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Doravirine/lamivudine/tenofovir disoproxil fumarate-induced hypertriglyceridemia in a newly diagnosed AIDS patient

A 44-year-old woman (male-to-female) affected by hypertension and asthma with history of unprotected sexual intercourse and inhalatory drug abuse was admitted to the emergency room complaining of nausea, headache, and convulsive status epilepticus. Brain computed tomography (CT) scan showed hypodense lesions in the left parietal lobe and left cerebellar hemisphere, compatible with a central nervous system opportunistic infection. Fourth-generation HIV test was positive and further confirmed by immunoblotting (baseline absolute lymphocyte count 1256 cell/μl; $CD3^+CD4^+$ count 52 cells/μl; $CD4^+/CD8^+$ ratio 0.06 with HIV-1-RNA: 407 000 copies/ml). Intravenous valproic acid, levetiracetam and lacosamide were started as antiepileptic therapy. Furthermore, intravenous mannitol was administered for the reduction of intracranial pressure resulting from cerebral edema. PCR for *Toxoplasma* spp. tested positive on whole blood sample, and even though cerebrospinal fluid analysis was unfeasible because of compressive phenomena on the left brain fourth ventricle, a diagnosis of neurotoxoplasmosis was made. Several active infections were also diagnosed, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hepatitis B virus (HBV) (because of the presence of HBs, HBe antigens, HBe antibodies and HBV-DNA 72UI/ml), cytomegalovirus (with detectable viremia) and pulmonary aspergillosis. Active and latent infection because of *Mycobacterium tuberculosis* was ruled out. Considering the need for prophylactic treatments and the presence of multiple active infections, the patient received secondary prophylaxis for SARS-CoV2 with a single dose of sotrovimab (VIR-7831). Treatment for pulmonary aspergillosis was started with isavuconazole, and trimethoprim–sulfamethoxazole was introduced for the treatment of neurotoxoplasmosis. Prophylaxis for *Mycobacterium avium* complex was also provided with oral azithromycin. Antiretroviral treatment (ART) with doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) association as fixed-dose combination single-tablet regimen (Delstrigo-Merck Canada Inc.) was initiated. Nevertheless, during the following routine blood test, an unexpected increase in triglyceride value was noted, which spiked up to 1719 mg/dl on the 15th day after the introduction of DOR/3TC/TDF. No sign or symptom of acute pancreatitis was detected at any time during hospitalization. A differential diagnosis was made between a previously undiagnosed familial hypertriglyceridemia and drug-related toxicity. A complete lipid profile was performed at admission revealing an isolated mild hypertriglyceridemia (admission triglyceride value 276 mg/dl, reference range <150 mg/dl); therefore, the first diagnostic hypothesis was excluded. In an attempt to identify the drug putatively responsible for the sudden increase in triglyceride levels, therapy was simplified with sequential sampling of blood triglycerides. No improvement was observed after isavuconazole, azithromycin or valproic acid suspension. Considering the whole therapeutic scheme, after a literature search for possible interactions and side effects, we safely assumed hypertriglyceridemia as unrelated side effect of any of the remaining drugs, including levetiracetam, lacosamide and trimethoprim–sulfamethoxazole [1,2]. This led us to evaluate the possible involvement of DOR/3TC/TDF. Considering the increased risk of acute pancreatitis because of hypertriglyceridemia, plasma apheresis was suggested. Nevertheless, the patient refused the treatment. The simultaneous interruption of DOR/3TC/TDF together with the introduction of gemfibrozil caused a rapid decrease in triglyceride levels (Fig. 1). According to fenofibrate effect on lowering triglyceride levels, reported, on a sample of 1113 patients with a 4 months median follow-up, a median reduction of triglycerides of 60% ($P < 0.001$) [3]. Conversely, our patient reported a reduction of 87.5% on triglyceride levels in less than 2 weeks, further reinforcing our hypothesis of a drug-induced isolated hypertriglyceridemia.

We therefore proceeded with a treatment re-challenge with DOT/3TC/TDF in combination with gemfibrozil, with a new rapid increase in triglyceride levels, implying a direct effect of DOR/3TC/TDF on triglyceride levels:

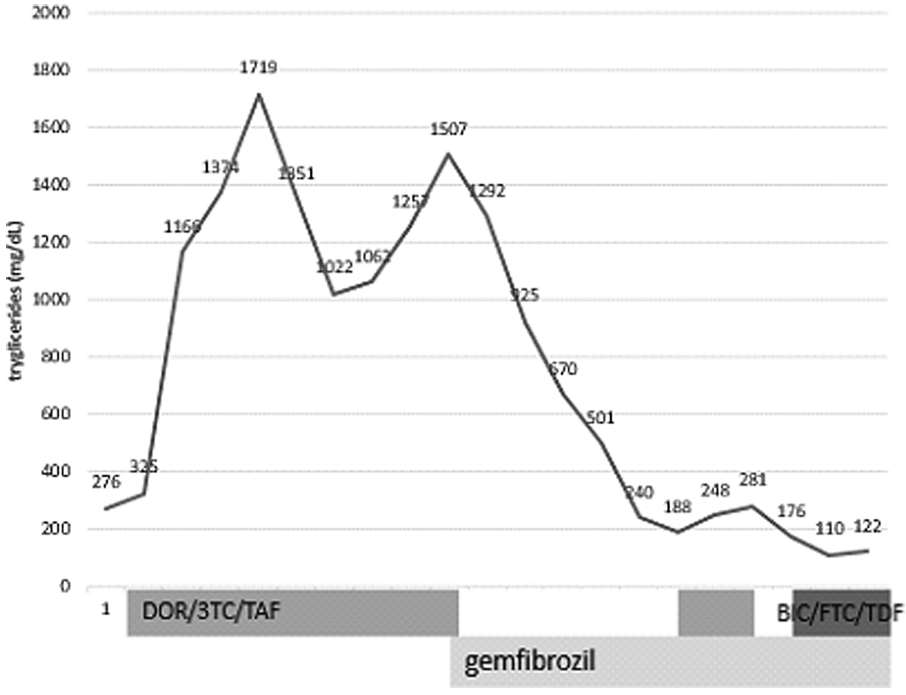

Fig. 1. Serum triglyceride assessment and concomitant treatment regimens.

complete normalization after DOR/3TC/TDF suspension in favor of bictegravir/emtricitabine/tenofovir alafenamide was registered.

We concluded that hypertriglyceridemia was a consequence of DOR/3TC/TDF administration. Paradoxically, comparative data from the registration trials DRIVE-AHEAD, DRIVE-FORWARD and DRIVE-SHIFT, found it to have, on average, a reducing effect on triglycerides, when compared with other ART regimens [4–6]. Hypertriglyceridemia (500–1000 mg/dl) has been reported among the rare side effects of patients treated with DOR/3TC/TDF (2/336, 0.6% of cases) [4]. Likewise, in the DRIVE-SHIFT-trial, 0.3% of patients showed an increase of triglyceride levels, that is, 1 of 391 in the first 24 weeks, and 1 of 377 in the period 24–48 weeks of treatment [6].

Due to multiple drug co-administration for the first time, no certain causal link can be attributable to the DOR/3TC/TDF alone. Nevertheless, the timing and magnitude of dramatic triglyceride level changes during challenging, suspension and re-challenging, makes it highly suggestive. However, the newly administered fibrate therapy makes the triglyceride response to re-challenge difficult to interpret.

Single-tablet regimens, such as DOR/3TC/TDF, favor compliance and are generally well tolerated. When compared with drug regimens containing protease inhibitors, ART including nonnucleoside reverse transcriptase inhibitor (NNRTIs) such as doravirine show a significant improvement in triglyceride levels, representing a good therapeutic option in patients with impaired lipid profile [7]. However, in rare cases, DOR/3TC/TDF can be associated with severe hypertriglyceridemia, as shown in our report.

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Conflicts of interest

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