Case Report

# An unusual case of recurrent pancreatitis in a human immunodeficiency virus patient

M. V. S. Subbalaxmi[1], Kiranmayee Narapaneni[1], Radhika Soanker[2], Ramakrishna Narayana[3]

Departments of [1]General Medicine, [2]Clinical Pharmacology and Therapeutics, [3]Radiology, Nizam's Institute of Medical Sciences, Hyderabad, Telengana, India

**Abstract**

Acute pancreatitis (AP) is a rare but life-threatening complication in human immunodeficiency virus (HIV) patients and poses great challenge in management. Drug toxicity and opportunistic infections (OIs) are the most frequently observed causes of pancreatitis in HIV patients in addition to the presence of comorbidities such as alcoholism, biliary disease and hypertriglyceridemia. Here, we report a case of acute-on chronic recurrent pancreatitis induced by nucleoside reverse transcriptase inhibitors and ritonavir which is successfully managed with unboosted atazanavir in combination with backbone regimen.

**Keywords:** Drug toxicity, human immunodeficiency virus, pancreatitis, ritonavir, unboosted atazanavir

**Address for correspondence:** Dr M. V. S. Subbalaxmi, Additional Professor, Department of General Medicine, Nizam's Institute of Medical Sciences, Hyderabad, Telengana, India.
E-mail: subbalaxmimvs@gmail.com

## INTRODUCTION

Acute pancreatitis (AP) in human immunodeficiency virus (HIV) is a rare but serious condition. The annual incidence of AP in non-HIV-infected population is relatively low (i.e., 17–30 cases/100,000 population compared to HIV-infected population).[1] Prior to the highly active antiretroviral therapy (HAART) era, Dutta *et al.* reported 14 cases of AP/100 HIV patients over a period of 1 year.[1] This exceedingly high rate was explained by the presence of comorbidities in their HIV population (alcohol and biliary disease), opportunistic infections (OIs) (such as cytomegalovirus, cryptosporidiosis and *Mycobacterium tuberculosis*) and drugs used for chemoprophylaxis (e.g., pentamidine, corticosteroids, sulphonamides, ketoconazole, isoniazid and metronidazole). Nucleoside reverse transcriptase inhibitors (NRTIs) such as didanosine, stavudine, zidovudine and non-NRTIs such as efavirenz are associated with an increased risk of AP. The adverse effects of protease inhibitors (PIs) over lipid metabolism led to greater risk of pancreatitis secondary to hypertriglyceridaemia. This causes difficulty for the physicians to construct an effective antiretroviral therapy (ART) regimen in such high-risk population. Here, we report a case of recurrent episodes of AP induced by NRTIs and ritonavir.

## CASE REPORT

A 44-year-old male, presented to General Medicine outpatient department of our hospital with complaints of recurrent episodes of severe abdominal pain and vomiting over the past 5 days. Pain was more in the epigastric region radiating to the upper back, increased with food intake and in supine position. Pain was less on bending forwards. On examination, he was weighing 60 kg and was afebrile.

| Access this article online | |
|---|---|
| Quick Response Code: | Website: www.jcsr.co.in |
| | DOI: 10.4103/JCSR.JCSR_73_19 |



**How to cite this article:** Subbalaxmi MV, Narapaneni K, Soanker R, Narayana R. An unusual case of recurrent pancreatitis in a human immunodeficiency virus patient. J Clin Sci Res 2019;8:207-10.

Pallor was observed and there was no evidence of clubbing, cyanosis, icterus, peripheral lymphadenopathy and pedal edema. The pulse rate was 88/minute, and blood pressure was 120/80 mmHg. Tenderness was noted in epigastrium and left hypochondrium with preserved bowel sounds. Other systemic examination was normal.

The patient was diagnosed to have HIV-1 15 years ago. CD4 count at that time was 582 cells/mm$^3$, and he did not receive any ART. He was apparently asymptomatic for the next 10 years when he was hospitalised with complaints of nausea, vomiting and severe epigastric pain after a binge of alcohol. His serum amylase and lipase levels were 909 U/L (normal = 40–140 U/L) and 1744 U/L (normal = 0–160 U/L), respectively. He was diagnosed to have alcohol-related pancreatitis and treated conservatively. The patient was discharged after 7 days with an advice of strict alcohol abstinence. His serum amylase and lipase levels decreased to 96 U/L and 140 U/L, respectively, after 4 weeks of discharge. At that time, CD4 count was 194 cells/mm$^3$ and HIV Ribonucleic acid (RNA) load was 66,400 copies/ml. He was started on ART with zidovudine 300 mg BD, lamivudine 150 mg BD and nevirapine 200 mg BD. Two months following the use of ART, he was hospitalised twice with AP which was treated conservatively and discharged. The patient was started on the same ART regimen following which he again developed AP. Drug-induced pancreatitis was suspected, and ART was stopped. After serum amylase and lipase levels normalised, the patient was advised ART regimen containing Tenofovir disoproxil fumarate (TDF) 300 mg OD, efavirenz 600 mg OD and emtricitabine 200 mg OD. The patient continued to develop recurrent episodes of AP in the next 2 years though he did not consume alcohol. He started taking ART irregularly in view of abdominal pain. Two years later, the patient developed symptoms of low-grade fever associated with dull-aching abdominal pain, loss of appetite and weight over 3 months duration. Contrast-enhanced computed tomography (CECT) abdomen revealed ileocecal thickening with mesenteric lymphadenopathy. Ileoceacal tuberculosis was diagnosed and antituberculosis treatment was prescribed for 6 months. In view of the virological failure with serum HIV RNA of 1,54,285 copies/ml and CD4 count of 139 cells/mm$^3$, he was started on second-line Combination anti-retroviral therapy (cART) comprising abacavir 300 mg BD, lamivudine 150 mg BD and atazanavir boosted with ritonavir 300/100 mg OD. The patient was on this ART for 2 months before the present hospitalisation.

During the present admission at our institute, investigations revealed normochromic normocytic anaemia with haemoglobin of 10.4 g/dL. Fasting and postprandial blood sugars were 210 mg/dL and 280 mg/dl, respectively, with Glycosylated hemoglobin ($HbA_1c$) of 7.7%. Renal and liver function tests were normal. Serum levels of calcium – 8.9 mg/dL, cholesterol – 168 mg/dL, high-density lipoprotein – 42 mg/dL, low-density lipoprotein – 96 mg/dL and triglycerides – 125 mg/dL were noted. Chest radiograph and electrocardiogram were normal. Abdominal ultrasonogram was suggestive of AP with Grade I fatty liver, and CECT abdomen revealed focal AP involving the head region with changes of chronic pancreatitis involving the body and tail of pancreas [Figure 1]. The patient was diagnosed to be having HIV-1 infection with diabetes mellitus with acute-on chronic recurrent pancreatitis triggered possibly due to ART i.e., zidovudine, tenofovir, efavirenz and ritonavir. Keeping in view of his clinical condition, an alternate regimen comprising abacavir 300 mg BD, lamivudine 150 mg BD and high-dose atazanavir without ritonavir 400 mg OD was started. The patient tolerated this regimen with improvement in CD4 count from 125 cells/mm$^3$ to 258 cells/mm$^3$, and viral load was significantly suppressed to <50 copies/ml over a period of 4 months. The patient symptomatically improved and gained weight of around 6 kg with no further episodes of AP for the past 1 year.

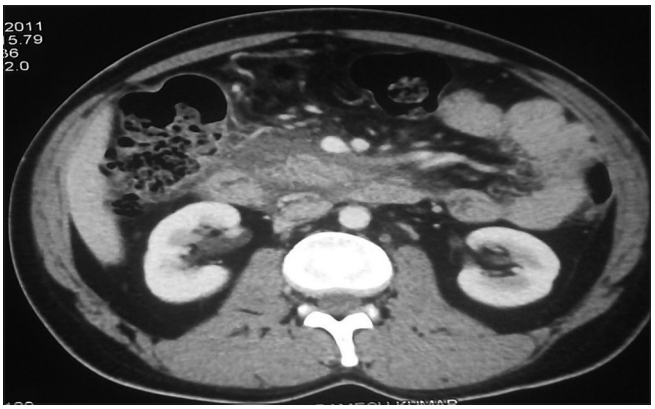

**Figure 1:** Axial section of contrast-enhanced computed tomogram of abdomen of the patient showing bulky head of pancreas with few small non-enhancing areas, peripancreatic fat stranding, minimal fluid collection and grossly atrophic body and tail suggestive of focal acute pancreatitis in the head region with chronic changes involving the pancreatic body and tail

## DISCUSSION

With the advent of HAART, transition has been noticed in the factors causing pancreatic disease in HIV patients from severe immunosuppression, OIs and drugs used for chemoprophylaxis to the newly emerged nucleotide analogues and metabolic derangements. The incidence of AP is widely variable among HIV-positive individuals and observed frequently due to multifactorial association. In addition

to the classic causes described for pancreatitis (alcohol and biliary disease), among HIV-infected individuals, there are specific pancreatic affections described such as HIV itself, severe immunosuppression, high viraemia, OIs, various medications used for the treatment of OIs and antiretroviral drugs. Of all the above causes, drugs are the most common cause for AP followed by OIs and HIV-specific tumours such as Kaposi sarcoma.

The risk of pancreatitis in HIV patients is increased in the presence of low CD4 counts. It is also evident that more advanced disease with higher viral load is further associated with greater risk. Recurrence of AP in our case is possibly due to antiretroviral drugs compounded by immunosuppression with CD4 count <200 cells/mm$^3$, which is consistent with data from prior studies.[2]

OIs commonly responsible for pancreatitis include cytomegalovirus, mycobacterium avium complex, tuberculosis, cryptosporidium, *Toxoplasma gondii*, *Cryptococcus* and *Candida*.[1]

The use of NRTIs, particularly didanosine and stavudine, is associated with an increased risk of pancreatitis.[3] These drugs on prolonged exposure can cause mitochondrial toxicity due to the inhibition of deoxyribonucleic acid (DNA) polymerase.[1] In our case, pancreatitis was triggered initially after starting zidovudine and nevirapine and later recurred with efavirenz and TDF.

PIs, mainly lopinavir and ritonavir, decrease the peripheral clearance of triglycerides, thus explaining its association with an increased risk of pancreatitis due to secondary hypertriglyceridaemia. Elevation of triglycerides in excess of 200% over baseline values is associated with AP in patients receiving ritonavir. This adverse effect on serum lipids was mainly dose related and can be observed as early as 1 week after the initiation of ritonavir.[4] The mechanisms by which ritonavir causes hypertriglyceridemia are not known. Although ritonavir inhibits CYP3A4 isomer of cytochromeP450, there is no definitive evidence that hyperlipidaemia occurs due to the inhibition of this enzyme. HIV infection itself is associated with hypertriglyceridemia, and the degree of hypertriglyceridemia inversely correlates with the CD4 count.[5] However, these levels remain normal in HIV patients who do not have manifestations of AIDS as noticed in our patient.

Drugs such as corticosteroids, acetaminophen, sulphonamides, cotrimoxazole, pentamidine, opioids and isoniazid have been reported to cause pancreatitis in HIV-infected patients. Drug-induced pancreatitis can be caused either by hypersensitivity reaction or by generation of toxic metabolite. The mortality rate in AP is around 10%–15%. About 80% cases are usually mild and 20% are severe in nature. The mortality rate is about 5% in mild cases, whereas it is about 98% in severe cases.

Based on demographics, personal and medical history in our case, the underlying pancreatic disease can be attributable to alcohol initially but was reasonably under remission with abstinence. The time sequence of initiation of ART medications (zidovudine, tenfovir (TDF), efavirenz and atazanavir/ritonavir) and the onset of pancreatitis are consistent with the diagnosis. It was further confirmed as the patient developed recurrent pancreatitis when re-challenged separately with zidovudine, TDF, efavirenz and atazanavir/ritonavir and eventually showed clinical and biochemical regression of pancreatitis after discontinuation of drugs implying definite temporal association with drugs.

Atazanavir, a potent HIV PI, undergoes hepatic metabolism by cytochrome P450. When co-administered with low-dose ritonavir (inhibitor of CYP3A4), plasma atazanavir levels are increased to levels that are associated with adequate viral load suppression. Thus, atazanavir/ritonavir is the most preferred boosted PI for initial cART because of its excellent pharmacokinetics, ease of dosing, potency and favourable resistance profile.[6] However, in the presence of ritonavir intolerance as in our case as evidenced by recurrence of pancreatitis, administration of high-dose unboosted atazanavir in combination with NRTI helps in achieving significant improvement of CD4 count, suppression of viraemia, prevention of OIs and successful remission of pancreatitis.

ART-induced pancreatitis should be considered as an important cause of pancreatitis in patients with HIV infection. Clinicians should be aware of the complications while prescribing ART and carefully monitor serum lipid levels and withhold offending drugs whenever possible.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to b`e reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES


1. Raza S, Chaudhry NA, Brown JD, Aghaie S, Rezai D, Khan A, *et al*. To study the clinical, biochemical and radiological features of acute pancreatitis in HIV and AIDS. J Clin Med Res 2013;5:12-7.
2. Dragovic G. Acute pancreatitis in HIV/AIDS patients: An issue of concern. Asian Pac J Trop Biomed 2013;3:422-5.
3. Chebane L, Bagheri H, Hillaire-Buys D, Géniaux H, Yahioui N, Laroche ML, *et al*. Drug-induced pancreatitis. A review of French spontaneous reports. Rev Med Interne 2015;36:573-8.
4. Danner SA, Carr A, Leonard JM, Lehman LM, Gudiol F, Gonzales J, *et al*. A short-term study of the safety, pharmacokinetics, and efficacy of ritonavir, an inhibitor of HIV-1 protease. European-Australian Collaborative Ritonavir Study Group. N Engl J Med 1995;333:1528-33.
5. Constans J, Pellegrin JL, Peuchant E, Dumon MF, Pellegrin I, Sergeant C, *et al*. Plasma lipids in HIV-infected patients: A prospective study in 95 patients. Eur J Clin Invest 1994;24:416-20.
6. Achenbach CJ, Darin KM, Murphy RL, Katlama C. Atazanavir/ritonavir-based combination antiretroviral therapy for treatment of HIV-1 infection in adults. Future Virol 2011;6:157-77.