

**THE PREVALENCE OF ACUTE PANCREATITIS IN HIV POSITIVE
MEDICAL IN-PATIENTS PRESENTING AT KENYATTA NATIONAL
HOSPITAL (KNH) WITH ACUTE UPPER ABDOMINAL PAIN.**

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**A Dissertation Submitted in Part Fulfilment of the Requirement
for the Degree of Masters of Medicine in Internal Medicine,
UNIVERSITY OF NAIROBI.**



DECLARATION

This thesis report is my original work and has not been presented for any award in any university

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To my loving husband Dr. Eren Oyungu for his constant support, and to my children Anthony and Gloria for teaching me the meaning of love and perseverance.

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ABBREVIATIONS

- ACE inhibitors:** Angiotensin converting enzyme inhibitors.
- ARDS:** Adult Respiratory Distress Syndrome.
- AIDS:** Acquired Immunodeficiency Syndrome.
- AP:** Acute pancreatitis.
- CMV:** Cytomegalovirus.
- CT scan:** Computed Tomography Scan.
- CRP:** C reactive protein.
- CD4:** Cluster of differentiation 4.
- CVS:** Cardiovascular system.
- CNS:** Central Nervous system.
- ERCP:** Endoscopic Retrograde Cholangiopancreatography.
- ECG:** Electrocardiogram.
- GIT:** Gastrointestinal system.
- HIV:** Human Immunodeficiency Virus.
- KNH:** Kenyatta National Hospital.
- LUQ:** Left upper quadrant.
- MRI:** Magnetic Resonance Imaging.
- NSAIDS:** Non steroidal anti-inflammatory drugs.
- NASCOP:** National AIDS and STD Control Programme.
- R/S:** Respiratory system.
- RIF:** Right iliac fossa.
- RUQ:** Right upper quadrant.
- SLE:** Systemic Lupus Erythematosus.
- SPSS:** Statistical Packages for Social Sciences.
- TTP:** Thrombotic Thrombocytopenic Purpura.
- U.O.N:** University of Nairobi.
- U/S:** Ultrasound.

ABSTRACT.

Background: AP is an inflammatory disease of the pancreas with variable involvement of remote organ systems. There are various theories put forward to explain the pathogenesis of acute pancreatitis, which remains unclear.

Acute onset of upper abdominal pain makes one suspect acute pancreatitis.

With the HIV pandemic, acute pancreatitis has been noted to be on the increase, due mainly to opportunistic infections, malnutrition and drug therapy used in HIV. Acute pancreatitis is potentially treatable if recognized early, but if diagnosis is delayed, it can be life threatening and it has a negative impact on HIV prognosis. Local published data on HIV associated acute pancreatitis are lacking and so this study has shed light on this important subject.

Objectives: To determine the prevalence of acute pancreatitis in HIV positive patients presenting with features of acute abdominal pain at Kenyatta National Hospital and correlate the presence of acute pancreatitis with extent of HIV disease and the presence of other evident acute pancreatitis risk factors.

Design: Cross sectional survey.

Setting: Medical and surgical wards of Kenyatta National Hospital, a tertiary referral hospital in Nairobi, Kenya.

Methods: Pretest counselling for HIV testing was undertaken in all consecutive patients with complaints of upper abdominal pain and in those who consented, the test was done. Those that tested positive for HIV by the Rapid HIV 1 and 2 assays were recruited into the study. They underwent a clinical examination and venous blood was drawn for serum amylase, lipase and CD4 lymphocyte count analysis.

A case of acute pancreatitis was defined as a patient with acute upper abdominal pain of less than seven days duration with serum amylase and /or lipase levels higher than the upper reference limit of the assay method used.

Results: The prevalence of HIV positivity in patients admitted with acute abdominal pain was 45.1%, and the prevalence of AP in those testing positive for HIV was 29.9%, based on serum amylase levels >125 u/l and/or serum lipase levels above 78 u/l. There was no significant difference in the clinical presentation in those with or without AP. However, patients reporting relief of pain with milk and food were unlikely to have AP (p value 0.02). There was no correlation between presence of acute pancreatitis and extent of HIV disease as depicted by CD4 counts. The presence of opportunistic infections, for example candidiasis and herpes zoster, as evident risk factors for AP did not differ between those with and without AP.

Conclusions: There was no statistically significant difference in the age, sex, mode of presentation, presence of opportunistic infections and CD4 counts in those with and without AP.

Recommendations: AP should be looked for in HIV positive patients with acute abdominal pain.

Further research is required to identify causes of AP in HIV positive patients in our setup and to determine the patient's clinical outcomes.

LITERATURE REVIEW

Acute pancreatitis is defined as an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems (1, 2, 3, 4). It is further classified into mild and severe forms. Mild acute pancreatitis is associated with minimal organ dysfunction and uneventful recovery while severe acute pancreatitis is associated with pancreatic necrosis and may lead to organ failure and/or local complications (1, 2, 3, 4).

Abnormal pancreatic exocrine and endocrine function can occur during an acute attack (5). In patients with interstitial or oedematous pancreatitis, the gland returns to histologic and functional normalcy after recovery if the patient survives. Endocrine function returns to normal soon after the acute phase, while exocrine function may take up to one year for full recovery (5, 6).

In patients with necrotising pancreatitis, permanent exocrine and endocrine insufficiency may develop immediately or on follow-up, depending upon extent of necrosis

AETIOLOGICAL FACTORS

The two most common causes of acute pancreatitis are alcohol abuse and biliary tract obstruction related to cholelithiasis. These two conditions account for 60 to 80 percent of all cases of acute pancreatitis (7).

Acute pancreatitis may also be caused by metabolic disorders, drugs, connective tissue diseases, infections, trauma or surgery (1, 2, 3, 4).

Metabolic causes include hypertriglyceridemia and hypercalcemia. For drugs, there are those for which association with acute pancreatitis is definite e.g. azathioprine, sulfonamides, thiazide diuretics, dideoxyinosine and tetracycline, while for other drugs the association is probable e.g. acetaminophen, nitrofurantoin, methyldopa,

metronidazole, non steroidal anti-inflammatory drugs and angiotensin converting enzyme inhibitors.

Approximately 2-5% of cases of acute pancreatitis are drug related. Drugs cause pancreatitis either by a hypersensitivity reaction or by generation of a toxic metabolite, although in some cases it is not clear which of these mechanisms is operative (4).

Connective tissue diseases associated with acute pancreatitis are those with vasculitis as part of their clinical syndrome e.g. systemic lupus erythematosus, necrotising angitis and thrombotic thrombocytopenic purpura.

Infections causing acute pancreatitis include viruses e.g. coxsackievirus, echovirus, cytomegalovirus, HIV and viral hepatitis; parasites e.g. ascariasis and bacteria e.g. mycoplasma, campylobacter and mycobacterium avium complex.

Congenital anomalies have also been associated with acute pancreatitis e.g. pancreas divisum, choledochocoele, as have other hereditary disorders like cystic fibrosis.

10-25% of cases are idiopathic.

PATHOGENESIS (1, 4)

The pathogenesis of acute pancreatitis is unclear but there are theories that try to explain the disease namely the autodigestion theory, the common channel theory and the lysosomal hydrolase theory.

In the autodigestion theory, the disease is thought to be initiated by toxic metabolites, which stimulate proteolytic enzymes within the pancreas, by damaging vesicles and granules in the pancreas. Trypsinogen is activated to trypsin, which then activates other proenzymes. The initial damage to the vesicles and granules may be due to oxygen radicals, endotoxins, exotoxins, ischemia, anoxia and direct trauma to the pancreas. After their activation, the enzymes attack the pancreas causing cell membrane

destruction. There is resultant oedema, interstitial haemorrhage, and vascular damage. Tissue necrosis factor released from this process inhibits activity of major organs of the body like the heart, brain and lungs, causing ARDS in the latter (1, 4).

In the common channel theory, there is supposedly a common channel with free communication between the common bile duct and the main pancreatic duct, allowing bile reflux from the common bile duct into pancreatic tissue, which starts the process of acute pancreatitis. This theory supposes obstruction of pancreatic duct, retention of enzymes, their activation and subsequent damage; a common channel though is infrequently encountered and obstruction of the main pancreatic duct usually produces pancreatic oedema rather than pancreatitis.

The autodigestion theory has largely eclipsed the common channel and obstruction of pancreatic duct theories (1,2,4).

A recent hypothesis to explain the intrapancreatic activation of zymogens is that these zymogens become activated by lysosomal hydrolases like cathepsin B in the pancreatic acinar cell itself. It is not clear however, whether the human acinar cell can provide the pH (about 3.0) necessary for activation of trypsinogen by lysosomal hydrolases. It is now believed that ischemia/hypoperfusion can alone result in activation of trypsinogen and pancreatic injury (1, 4).

INCIDENCE

Between 1960 and 1980, the incidence of acute pancreatitis increased 10-fold globally. (8) The incidence of acute pancreatitis in the West varies from 4.8 to 24.2 cases per 100,000 people in the population [9]. Accurate assessment of disease incidence is however difficult since mild disease may be missed and similarly, death may occur before the diagnosis is made in severe and fulminant attacks. In some reports, for

example, the diagnosis of acute pancreatitis was not made until autopsy in 10 percent of patients [10,11].

The male to female ratio in incidence is 1:1. However in females, the commonest cause of acute pancreatitis is biliary stones, while in males, it is alcohol abuse (1, 3).

No published incidence data is available from Africa.

DIAGNOSIS

A diagnosis of acute pancreatitis is made following assessment of the clinical presentation, laboratory workup and /or radiological investigations.

CLINICAL PRESENTATION

Patients with acute pancreatitis present with mild to severe epigastric pain, with radiation to the flank, the back, or both. Classically, the pain is characterised as constant, dull and boring, and is worse when the patient is supine. The discomfort may lessen when the patient assumes a sitting or fetal position. A heavy meal or drinking binge often triggers the pain. Nausea and nonfeculent vomiting are present in 75 to 90 percent of patients. (12)

However, painless pancreatitis although uncommon is a definite and well recognised entity, particularly in the setting of peritoneal dialysis, postoperative situations, especially renal transplant, Legionnaires disease and in some cases may present as subcutaneous fat necrosis (panniculitis) (11).

Physical Examination

The spectrum of severity of acute pancreatitis is reflected on physical examination. Between 50 and 90 percent of patients have signs of abdominal

distension or muscle spasms with epigastric pain and left upper-quadrant tenderness (12,13). There are patients though with abdominal findings out of proportion with the severity of pain (less tenderness in comparison to degree of pain reported by the patient). Other signs are fever, tachycardia and jaundice. Often the patient is restless and dehydrated on presentation (11,14). The clinical presentation of AP in the HIV infected patients is similar to that in immunocompetent patients (60).

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Laboratory Diagnosis

Amylase: Serum amylase levels in patients with pancreatitis vary depending on the severity of the disease. On average, during uncomplicated cases, the serum amylase level starts increasing from two to 12 hours after the onset of symptoms and peaks at 12 to 72 hours. It usually returns to normal within one week (15,16). Although serum amylase is the most widely used method of diagnosing pancreatitis it is not sufficiently sensitive or specific (75 to 92 % and 20 to 60 % respectively). The advantages of amylase testing are that it is an inexpensive, easily available and robust assay (17). However, a variety of nonpancreatic conditions cause increased amylase levels, some of which form the differential diagnosis of acute pancreatitis (18). These include renal insufficiency, salivary gland lesions e.g. mumps, calculus and irradiation sialadenitis; "Tumour" hyperamylasaemia e.g. in carcinoma of the lung and oesophagus, breast and ovarian carcinoma; in biliary tract disease e.g. cholecystitis; in diabetic ketoacidosis; in intraabdominal disease e.g. perforated or penetrating peptic ulcer, intestinal obstruction or infarction, peritonitis, ruptured ectopic pregnancy and chronic liver disease.

Plasma amylase is derived from the pancreas and salivary glands. It is rarely necessary to identify the isoenzyme components in plasma, but they can be distinguished by electrophoresis, or by using an inhibitor derived from wheat germ. Possible indications for isoenzyme determination include; a) the coexistence of mumps or renal failure which complicates the interpretation of high activities due to acute pancreatitis and; b) the possibility of chronic pancreatic disease, in which low activities may be found. Some laboratories now measure the plasma 'pancreatic' amylase activity using a method that incorporates wheat germ rather than starch. The different substrates affect the results and it is important to interpret the result against the reference range from the same laboratory (19).

Lipase: Lipase levels increase within four to eight hours of the onset of clinical symptoms and peak at about 24 hours. Levels decrease within eight to 14 days. The specificity (50 to 99 percent) and sensitivity (86 to 100 percent) of lipase measurements are better than those of amylase measurement, particularly in detecting alcoholic pancreatitis (17). The specificity of lipase measurement, as well as amylase measurement, may be improved by raising the threshold to at least three times the upper limit of the normal reference values (18).

Lipase elevations usually parallel those of amylase, but increases in lipase activity may occur sooner or later than increases in amylase activity, and lipase may rise to a greater extent. In acute pancreatitis, normoamylasaemia may occur in up to 20% of patients (20) and for this reason it is suggested that the two assays complement and not exclude each other and that both enzymes be assayed (20).

Trypsin/Elastase: Based on median sensitivities and specificities, an elevated trypsin level has a better likelihood ratio for detecting pancreatitis than the amylase level and is probably the most accurate serum indicator for acute pancreatitis (21). The acinar cells of the human pancreas synthesise two different trypsins (I and II), in the form of the inactive proenzymes (or zymogens), trypsinogens I and II, which are stored in zymogen granules and are secreted into the duodenum under the stimulus of either the vagus nerve or the intestinal hormone cholecystokinin. Trypsinogen I is present at about twice the concentration of trypsinogen II (20).

In healthy individuals, free trypsinogen is the major form found in serum. After an attack of acute pancreatitis, serum immunoreactive trypsin rises in parallel with serum amylase activity to peak values ranging from two to four hundred times the upper reference limit. The distribution of the different forms of trypsin appears to be related to the type and severity of acute pancreatitis. Thus in the mildest form of acute pancreatitis, 80 to 99 % of the immunoreactive trypsin exists as free trypsinogen I, with smaller proportions existing as bound trypsin I. In the more severe forms, in which mortality ranges from 20% to more than 50%, the proportion of free trypsinogen I may be as low as 30% of the total, with appreciable proportions existing as the α 1 antitrypsin and α 2 macroglobulin bound trypsin (20). However, a serum trypsin assay is not widely available and therefore is not routinely used.

The elastase level has not proved to be better than trypsin or lipase levels in assisting the diagnosis of acute pancreatitis.

Radiologic Studies

Ultrasonography: Ultrasonography is an acceptable study for initial evaluation when biliary causes are suspected. Pancreatic ultrasonography has various advantages: it is noninvasive, relatively inexpensive and may be performed at the bedside. The sensitivity of this test in detecting pancreatitis is 62 to 95 percent (22, 23). However, in 35 percent of cases, the pancreas is obscured secondary to bowel gas (17).

Computed Tomography (CT): The contrast-enhanced CT scan provides the best imaging of the pancreas and surrounding structures. A CT study may be useful when other diagnostic studies are inconclusive, when the patient has severe symptoms, when fever is present or in the face of persistent leukocytosis that suggests secondary infection (24). In addition, CT scanning is especially helpful in assessing complications related to acute pancreatitis or as a follow-up study in patients who are clinically deteriorating. The CT findings in pancreatitis may show inflammation characterized by diffuse or segmental enlargement of the pancreas, with irregular contour and obliteration of peripancreatic fat, necrosis or a pseudocyst (17). CT scan may be normal in up to a third of patients with acute pancreatitis (25,28).

Endoscopic Retrograde Cholangiopancreatography (ERCP)

ERCP has a limited role in management of acute pancreatitis. It is primarily indicated in patients with severe disease who are suspected of having biliary obstruction (26). This procedure is sometimes done to enable endoscopic sphincterotomy and remove impacted stones. The risks of performing ERCP with

sphincterotomy include precipitating an acute episode of pancreatitis, introducing infection and causing haemorrhage and perforation. At least one study has shown that patients with severe biliary pancreatitis show a reduction in morbidity and mortality with early (less than 24 hours) ERCP (27).

MRI: In many centers MRI is used mainly to clarify problems not fully evaluated with CT scan and U/S, particularly if there is a conflict between their findings (57).

OTHER SUPPORTIVE TESTS:

These are tests done in the workup of a patient suspected to have acute pancreatitis but not for diagnosis. They include; full blood count whereby a rise in WBC count may indicate infection; blood sugars- hyperglycaemia secondary to decreased insulin release and also due to catecholamine and cortisol release is common; blood calcium levels are done since 25% of cases have hypercalcaemia; Serum triglycerides are found to be increased in 10-25% of cases; liver enzymes and blood bilirubin are increased while serum albumin is decreased in cases of acute pancreatitis; arterial blood gas analysis may show hypoxia in severe forms of acute pancreatitis while ECG changes similar to those of myocardial ischaemia e.g. ST segment elevation and T wave inversion may be seen (1,4).

C reactive protein (CRP)

This is an acute phase reactant, synthesised in the liver, whose level in plasma can rise dramatically after myocardial infarction, stress, trauma, infection, inflammation. The increase occurs within 24 to 48 hours, and the level may be 2000 times above normal. Because the increase is nonspecific, however, it

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cannot be interpreted without a complete clinical history, and even then only by comparison with previous values. Because CRP is normally present in plasma at a mean concentration of less than 800 μ g/dl, sensitive immunochemical methods are required for its detection (20, 28).

Plain Radiographs: Plain radiographs may support the diagnosis of acute pancreatitis when certain findings are present (13). Of these findings, a gas-filled duodenum (sentinel loop) secondary to obstruction is the most specific for pancreatitis (13). However, none of the radiologic abnormalities on plain films can be used for specific diagnostic purposes.

MISDIAGNOSIS

The clinical diagnosis of pancreatitis is difficult to make and is frequently missed. Misdiagnosis rate as high as 43 percent have been reported and in some cases, the diagnosis is made at autopsy (10, 11).

The reasons for misdiagnosis and underdiagnosis include; a) lack of clinical suspicion due to atypical presentation without overt clinical manifestation e.g. absence of abdominal pain which occurs in 10-15% of cases; b) serum amylase has limited sensitivity and specificity when used as a diagnostic test routinely in clinical practice; c) serum amylase is useful only for a short while during the period of the illness (acute pancreatitis) and d) there are no pathognomonic symptoms and signs of acute pancreatitis (10,12).

MORBIDITY AND MORTALITY

Most complications of acute pancreatitis and subsequent deaths occur within two weeks of onset of pain. Secondary pancreatic infection is the most common cause of death in acute pancreatitis, accounting for 70 to 80 percent of deaths (8, 29). Complications frequently manifest as necrosis and organ failure, which often includes the cardiovascular, pulmonary and renal systems (29). Cardiovascular complications may reflect bleeding into the retroperitoneal space and decreased vascular resistance. Pulmonary insufficiency may range from mild atelectasis to life-threatening adult respiratory distress syndrome. Acute renal failure defined as a twofold creatinine rise may ensue secondary to cardiovascular collapse and hypotension, resulting in acute tubular necrosis (21). Complications are more common in patients with severer, necrotic disease and with other underlying pathology, for instance obesity, pre-existing hypertriglyceridaemia, and immunosuppression. In one study by Cappel and Marks (60), HIV infected patients were more likely to have a severe hospital course, partly due to other major illnesses present but also due to increased complications from AP, with a higher mortality compared to HIV negative patients (20% versus 11% respectively).

CT scanning may detect late complications of pancreatitis. Complications that usually occur after three weeks include pseudocysts and abscess formation. Pseudocysts occur in about 1 to 8 percent of cases. Abscesses occur in 1 to 4 percent of patients (8).

ACUTE PANCREATITIS AND HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

The incidence of acute pancreatitis is increased in patients with HIV for three main reasons; i) the high incidence of infections involving the pancreas, such as infections with *Mycobacterium avium* complex, cryptosporidium, cytomegalovirus; ii) the frequent use by patients with HIV/AIDS of medication such as didanosine, pentamidine, and trimethoprim-sulfamethoxazole which predispose to acute pancreatitis; iii) chronic malnutrition from poor oral intake due to gastrointestinal disease, nausea and vomiting, and even side effects from medications taken. Malnutrition is known to cause pancreatitis (55). Common aetiologies of acute pancreatitis, for example alcohol overindulgence and biliary calculi do still afflict HIV infected individuals aside from these predispositions.

Acute pancreatitis has been reported to occur in between 5-22% of HIV infected individuals (33, 46, 48, 50, 52,). In a retrospective study by Muller (58), 17% of 53 HIV positive children followed up over a six year period developed acute pancreatitis, giving an annual incidence of 3%.

Carroccio et al did a case control study of 47 HIV infected children in order to find out the incidence of acute pancreatitis in these patients. They found that 15% of HIV-infected children had biochemical evidence of pancreatic involvement (raised serum amylase and lipase levels); however, this condition was unrelated to clinical signs of pancreatitis. Neither drug administration nor opportunistic infections seemed to determine the increased serum pancreatic enzyme levels (52).

A retrospective study in Spain by Munoz et al (41) looked at the aetiology and evolution of 40 episodes of acute pancreatitis in 28 patients infected with the human immunodeficiency virus (HIV). AIDS criteria were met by 89.3% of these patients. Acute pancreatitis secondary to AIDS associated cholangitis occurred in 35.7% of episodes. Opportunistic infections accounted for 32.5% of episodes, drug use for 22.5% and biliary lithiasis for 5% of episodes of acute pancreatitis. Sixty percent of episodes were severe in nature and the mortality rate reached 30%.

Dutta and others examined records of 321 HIV positive patients admitted in 1993-1994 at Sinai Hospital Baltimore (John Hopkins University hospital), looking at the incidence of acute pancreatitis and aetiological factors associated with acute pancreatitis in these patients. 45 patients developed acute pancreatitis in the one year of study. A statistically significant negative correlation was found between serum pancreatic enzyme level and the CD4 lymphocytes ($p < 0.05$, $r = -0.2$ for serum amylase, $p < 0.05$, $r = -0.15$ for serum lipase) (48). Patients with asymptomatic HIV infection or CD4 lymphocyte count $> 500/\text{mm}^3$ did not develop asymptomatic hyperamylasaemia or acute pancreatitis. The presence of gallstones, pentamidine therapy, infection with pneumocystis carinii and mycobacterium avium intracellular correlated significantly ($p < 0.001$) with the diagnosis of acute pancreatitis(48).

The conclusion was that the results suggested a high incidence (14%) of mild to moderately severe acute pancreatitis. In addition, marked reduction in CD4 lymphocyte count was associated with increase in serum pancreatic enzyme levels (amylase, lipase activity) which the authors suggested could be due to pancreatic gland inflammation or altered pancreatic enzyme turnover (48).

HIV positive patients have been known to present with chronic abdominal pain and been subsequently diagnosed to have acute pancreatitis (33, 34).

However hyperamylasaemia has also been reported in about half of HIV infected patients without specific symptoms of pancreatic disease and autopsy examinations of AIDS patients often reveal pancreatic abnormalities (52).

Among the infectious causes of acute pancreatitis, cytomegalovirus is very common in advanced stages of AIDS, with the gastrointestinal tract being the second most commonly involved organ after the retina (32). Autopsy studies have shown that CMV is the most common pathogen that involves the pancreas in AIDS patients (32). Antemortem diagnosis of CMV pancreatitis requires a high index of suspicion, and may be achieved by demonstrating inclusion bodies within the pancreatic parenchyma and viral culture of the pancreatic tissue (35,36). Mycobacterium tuberculosis infection of the pancreas has also been reported in HIV positive patients (37). In several reports, acute pancreatitis has been found to be caused by the HIV virus itself (38,39,40,41).

Other systemic diseases like Kaposi sarcoma and lymphomas have been reported to cause acute pancreatitis (50).

Drugs are common causes of acute pancreatitis (60) in HIV infected patients. These include both antiretroviral drugs and other drugs prescribed for various opportunistic infections (64). Among the ARVs, several nucleoside reverse transcriptase inhibitors (NRTIs) have been implicated as causative agents in acute pancreatitis and these include didanosine, stavudine and zalcitabine

(42,43,65,66,67,68). AP has however not been reported with the newer NRTIs for instance Tenofovir Disoproxil fumarate (65). Among the protease inhibitors, acute pancreatitis has been reported to occur in some patients on ritonavir, Kaletra (lopinavir / ritonavir combination) and nelfinavir (44,51,65). There are reports of AP resulting from hydroxyurea use (45), as well as with combination (triple) ARV therapy (46,47).

Other than ARVs, there are pharmacological agents frequently prescribed to HIV infected patients that have a definite association with pancreatitis, in that acute pancreatitis develops with drug treatment, disappears upon drug withdrawal, and recurs with rechallenge. Additional evidence for this association may have also come from comparison of treated and untreated groups, or from experimental data. These drugs include sulfonamides (69,70,71), pentamidine (72,73,74), pentavalent antimony (75,76,77), corticosteroids (78,79) and octreotide (80).

For some drugs there has been inadequate or contradictory evidence to support an association with AP and these include isoniazid, rifampicin, erythromycin, intravenous lipid emulsion and paramomycin (81,82,83,84,85,86).

Pancreatic disease has been associated with renal disease, with a presentation similar to hepatorenal syndrome, whereby there is renal failure which cannot be reversed easily with all the current known treatment strategies. The pancreato-renal syndrome has been described in association with combination antiretroviral therapy in HIV infection (49).

In the HIV infected patient, pancreatic evaluation by imaging techniques may disclose acute pancreatitis even in the absence of abdominal pain (53).

JUSTIFICATION

HIV infection is increasing in prevalence in Kenya with an estimated 2.2 million Kenyans infected with HIV/AIDS (54). Studies in the West reveal a prevalence of acute pancreatitis of between 4 and 22% in the HIV infected population (33,46,48,50,52) compared to the HIV negative individuals where it stands at 0.004 to 0.024% (4.8 to 24.2 per 100,000 (9). One aim of this study therefore was to find out the prevalence of acute pancreatitis in HIV positive patients presenting with acute abdominal pain in a tertiary referral hospital in Kenya and see how these compared with prevalence rates from the West.

Acute pancreatitis can be fatal even in those patients who are immunocompetent. Mortality is related to the severity of the disease, and HIV patients with lower CD4 counts experience frequent attacks of acute pancreatitis and much more severe disease (41, 48). Acute pancreatitis therefore is seen to impact negatively on HIV prognosis, yet if diagnosed, it is potentially treatable. Thus it was necessary to find out the prevalence of acute pancreatitis in HIV positive patients presenting with acute abdominal pain in our setup, so as to reemphasize the need to be more aggressive in screening for this condition in order to improve the patients' outcome.

With increasing use of antiretroviral therapy (ARVs), it is expected that the clinical status and outcome of HIV positive patients will improve, possibly leading to less incidence of acute pancreatitis, since the incidence has been negatively correlated with CD4 counts in some studies. On the other hand, certain ARVs for example NRTIs like didanosine, zalcitabine and stavudine and a few protease inhibitors like ritonavir and lopinavir, are known to predispose to development of acute pancreatitis. It was therefore our aim to

find out if ARV therapy was associated with an increase or decrease in the occurrence of AP.

There is no published data from Africa available on the subject of HIV associated AP, hence the results of this study form a baseline for further research on this subject.

OBJECTIVES

Main objective

To determine the point prevalence of acute pancreatitis in HIV positive patients presenting with features of acute abdominal pain at Kenyatta National Hospital and to correlate the presence of acute pancreatitis (AP) with extent of HIV disease and with the presence of other evident AP risk factors.

Specific objectives

- 1) To determine the profile of serum amylase and lipase in HIV positive patients presenting with acute abdominal pain.
- 2) To document CD4 lymphocyte counts in these patients.
- 3) To describe the presence of other evident risk factors for acute pancreatitis other than HIV in these patients.

PATIENTS AND METHODS

STUDY DESIGN

Cross sectional survey.

STUDY SITE

The study was carried out at Kenyatta National Hospital, which is a tertiary referral hospital. In-patients in the medical wards who fit the case definition were recruited into the study.

STUDY POPULATION

All adult patients admitted at KNH medical and surgical wards during the study period with acute upper abdominal pain.

CASE DEFINITION

A case was defined as a patient admitted with acute upper abdominal pain who tested positive for HIV.

OTHER TERMINOLOGIES

Acute abdominal pain was defined as sudden onset of pain in the upper abdomen namely the epigastrium, right and left hypochondrium, of less than seven days duration, with or without radiation to the back, shoulders, flanks and lower abdomen and with or without nausea and vomiting.

HIV status was determined by using the Rapid HIV 1/2 assay test which has a sensitivity and specificity of 99.9% (56).

Acute pancreatitis was defined as a rise in serum amylase and /or lipase levels above upper reference limits of the assay method used. For amylase the reference range was 25 to 125 u/l while for lipase this was 8 to 78 u/l.

SAMPLING

Consecutive patients screened were recruited until the required sample size was attained. Although there is an inherent selection bias in consecutive sampling as opposed to random sampling, our results in regard to similarity in demographics of selected HIV positive patients and screened HIV negative patients makes selection bias unlikely (**pages 28-29, results**).

INCLUSION CRITERIA

- Patients with HIV infection and acute abdominal pain.
- Written informed consent by the patient.

EXCLUSION CRITERIA

- Failure to give written informed consent.

SAMPLE SIZE.

The sample size was 144, which was calculated based on the estimated prevalence of acute pancreatitis in HIV patients of 10%, the desired accuracy 10% and a p value of 0.05, all aimed at giving the study a power of 80% (**see Appendix x for formula**).

MATERIALS AND METHODS

PATIENTS

On the post admission day, all medical and surgical wards were visited by the principal investigator who perused all the files of new admissions (**Appendix i**). The files of patients admitted with acute onset of upper abdominal pain were identified and patients traced to their respective rooms and beds. A preliminary history and physical evaluation was done using a specific proforma, whereby demographic data, clinical features and admitting diagnosis was entered (**Appendix ii**). Consent to undertake a HIV test was sought from the patient after pretest counselling during which the benefits of undertaking the test were outlined (**Appendix iii**). Those who consented had a rapid HIV assay done. Consent was thereafter sought from the HIV positive patients for recruitment into the study after explanation regarding the purpose of the study (**Appendix iv**). Those who declined to join the study still had demographic data taken, with presenting clinical features being recorded and possible risk factors for acute pancreatitis as per history (**Appendix v**). This was done to evaluate selection bias.

Those who consented to joining the study then underwent a detailed history taking, with history of alcohol use and antiretroviral therapy being recorded and a physical examination, whereby vital signs, presence of evident opportunistic infectious, for example candidiasis and herpes zoster and systemic examination with special regard to abdominal examination findings was done (**Appendix vi**). Any other confirmed opportunistic infection was also recorded, for example presence of tuberculosis confirmed on sputum studies. Venous blood was drawn for serum amylase and lipase levels estimation, and for CD4 cell counts as outlined in laboratory methods below.

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LABORATORY METHODS

Those who consented to HIV testing had 20 μ l of capillary blood obtained under aseptic technique by pricking the side of the fingertip which was then put in a capillary tube and then analyzed as per the guidelines in the Instant Screen rapid HIV/2 Assay for whole blood, serum or plasma (**Appendix vii**).

Ten milliliters of venous blood was taken from each HIV positive patient from the antecubital fossa using aseptic technique, eight millilitres of which was put in a plain bottle, was allowed to clot, then the sample was centrifuged at 2000 rpm and serum separated and stored at -20 degrees centigrade until analysis was done. Serum amylase and lipase were estimated by turbidimetric methods on an autoanalyser using commercial reagents (**Appendix viii**). Two millilitres of blood was put in a citrated bottle for CD4 counts which were estimated using monoclonal antibodies for detecting human antigens on the CD4+ve cells by use of flow cytometry (**Appendix ix**).

DATA ANALYSIS

Data were collected using standard data sheets (**Appendix v and vi**) and coded. It was entered into a computer using SPSS version 10. It was cleaned and verified before analysis using the SPSS version 10. It was then summarised into means, ranges, standard deviation and medians.

The point prevalence of acute pancreatitis was calculated by the use of the formula below:

$$\text{Point prevalence of AP} = \frac{\text{Cases}}{\text{Cases} + \text{non cases}}$$

Stage of HIV infection as portrayed by the CD4 counts is correlated with the presence or absence of acute pancreatitis.

Association was examined using chi square test for categorical data and a p value of 0.05 is taken as significant. The student t-test and Pearson's correlation was used for continuous variables. The level of significance was a p value of 0.05.

DURATION OF STUDY

The study was undertaken over six months, from August 2004 to January 2005. Patient recruitment continued until the desired sample size was achieved.

PATIENT CONSENT

It was ensured that every patient fully understood the nature of the study. Informed written consent was sought from each patient /guardian for those who were under 18 years of age (Appendix i).

ETHICAL CONSIDERATIONS

Permission to carry out the study was sought from the Kenyatta National Hospital Scientific and ethical review committee.

Patients were enrolled in the study only after giving informed written consent.

It was ensured that all patients who underwent a HIV test were pretest counseled.

Post test counseling was done for all patients, whether they tested positive for HIV or not.

All who tested positive for HIV were referred to the newly established comprehensive care clinic for institution of antiretroviral therapy.

All information obtained about patients was handled with the utmost confidentiality and used only for the intended purpose. Results were also communicated to the ward caregivers for proper management of patients.

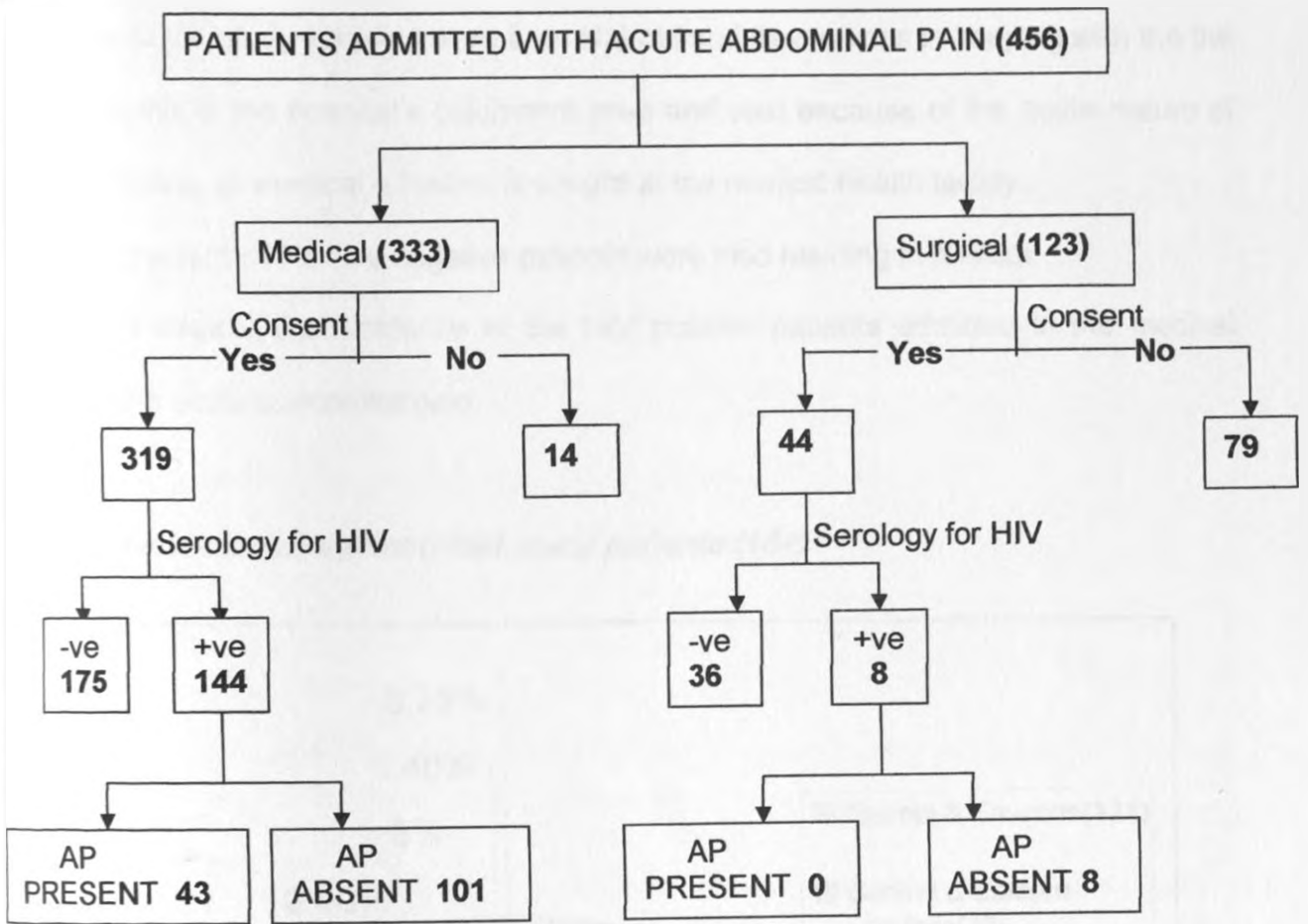
RESULTS

During the study period, 3889 admissions were screened (2508 from medical and 1381 from surgical wards). Of the 456 (11.7%) patients admitted with acute abdominal pain, 333 (13.3%) were from medical wards while 123 (9%) were from surgical wards.

Of the 123 surgical patients, 94 were males and 29 were females (male to female ratio 3.2:1). Most of the surgical patients approached did not consent to enter the study citing the fact that they were already aware of their operative diagnosis, and hence only 44 were screened for HIV and 8 tested positive. None of the eight patients had biochemical evidence of AP. The eight constituted only 4% of the entire HIV population recruited and analysis with and without them did not show any differences, thus the data presented below refers only to the medical patients.

Among the 333 medical patients (13.3 %) who had acute abdominal pain, 319 gave consent for HIV testing, 131 of whom were males while 188 were females, with a male to female ratio of 0.7:1. 175 patients tested negative while 144 tested positive, giving a HIV prevalence of 45.1 % in those patients admitted with acute abdominal pain. 14 patients declined to give consent for HIV testing, two of whom already knew their serostatus (positive).

Flow chart indicating how recruitment and handling of patients was undertaken



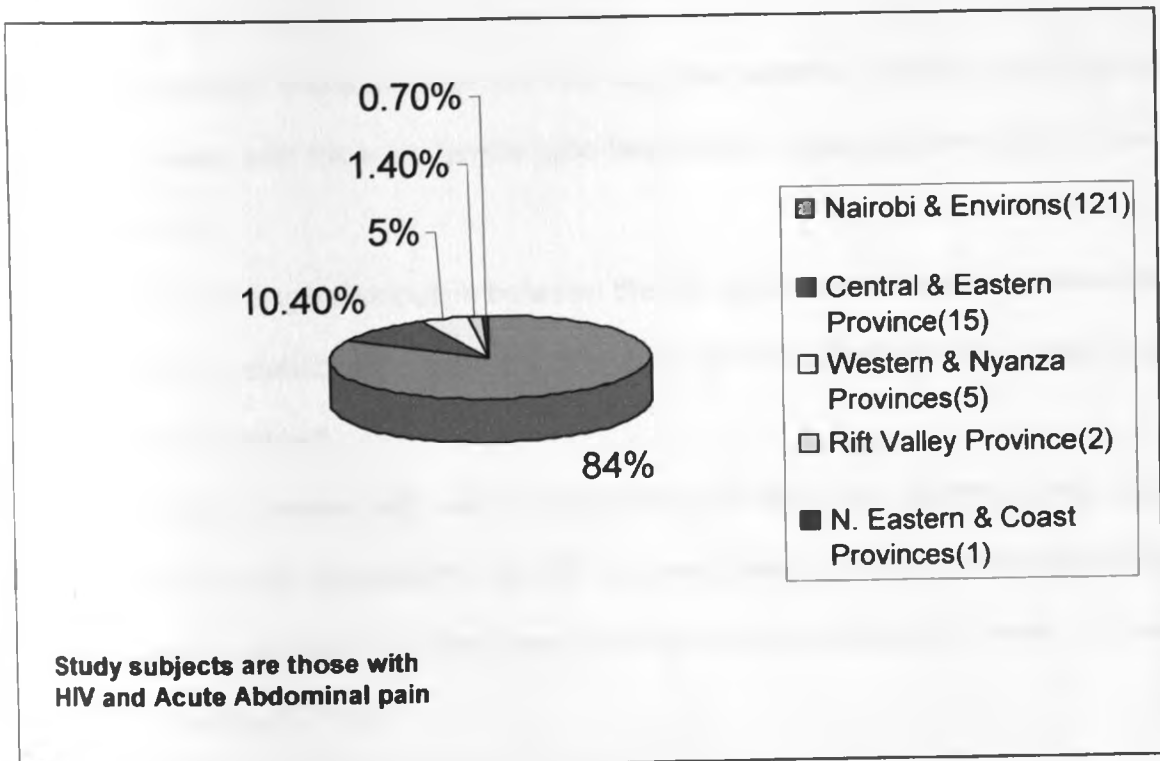
RESIDENCE

Majority of the study subjects were from Nairobi and its environs in keeping with the the fact that this is the hospital's catchment area and also because of the acute nature of this condition, so medical attention is sought at the nearest health facility.

Fifty six percent of the HIV negative patients were also residing in Nairobi.

Figure 1 depicts the residence of the HIV positive patients admitted in the medical wards with acute abdominal pain.

Fig 1: Residence of the recruited study patients (144)



AGE AND GENDER DISTRIBUTION

The age of the 144 HIV positive study subjects ranged from 18 to 75 years with majority of patients falling in the 25-34 year age group (see figure 3). The mean age was 32.0 years (SD + 9.2 years).

There were 52 males (36.1%) and 92 females (63.9%) giving a male to female ratio of 0.6:1.

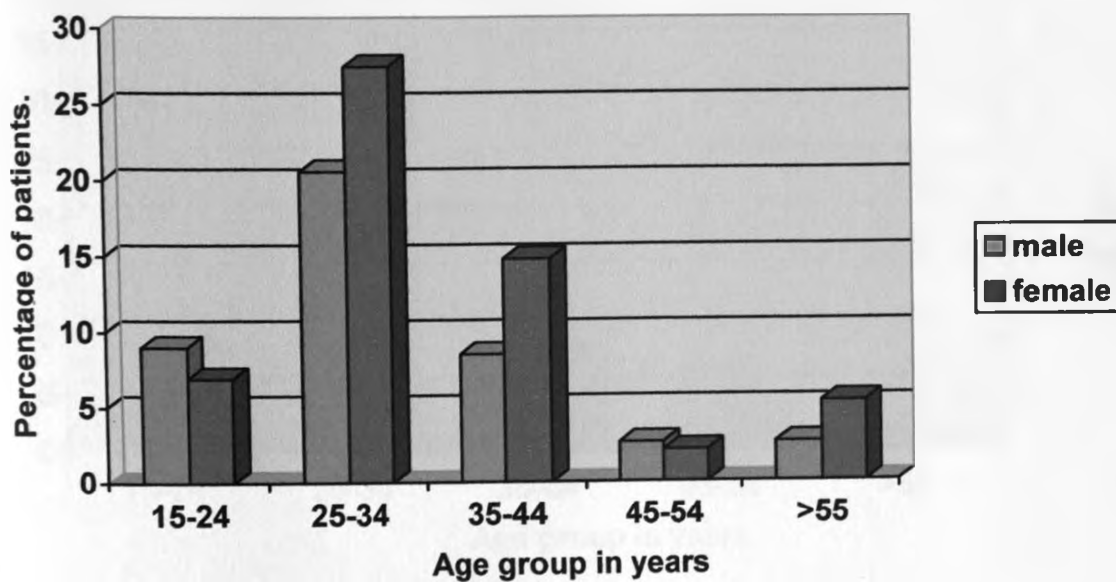
There was no gender differences in the age distribution, the means being 33.3 years (SD ± 9.72) for males and 31.4 years (SD ± 8.1) for females respectively (p=0.34).

The age and gender distribution for the HIV negative patients compared with that for the HIV positive ones, with the male:female ratio being 0.8:1 and mode being 25-34 years age group (figure 2).

A comparison of the age distribution between the HIV positive and negative groups showed that there was no statistically significant difference (p=0.22), indicating that study subjects selection was not biased.

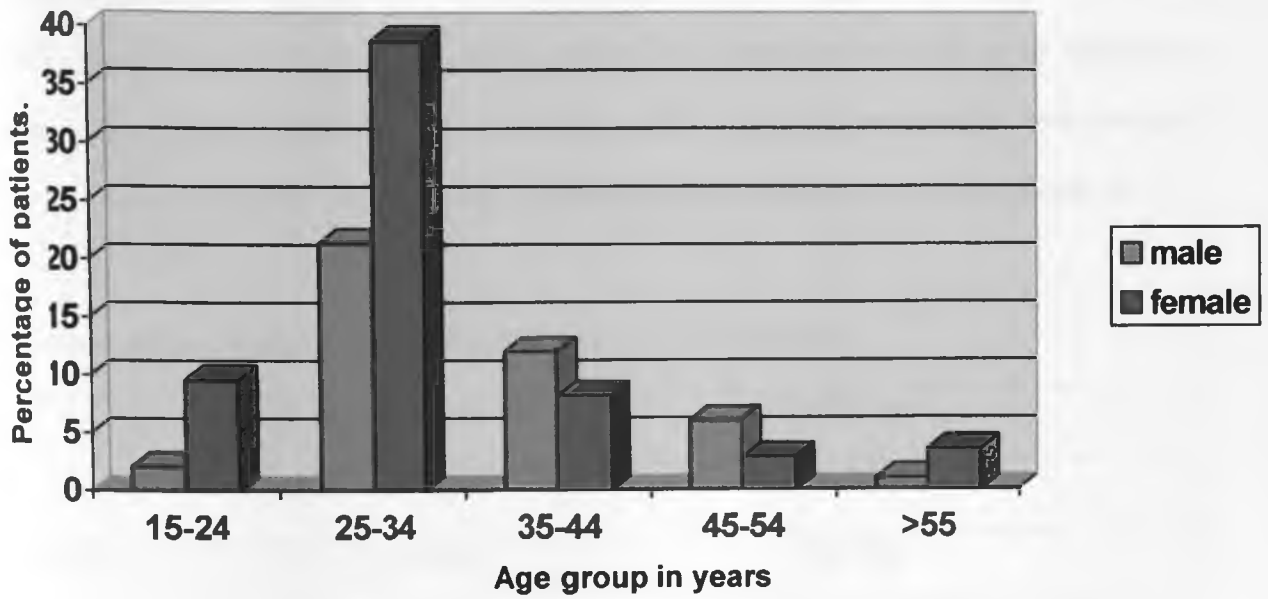
While only those patients with acute abdominal pain and HIV became study subjects, demographic data was available for the HIV negative patients and non-consenters from the medical records (appendix v), and these was used for comparisons in order to show if a selection bias existed or not.

Fig 2: Age and gender distribution of HIV negative patients and nonconsenters (189).



There were more females than males in all age groups in the HIV negative patients and non-consenters except in the 15-24 years age group.

Figure 3: Age and Gender distribution of the study subjects (144 patients).



ADMITTING DIAGNOSIS OF THE HIV POSITIVE AND NEGATIVE PATIENTS

Over half of the patients in both the HIV positive and HIV negative groups had a main admitting diagnosis of acute PUD, either alone or in combination with other diagnosis including pneumonia, acute confusional states, acute tonsillitis, meningitis, enteritis and puerperal sepsis, hepatitis, febrile illness, intestinal obstruction among others (table 1).

Table 1: Admitting diagnosis for the HIV +ve and -ve patients

Dx	HIV +ve	HIV -ve
	n (%)	n (%)
Acute PUD	65 (45)	96 (53)
Acute Gastritis	20 (14)	18 (9.1)
Acute GE	22 (15)	12 (6)
Acute PUD and other	13 (9)	20 (10.3)
Acute Gastritis and other	9 (6)	24 (12.6)
Acute GE and other	4 (3)	0 (0)
Peritonitis	4 (3)	0 (0)
Acute pancreatitis	0(0)	0(0)
Other	7 (5)	19 (9)

Acute gastroenteritis as an admitting diagnosis on its own or in combination with other diagnosis was more common in the HIV positive patients than in the HIV negative, (26% vs 12% respectively), and the difference was statistically significant ($p=0.04$).

PREVALENCE OF ACUTE PANCREATITIS IN THE STUDY SUBJECTS

Forty three of the one hundred and forty four study subjects had acute pancreatitis, based on serum amylase and/or lipase levels, giving a prevalence rate of acute pancreatitis of 29.9% in HIV patients presenting with acute abdominal pain in the medical wards. When only those patients who had both raised amylase and lipase levels were analysed, the prevalence of AP became 22.9%.

Of those with AP, 32.6% were males while 67.4% were females (see table 2). These differences in sex distribution were present from the outset as seen in all those patients recruited into the study, whereby 36.1% were males while 63.9% were females.

Table2: AP status by gender

PANCREATITIS	MALE		FEMALE	
	No.	%	No.	%
Positive (43)	14	32.6	29	67.4
Negative (101)	38	37.6	63	62.4

The male to female ratio of the patients with AP was 0.5:1. This gender difference however was not statistically significant ($p=0.56$).

ADMITTING DIAGNOSIS IN THOSE WITH ACUTE PANCREATITIS

Most of those patients with AP (60.5%) were admitted with a diagnosis of acute PUD. In 8 patients with AP (18.6%), the admitting diagnosis was acute gastritis. This compared well with the admitting diagnosis for the entire group of HIV positive patients in whom the admitting diagnosis was acute PUD and gastritis in 54% and 20% of the patients respectively.

Five (11.6%) and four (9.3%) of those with AP had an admitting diagnosis of gastroenteritis and other conditions (hepatitis, acute febrile illness) respectively. It was notable that none of the study subjects had AP as the admitting diagnosis.

CLINICAL FEATURES OF THE 144 HIV POSITIVE STUDY SUBJECTS

Duration of pain ranged from one to seven days, with a median of 6 days and mean of 5.5 days. The mean pain duration for those with AP was 5.7 days and for those without 5.4 days. There was no statistical difference in pain duration between those with and without AP ($p=0.48$).

Most patients (98.6%) reported having epigastric pain. In addition, 17.4% had RUQ pain and 6.9% had LUQ, on their own or in various combinations and there was no difference in terms of pain location in those with or without AP (p value=0.36)

Majority of the patients (50.7%) described the pain as burning in character, while 25% reported the pain as colicky and 7.4% as dull in nature. The rest (6.9%) gave various descriptions to their pain including boring, pricking and throbbing (P values for differences

in pain character between those with and without AP were 0.66, 0.50, and 0.54 for burning, colicky and dull pain respectively).

One hundred and twenty nine patients (89.6%) reported nausea and / or vomiting, with a mean duration of 5.0 days. There was no statistical difference in mean duration of vomiting between those with and without AP (p value =0.55).

Fifty one of the study subjects (35.4%), had pain radiation to various sites, as depicted in table 3 below.

Table 3: Pain radiation sites in study subjects

	AP Present (%)	AP Absent (%)	P Value
Back	14(73.6%)	19 (59.3%)	0.078
Right Hypochondrium	2 (10.5%)	1(3.1%)	
RIF	1 (5.3%)	6 (18.7%)	
Left subcostal	1 (5.3%)	2 (6.3%)	
Paraumbilical	0 (0%)	2 (6.3%)	
RUQ and Back	1 (5.3%)	2 (6.3%)	

Majority of patients reported radiation of pain to their back, this being 73.6% in those with AP and 59.3% in those without AP. This difference however was not statistically significant (p=0.078).

OTHER CLINICAL FEATURES IN STUDY SUBJECTS

Only seven patients (4.9%), reported relief of pain with change in position. A significant number (70 patients or 48.6%) reported being dizzy in the course of their illness and 9 (6.3%) were confused at the time of their admission, but no patient was in a coma. Relatively few patients (28 or 19.4%) reported history of alcohol use (see table 4). However the amount of alcohol taken and temporal relationship was not quantified, therefore no conclusions regarding its role in AP causation can be reached. Only five patients (3.5%) were on ARVs and no further analysis on these patients was done.

About two thirds of the study subjects had fever (temperature $>37.2^{\circ}\text{C}$), majority (94.4%) had a normal pulse rate (60-100 beats per minute), while most (88.2%) were tachypnoeic. 20.1% of the study subjects had low BP (BP $<90/60$ mmhg). None of the vital signs showed a statistically significant difference in those with and without AP.

Table 4: Other clinical features in the studied 144 subjects

Variable	AP +ve n (%)	AP - ve n (%)	P Value
Relief by milk & food	2 (4.7)	20 (19.8)	0.02
Hx of alcohol use	7 (16.3)	21 (20.8)	0.53
Current ARV use	1 (2.3)	4 (3.8)	

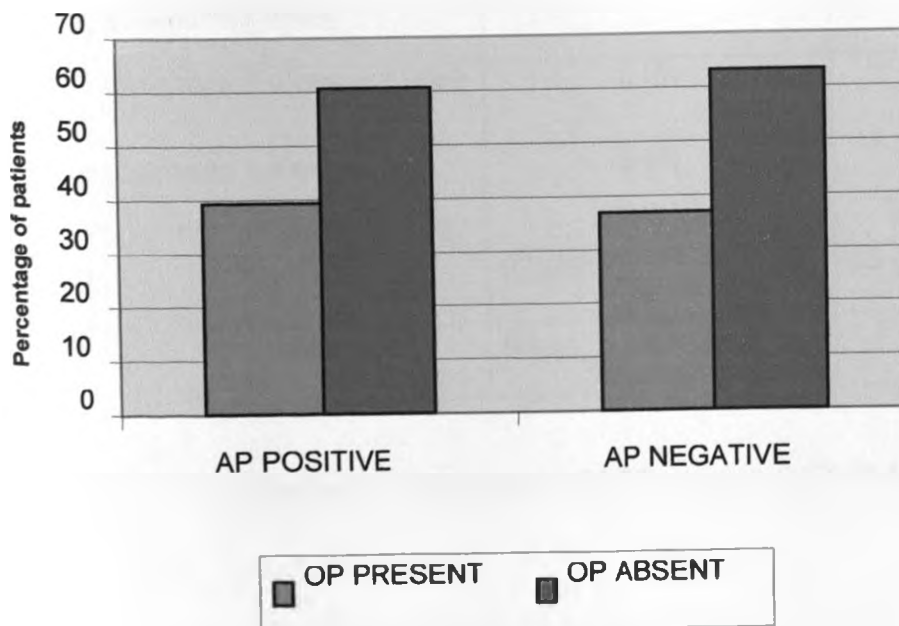
From the table above it is evident that more AP negative patients reported relief of their pain by food and milk than did those with AP, with a statistically significant p value of 0.02.

OPPORTUNISTIC INFECTIONS IN STUDY SUBJECTS

In this study, there was active search for opportunistic infections especially by means of laboratory and radiological workup but we relied on available medical records and physical examination findings by the principal investigator to document any gross opportunistic infection present in the study subjects. Most of the study subjects did not have opportunistic infections (62.7% versus 62.8% in those with and without AP respectively, table 5 and figure 4).

Of those who had, the most frequent infection was oral candidiasis, in 25.6% and 25.7% of AP positive and AP negative subjects respectively ($p=0.88$).

Fig 4: Presence of opportunistic infections in the study subjects.



There was no difference in the presence of opportunistic infections among those with AP and those without, the percentages being 39.5% and 36.6% among AP and non AP respectively ($p=0.74$).

Table 5: Opportunistic infections found in study subjects.

OPPORTUNISTIC INFECTION	AP PRESENT	AP ABSENT
	n (%)	n (%)
Oral Candidiasis	11 (25.6)	26 (25.7)
Tuberculosis(sputum positive)	2 (4.7)	1 (0.9)
Herpes Zoster	2 (4.7)	2 (1.8)
Other(molluscum contagiosum, folliculitis)	1 (2.3)	7 (6.8)
Oral candidiasis & Herpes Zoster	0 (0)	1 (1)
Oral candidiasis & Other	0 (0)	1 (1)
None	27 (62.7)	63 (62.8)
Total	43	101

Other opportunistic infections accounted for 11.7% versus 9.5% in those with and without AP respectively.

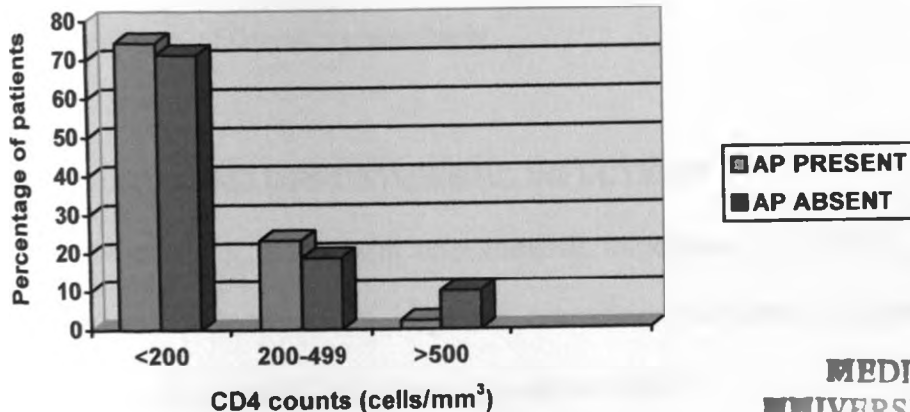
ACUTE PANCREATITIS AND CD4 COUNTS

Majority of the study subjects had CD4 counts $<200/\text{mm}^3$ (72.2%), 20.2% had CD4 counts between 200 and $499/\text{mm}^3$ while 7.6% had CD4 counts above $500/\text{mm}^3$.

Of those with AP, 74.4% (32) had CD4 counts $<200/\text{mm}^3$ and this compared well with those without AP (71.3% or 72) as depicted in **figure 5**. In the range of CD4 counts between 200 and 499, 23.3% (10) of the patients had AP while 18.8% (19) did not, while for CD4 counts above $500/\text{mm}^3$, only one patient (2.3%) had AP while 10 (9.9%) did not.

There was no increase in percentage of patients with acute pancreatitis with decreasing CD4 counts (see **figure 6**).

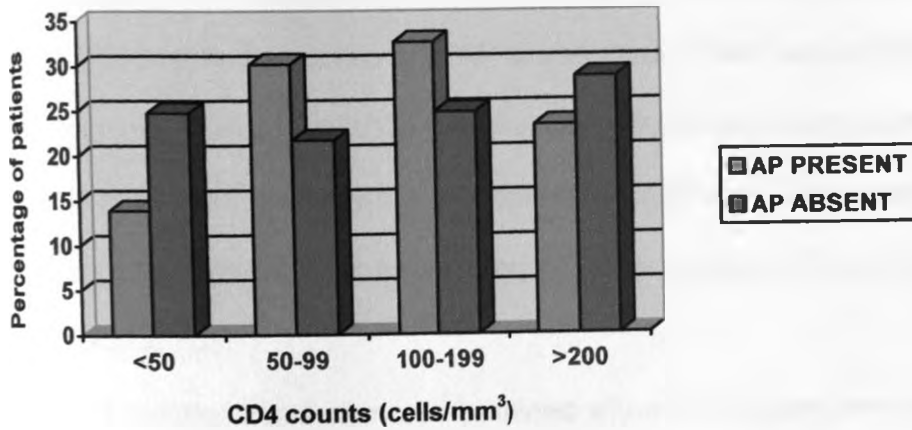
Fig 5: CD4 counts in the patients with and without AP



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There was no statistical difference in the CD4 counts in those with and without AP ($p=0.27$)

Fig 6: Proportion of patients with CD4 counts below 200/mm³.



Though most patients with AP had CD4 counts lower than 200/mm³, there was no increase in number of patients with AP with decreasing CD4 counts, with percentage of patients with AP being 23.3%,32.6%,30.2% and 13.9% for CD4 counts of >200/mm³,100-119, 50-99 and <50/mm³ respectively.

CD4 COUNTS AND OPPORTUNISTIC INFECTIONS

Of the 54 study subjects with opportunistic infections, 48 (88.9%) had CD4 counts less than 200/mm³. There was a negative correlation between decreasing CD4 counts and increase in opportunistic infections, (p value 0.002).

CORRELATION BETWEEN CD4 COUNTS < 200/MM³ AND SEVERITY OF AP

The severity of AP as depicted by the enzyme levels was correlated with the CD4 counts for the 43 patients diagnosed with AP in this study. There was a positive correlation with a Pearson's R coefficient of 0.375 and p value of 0.013 which was statistically significant, but when analysis was done for the 32 patients with AP and CD4 counts below 200/mm³, this positive correlation was not as evident, with the Pearson's R coefficient becoming -0.055 and p value 0.763.

The same positive correlation was obtained when CD4 counts were analysed versus lipase levels for all patients with AP, whereby the Pearson's R coefficient was 0.319 and p value was 0.037, but on analysis of only those with CD4 counts below 200/mm³, the R value became 0.008 and p value 0.966.

DISCUSSION

The prevalence of acute pancreatitis in HIV positive patients presenting with acute abdominal pain in our study was 29.9%. This implies that every one in three HIV positive patients admitted with acute abdominal pain has AP, so clinicians should consider it a differential diagnosis in such patients. Acute pancreatitis has been reported to be more common in HIV patients than in the immunocompetent with a prevalence of between 5 – 22%. Dutta et al in Baltimore (48) in 1997 reported a prevalence of 14% in 321 HIV positive patients, while Cappel and Marks in their study showed a prevalence of 5% (60). Dowell, S and others in 1989 showed a 22.5% prevalence of acute pancreatitis in HIV positive patients with suggestive clinical features (61). The higher prevalence in our study could be explained by the fact that patients in the developing world are at risk of more infections, which in the immunocompromised can involve the pancreas especially in the setting of low CD4 counts as was the case in our study.

Dutta's study had a different design from our study in that he and his colleagues did a retrospective analysis of all HIV positive patients regardless of their abdominal symptomatology and did an analysis of those who had biochemical evidence of AP, whereas ours was a cross sectional study of HIV positive patients with abdominal symptoms. Thus had they analysed a larger sample of symptomatic patients, their prevalence of AP in these patients may have approached what we got.

A higher prevalence in our study could also have been as a result of misclassification since we did not investigate for other causes of hyperamylasemia and thus classified everyone with raised serum amylase as having acute pancreatitis, which may not have been the case.

Serial enzyme assays would have helped us reach a more definitive diagnosis of AP, but we were not able to do this due to logistic and financial constraints.

Majority of our study subjects (72.2%) fulfilled the CDC criteria as having AIDS based on the CD4 counts $<200/\text{mm}^3$. Of those diagnosed to have acute pancreatitis, 74.4% had CD4 counts $<200/\text{mm}^3$, which was comparable to data from other published studies. Parithivel V.S et al in 1999 in USA in their retrospective review of 54 HIV/AIDS patients admitted with AP, showed that 89% of their study subjects had CD4 counts $<200/\text{mm}^3$ in blood (59), while in 2003, Gan I et al in British Columbia in another retrospective study of 73 HIV infected patients with AP found that 83.6% of the patients had AIDS, based on CD4 counts (62). Our figures, though slightly lower still show a majority of our patients being in the AIDS category. However as majority of those with and without AP in our study had AIDS (72.2%), a low CD4 count alone does not appear to be a major risk factor for development of AP. Most of the studies in literature have analysed patients with acute pancreatitis only, so there is no identifiable explanation as to why one patient would get AP while another does not, yet they have similar CD4 profiles. There may be other underlying factors in our setup which need to be looked into, such as malnutrition which is known to predispose to AP (55). There is therefore need for further research to identify the causes of AP in HIV positive patients in our setup.

There was a positive correlation when serum enzyme levels depicting severity of disease were correlated with CD4 counts in those with AP in our study, ($r=0.375$, $p=0.013$ for serum amylase, $r=0.319$, $p=0.037$ for serum lipase). However when only those with CD4 counts

<200/mm³ were analysed, the positive correlation became less obvious, ($r=-0.055$, $p=0.763$; $r=0.008$, $p=0.966$ for amylase and lipase respectively). Dutta and others in their study showed a statistically significant negative correlation between serum pancreatic enzyme levels and CD4 lymphocytes ($P<0.05$ for serum amylase, $P<0.05$ for serum lipase) (48). Lower CD4 counts were thus associated with higher enzyme levels, implying that patients with lower CD4 counts develop severer disease (AP). The findings in our study suggest the opposite and could be explained by the fact that it requires an intact immune system to mount a good inflammatory response with resultant high pancreatic enzyme levels. Further research however is required to validate these findings which may consequently have a bearing on the use of ARVs, as immune reconstitution may be associated with increase in the presence and severity of AP.

The male to female ratio in our study subjects was 0.6:1 which compared well with that for KNH medical admissions for the year 2002 and 2003 (0.7:1). The HIV positivity was however higher at 45.1% compared to 18.5% for medical admissions at KNH in 2003. This may be because ours was a select group with admitting diagnoses that could have been HIV related, for instance gastroenteritis. The other possibility is that of underdiagnosis of HIV, as discharge summaries from which hospital data on HIV is recorded may have been incomplete.

The mean age of all the study subjects was 32 years while those with acute pancreatitis were slightly younger at 30.3 years of age and those without AP had a mean age of 32.8 years. This difference was however not statistically significant ($p=0.44$). This compared well

with results from a study by Parithiel et al (59) in which 65% of the HIV patients who had AP had an age less than 40 years. In our study, 55% of the study subjects were aged between 15-29 years. Data from NASCOP also shows that majority of HIV positive patients in Kenya (75%) fall in this age group which shows that the burden of HIV disease is in the young productive age group and that our data was representative of our HIV population.

The mode of presentation in patients diagnosed to have acute pancreatitis did not differ significantly with those without acute pancreatitis, in terms of pain location, character of pain and presence of nausea and vomiting. It is thus evident that as described by Cappell et al (60), the diagnosis and management of acute pancreatitis in HIV infected patients remains a challenging problem. However we did demonstrate in this study that patients reporting relief of their pain by food and milk were unlikely to have AP and these differences reached statistical significance ($p=0.02$). A further study to validate this finding would be useful so as to show if this characteristic can be used as a predictor of who will have or not have AP in the setting of HIV positivity and acute abdominal pain.

Most of the patients diagnosed with AP in this study had no clinical characteristic differentiating them from those without AP. Pain radiation for instance was to similar locations in both groups of patients. The most common pain radiation site was the back in 73.6% of those with AP and 59.3% of those without AP, but these differences were not statistically significant ($p=0.078$). The pain of AP is said to worsen with lying in a supine position and be relieved by sitting forward or lying in a fetal position but in our study, a change in position only relieved pain in 4.9% (7) of the patients (numbers too small to

subject to statistical analysis). This study has shown that patients may have AP even with an atypical presentation.

It is noteworthy that no patient in our study had an admitting diagnosis of AP; the most common admitting diagnosis was acute PUD, acute gastritis and gastroenteritis (45%, 4% and 15% of patients respectively). In literature misdiagnosis has been reported to occur in up to 43% of cases of AP (10,11,12), mainly due to atypical presentations, use of serum amylase as a diagnostic tool yet this has a limited specificity and sensitivity and is useful for a short time; and the fact that there are no pathognomonic symptoms and signs of AP. The reason for the misdiagnosis in our study could have been as a result of clinicians not considering AP to be a primary or even differential diagnosis in these patients.

The presence of opportunistic infections in those with and without AP did not show statistical difference ($P=0.74$). Even an analysis of each individual opportunistic infection did not show a difference in those with or without AP. The various infections noted from patient records, for example *Mycobacterium tuberculosis* and candidiasis are likely causes of acute pancreatitis (1,2,3,4). Some of the organisms that may cause gastroenteritis in these patients, for example cytomegalovirus and cryptosporidium may also cause AP. We did not however in our study actively search for aetiological causes of acute pancreatitis by means of further laboratory workup. Further research to show the causes of AP in our setup would be useful as appropriate management for the specific cause can be given such as antivirals for CMV.

The mean pain duration for the patients with AP in this study was 5.4 days while the median was five days. The kinetics of serum amylase is such that by the fifth day the level in serum is declining. However lipase levels were likely to have been in the diagnostic range as levels decline from day 8-14, thus it would have selected out those with amylase levels that had returned to normal but still had AP. Those with marginal amylase and lipase levels most likely due to the late presentation were diagnosed to have AP in our study and were still likely to have the disease despite the lower enzyme levels. Thus our prevalence rates of AP in HIV positive patients with acute abdominal pain are likely a reflection of the true prevalence in our setup since we used both assays of lipase and amylase.

Only five patients in this study were on ARVs. ARVs have been known to contribute to the increased prevalence of AP in HIV positive patients. Our study demonstrated a high prevalence of AP in HIV patients with acute abdominal pain but with little ARV use. We expect a rise in prevalence of AP in HIV positive patients with the current scaling up of ARV use in Kenya. This therefore raises another subject for future studies.

In conclusion, this study has shown a high prevalence of AP in HIV positive patients admitted with acute abdominal pain, whose mode of presentation does not differentiate them from those without AP and whose CD4 counts do not differ from those of HIV positive patients without AP.

CONCLUSIONS

HIV positivity for the patients admitted with acute abdominal pain in this study was 45.1%.

Prevalence of acute pancreatitis in HIV positive patients admitted with acute abdominal pain was 29.9%.

There was no statistically significant difference in the age, sex, mode of presentation, presence of opportunistic infections and CD4 counts in the two groups of patients, that is those with or without acute pancreatitis.

Opportunistic infections were more in those with lower CD4 counts (p value 0.002).

The serum amylase and lipase levels showed no negative correlation with CD4 counts (p values 0.763 and 0.0.966 respectively).

STUDY LIMITATIONS.

Not being able to do CT Scan for diagnostic purposes was a limitation especially because some patients may have had marginal amylase and lipase levels yet have acute pancreatitis, leading to misclassification.

Patients came to hospital late by which time pancreatic enzymes may no longer have been elevated above the diagnostic cut-off values, which may have influenced the results of actual prevalence of AP.

RECOMMENDATIONS

Evidence of acute pancreatitis should be sought in HIV positive patients presenting with acute abdominal pain.

Further research is needed in HIV positive patients presenting with acute abdominal pain to identify the causes of AP in these patients.

Research on HIV positive patients presenting with acute abdominal pain to identify causes of AP should also incorporate investigations to rule out other causes of hyperamylasemia as this may have influenced the prevalence rate in our study.

Further studies need to be done to determine the correlation between CD4 counts and severity of acute pancreatitis.

Follow-up studies should be done to look at the natural history of AP in HIV.

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APPENDIX I

WARD AMISSIONS SCREENING

Ward:

Medical:

Surgical:

Number of admissions:

Number with acute upper abdominal pain:

APPENDIX II

Case screening proforma

Name: _____

Sex: Age:

Occupation: _____ Residence: _____

Clinical features: Pain: _____

Abdominal findings: _____

Admitting diagnosis: _____

APPENDIX III

Consent form 1

Patient Information about the study and Consent form for HIV testing.

I am Dr. Njiru and am carrying a study on patients who have acute abdominal pain to find out how many could be suffering from acute pancreatitis. The pancreas is an important organ that produces juices that assist us in digesting food. I wish to find out the HIV status of these patients because it is known that HIV positive patients suffer from much more severe form of acute pancreatitis, so their disease needs to be recognized early and treated aggressively. HIV is spread through various ways including from a infected partner, through blood transfusions though this is an uncommon mode since blood is screened, sharing of contaminated needles and from a pregnant mother to her unborn child. Joining this study will mean that you will be aware of your HIV status and if positive can access antiretroviral medication from our comprehensive care clinic, be educated on how to reduce transmission to sexual partners and future children . If negative, you will be educated on how to stay negative. Furthermore, testing for the presence of acute pancreatitis will ensure your primary physicians are better placed to treat you.

Then:

I have explained to the patients all about HIV testing: Name:

Signature:

I have fully understood the importance and implications of having a HIV test,
as explained to me by the investigator: Signature:

APPENDIX IV

Consent Form 2

Patient information and consent form for the study (for HIV positive patients).

I am carrying out a study on presence of acute pancreatitis in patients with HIV and acute abdominal pain. Acute pancreatitis is a disease affecting the pancreas, an organ that produces chemicals that help us digest food. The disease prevents the organ from carrying out this function. Patients usually have abdominal pain when they have this condition.

Then:

If you agree to take part in the study, a full medical history will be taken, physical examination will be done and a number of investigations will be carried out on a blood sample taken from you

10mls of blood will be taken for serum amylase and lipase determination and CD4/CD8 cell counts. There will be minimal pain when taking the blood from you.

If any disease is detected it will be treated promptly. All information obtained is strictly confidential and will not be revealed to other persons without your prior consent. The quality of medical care given to you in this Hospital will not be compromised by your refusal to participate in this study.

Participation in the study is voluntary and you are free to withdraw at any time.

I _____ of _____ understand the above and give my consent participate in the study.

Signed _____

Date _____

I confirm that I have adequately explained to the patient the above.

Investigator _____

Date _____

APPENDIX V

Data sheet (for HIV negative and no consenting patients):

Number: Name:

Sex: Age:

Occupation:

Residence

Brief history:

1. Pain: Duration:

 Location:

 Character:

 Radiation:

 Relieving factors:

2. Nausea&/or vomiting: duration:

 Aggravating factors:

Systemic enquiry:

Yes

No

If yes, duration

R/S: Cough

 Chest pain

 Difficulty in breathing.

CVS: Palpitations

 Easy fatiguability.

CNS: Dizziness

 Confusion.

 Coma.

Hx of alcohol use:

Hx of ARV use (current):

Physical findings:

 General condition:

 Vital signs: Temp

 Pulse

 Respiratory rate

Blood pressure

Systemic examination:

Abdomen.

R/S

CVS

CNS

Other significant clinical problem found in patient; e.g. Opportunistic infections:

HIV status for those tested-negative:

APPENDIX VI

DATA SHEET FOR HIV POSITIVE PATIENTS:

Study No.

Name:

Sex: Age:

Occupation:

Residence

Brief history:

1. Pain: Duration:

 Location:

 Character:

 Radiation:

 Relieving factors:

 Aggravating factors:

2. Nausea &/or vomiting: Yes No If yes, duration:

Systemic enquiry: Yes No If yes, duration

CNS:Dizziness

 Confusion.

 Coma.

Hx of alcohol use:

Hx of ARV use (current):

Physical findings:

 General condition:

 Vital signs: Temp

 Pulse

 Respiratory rate

 Blood pressure

Opportunistic infections (if recorded in file):

Systemic examination:

Abdomen:	Parameter	Yes	No
	Soft		
	Tender		
	Rebound tenderness		
	Free fluid		
	Distended		
	Bowel sounds		
	Other (specify) _____.		
	CNS:	Unconscious	

Investigations:

Rapid HIV1 /2 Assay: Positive:

CD4 counts (cells/mm³):

Serum amylase levels (μ/l):

Serum lipase levels (μ/l):

APPENDIX VII

INSTANTSCREEN.RAPID HIV1/2 ASSAY FOR BLOOD, SERUM OR PLASMA.

Those who consented to the study had HIV testing done, whereby 20 μ l of blood obtained under aseptic technique by pricking the side of the fingertip was put in a capillary tube which then was transferred into a mixing bottle and a diluent solution added to it and shaken vigorously for at least 10 seconds, after which the mixture was transferred into a test device and a detector solution (solution 2) which had been shaken to resuspend all the sediments was added to it. After the solution had been absorbed, all the wash solution was emptied into the test device. The test device was then opened by twisting both halves against each other and the test membrane was removed by using the upper half of the device as a tool.

Results were read from the membrane, with one blue dot on the left of the membrane denoting a negative result, two blue dots a positive result and if no blue dot this indicated an incorrectly performed test or a problem with the sample e.g. antibody degradation ,thus the test was repeated.

APPENDIX VIII

AMYLASE ANALYSIS:

100 μ l of serum is mixed with a preincubated sample of the test solution containing 2-chloro-4-nitrophenyl- α -D maltotriose (CNP3). α Amylase hydrolyzes the CNP3 to release 2-chloro-4-nitrophenol (CNP2), maltotriose and glucose. The rate of formation of the 2-chloro-4 nitrophenol can be detected spectrophotometrically at 404 nm to give a direct measurement of α - amylase activity in the sample.

TURBIMETRIC ASSAY OF LIPASE.

Principle and procedure:

Lipase catalyzes the hydrolysis of fatty acids from an emulsion of oleic acid with a simultaneous increase in the turbidity of the reaction mixture. In practice, 100 μ l aliquot of serum is added to a preincubated stabilized triolein emulsion containing sodium deoxycholate (35mmol/l) , CaCl(100 μ mol/L) and porcine colipase (6mg/L) at pH 9.2 with TRIS buffer at 26 mmol/L and triolein at 300 μ l/L. Assay temperature is 30oc. Absorbance at 340nm is read after 4 min. The absorbance per minute is taken as a measure of lipase activity. This method requires the use of a lipase calibrator. The commercially available Roche Diagnostics kit can be optimized by supplementing the deoxycholate concentration from 19 to 35 mmol/L and the colipase from 3 to 6 mg/L (Refer to the kit insert).

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APPENDIX IX

CD4 CELL COUNTS; MONOCLONAL ANTIBODY TESTING BY BIO1 FROM BIOTECHNOLOGIE DIAGNOSTICI (BIO-D)

METHOD;

Add 100 μ l of whole blood to a staining tube. To this tube add 10 μ l of CD4PE REAGENT. Mix gently and incubate 20-30 minutes at 2-8 degrees centigrade. Add 2 mls of BIO LISANTE (code BDL001). Vortex tube gently (no more than 2 seconds) then incubate for 10 minutes at room temperature in the dark. Wash cells two times with 3 mls of PBS. Resuspend cells in 0.5 - 1 ml of PBS and analyse by flow cytometry as outlined below.

FLOW CYTOMETRY ANALYSIS:

CD4PE immunofluorescence analysis can be performed on a flow cytometer equipped with an excitation source of 488nm and fitted with logarithmic amplifiers

CD8 cell counts follow the same procedure as for CD4 counts except that to the blood is added CD8PE reagent and not the CD4PE reagent.

APPENDIX X

SAMPLE SIZE CALCULATION:

The minimum sample size is 100. This is calculated using the following formula

$$n = \frac{(Z_{1-\alpha/2})^2 P (1-p)}{d^2}$$

Where n = sample size

Z = standard normal division

P = Estimated prevalence of the characteristics (10%) for AP in HIV positive patients.

d = desired degree of precision or accuracy (10%)

$(Z_{1-\alpha/2}) = 1.96$, corresponding to a significance level of 0.05.

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