10 (6–48) months of tenofovir exposure. pRTA with hyperchloremic NAGMA was a recognized complication, except for one case, wherein the patient had distal RTA [7]. In the present case, trans-tubular potassium gradient and urine protein-creatinine ratio were significantly elevated, the same were indicative of severe renal damage compared to previously reported instances. Following tenofovir withdrawal and the administration of suitable treatment modalities, all the previous series reported favorable outcomes in the form of normalization of laboratory results, improvement in signs and symptoms, and improvement in the overall clinical condition of patients, exception is our case. Multi-organ dysfunction, the insidious onset of impending meningoencephalitis, and DCLD are all strong predictors of death in our patient. In addition, we strongly believe that TDF-induced FS and pRTA definitely complicated the clinical course of our patient, resulting in prolonged hospitalization, and ultimately which might have contributed to the death of our patient.

Data suggests an equivalent *in vivo* potency of tenofovir alafenamide fumarate (TAF) to TDF at 30-fold lower doses, resulting in 91% lower plasma tenofovir concentrations [9]. As documented in previous studies, a switch from TDF to TAF does result in a significant reduction in proteinuria, albuminuria, and an improvement in bone mineral density, albeit minimal change in eGFR [10-12]. Thus, TAF seems to have a better safety and tolerability profile. This switch from TDF to TAF was sought in our patient; meanwhile, she landed up developing DCLD. On Naranjo's assessment [13], this particular incidence scored 8 of 13 points, indicating a "probable" association between TDF exposure and the development of FS, pRTA, and NDI. The severity of the reaction was documented as "severe (level - 7)" on Hartwig's adverse drug reaction severity assessment scale.

CONCLUSION

TDF-induced FS can lead to developement of hypokalemic paralysis (manifested as muscle wasting) and pRTA, this ultimately can complicate the clinical course of patients. This ADR can cause a serious renal damage (acute renal failure), hence, patient-focused clinical management review is crucial. Clinicians must routinely monitor patients receiving TDF for urine analysis, creatinine, and electrolytes for timely diagnosis of potential renal damage secondary to FS, pRTA, and NDI.

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