CLINICAL VIGNETTE

Peripheral Mononeuropathy on TDF-FTC for PrEP

Daniel Puneky, MD and John David Fernandez, MD

David Geffen School of Medicine at UCLA

Case

A 38-year-old patient presented for initiation of Pre-Exposure Prophylaxis for HIV infection (PrEP). His past medical history was only notable for hyperlipidemia and migraine headaches. He had not taken PrEP previously. He received appropriate counseling and laboratory testing including negative 4th generation HIV antigen/antibody testing. He was initiated on the daily PrEP regimen tenofovir disoproxil fumarate-emtricitabine (TDF-FTC; brand name: Truvada) 300-200 mg PO Daily.

At his one month follow up, he reported good adherence with the medication, but experienced symptoms including nausea, loose stools, headache and mild wrist and ankle joint pain that resolved within two weeks after starting PrEP. He also reported new paresthesias in the left shin and thigh. They improved with standing and walking but worsened with running. He denied back pain and had not started any other medications, supplements or herbs. He follows a varied diet with no recent dietary changes. His physical exam was notable for mildly reduced sensation to vibration in the left lateral lower leg. Strength was 5/5 at the bilateral hip, knee and ankle, and range of motion intact. The neurologic exam was otherwise normal, and his skin was normal in appearance without rashes. Vital signs and BMI were also within normal limits. His lab testing was significant only for ANA 1:640. Negative labs included CBC, CMP, 4th gen. HIV Ag/Ab, RPR, HCV, Vitamin B12, TSH, ESR, CRP, urinalysis, gonorrhea, and chlamydia NAAT (from urine, rectal swab and pharyngeal swab). TDF-FTC was discontinued, and the patient was referred to Rheumatology for evaluation of the elevated ANA.

At his two month follow up after medication initiation, het reported that the left leg paresthesia resolved about 2 weeks after stopping TDF-FTC. Rheumatology did not find evidence for connective tissue disease despite the ANA. Following extensive counseling and discussion with the patient, a retrial of TDF-FTC was started. Within a couple of days of resuming the medication the paresthesia returned and again resolved with discontinuation. He was then referred to Neurology, adverse medication effect was thought to be most likely given the timing. The transient peripheral nerve injury and extrinsic compression of the common peroneal nerve. Neurology recommended no additional evaluation, although EMG/NCS was recommended if symptoms returned.

The patient continued to meet indication for PrEP. To avoid TDF-FTC, tenofovir alafenamide-emtricitabine (TAF-FTC; brand name: Descovy) 25-200mg PO Daily was discussed but was not started as it has similar side effect profile to TDF-FTC, with concern his symptoms would return. He was started on monthly long acting injectable cabotegravir 600mg IM, which he tolerated well.

Discussion

In 2022, it was estimated that worldwide 39 million people were living with HIV, with 1.3 million annual new infections occurring.[1] In 2021 the United States, estimate was approximately 1.2 million people living with HIV with 36,136 new annual diagnoses.[2,3] Advancements in HIV treatment have significantly improved patient outcomes, enhanced quality of life and prolonged survival. However, despite considerable effort, development of a preventive vaccine or definitive cure for HIV infection remains elusive. In 2010, Grant et al demonstrated that daily oral PrEP was a highly effective strategy to prevent the transmission of HIV.[4] In 2019, TAF-FTC was approved as an alternative option for PrEP in cis-men and trans-women.[5] In 2022 long-acting injectable CAB was approved for PrEP in cis-men, trans-women and cis-women.[6]

TDF and TAF are nucleotide reverse transcriptase inhibitors (NRTIs) and FTC is a nucleoside reverse transcriptase inhibitor. They inhibit viral replication by interfering with HIV viral RNA dependent DNA polymerase. CAB is an integrase strand transfer inhibitor (INSTI). It blocks the strand transfer step of retroviral DNA integration into the host genome by binding to the HIV integrase active site. Zidovudine (AZT) was approved in 1987, as the first drug for treatment of HIV in the US.[7] It is a member of the NRTI class and known to cause myopathy. Other early medications in this class—including zalcitabine, fialuridine, lamivudine, stavudine and fialuridine—are known to cause peripheral neuropathy.[8] With the exception of lamivudine (3TC) none of these agents are in use today at least in part due to adverse effects.

The most common adverse effects of TDF-FTC and TAF-FTC are dizziness, nausea and diarrhea.[5] The most common adverse effects of CAB are injection site reactions, diarrhea, and headache.[6] Up to 5% of patients in clinical trials studying TDF-

FTC in combination with other anti-retroviral agents for the treatment of HIV developed paresthesia and/or peripheral neuropathy. These start symmetrically in the lower extremities and can ascend to the upper extremities.[9] These side effects were not present in PrEP studies or post-marketing data. Clinically, this is not commonly associated with TDF-FTC. There is only one single case report of atypical peripheral neuropathy with TDF-FTC for PrEP.[10] This described a 24-year-old female participating in a clinical trial studying the use of TDF-FTC for PrEP in cis-women (FEM-PrEP). She developed progressive weakness and tremor as well as postural dependent numbness that differed from typical TDF-FTC-related neuropathy. Extensive evaluation did not reveal another plausible cause, and her symptoms resolved with medication discontinuation. While her presentation is dissimilar from our patient's neuropathy, it illustrates an unusual neuropathic presentation with TDF-FTC.

In conclusion, our patient demonstrates an atypical adverse effect of TDF-FTC rarely seen when used for PrEP. While significant advancements have been made in HIV treatment and prevention, providers prescribing PrEP should be aware of the potential for atypical side effects, including unusual neuropathic presentations. These rare adverse effects, reinforce the importance of careful monitoring and individualized patient management. Healthcare providers should be vigilant for unexplained symptoms in patients on these medications which need thorough evaluation. If a more plausible etiology is not uncovered, a trial of drug discontinuation is reasonable. Fortunately for our patient, new options, such as injectable CAB, were available as an alternative to TDF-FTC. These should be considered in patients with neurological or severe adverse effects from tenofovir-based PrEP regimens. Proactive prevention efforts should be continued for these individuals, ensuring best possible care.

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