MAJOR ARTICLE

Pancreatitis Treated with Didanosine and Tenofovir Disoproxil Fumarate

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Pancreatitis occurs in up to 7% of patients infected with human immunodeficiency virus who are treated with standard doses of didanosine. Tenofovir disoproxil fumarate increases the plasma levels of didanosine and, thus, the combination of these agents may increase the risk of pancreatitis. Four cases of pancreatitis that occurred during administration of this drug combination are examined, including 1 that resulted in death.

Patients infected with HIV have a risk of pancreatitis estimated to be 35–800 times greater than that of the general population [1–3]. The incidence and prevalence vary according to the population studied and method of data collection, but the risk clearly increases as the stage of HIV disease advances [4, 5]. The most common risk factors include a history of pancreatitis, alcohol use, treatment with medications known to cause pancreatitis, opportunistic infections, hypertriglyceridemia, and cholelithiasis [1–6].

It is well established that didanosine is associated with an increased risk of pancreatic inflammation [7, 8]. Pancreatitis occurs in up to 7% of patients receiving recommended doses of didanosine and in up to 10% of those receiving higher doses [9,10]. Drugs with overlapping toxicities, as well as agents that increase the plasma or intracellular levels of didanosine, heighten the risk of pancreatitis. For example, Havlir et al. [11] and Moore et al. [6] showed that the addition of hydroxyurea (which depletes the pool of competing natural nucleosides and elevates intracellular didanosine levels) to a combination of didanosine and stavudine increases the risk of pancreatitis. There have also been several recent reports suggesting an increased incidence of pancreatitis in HIV/hepatitis C virus (HCV)–coinfected patients taking didanosine and ribavirin together [12–14]. Ribavirin promotes the conversion of didanosine to its active triphosphorylated metabolite (ddATP), and concentrations of ddATP are ~2-fold higher in cells exposed to ribavirin than in those exposed to didanosine alone [15].

Tenofovir disoproxil fumarate (DF) significantly increases the maximum concentration of didanosine [16]. These effects are seen both with the buffered and enteric-coated (EC) formulations of didanosine (Bristol-Myers Squibb, written communication to HIV-treating professionals, 7 May 2002). When coadministered with tenofovir DF, the area under the curve (AUC) of didanosine increases by 46% when taken without food and by 60% when taken with food. In contrast, didanosine has no effect on the AUC of tenofovir DF.

The interaction between these 2 drugs may result in increased incidence of didanosine-associated pancreatitis. Four cases of pancreatitis, 1 of which resulted in death, attributed to elevated didanosine levels due to tenofovir DF are reviewed in the following case reports.

CASE REPORTS

Case 1. A 27-year-old, HIV-infected ($CD4^+$ cell count, 9 cells/μL; HIV RNA load, >750,000 copies/mL) Asian man with a history of cryptococcal meningitis

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and disseminated *Mycobacterium avium* complex infection initiated HAART with lopinavir-ritonavir (400/100 mg b.i.d.), tenofovir DF (300 mg q.d.), and didanosine EC (400 mg q.d.). At the time, his weight was 60 kg.

Six months after initiating treatment, the patient presented with a 2-day history of nausea and vomiting with no abdominal pain. Results of a review of systems were otherwise negative, and he denied alcohol use. In addition to HAART, his medicines included epoetin alfa, azithromycin, rifabutin, fluconazole, and trimethoprim-sulfamethoxazole.

He had lost 10 kg since beginning HAART. He was afebrile, tachycardic, and hypotensive. Physical examination revealed a moderately ill-appearing, cachectic man who had a soft abdomen with normal active bowel sounds, minimal epigastric tenderness, and no hepatosplenomegaly.

Remarkable laboratory results included a sodium level of 124 mmol/L, a bicarbonate level of 16 mmol/L, a creatinine level of 0.9 mg/dL, an aspartate aminotransferase level of 89 U/L, an alanine aminotransferase level of 46 U/L, an albumin level of 1.2 g/dL, a lipase level of 140 U/L, a lactate level of 5.9 mmol/L, a total bilirubin level of 5.3 mg/dL, a triglyceride level of 209 mg/dL, a $CD4^+$ cell count of 33 cells/μL, and an HIV RNA load of <50 copies/mL.

The patient was admitted to the University of California, San Diego Medical Center with acute pancreatitis and lactic acidosis and was placed on bowel rest. Clinically, he did not appear septic, and all cultures were negative for bacterial, fungal, and viral growth. His antiretroviral medications were discontinued. By hospital day (HD) 3, he had become anasarcic. CT performed on HD 4 revealed ascites, pleural effusions, and a 4×3–cm ring-enhancing fluid collection anterior to the pancreas; there was no evidence of cholelithiasis (figure 1*A*). Peritoneal fluid revealed a total protein level of 500 mg/dL, an amylase level of 250 U/L, a lipase level of 546 U/L, and a serum ascites albumin gradient of 0.2 U/L.

By HD 5, the nausea and vomiting had resolved, and the patient was hungry. He tolerated clear liquids for 1 day and then became symptomatic again. On HD 8, he became hypothermic, hypotensive, and hypoxemic. He was transferred to the intensive care unit, and a second paracentesis revealed a peritoneal fluid amylase level of >1000 U/L. His serum lipase level increased to 562 U/L, and his lactate level was 3.2 mmol/L.

He developed adult respiratory distress syndrome and required mechanical ventilation with vasopressor support. A second CT scan on HD 9 revealed near-total pancreatic necrosis with multiple pseudocysts (figure 1*B*). The patient died on HD 12.

Case 2. A 40-year-old white woman with a >10-year history of HIV infection started receiving antiretroviral combination of lopinavir-ritonavir (400/100 mg b.i.d), amprenavir (750 mg b.i.d.), lamivudine (150 mg b.i.d.), and didanosine (250-mg buffered tablet q.d.). Her baseline weight was ~50 kg, her $CD4^+$ cell count was 61 cells/μL, and her HIV RNA load was 15,400 copies/mL. Seven months later, didanosine was changed to didanosine EC (400 mg q.d.). Another 10 months later, because of virologic failure, her regimen was modified to lopinavir-ritonavir (400/100 mg b.i.d.), lamivudine (150 mg b.i.d.), didanosine EC (400 mg q.d.), tenofovir DF (300 mg q.d.), and delavirdine (600 mg b.i.d.). She was instructed to take the didanosine EC on an empty stomach and to separate the dosing with tenofovir DF by 2 h.

Three months after initiating treatment, the patient complained of anorexia but was otherwise asymptomatic. Her weight had decreased to 38 kg. Her serum lipase level was elevated at 434 U/L. The serum lactate level was not measured at that time. Her creatinine level was 0.9 mg/dL.

One month later, the patient complained of anorexia, nausea, and vomiting; however, she reported no abdominal pain. Her weight had further decreased to 35 kg. Her creatinine level was 1.1 mg/dL. Her serum lipase level had increased to 638 U/L, and her antiretroviral regimen was discontinued. Abdominal ultrasound showed mild left hydronephrosis and cholelithiasis, which consisted of several small calculi in the gallbladder. While receiving HAART, her highest $CD4^+$ cell count was 97 cells/μL. Serum triglyceride levels were either normal or minimally elevated throughout her treatment course.

During the next month, the patient's symptoms improved, but her lipase level increased to a peak of 1947 U/L. A CT scan revealed no evidence of phlegmon or other intraabdominal abnormalities. Her creatinine level remained at 1.1 mg/dL.

Three months later, her weight increased to 48 kg, and her lipase normalized. The patient started receiving a new regimen (saquinavir hard-gel capsules, 1000 mg b.i.d.; lopinavir-ritonavir, 400/100 mg b.i.d.; lamivudine, 150 mg b.i.d.; and tenofovir DF, 300 mg q.d.) that she has tolerated for 2 months.

Case 3. A 48-year-old, HIV-infected Hispanic man started receiving abacavir (300 mg b.i.d.), didanosine EC (400 mg q.d.), and tenofovir DF (300 mg q.d.). His HIV RNA load was 2000 copies/mL, and his $CD4^+$ cell count was 295 cells/μL. He weighed 90 kg. The patient had a history of arterial occlusive disease, hyperlipidemia, hypertension, lipodystrophy, hypogonadism, anxiety, and depression. His other medications included warfarin, benazepril, atorvastatin, bupropion, paroxetine, zolpidem, alprazolam, clonazepam, celecoxib, zonisamide, testosterone gel, and a multivitamin. He denied alcohol use.

One month after treatment was started, the patient had tolerated the regimen well, except for occasional diarrhea. His fasting triglyceride level was 282 mg/dL and subsequent nonfasting glucose level was 140 mg/dL.

Two months later, the patient presented to the emergency department with complaints of generalized fatigue, polyuria, and polydipsia. He did not report any abdominal pain, nausea,

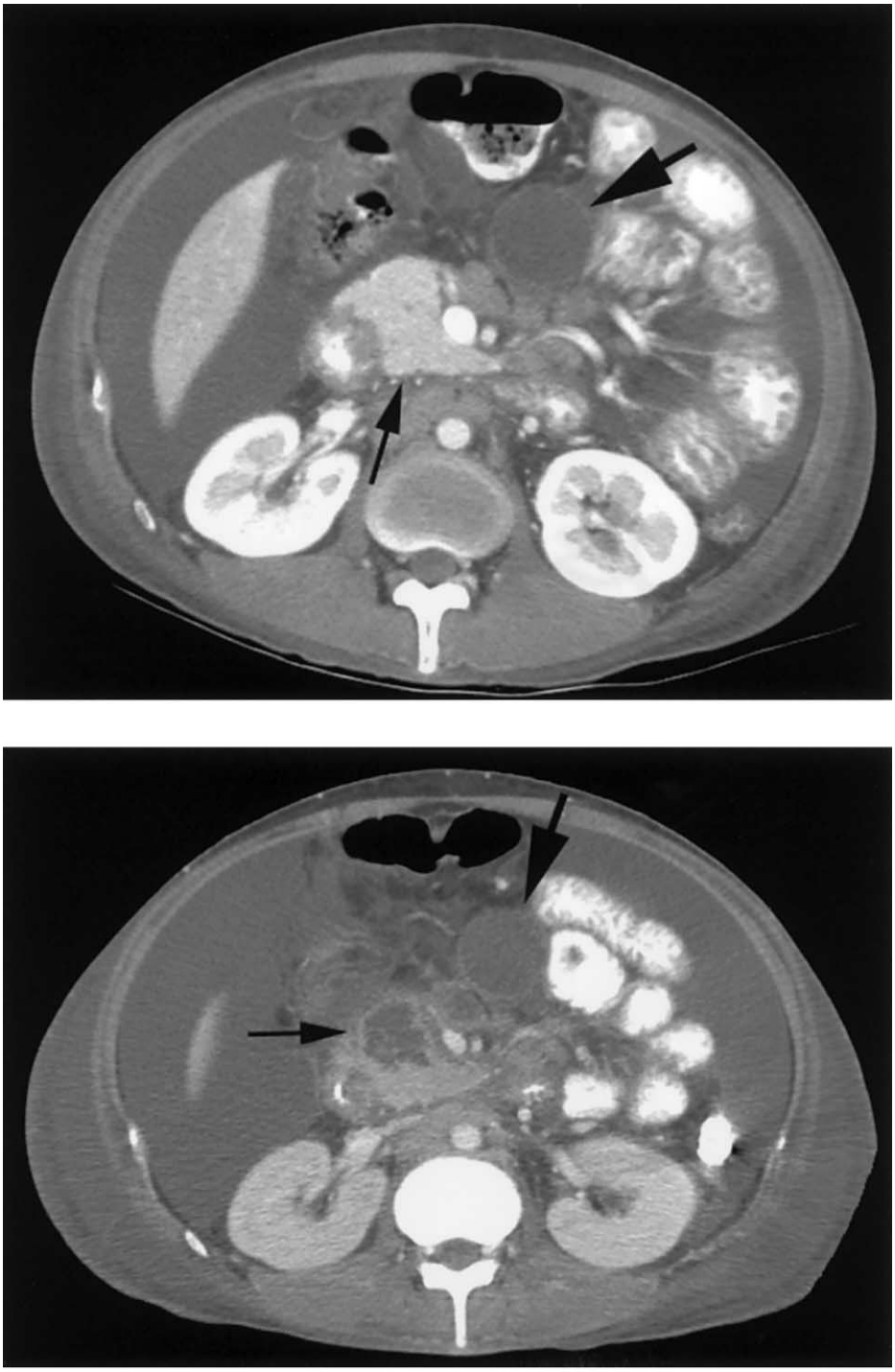

Figure 1. *A,* CT scan from hospital day 4. The *small arrow* indicates a normal pancreas (compare with *B*). The *large arrow* points to the cyst that was subsequently thought to be a pseudocyst. Also, note the large amount of ascites around the liver. *B,* CT scan from hospital day 9. The *small arrow* now indicates the necrotic pancreas. The *large arrow* points to the same cyst indicated in *A.* Note the increase in the amount of ascites.

or vomiting. His creatinine level was 1.3 mg/dL, serum glucose level was 367 mg/dL, triglyceride level was 282 mg/dL, and serum lipase level was 2907 U/L. An ultrasound examination revealed mild pancreatitis and mild peripancreatic inflammatory changes. There was no evidence of cholelithiasis. Pancreatitis was diagnosed on the basis of his elevated lipase level and the ultrasound findings, and his antiretrovirals were stopped.

Within 3 weeks, his symptoms resolved, and his laboratory values began to normalize. Two months later, the patient resumed antiretroviral therapy with tenofovir DF, abacavir, and

ritonavir-boosted saquinavir (hard-gel capsules). He has tolerated the new regimen well for 3 months, with no recurrence of hyperglycemia or pancreatitis.

Case 4. A 49-year-old Hispanic man with a 17-year history of HIV infection started receiving tenofovir DF (300 mg q.d.), didanosine EC (400 mg q.d.), and lopinavir-ritonavir (400/100 mg b.i.d.). His $CD4^+$ cell count was 179 cells/μL, and his HIV RNA load was 6520 copies/mL. He had no history of alcohol abuse or cholelithiasis. Three months after the initiation of therapy, he began to complain of nausea and anorexia. His amylase and lipase levels were normal, and his triglyceride level was 298 mg/dL. During the next 2 months, nausea persisted, and the patient lost weight. His amylase and lipase levels remained normal.

Five months later, the patient was hospitalized for pneumonia complicated by respiratory failure and pancreatitis, which was determined to be secondary to his antiretroviral therapy. Ultrasonography revealed an echogenic liver likely due to fatty infiltration and a distended gallbladder with associated thickening of the gallbladder wall. A CT scan of the abdomen showed that the gallbladder was normal. Before discontinuing HAART, his $CD4^+$ cell count had increased to 295 cells/μL, and his HIV RNA load was 483 copies/mL. At his follow-up appointment after discharge, he had lost a total of 20 kg from his peak weight of 96 kg, his lipase level was still elevated at 1055 U/L, and his triglyceride level was 134 mg/dL. His creatinine level was 1.4 mg/dL.

Two months later, the patient resumed antiretroviral therapy with tenofovir DF, lamivudine, and lopinavir-ritonavir. After 4 months of receiving this regimen, his lipase level was normal, and he remains asymptomatic.

DISCUSSION

These 4 cases of pancreatitis highlight the potential dangers of using didanosine and tenofovir DF together in antiretroviral regimens. In each case, pancreatitis was diagnosed on the basis of either clinical or imaging findings in association with elevated pancreatic enzyme levels. Other risk factors for acute pancreatitis (such as previous history of pancreatitis, cholelithiasis, receipt of drugs associated with pancreatitis, hypertriglyceridemia, and alcohol use) were evaluated for each patient. In case 2, cholelithiasis was present when pancreatitis was diagnosed. When antiretroviral therapy was discontinued, however, symptoms resolved. In cases 1, 3, and 4, no potential cause of pancreatitis was found other than the patients' antiretroviral medications.

Three of the 4 patients had $CD4^+$ cell counts of <200 cells/μL when they developed pancreatitis. A significant correlation between the risk of pancreatitis and a low $CD4^+$ cell count has been reported elsewhere and may have played a role in these cases [4, 6, 17].

Two of the 4 patients had significant involuntary weight loss documented before their episodes of pancreatitis, and another had weight loss documented at the time of his pancreatitis. Two patients weighed <60 kg when they received a diagnosis of pancreatitis. This weight loss likely predisposed them to even greater didanosine toxicity as their weight decreased to <60 kg, the weight at which the recommended daily dose of didanosine should be reduced from 400 mg to 250 mg [7]. Although there are many reasons that these patients may have lost weight (e.g., HIV infection–related wasting, hypogonadism, and depression), the weight loss may have been due to symptomatic hyperlactatemia, which is also a well-known long-term complication of didanosine therapy [7]. A lactate level was measured only in case 1; it was found to be elevated at the time of admission, before the patient developed multiorgan failure. The elevated level therefore likely reflected ongoing drug-induced toxicity.

Of note, 3 of the 4 patients were receiving regimens that included lopinavir-ritonavir. This boosted protease inhibitor increases the AUC of tenofovir DF by 34% [18]. The interaction between lopinavir-ritonavir and tenofovir, coupled with that between tenofovir DF and didanosine, may have increased the plasma levels of didanosine even further. Lopinavir-ritonavir has been associated with pancreatitis, including some fatal cases [19]. The direct and indirect roles of lopinavir-ritonavir in these cases of pancreatitis is uncertain; however, it is important to note that 2 patients have resumed alternative lopinavir-ritonavir–containing regimens and have not experienced a recurrence of pancreatitis.

The patient in case 2 was receiving delavirdine—a potent inhibitor of the cytochrome P450 system—when he received a diagnosis of pancreatitis. Delavirdine's effects on didanosine depend on the timing of their coadministration. For the buffered formulations of didanosine, simultaneous administration with delavirdine results in an ~20% decrease in the AUC of both agents, relative to their administration 1 h apart [20]. The didanosine EC package insert states that the results associated with buffered didanosine may be applied to didanosine EC and that no clinically significant interaction has been observed between delavirdine and didanosine EC. Tenofovir is not metabolized by the cytochrome P450 system and does not interact with delavirdine [18]. It therefore seems unlikely that delavirdine played any role in the development of pancreatitis in this patient.

The recommended dose of didanosine is 400 mg daily for patients weighing >60 kg. For persons weighing <60 kg, the recommended dose is 250 mg every day. Recent data suggest that a didanosine EC dose of 250 mg administered to patients weighing >60 kg who are also taking tenofovir DF yields plasma

levels similar to the 400-mg dose of didanosine EC without tenofovir DF [21]. Currently, there are no pharmacokinetic data for patients weighing <60 kg who are receiving tenofovir DF and didanosine or the combination of lopinavir-ritonavir, tenofovir DF, and didanosine. Clinicians should also be aware that both didanosine and tenofovir DF are renally cleared, and doses must be reduced in cases of renal insufficiency or failure.

The exact mechanism by which tenofovir DF increases didanosine levels is unclear. Flaherty et al. [22] studied the pharmacokinetics of didanosine and tenofovir DF in healthy volunteers for 7 days. A 40% increase in urinary recovery of didanosine was observed, which suggests that greater bioavailability, rather than reduced clearance, is the mechanism for increased plasma levels. Rodman et al. [23] evaluated the interaction between tenofovir DF and didanosine at the cellular level in both quiescent and stimulated human PBMCs. The phosphorylated metabolites of both drugs (TFVpp for tenofovir DF and ddATP for didanosine) were measured in the presence and absence of the drugs in concentrations that reflected the range seen in patients who were receiving recommended doses. No interaction was found, indicating that altered intracellular metabolism is not the mechanism of elevated didanosine levels.

Mitochondrial dysfunction by means of DNA polymerase γ inhibition is thought to play a significant role in didanosine-associated complications (e.g., pancreatitis, hyperlactatemia, and peripheral neuropathy) [24–28]. In vitro studies comparing nucleoside reverse-transcriptase inhibitors (NRTIs) have demonstrated that didanosine is second only to zalcitabine in its ability to inhibit mitochondrial function [29–31]. The in vitro mitochondrial toxic effects and in vivo clinical toxicities of didanosine have also been shown to be concentration (dose) dependent [7, 32]. The drug interaction between tenofovir DF and didanosine (and lopinavir-ritonavir) and the mitochondrial toxicity observed may be a result of elevated didanosine levels.

The 3 patients who survived their pancreatitis have thus far tolerated rechallenges of tenofovir DF–containing regimens that do not include didanosine. Tenofovir DF has been shown in vitro to be one of the least damaging NRTIs to mitochondria. In clinical trials, tenofovir DF has had low rates of long-term clinical complications due to mitochondrial toxicity [32, 33].

CONCLUSIONS

The elevated didanosine levels that tenofovir DF induces likely predisposes patients taking these 2 NRTIs together to a higher risk of pancreatitis than would didanosine alone. For patients receiving didanosine and tenofovir DF, it is imperative that clinicians administer didanosine at 250 mg every day and maintain a high index of suspicion for pancreatitis and other didanosine-related complications. Until more safety and pharmacokinetic data are available, coadministration of didanosine and tenofovir DF should be avoided for patients with any of the following characteristics: weight of <60 kg, renal impairment, or current therapy with lopinavir-ritonavir. The 4 cases demonstrate the importance of vigilant surveillance for drug toxicity, especially for new, untested combinations of medications with narrow therapeutic windows.

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An error appeared in an electronic article published in the 1 September 2003 issue of the journal (Blanchard JN, Wohlfeiler M, Canas A, King K, Lonergan JT. Pancreatitis treated with didanosine and tenofovir disoproxil fumarate. Clin Infect Dis 2003; 37:e57–62). The title should read "Pancreatitis with didanosine and tenofovir disoproxil fumarate" (*not* "Pancreatitis treated with didanosine and tenofovir disoproxil fumarate"). The journal regrets this error.

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