Correspondence - Letter to the editor

Pancreatitis in an HIV-infected person on a tenofovir, didanosine and stavudine containing highly active antiretroviral treatment

Short title : Tenofovir and pancreatitis

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Sir,

The use of tenofovir disoproxil fumarate (DF), is known to increase didanosine (ddI) levels [1-3]. To our knowledge, only one case of pancreatitis due to the concomitant use of both drugs has been reported so far [4]. We describe a second patient who developed pancreatitis, while receiving tenofovir DF, didanosine enteric-coated (ddI EC) and stavudine (d4T), as part of a highly active antiretroviral treatment (HAART).

A 33-year-old, African, HIV seropositive woman was hospitalised because of a two day history of epigastric and left hypochondric pain, irradiating to the back. The HIV infection was diagnosed in 1994 and she had been on HAART since 1999. Five months before the current event, her treatment was switched to lopinavir/ritonavir (400/100 mg BID), d4T (30 mg BID), and ddI EC (250 mg QD, two hours before breakfast). One month before the current event, tenofovir DF (300 mg QD in the evening) was added. Her body weight on admission was 51 kg. Clinical examination revealed tenderness in the left hypochondric region. Laboratory tests showed following results: amylase 11395 U/L (normal range: 24-72), lipase 88870 U/L (normal range 13-300), aspartate aminotransferase 565 U/L (normal range: 5-40), alanine aminotransferase (normal range: 7-56), gamma-glutamyltransferase 320 U/L (normal range: 11-29), alkaline phosphatase 208 U/L (normal range: 36-95) and lactate dehydrogenase 1908 U/L (normal range: 313-618). Renal function was normal. The CD4+ lymphocyte count was 153/mm^3 and viral load less then 50 copies/ml. Abdominal ultrasound examination showed an oedematous pancreas. The gallbladder, bile and pancreatic ducts were normal. The antiretroviral therapy was discontinued, followed by a swift decrease of the pancreatic and liver enzyme serum concentrations. Seven days after the initial presentation, all symptoms had resolved.

As in the previous case report [4], our patient received a HAART regimen containing d4T, ddI and tenofovir DF. She survived and recovered fully, unlike the first case in which multiple organ failure developed, leading to death.

In healthy volunteers, the administration of 400mg ddI and 300 mg tenofovir DF within two hours resulted in a 28% increase of the maximal ddI concentration and an increase of the area under the curve with about 40% [1,2]. Moreover the administration of ddI EC 250 mg with tenofovir DF staggered or simultaneously with or without a meal resulted in similar drug exposures to a 400 mg dose of ddI EC alone [3]. In our patient, the ddI dosage was reduced to 250 mg, because of low body weight and was taken twelve hours before tenofovir DF. It is clear that maximising the interval between the intake of tenofovir DF and ddI and adjusting the dosage of ddI according to body weight are not enough to avoid ddI related side effects.

Treatment regimens combining ddI and d4T potentially increase mitochondrial toxicity [5] and the risk of developing pancreatitis [6]. Moreover, tenofovir DF is potentially nephrotoxic [7] and d4T clearance decreases in subjects with impaired renal function [8]. Therefore, while awaiting results of larger scale interaction studies between d4T, ddI and tenofovir DF (including also individuals with low body weight), we propose to avoid this combination in HAART regimens.

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