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Case report - Tenofovir induced bone disease in HIV positive patients at ART center of a tertiary care hospital

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Abstract

Tenofovir Disoproxil Fumarate (TDF) is an adenine analogue reverse transcription inhibitor used in first-line treatment as well as is also a part of second line treatment of HIV infection. There have been reporting of sporadic cases of Fanconis syndrome/ proximal renal tubule pathy (PRT), PRT with multiple insufficiency fractures and isolated bone disease, including osteomalacia and osteoporosis as adverse drug reactions linked with use of Tenofovir. In present case 60 years', female patient living with HIV, was diagnosed as suffering from variable degree of Fanconissymdrome and its complication of hypophosphatemicosteomalacia, on basis of serum creatinine, serum phosphate and serum alkaline phosphatase levels. Tenofovir was discontinued and patient was prescribed an alternate regimen. Patient improved symptom matically in period four months, while laboratory parameters were still recovering. A periodic monitoring of renal functions is recommended in patients treated with tenofovir based Anti-retroviral Treatment (ART) regimen.

Keywords: Tenofovir, Fanconi Syndrome, Adverse Drug Reaction.

Introduction

Human Immunodeficiency Virus (HIV) is an infection that attacks the CD4 cells and CD4 count below 200 is considered as Acquired Immunodeficiency Syndrome (AIDS) [1].

At the end of 2019, at global level, 38.0 million people were living with HIV. In India, there were 23.49 lakh People Living with HIV (PLHIV) including 3.4%Children Living with HIV (CLHIV) and 20.52 thousand pregnant women. In 2019 New HIV infection cases were 69.22 thousand and AIDS related deaths were58.96 thousand [2].

HIV patients who are taking Anti-Retroviral Therapy (ART) and are virally suppressed do not transmit HIV and so World Health Organization (WHO) recommended that all people living with HIV should be treated with ART [1]. Approved ARV medicines are divided into seven drug classes based on how each drug affects the HIV life cycle, including [3].

- Nucleoside Reverse Transcriptase Inhibtiors (NRTI): Zidovudine (AZT), Stavudine, Lamivudine (3TC), Emtricitabine and Didanosine
- Non-Nucleoside Reverse Transcriptase Inhibitors: Efavirenz (EFV), Nevirapine (NVP), Etravirine, Rilpivirine
- Nucleotide Reverse Transcriptase Inhibitors (NRTI): Tenofovir
- Protease Inhibitors: Saquinavir, Indinavir, Nelfinavir, Ritonavir, Fosamprenavir. Atazanavir, Darunavir
- Entry/Fusion Inhibitors: Enfuviritide
- CCR5 inhibitors: Maraviroc
- Integrase Inhibitors: Raltegravir, Dolutegravir (DTG), Elvitegravir

First-line ART should consist of two NRTIs plus a NNRTI and recommended combinations are: TDF + 3TC + EFV; AZT + 3TC + EFV; AZT + 3TC + NVP; TDF + 3TC + NVP [3]. In 2019, WHO recommended the use of DTG-based or low-dose efavirenz for first-line therapy [1]. DTG should also be used in 2nd line therapy, if not used in 1st line due to its efficacy and the low risk for neural tube defect [1]. Darunavir+ ritonavir is recommended as drug in third- line or an alternative second-line therapy [1]. By June 2020, transition to DTG had been implemented with an expectation of better tolerability, higher efficacy, and lower rates of treatment discontinuation [1].

ARV medicines improve longevity and reduce the risk of HIV transmission but, lead to side effects which may be serious. However, the benefits of HIV medicines far outweigh the risk of side effects. Different ARV medicines can cause different side effects and people taking the same ARV medicine may experience different side effects and these side effects may last only a few days or weeks or could be a chronic. Some side effects can appear in short term after therapy, while other side effects appear after months or years of starting a medicine [3].

Tenofovir Disoproxil Fumarate (TDF) is an adenine analogue reverse transcription inhibitor mainly used in first-line treatment as well as is also a part of second line treatment of HIV infection. Its use has been linked to sporadic cases of Fanconis syndrome/ proximal renal tubulopathy (PRT), PRT with multiple insufficiency fractures and isolated bone disease, including osteomalacia and osteoporosis [4]. We are reporting here a case of PRT with bone disease.

Case

A 60 years, married, female patient was diagnosed as HIV positive and simultaneously diagnosed with extra-pulmonary tuberculosis on 19/03/07. Base line reports as on 06/03/07 were: Hb [mg/dl] - 9.4; TLC [cells/ mm] - 96800; S. creatinine [mg/dl] - 0.55. She took Anti-Kochs treatment (AKT) from 07/04/2007-15/05/2008. Patient completed the AKT and was cured. Then after,

patient was started on first line ARV regimen containing Fixed Dose Combination (FDC) of Stavudine + Lamivudine + Nevirapine (30+150+200 mg) two times a day on 29/05/2008 at ART center of a tertiary care hospital.

On 13/05/13 patient regimen was substituted to Zidovudine + Lamivudine + Nevirapine (300+15+200 mg) two times a day, as per National AIDS Control Organization (NACO) guideline. Due to immunological failure i.e.,<200 CD4 cells /c. mm, on 12/03/14 regimen had to be switched to Tenofovir + Lamivudine [300+300 mg] OD and Atazanavir+ ritonavir [300+100 mg]. CD4 counts as on 9/03/14 was 84 cells/mm^3. With treatment change the CD4 cell count raised to 376 cells/c. mm as on 11/09/14.

On 25/07/2020, patient consulted private practitioner (rheumato logist) with the complaint of back pain, ankle pain and difficulty in walking.Patient was diagnosed as suffering from tenofovir induced hypophos phatemi costeo malacia on basis of reports: Serum phosphorus- 1.8 mg/dl [2.5-4.5] [Hypophosphate Mia]; Serum creatinine- 1.76 mg/dl [.40-1.40]; Serum alkaline phosphatase- 371 IU/L [40-129]; S. PTH- 92.60 pg./ml [15-68.3]. Patient was treated with oral calcium, sodium bicarbonate, acetaminophen, bisphosphonates and vitamin D supplements. All medications were prescribed for one month.

Diagnosis was confirmed at ART center of a tertiary care hospital at time of follow-up visit with help of laboratory investigations (01/08/2020) :S. Urea- 37 mg/dl [10-45]; Serum creatinine- 1.50 mg/dl [0.6-1.4]; Serum alanine amino transferase- 37 IU/L [0-34]; Serum aspartate amino transferase- 30 IU/L [0-31]; Serum alkaline phoaphatase- 667 IU/L [39-118]; Bilirubin [total]- 2.46 mg/dl [0.2-1.2]**;** Haemoglobin- 12.10 gm/dl**;** White blood cell- 8.90*1000 c.mm**;** Platelet- 481.00*1000 c.mm**;** Last viral load (07/08/2020)- <20 copies/ ml i.e. result not detected**;** CD4 cell count- 533 cells/c. mm.

Because of significant changes in Serum alkalinephosphatase this case was reported to State AIDS Clinical Expert Panel (SACEP), for recommendation to change treatment regimen.

On 15/08/2020 it was recommended from SACEPto change the drug regimen totablet Abacavir [300] 1BD, tablet Lamivudine [150] 1OD, tablet Atazanavir + ritonavir [300+100] 1OD. On subsequent follow up visits patient showed symptom matic improvement (complete symptom matic improvement in 4 months of discontinuing the medication) as well as laboratory investigations showed improving values for S. ALP, as shown in Table 1.

Table 1: Laboratory investigations at follow- up visit.

Laboratory parameters	[01/09/2020]	[03/03/2021]
S. Creatinine [0.6-1.4 mg/dl]	1.10 mg/dl	1.28 mg/dl
S. Urea [10-45 mg/dl]	22 mg/dl	25.50 mg/dl
S. AST [0-31 IU/L]	21 IU/L	22.80 IU/L
S. ALT [0-34 IU/L]	12 IU/L	16.40 IU/L
S. ALP [39-118 IU/L]	530 IU/L	262 IU/L

Case have been reported via Vigiflow to the Indian Pharmacopoeia Commission (IPC), the National Coordination Center (Ghaziabad), under Pharmacovigilance Programme of India, as tenofovir induced hypophosphatemicosteomalacia. Here, the WHO-UMC causality assessment [5] is propable and Naranjo score [6] is +4 (possible).

Discussion

Tenofovir disoproxil fumarate (TDF) is an adenine analogue reverse transcription inhibitor widely used in first-line treatment of human immunodeficiency virus

(HIV) infection. Its use has been linked to SporadicFanconis syndrome/ Proximal renal tubulopathy (PRT), PRT with multiple insufficiency fractures and isolated bone disease, including osteomalacia and osteoporosis [4].

Fanconi syndrome is associated with excess excretion of glucose, bicarbonate, phosphates,uric acid, potassium, and amino acids and giving rise to complications like electrolyte abnormalities, acid-base disturbances and hypo phos phatemi costeo malacia [7]. It can be caused by congenital or acquired diseases or by drug [8]. There are three mechanisms explaining antiviral agent– induced renal injury: transporter defects, apoptosis, and mitochondrial injury. Mitochondria damage plays an important role inTDF induced PRT. There is decrease in mitochondrial DNA replication due to inhibition of Mitochondrial DNA polymerase. Underlying Mitochondrial DNA mutations or polymorphisms makes small percentage of individual more susceptible to renal toxicity [8]. Secretory transporters, such as organic anion transporter (OAT) and multidrug resistance-associated protein (MRP) of renal proximal tubule contribute to concentrate potential cytotoxin sin intra-tubular space. There is an increase in drug-induced renal tubular cytotoxicity in cells expressing OAT1 as compared to cells lacking the transporter and tenofovir is having high affinity for OAT1. Also renal toxicity is associated with MRP2 polymorphisms and even attributed to an interaction of the protease inhibitor with MRP2- or MRP4-mediated export. This forms the genetic basis of the nephrotoxicity due to tenofovir. However, the reason for the association of tenofovir-induced proximal tubular damage with these secretory transporters is currently unclear [8].

Patients having Fanconis syndrome usually present with normal glomerular function, pain, muscle weakness, increased fracture risk and decreased quality of life. Often diagnosis is delayed.

Treatment of Fanconi syndrome and itscomplications involves treating the cause.The National Institute of Health guidelines, thus recommends that for patients specifically on tenofovir, both basic chemistry (alanine aminotransferase, aspartate aminotransferase, bilirubin and alkaline phosphatase) and urinalysis should be done every 6 months, to have early diagnosis of the disease and take corrective measures [7].

Case is of 60years'/F patient living with HIV, with variable degree of Fanconissymdromeand its complication of hypophosphatemicosteomalacia. It's diagnosed on basis of serum creatinine, serum phosphate and serum alkaline phosphatase levels. Patient started tenofovir + lamivudine and atazanavir + ritonavir regimen on 12/02/14 and become symptom matic on 25/07/2020. Patient complained for back pain, ankle pain and difficulty in walking. However, patient was female of age 60 years. Such complains may be due to additive effect of post-menopausal osteoporosis as well as age related wear and tear of tissue along with decreased renal function. Moreover, regimen consisted of TDF as well as ritonavir (RTV)as a booster and RTV effects the human organic anion transporters 1 and 3 (hOAT 1 and hOAT3) and/ or multidrug resistance proteins 2 and 4 (MRP2/4) leading to elevated tenofovir plasma concentrations [9]. It has also been implicated that RTV may impair p-glycoprotein-mediated efflux of TDF, increase p-glycoprotein expression and decrease intestinal TDF hydrolysis, thereby increasing TDF absorption through the gastrointestinal tract. This interaction between RTV and TDF augments tenofovir-

relatedadverse effects [9]. Regimen was changed on 15/08/2020 and simultaneous treatment with Vitamin D3, calcium, bisphosphonates, sodium bicarbonate was also given. Patient showed symptomatic improvement as well as serum creatinine and alkaline phosphatase were becoming normal at subsequent investigations.

TheAdverse Drug Reactions (ADRs) was reported as non-serious ADRs with tablet tenofovir + lamivudine as suspected medications. There was a time relation to the medication intake, a positive DE challenge, presence of objective evidences as well as it's a known pharmacological phenomenon.

The alternative cause was present as 'others – age' so the WHO-UMC causality assessment was probable and Naranjo score was+4 (possible).

The rapid withdrawal of the drug usually reverses the renal damage; however, some amount of damage may persist. Some patients need surgery to recover pathological fractures secondary to Fanconi syndrome [8].

There have been sporadic cases of tenofovir induced bone disease world-wide [10, 11]. Hence reporting of such cases can aid in identifying the risk factors for this occurrence. In addition to exposure to TDF, older age and presence of comorbidities are significant predictors of renal function abnormalities and thus bone disease [12].

There is a genetic basis for renal toxicity due to tenofovir [8, 13] so a prior genetic evaluation can help in decision making for HIV treatment in the particular patient. However, this can prove to be a costly option. Tenofovir alafenamide is prodrug that has improved renal safety.

Pharmacokinetic studies suggest a better renal tolerance of tenofovir alafenamide because tenofovir plasma concentrations are lower after tenofovir alafenamide administration. As an alternative to TDF, tenofovirala fen amide may be used.

But its evaluation under special circumstances, long term safety on renal toxicity, as well as use in patients with the chronic kidney disease patients is needed to lead to its inclusion in the routine use [14].So only recommended option remains screening patients prior to starting tenofovir in order to record baseline renal function, and then monitoring renal function every 3-6 months. If abnormalities arise, confirmation of the diagnosis should be done by laboratory and radiological tests and cessation of tenofovir and switching to another agent should be considered [6].

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