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CASE REPORT

Neurological syndrome in an HIV-prevention trial participant randomized to daily tenofovir disoproxil fumarate (300 mg) and emtricitabine (200 mg) in Bondo, Kenya

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Abstract: Side effects of antiretroviral drug use by HIV-positive patients have been extensively studied; however, there are limited data on the side effects of antiretroviral drugs used as an HIV prophylaxis among healthy, HIV-negative individuals. Here we report on an unusual neuropathy in a 24-year-old participant in the FEM-PrEP trial. This was a Phase III randomized, double blind, placebo-controlled trial to test the safety and effectiveness of tenofovir disoproxil fumarate (300 mg) and emtricitabine (200 mg) (TDF-FTC) to prevent HIV. At the eighth week of taking TDF-FTC with moderate adherence, the participant complained of mild paresthesiae, numbness, and a tingling sensation in her upper limbs that was associated with pain and cold. After an additional 4 days, she developed a disabling weakness of her upper limbs and tremors in her hands. The study product was discontinued, and within 2 weeks she was free of all symptoms. One month after restarting the drug, she complained of posture-dependent numbness of her upper limbs. Results of clinical and neurological exams, laboratory tests, and magnetic resonance imaging are described here.

Keywords: pre-exposure prophylaxis, toxic neuropathy, NRTI

Introduction

Pre-exposure prophylaxis (PrEP) is an HIV prevention approach in which HIV-negative people take antiretroviral medication to minimize their risks of HIV acquisition.[1–5] Although the side effects of antiretroviral drug use by HIV-positive patients have been extensively studied, only limited data have been published on side effects of antiretroviral drugs when used as PrEP agents in healthy, HIV-negative people.[6–10] Unusual and rare symptoms potentially associated with PrEP are useful to report. Herein, we report a probable case of toxic neuropathy in a participant in the FEM-PrEP trial, a randomized, double-blind, placebo-controlled safety and effectiveness trial of daily oral tenofovir disoproxil fumarate (300 mg) and emtricitabine (200 mg) (TDF-FTC) given as PrEP against HIV-1 acquisition.[11] Enrolled participants were healthy HIV-negative women, between 18 and 35 years, who were at high risk of acquiring HIV infection. They were to visit the clinic every 4 weeks for up to 60 weeks to receive HIV-prevention counseling, obtain a resupply of study pills, and have their safety monitored.

The trial was approved by all applicable ethical and regulatory committees and was registered on clinicaltrials.gov (number NCT00625404).[12] All participants gave their informed consent before screening and enrolment.

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Case presentation

The participant we describe here was a healthy 24-year-old woman (height 174 cm, weight 56 kg) with no history of drug allergy and alcohol use. Laboratory tests conducted during screening on July 17, 2009, found that she was negative for HIV, syphilis, and hepatitis B. Her hepatic enzymes and creatinine clearance were within normal limits.

After about 8 weeks of taking TDF-FTC, this participant complained of mild paresthesiae, numbness, and a tingling sensation in her upper limbs that was associated with pain and cold. The symptoms did not affect her daily activities, physical examination was normal, and she had not taken any medications that are known to cause peripheral neuropathy upon interaction with TDF-FTC. After an additional 4 days, she developed a disabling weakness of her upper limbs and bilateral weakness of power grip of grade 3–4 and fine tremors in her hands at rest and with activity. Neurological examinations found normal orientation in time and place as was her pupillary light reaction and fundoscopy. Muscle tone, reflexes, and somatic sensations were also normal, but there was a mild deviation of the mouth and the tongue to the left, on protrusion.

After trial closure, analysis of her plasma and intracellular drug levels at week 4 and 8 were consistent with moderate adherence to TDF-FTC.[11,13] At week 10, TDF-FTC was temporarily withheld due to safety concerns and as per the study protocol. The participant was given oral Neurorubine® (Vitamins B1, B6, and B12; Mepha Ltd, Aesch, Switzerland) for 2 weeks. Within 2 weeks after stopping the study drug, she was free of all symptoms. At week 12, she was restarted on the study drug according to the protocol. However, 1 month after restarting the pill, the participant complained of other neurological symptoms of posture-dependent numbness of her upper limbs. The numbness occurred while bending down and resolved after assuming an upright posture. She did not experience the earlier disabling muscle weakness or tremors. Her neurological exam was normal, and she continued taking the study drug. Her drug levels at week 24 (analyzed on stored samples after study closure) were consistent with low adherence to TDF-FTC.

At week 25, the study team decided to withdraw the study drug until neurologic exploration was completed. At week 28, the participant reported having taken a traditional herbal medicine, orally as a single dose. The nature of the herbal medication could not be determined by the study team.

At week 29, the magnetic resonance imaging (MRI) of her brain and cervical spine was found to be normal. Blood tests (performed at that time) revealed her lactate dehydrogenase was elevated at 514 U/L (normal range: 230–460), but her aldolase and creatinine phosphokinase were normal. The neurologist – with extensive experience in the treatment of HIV-infected patients – who assessed the participant observed:

> The clinical manifestation in this patient was not the usual peripheral neuropathy known in patients receiving TDF-FTC. A typical TDF-FTC-related neuropathy starts with feet and only later goes to upper extremities. The fact that the paresthesiae occurs when the patient bends forward (Lhermitte's sign) suggests a possible lesion of the cervical spine, though MRI findings were normal.

In addition to the study drug, Neurorubine®, and the unknown herbal medication, the participant reported taking the following medications: 1) medroxyprogesterone acetate, from enrolment throughout the study period; 2) ibuprofen at week five for one day; 3) amoxicillin/clavulanic acid at week seven for 10 days; and 4) diclofenac at weeks 9 and 10 for 3 and 7 days respectively.

Overall, for safety concern, the participant was managed as if she was assigned the TDF-FTC arm. The clinical team decided not to un-blind the participant's study group allocation, because this would not influence clinical case management. The participant's postural numbness gradually improved and was completely resolved by her week 36 visit. The participant finished study follow-up on September 28, 2010. Her symptoms did not reoccur after she discontinued the study pill.

After trial closure, levels of vitamin B12 on her stored blood samples at weeks 4, 8, 12, and 16 all showed normal values: 625, 727, 744, and 791 ng/L respectively (normal range: 239–931 ng/L).

Discussion

Peripheral neuropathy is an established adverse reaction of both TDF and FTC. It occurs in 5% of patients receiving these drugs in clinical trials.[14] Based on established etiological clues, the clinical picture described in our case suggests toxic neuropathy from TDF-FTC. First, onset of neuropathy occurred after 8 weeks of TDF-FTC initiation. Secondly, symptomatic improvement was noted after discontinuation of the drug, thus permitting resumption of TDF-FTC. Low adherence after re-challenge (restart) likely contributed to the mild symptoms the participant reported. Thirdly, elevated lactate levels as a result of mitochondrial toxicity have been associated with nucleoside reverse transcriptase inhibitor-mediated neuropathy.[15,16]

Regarding the additional medications – medroxyprogesterone acetate, ibuprofen, amoxicillin/clavulanic acid – the participant received prior to the onset of her neuropathy, none is known or plausibly neurotoxic.

Lumbar puncture and a nerve conduction study were not performed. Other differential diagnoses could include acute disseminated encephalomyelitis (ADEM) or an attack of multiple sclerosis. However, the patient showed no signs of cognitive impairment, which often occurs in patients with ADEM.[17] A normal brain MRI scan supported neither ADEM nor multiple sclerosis.[18] The myelopathy component of ADEM was a possibility, but symptom progression was not consistent with ADEM.[19]

To our knowledge, multiple neurological dysfunctions, as observed in this patient, have not been described during the post-marketing experience with TDF-FTC. Health care providers should be aware of this potential toxicity, and appropriate monitoring should be implemented due to the increasing use of PrEP.

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Disclosure

The authors report no conflict of interest in this work.

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