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A Case-control Study of HIV-associated Pancreatic Abnormalities during HAART Era. Focus on Emerging Risk Factors and Specific Management

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Abstract

Introduction: The epidemiological and clinical features of HIV-associated pancreatic abnormalities are expected to change after HAART introduction.

Patients and methods: The frequency, risk factors, and clinical and therapeutic features of pancreatic alterations were assessed in an observational case-control study.

Results: Nine hundred and 20 were evaluated for pancreatic abnormalities in a case-control study including the whole follow-up period of each considered patient; 128 subjects with high and prolonged laboratory anomalies were assessed, to outline the profile of pancreatic disease before and during the HAART era. Compared with controls, the 334 patients (36.3%) who experienced at least one episode of confirmed pancreatic laboratory abnormality had a longer duration of seropositivity, exposure to protease inhibitors, a more frequent immunodeficiency, AIDS diagnosis, liver or biliary disease, and hypertriglyceridemia, while no relation was found with antiretroviral administration, and the duration of nucleoside analogue use. Among these 334 patients, high and prolonged laboratory alterations eventually associated with signs of organ involvement occurred in 128 cases, and were related to the administration of didanosine, stavudine, lamivudine, pentamidine, cotrimoxazole, or anti-tubercular therapy, substance or alcohol abuse, opportunistic infections, liver or biliary disease, a protease inhibitor-based HAART, and hypertriglyceridemia. However, no difference was noticed between the 32 patients with clinical and/or imaging evidence of pancreatic involvement and the remaining 96 asymptomatic cases, as to the same risk factors. Although recurrences of enzyme alterations involved >70% of patients, in only 33.8% of cases a change of antiretroviral or antimicrobial therapy was necessary. An acute but uncomplicated pancreatitis occurred in 7 patients of 26 overall symptomatic subjects. A 2-4-week gabexate and/or octreotide administration (performed in 59 cases of 128), attained a significant laboratory, clinical, and imaging cure or improvement in 71.2% of cases, with a better success rate of combined versus single therapy; a reduced tendency to disease recurrences, and a better tolerability of antiretrovirals were also noticed.

Conclusions: Epidemiological and pathogenetic studies are needed to assess pancreatic abnormalities especially in the HAART era, and their consequences on continued antiretroviral and antimicrobial therapy. The antiretroviral management and the indication to gabexate and/or octreotide administration in the different clinical and laboratory situations, warrant controlled investigation.

Key words: HIV infection, serum amylase-lipase, case-control study, antiretroviral therapy

Introduction

Clinical and laboratory abnormalities of pancreas are persisting but still underestimated problems in the management of HIV disease. Moreover, the spectrum of potential risk factors for pancreotoxicity is expected to significantly change over time, especially after the introduction of combined antiretroviral therapy, which significantly modified the natural history of HIV disease, leading it into a predominantly chronic, treatable disorder characterized by a sharp drop of immunodeficiency-related complications, and a concurrent increase of drug-associated long-term toxicity. In the era which preceded the introduction of highly active antiretroviral therapy (HAART) opportunistic infections, AIDS-related cancer, the use of nucleoside analogues, pentamidine or other antimonials, cotrimoxazole, dapsone, antitubercular or other anti-infective drugs, antineoplastic chemotherapy and diuretics, were suspected to support acute or chronic pancreatic injury [1-15]. On the other hand, the introduction of HAART in mid-1996 led to a remarkable drop of AIDS-related conditions and reduced the need of antiinfective therapy and chemoprophylaxis, but in the meantime a broad spectrum of risk factors for pancreas metabolism remained or emerged, such as the continued use of nucleoside analogues as a part of HAART, the administration of antiretroviral agents belonging to novel classes (i.e. protease inhibitors and non-nucleoside reverse transcriptase inhibitors), frequent lipid, glucose, and other metabolic abnormalities, hepatic steatosis, lactic acidosis syndrome, and other long-term drug toxicity promoted by HAART, joined their pathogenetic role to the above-mentioned conditions during the last five year [13, 16, 17]. Moreover, as suspected since early HIV pandemic by histopathologic studies [5, 16], HIV itself might play a direct pancreotoxic

role, as confirmed by the recent finding of macrophages bearing the specific CCR-5 receptor in the cell infiltrate of chronic pancreatitis [18]. Finally, a number of factors not necessarily related to HIV infection but possibly concurrent, have to be taken into account: chronic liver of biliary disease, alcohol abuse, familiary dyslipidemia, hypercalcemia, and regional ischemia may have an increased frequency in HIV-infected patient population [5, 11, 13, 19]. To the best of our knowledge, no literatures evidences dealing with the epidemiology, risk factors, and management of HIV-associated pancreatic abnormalities have been published, since HAART became the standard of care for HIV disease. On our opinion, both clinical and subclinical (i.e. laboratory) pancreatic abnormalities deserve a careful epidemiological and clinical re-evaluation in the HAART era, in order to identify the present frequency of known and novel risk factors, weight their role and clinical significance (as to the development of acute pancreatitis, or contraindications to the use of a broad spectrum of potentially pancreotoxic drugs), and to provide effective treatment and prevention (if needed and proven effective).

Aim of our study was therefore to assess the frequency, possible supporting factors, severity and clinical features, efficacy of eventual treatment, and outcome of pancreatic abnormalities found through an observational case-control study carried out during the year 2000 in our cohort of 1017 HIV-infected patients followed for at least 12 months.

Patients and Methods

One thousand and 17 overall HIV-infected patients followed at our tertiary care reference centre during the year 2000 since 12 months or more, had an at least quarterly laboratory workout, including serum amylase, pancreatic isoamylase, and lipase levels measured by commercial test kits and an automated analyser (with an upper normal range value of 220, 120, and 270 mg/dL, respectively). Macroamylasemia was evaluted with a cellulose acetate electrophoresis, in subjects with isolated and persistingly raised total amylase levels. Of 1017 patients, 903 (88.8%) received combined antiretroviral drugs since 12 months or more. After excluding from assessment 97 patients who had compliance levels with prescribed controls and/or medications below 90% (as evaluated by monthly clinical controls, direct drug prescription and accountability, and spontaneous patients' declarations), the 920 evaluable subjects (813 receiving antiretrovirals: 88.4%), were assessed for eventual laboratory and clinical pancreatic abnormalities in a case-control observational study including the entire follow-up period of each considered patient, and aimed at identifying possible risk factors and clinical features of pancreatic anomalies in the setting of HIV disease. Duration of HIV disease and antiretroviral therapy were considered at the time of the first appearance of altered serum pancreatic enzymes. Furthermore, all patients with elevated laboratory pancreatic abnormalities (as defined by an at least three-fold increase of serum pancreatic isoamylase and/or lipase levels) [20], were further assessed from an epidemiological, clinical, instrumental, therapeutic, and outcome point of view, in order to outline the profile of pancreatic disease before and during the HAART era, after obtaining their informed consent.

The statistical evaluation was carried out by Student t test (for continuous variables), and Mantel-Haenszel chi-square test and Fisher exact test (for categorical variables), with significance levels set at $p<0.05$.

Results

In the whole patient cohort of 920 evaluable subjects, even 334 of them (36.3%) experienced at least one episode of alteration of at least two serum pancreatic enzymes (serum amylase, plus pancreatic isoamylase and/or lipase), throughout their entire follow-up period (mean 30.6 ± 15.8 months; range 12 to 182 consecutive months). The demographic, epidemiological, clinical, laboratory, and therapeutic features of these patients were compared with those of the remaining 586 subjects who never showed serum pancreatic enzyme alterations, in a 1 : 1.75 case-control study. When comparing the 334 patients experiencing at least one episode of confirmed serum pancreatic abnormality with the remaining 586 control subjects who did not, the only variables which showed a significant relationship with the development of occasional pancreatic disturbances were the overall duration of known HIV seropositivity ($p<0.0001$), a prior or concurrent diagnosis of full-blown AIDS ($p<0.0001$) (but not HIV-related tumors; data not shown), a more severe immunodeficiency, as expressed by a greater frequency of a CD4+ lymphocyte count <200 cells/μL ($p<0.004$), the duration of protease inhibitor-based HAART, a concurrent chronic biliary or liver disease (either viral or alcoholic in origin), and the occurrence of hypertriglyceridemia (serum triglyceride levels above 172 mg/dL) in at least one occasion ($p<0.0001$ for these last three variables), while no significant correlation was shown with all considered demographic and epidemiological parameters (age, gender, type of risk for HIV infection), the percentage of patients treated with antiretroviral drugs, and also the comprehensive duration of nucleoside analogue administration (Table 1). No case of macroamylasemia was detected in the 334 patients with elevated serum amylase levels.

One hundred and 28 patients out of 334 (13.9% of the whole cohort, and 38.3% of subjects with at least one episode of pancreatic laboratory abnormality), experienced an at least three-fold increase of serum pancreatic enzymes persisting for 6 months or more (a situation predictive for the development of acute pancreatitis) [20], in association with clinical and ultrasonographic and/or contrast-enhanced CT signs of pancreatic involvement identified in 32 patients only (3.5% of the whole cohort, and 25% of patients with elevated and persisting laboratory abnormalities). Compared with the remaining 206 patients with isolated and low-level pancreatic laboratory abnormalities, these 128 patients with high and prolonged laboratory alterations (either associated with signs and symptoms of organ involvement, or not), showed a significant correlation with concurrent use of didanosine, stavudine,

Table 1. Demographic, epidemiological, therapeutic, laboratory, and clinical features of the 334 patients with at least one confirmed serum pancreatic abnormality (i.e. elevated amylase plus either pancreatic isoamylase or lipase levels), compared with those of the 586 patients who never experienced these laboratory alterations, during the whole patients' follow-up at our centre.

Features	Patients with at least one episode of serum pancreatic enzyme abnormality (n = 334)	Patients who never experienced serum pancreatic enzyme abnormalities (n = 586)	*P* value
Age (years±SD)	36.1 ± 8.2	35.7 ± 8.4	n.s.
Gender (males / females)	222 / 112	398 / 188	n.s.
Type of exposure to HIV infection[a]	197 / 71 / 57 / 4 / 5	353 / 116 / 104 / 3 / 10	n.s.
Duration of known HIV disease (months ±SD and range)	33.1 ± 16.8 (12-182)	27.2 ± 14.3 (12-177)	<.0001
n. (%) of patients receiving antiretrovirals in the year 2000	301 (90.1%)	512 (87.4%)	n.s
n. (%) of patients with a diagnosis of full-blown AIDS	81 (24.3%)	77 (13.1%)	<.0001
n. (%) of patients with a CD4+ lymphocyte count <200 cells/μL	109 (32.6%)	139 (23.7%)	<.004
Comprehensive duration of antiretroviral therapy including nucleoside analogues[b] (months±SD and range)	26.2 ± 13.6 (12-168)	24.5 ± 15.2 (12-154)	n.s.
Comprehensive duration of protease-inhibitor-based HAART (months ±SD and range)	19.2 ± 12.9 (12-61)	15.3 ± 12.6 (12-53)	<.0001
n. (%) of patients with a concurrent chronic hepatitis or biliary disorders	112 (33.5%)	120 (20.5%)	<.0001
n. (%) of patients with at least one occurrence of hypertriglyceridemia (serum triglyceride levels >172 mg/mL)	139 (41.6%)	107 (18.3%)	<.0001

[a] i .v. drug use, heterosexual exposure, homo-bisexual exposure, administration of contaminated blood or blood derivatives, congenital infection.
[b] including zidovudine, didanosine, zalcitabine, lamivudine, stavudine, and abacavir.

lamivudine, pentamidine, cotrimoxazole, anti-tubercular therapy or their combination for at least 6 months ($p<0.05$ to $p<0.0001$), substance or alcohol abuse for 6 months or more ($p<0.03$), opportunistic infection with potential pancreatic involvement (cytomegalovirosis, mycobacteriosis and cryptosporidiasis) ($p<0.02$), chronic liver or biliary disease ($p<0.01$), a concurrent protease inhibitor-based HAART ($p<0.04$), hypertriglyceridemia of at least 6 months' duration ($p<0.01$), or a combination of two or more of these predisposing factors ($p<0.004$), while the overall duration of known seropositivity and antiretroviral therapy did not show relevant differences between the two study groups (data not shown). However, no difference was detected in the spectrum of risk factors between the 32 patients with clinical, ultrasonographic, and/or CT signs of pancreas involvement (pancreatic edema, heterogenic echogenicity, or organ enlargement), and the remaining 96 cases who had an apparently asymptomatic elevated and prolonged pancreatic enzyme alteration, as to the above-mentioned presumed risk factors (Table 2).

Of the 334 overall HIV-infected patients with pancreatic abnormalities, 234 (70.1%) experienced two to 18 different recurrences of enzyme alteration during their whole follow-up period, but only 113 subjects (33.8%) needed modification of underlying antiretroviral or antimicrobial therapy, including nucleoside analogues, pentamidine, cotrimoxazole, antitubercular drugs, or a protease inhibitor-based regimen (due to persistent or increasing hypertriglyceridemia), and all of them were able to continue an adequate antiretroviral therapy. Furthermore, 26 overall patients experienced mild-to-moderate gastrointestinal symptoms and abdominal pain, while a full-blown acute pancreatitis occurred in 7 patients only (as documented by clinical and instrumental assessment), but no episode required surgery, or had a complicated or lethal course. Notably, all patients who needed a switch of concurrent pharmacologic treatment or suffered from signs and symptoms of pancreatitis were part of the group of 128 patients with elevated and prolonged laboratory anomalies ($p<0.0001$ versus all other patients with isolated and low-level pancreatic alterations).

In 59 patients (46.1% of the group with high and prolonged laboratory anomalies with or without clinical and/or instrumental alterations), a specific treatment was attempted with i.v. gabexate mesilate at 100-400 mg/day in 36 cases, with subcutaneous octreotide (0.3-0.9 mg daily) in 11 patients, and with an association of these two drugs in the remaining 22 subjects, together with supportive treatment consisting of fluid and nutritional management, and eventual pain treatment. Forty-two overall patients (71.2% of the whole

Table 2. Among the 128 patients with an at least three-fold increase of serum pancreatic enzymes persisting for 6 months or more, the 32 cases with accompanying clinical and ultrasonographic and/or contrast-enhanced CT signs of pancreatic involvement are compared with the remaining 96 patients with an apparently asymptomatic elevated and prolonged specific hyperamilasemia and/or hyperlipasemia, according to some presumed risk factors. No significant differences were found between the two groups according to the examined variables.

Presumed risk factors	Patients with clinical and/or instrumental signs of pancreatic involvement (n = 32)	Patients with an apparently asymptomatic elevated and prolonged pancreatic laboratory alterations (n = 96)
n. (%) of patients who used didanosine, stavudine, lamivudine, pentamidine, cotrimoxazole, antitubercular therapy or their combination for 6 months or more	14 (43.7%)	41 (42.7%)
n. (%) of patients experiencing drug or alcohol abuse for 6 months or more	9 (28.1%)	29 (30.2%)
n. (%) of patients suffering from Cytomegalovirus, mycobacterial, or *Cryptosporidium* infection	12 (37.5%)	31 (32.3%)
n. (%) of patients with chronic liver and/or biliary tract disease	16 (50%)	50 (52.1%)
n. (%) of patients on protease inhibitor-containing HAART	19 (59.4%)	51 (53.1%)
n. (%) of patients with hypertriglyceridemia since 6 months or more	11 (34.4%)	35 (36.4%)

group), obtained a significant improvement of all serum pancreatic enzymes (as assessed by a drop of 50% or more of their serum levels), associated with complete resolution of signs and symptoms and an ameliorement or a disappearance of instrumental pathologic findings (when present), after 2.3 ± 0.7 weeks (range 2-4 weeks) of treatment. The combined administration of gabexate and octreotide seemed to obtain a significantly more elevated success rate (19 patients out of 22: 86.4%), compared with that of single treatment regimens ($p<0.05$). Although 12 patients out of the 59 treated with gabexate and/or octreotide (20.3%) experienced increased nausea (probably attributable to drug side effects), treatment was never suspended due to these possible adverse events. Compared with untreated patients, those who received gabexate and/or ocreotide had a subsequent better tolerability of antiretroviral therapy (either modified or not after pancreatic enzyme alteration) ($p<0.03$). Unfortunately, an elevated relapse rate was found also among treated cases, with 19 patients of 59 (32.2%) developing at least one novel episode of laboratory and clinical or instrumental pancreatic involvement in the subsequent 4-10 months, regardless of the efficacy of previous treatment with gabexate and/or octreotide. However, a clear tendency towards a lower recurrence rate was shown in the treated versus the untreated patient group (32.2% versus 43.5%) (even after control for concurrent risk factors), although the first one had a more severe initial laboratory and clinical picture, possibly predisposing to subsequent disease flare-up.

Discussion

Despite the radical change of the natural history of HIV disease and AIDS occurred in the last 5 years thanks to HAART, HIV-infected patients continue to have multiple potential risk factors for subclinical or clinical pancreatic involvement, including the administration of directly or indirectly pancreotoxic drugs (i.e. nucleoside analogues, pentamidine, cotrimoxazole, protease inhibitors, non-nucleoside reverse transcriptase inhibitors, antitubercular compounds, and many others) [6-8, 10, 13, 15], alcohol or substance abuse, antiretroviral therapy-related hyperlipidemia, concomitant chronic liver or biliary disorders (including sclerosing cholangitis or regional malignancies) [14, 19], opportunistic diseases, and HIV infection itself, although the both frequency and role of each supporting factor has been poorly investigated [1-5, 9, 11-13, 15], especially after HAART introduction. When considering direct drug-related toxicity, didanosine, zalcitabine, stavudine, hydroxyurea, i.v. or aerosolized pentamidine, sulphonamides and their associations, cytotoxic drugs, isoniazid and other antitubercular drugs, furosemide and thiazides, all of them were related with pancreatic laboratory and/or clinical abnormalities during HIV disease, although acute pancreatitis was reported predominantly after pentamidine or didanosine administration [4-10, 21]. However, both frequency and severity of related signs and symptoms (abdominal pain with predominant back irradiation, diarrhea, nausea, and vomiting), prove very low [5, 13], and diagnostic imaging may be hampered by co-existing pathologies and meteorism for ultrasonography [22]. Therefore, although the overall frequency of pancreatic abnormalities was estimated 35-800 times greater than in the general population [12, 13], full-blown acute pancreatitis remained a somewhat rare finding in HIV-infected patients through years [5, 9, 13], and severe or fulminant disease has been reported in few cases, especially drug-induced episodes [8, 10, 13]. As

a consequence, most of HIV-associated pancreatic lesions were missed during lifetime, and discovered only after death [5, 16]. An extensive necropsy survey published in pre-HAART era (year 1994) and reporting all literature studies based on autopsy findings carried out since 1987, pointed out a pancreatic involvement in 254 cases of 749 necropsy studies (33.9%) [5]: the majority of diagnoses included opportunistic infections (121 cases) (predominantly due to Cytomegalovirus, *Mycobacterium avium-intracellulare*, *Cryptococcus neoformans*, *Mycobacterium tuberculosis*, and *Toxoplasma gondii*), followed by cytstosteatonecrosis (25 subjects), and AIDS-related tumors (22 cases). A recently published necropsy study reporting data on patients deceased in the year 1995 (again before HAART introduction), disclosed a very high (90%) frequency of pancreatic involvement (usually asymptomatic during life), and a broad spectrum of morphological abnormalities, including some possibly related to HIV itself [16]. A small number of studies focused on symptomatic, acute pancreatitis in HIV-infected patients, all lacking consideration of antiretroviral drugs other than nucleoside analogues [9, 12, 13, 15, 21]. In fact, clinical pancreatic disorders found during the pre-HAART era, generally resulted from an extended exposure to multiple medications and concurrent HIV-related disorders, which might act as reciprocal confounding factors. Among 321 patients followed during the years 1993-1994, even 45 individuals (14%) had a symptomatic acute pancreatitis documented by laboratory and instrumental examination; a significant correlation was found with a lower CD4+ lymphocyte count, presence of gallstones, active i.v. drug addiction, pentamidine administration, and some AIDS-related opportunistic infections [12]. In a recently published study, Moore et al. [15] investigated the role of nucleoside analogues and that of combined hydroxyurea, and found a significantly increased risk of pancreas abnormalities with the association didanosine-hydroxyurea (6.25 cases per 100 person-years: a 4-fold rise compared with didanosine alone), while the association didanosine-stavudine did not add risk. Surprisingly, drugs other than nucleoside analogues and hydroxyurea were not considered and the female gender appeared more interested, while the role of a concomitant reduced CD4+ count was confirmed [15]. On the whole, in the pre-HAART period HIV-associated immunodeficiency proved an independent predictor of pancreatitis and its prognosis, despite clinical manifestations were usually comparable with those found in the general population [9, 12, 13, 15, 21]. In the different examined (and not always comparable) case series, the global frequency of full-blown pancreatisis was usually lower than that reported by Dutta et al. [12], i.e. from 1.3% 15 to 5% [9], with a maximum incidence (14.2%) disclosed by Dowell et al. [21]. In this last study, a clear relationship with CDC disease staging, biliary tract disease, elevated serum triglyceride levels, cryptosporidiosis, and pentamidine or isoniazid therapy, were pointed out [21]. On the other hand, the incidence of isolated laboratory pancreatic abnormalities showed a notably extended range of frequency, always during the years preceding the introduction of HAART (7.8% up to 63% of examined cases), although also these studies are not comparable as to patient selection, duration of follow-up, and laboratory workout [1, 2, 4, 11, 23, 24]. One study linked hyperamylasemia with the male gender, drug abuse, AIDS, and a low CD4+ count, but not with prior liver-biliary disease, and nucleoside analogue use [11]. A relationship between the frequency of serum pancreatic enzyme alterations and an advanced HIV disease staging was confirmed by Dutta et al. [12]. Also in pediatric patients, a completely asymptomatic rise of serum pancreatic enzymes was noticed in 10 of 47 examined children (but pancreatic isoamylase and lipase were abnormal in only 6 and 7 cases, respectively); no correlation with disease staging, administered drugs, underlying diseases, and other presumed risk factors, were found in this population [25]. In a more recent study, asymptomatic mild-to-moderate rise of serum amylase-lipase levels were found in even 60% of 86 examined patients, but this frequency dropped to 14% only when an at least two-fold enzyme elevation was considered; an association with chronic HBV or HCV hepatitis, antiretroviral therapy, and i.v. cotrimoxazole use were underlined [24]. Since the simple measurement of amylasemia is much less specific than serum pancreatic isoamylase and lipase assessment [23, 26] and macroamylasemia has been also reported in HIV-infected subjects [23, 26, 27] (but not in our cohort), the combination of hyperamilasemia with either elevated pancreatic amylasemia or lipasemia was selected for evaluating laboratory abnormalities in our series, allowing a better estimate of this phenomenon. Already in the pre-HAART era, both endocrine abnormalities (leading to a poor glucose tolerance and possibly diabetes mellitus), and exocrine dysfunctions (potentially responsible for nutrient and especially fat malabsorption), were noticed in both adults and children [3, 5, 28, 29]. In particular, a 1992 Italian survey showed elevated levels of trypsin and elastase-1 in 56.3% and 25% of examined patients respectively, in absence of signs and symptoms of pancreatisis, while again an inverse relationship was found with the severity of HIV-associated immunodeficiency [3]. All these disturbances are now much more difficult to monitorize and attribute to an eventual pancreatic involvement, since the introduction of HAART generated a broad spectrum of metabolic abnormalities involving glucose, insulin, triglyceride and cholesterol metabolism, and multiple other metabolic and endocrinologic pathways: they include the lipodystrophy and fat redistribution syndrome [17, 30], and multiple other disorders such as drug-induced diabetes, hepatic steatosis, lactic acidosis, mitochondrial damage, and osteopenia. For instance, a reduced pancreatic lipolytic activity was shown in patients with HAART-associated hypertriglyceridemia [31].

Our experience confirms an apparently high rate of at least occasional pancreatic isoamylase and/or lipase alteration, interesting 36.3% of 920 patients evaluated for a period extending up to 182 months, and including both pre-HAART and HAART era. According to the study design, isolated serum amylase abnormalities have been therefore excluded from our series. When comparing these patients with all other HIV-infected subjects acting as controls, no association was demonstrated with gender, type of HIV exposure, HIV-relat-

ed malignancies, antiretroviral treatment as a whole, and duration of nucleoside analogue administration, but the duration of known HIV infection, a diagnosis of AIDS, a severe immunodeficiency, a concomitant hepatic or biliary disease, the length of protease inhibitor administration in HAART regimens and the usually protease-inhibitor related occurrence of hypertriglyceridemia 17 showed a significant relationship with occasional pancreatic enzyme abnormalities. When evaluating patients at high risk of developing an acute pancreatitis [20], 128 patients (13.9%) were found with an increase of serum pancreatic enzymes of >3-fold persisting for at least 6 months, although the majority (76.6%) of these patients were virtually asymptomatic, and clinical plus instrumental signs were identified in 32 cases only. The administration of didanosine, stavudine, lamivudine, pentamidine, cotrimoxazole, anti-tubercular drugs or their combination for at least 6 months, chronic substance or alcohol abuse, opportunistic infections with a potential pancreatic target, persisting liver or biliary disease, a protease inhibitor-based HAART, prolonged hypertriglyceridemia, or multiple concomitant risk factors, proved significantly more frequent in these 128 patients with high and prolonged laboratory alterations (either symptomatic or not), versus the remaining 206 patients with occcasional and low-level pancreatic laboratory alterations. Compared with literature studies dealing with elevated pancreatic enzymes in absence of signs and symptoms [1-4, 11, 23, 24], no link with the male gender and drug addiction [11] was found by us, while AIDS and HIV-related immunodeficiency confirmed their supporting role [3, 11, 12]. Also nucleoside analogue, other drug use, and underlying liver or biliary disease were often [24] (but not always) [11, 25] found as supporting factors by literature surveys. Like the study of Carroccio et al. [25], among our 15 pediatric patients, only 5 cases of occasional and asymptomatic rise of serum isoamylase and lipase were observed.

However, in our series both duration of seropositivity and antiretroviral therapy did not seem to play a role in supporting elevated and prolonged pancreatic disorders. Surprisingly, the same presumptive rik factors did not show a significantly different distribution between the 32 patients with clinical and instrumental signs of pancreas involvement, and the 96 subjects who experienced asymptomatic elevated and prolonged enzyme alteration. Although recurrences of pancreatic enzyme abnormalities interested over 70% of patients throughout a prolonged follow-up, a change of a possibly pancreotoxic anti-HIV or antimicrobial therapy was deemed necessary in around one third of cases with elevated and prolonged laboratory alterations, and even persisting or recurring laboratory pancreatic abnormalities did not hamper the conduction of an effective anti-HIV therapy (either modified or not). A clearly symptomatic disease and a true acute pancreatitis remained rare events (involving 26 and 7 patients, respectively), and did not alter HIV disease course, as to sequelae or lethal outcome. This low number of cases did not allow comparison with prior studies focusing on acute pancreatitis [9, 12, 13, 15, 21], although the reduced incidence of immunodeficiency and AIDS-related opportunism might have played a role in the HAART period considered by our study, while the continued administration of nucleoside analogues (excluding hydroxyurea in our series) [15], substance or alcohol abuse, liver or biliary tract disease, and the emerging role of dyslipidemia (already registered by Dowell et al.) [21], are expected to become major risk factors in the next few years. Since patients with HIV infection continue to have asymptomatic (more than symptomatic) serum pancreatic enzyme elevation, which can persist or recur for a long time [5, 13, 23, 24], often regardless of antiretroviral therapy evolution (from the nucleoside analogue period up to the HAART era), both clinical significance and practical consequences of these alterations throughout the HIV pandemic and the implications on patients' health, and antiretroviral and other concurrent treatment, remain largely unknown. Clinical problems essentially concern the real risk of development of a symptomatic or an acute, severe disease in patients with prolonged and/or elevated laboratory abnormalities and one or more concurrent risk factors, as well as the selection of patients candidates to benefit from a specific pharmacologic treatment (such as that with gabexate and/or somatostatin analogues). A final point of debate is the strategy for the management of long-term, asymptomatic, paucisymptomatic, or even slightly symptomatic pancreatic disease: while specific recommendations or expert guidelines are lacking for HIV-infected patients, an attempt to substitute the most pancreotoxic drugs (if any) should be done, and careful laboratory and instrumental monitoring implemented, but no definite strategies are to date outlined regarding simple long-term observation and monitoring, supportive treatment, change of underlying treatment, or criteria for the administration of specific therapy. Although both antisecretory compounds (such as somatostatin and its derivatives, such as octreotide), and antiprotease drugs (such as gabexate mesilate, administered at 900 mg/day in severe acute pancreatitis) [32], proved effective in reducing mortality and complications of acute pancreatitis respectively, their administration is now standard of care for patients suffering from an acute, severe disease [32, 33], but only very limited and anecdotal informations are available regarding their possible efficacy and safety in other conditions [34], including both acute disease and especially prolonged, elevated rise of serum pancreatic enzymes in HIV-infected patients. In particular, while octreotide proved useful in non-HIV-related pancreatitis [33] and in some other HIV-associated conditions (like refractory diarrhea) [35], the same drug seemed even implicated in causing acute pancreatitis during AIDS [36]. In our own therapeutic experience, when elevated and prolonged or symptomatic pancreatic disease was of concern, low-dose gabexate and/or octreotide treatment was attempted, despite lack of literature data regarding efficacy and safety in HIV-infected patients concurrently treated with antiretrovirals: 71..2% of the 59 treated patients obtained a satisfactory and sustained laboratory, clinical, and instrumental response within 2-4 weeks without relevant adverse events, with the gabexate-octreotide combination showing better activity than single agent adminis-

tration. Moreover, despite a more severe baseline laboratory and clinical situation, a tendency towards a lower recurrence rate was seen among treated patients versus untreated ones, as well as an improved tolerability to continued or changed antiretroviral regimen.

In conclusion, extensive epidemiological and pathogenetic studies are strongly needed to assess the frequency and clinical significance of laboratory or clinical pancreatic abnormalities especially in the HAART era, which may add risk factors for this complication. The risk of these alterations to evolve into a severe and potentially life-threatening disease, and their consequences on continued antiretroviral and antimicrobial therapy administration, have to be carefully considered. The indication to gabexate and/or somatostatin analogue administration in the different clinical and laboratory situations, and the recommendations for the concurrent use of a number of potentially pancreotoxic compounds in asymptomatic or paucisymptomatic HIV-infected patients with elevated or persistent pancreatic enzyme anomalies, are challenging problems which warrant further investigation via extensive, controlled studies.

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