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A. E. O. OTEDO, J. O. OTIENO, C. F. OTIENO and G.O. OYOO

ABSTRACT

***Background*: AIDS (acquired immunodeficiency syndrome) related cholangiopathy results from the inflammation of biliary tree and gall bladder. It is an uncommon manifestation of advanced HIV/AIDS that was associated with poor prognosis prior to the anti-retroviral therapy era. It commonly presents with biliary tree pain. Jaundice is uncommon and other symptoms include fever and vague abdominal pains. Patients have low CD4+ cell counts of between 50-200 cells/μl. It is rarely fatal but presents with marked epigastric pain, which affects the quality of life. Management is mainly conservative or surgical in selected cases.**

***Objective*: To describe AIDS-related cholangiopathy and the associated ultrasound features, immunological and biochemical markers in a cohort of HIV positive patients.**

***Design*: Longitudinal, consecutive entry, prospective study.**

***Setting*: Kisumu District Hospital medical and surgical wards, Mater and Nairobi west hospitals between January 2001 and May 2007.**

***Subjects*: Seventy nine patients with cholangiopathy/ cholecystitis were included in the study.**

***Intervention*: Antibiotics, analgesics, intravenous fluids/or surgery was offered to the patients.**

***Main outcome measures*: Clinical, biochemical and ultrasound features, management (surgical or conservative), CD4+ cell counts.**

***Results*: One hundred and two (42 males and 60 females) patients were screened. Twenty three (ten males and 13 females) patients were excluded. Seventy nine (32 males and 47 females) patients were included in the study. Their mean age was 38.8 ± 11.5 (17-70) years. The mean CD4+ cell count and white cell count were 122.4 ± 85.8 cells/μl (3.0-380) and 12.8 ± 4.5 X10^3/μl respectively. Mean ALT, AST and alkaline phosphatase were 413.4 ± 126.4 IU/L (range 160-800), 340.5 ± 113.3 IU/L (range 92-562) and 678.8 ± 535.9 IU/L (range 55-2790). Ultrasound showed varied features: Isolated dilated intrahepatic bile ducts in eight patients, enlarged gall bladder with thickened wall (cholecystitis) in thirty one patients, thickened common bile duct wall and cholecytitis and dilated intrahepatic and common bile duct, ten each, eleven had cholecystitis and gallstones and nine had normal ultrasound scan. The co-morbidities include; PTB in four patients, six had pneumocystis jiroveci pneumonia, two had cryptococcus meningitis, three had cryptosporidium/ microsporidium, ten had oral candidiasis, four had Kaposi's Sarcoma, seven had herpes zoster virus, one had broncho-pneumonia, ten had diarrhoea and thirty two had no infections. Seven patients had cholecystectomy done successfully and 72 patients were managed conservatively.**

***Conclusion*: AIDS- related cholangiopathy has diffuse biliary tree abnormalities. The patients had very low mean CD4+ cell counts signifying severe immunosuppression. The co-morbidities were observed to occur at very low CD4+ cell counts. Management is both conservative and surgical.**

INTRODUCTION

Biliary duct abnormality in patients with HIV/AIDS (AIDS cholangiopathy/cholangitis) was first described in 1988 by Mangulis *et al* (1). It results from inflammation of gall bladder and biliary tree. It is an uncommon manifestation of advanced HIV/AIDS and commonly presents with billiary tree pain. Jaundice is rare and cholangiopathy occurs at very low CD4+ cell counts of 50-200 cells/μl (1). There can be a spectrum of involvement ranging from acute acalculous cholecystitis to papillary stenosis with bile duct obstruction or a diffuse disease with sclerosing cholangitis-like picture with gall bladder involvement (1, 2). This was further characterised endoscopically by endoscopic retrograde cholangio-pancreatography (ERCP) in the late 1980's (2). AIDS related cholangiopathy/cholangitis has been reported in few series and reports. It causes a lot of morbidity due to the pain which reduces the quality of life of patients (3).

The aetiology of AIDS cholangiopathy/cholangitis remains unclear. The likely causes include opportunistic infections like cryptosporidium, cytomegalovirus (CMV) and microsporidium and rarely, Kaposi's sarcoma (3). AIDS cholangiopathy/cholangitis is rarely fatal and other AIDS-related illnesses and progression of immunodeficiency are the usual causes of death for these patients (4–7). AIDS cholangiopathy/cholangitis may present with less acute right upper quadrant pain, fever and nausea with cholestatic liver enzyme abnormalities. In acute acalculous cholecystitis, ultrasound, C-T Scan or MRI scan shows a thickened gall bladder wall in the absence of cholelithiasis. In patients who are fit for anaesthesia, cholecystectomy is usually required and HIV/AIDS is not a reason to defer surgery (8–11). Some of the patients can be asymptomatic and this makes the prevalence of this disease entity unknown (5). Indeed, the prevalence of HIV/AIDS cholangiopathy is poorly understood and data are scanty.

Longitudinal studies evaluating the prevalence of cholangitis/cholangiopathy or other hepato-biliary disorders in HIV/AIDS patients in sub-Saharan Africa is scanty hence the rationale of this study.

MATERIALS AND METHODS

One hundred and two (42 males and 60 females) patients with cholecystitis/cholangitis were screened. These were patients who presented with marked right upper quadrant pain with or without jaundice. The patients included were HIV positive and had cholecystitis/cholangiopathy. The patients excluded had cholangitis/cholecystitis and were HIV negative or declined HIV testing. Twenty three patients were excluded (20 HIV negative, three declined HIV test).

A total of 79 patients (32 males and 47 females) who were seen over a period of 50 months (January 2003 – May 2007), were recruited into the study. The study was conducted at Kisumu District Hospital (medical outpatient clinic, medical and surgical wards) and Nairobi Rheumatology Clinic and Mater Hospital. It included all the patients who were consecutively enrolled and met the inclusion criteria. The ethics and standards committee at the Kisumu District Hospital approved the study. A signed, informed consent was obtained from each patient, and < 18 year olds, signed by parent or guardian. Some, nine, were patients with known HIV positive sero-status and others (70), were newly diagnosed and diagnostic counselling and testing (pre- and post-) was done and sustained. The following information was obtained from each patient and their records: Socio-demographic data, abdominal ultrasound scan, eight millilitres of blood taken under aseptic condition from the cubital fossa. The patients were clinically examined for fever, jaundice, right upper quadrant pain and opportunistic infections and other co-morbidities by one of the authors (MDs).

The eight millilitres of blood which was drawn from each patient was divided into two equal aliquots of four millilitres each. Serum was separated from one aliquot soon after collection and used for serology for HIV (human immunodeficiency virus) and hepatitis B virus surface antigen (HBsAg) by ELISA test. The other four millilitres of whole blood was used for analysis of CD4+ cell count, complete blood count, liver function tests- alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP). CD4+ cell count was done using the FACS (fluorescent activated cell sorter) flow cytometry count method. The FACS flow cytometry machine has a sensitivity of 1-2000 cells/μl. Complete blood count was done by coulter counter machine.

ALT and AST analysis was done using the technicon RA 1000 machine (Technicon RA systems No. sm – 0034 D91 and No. sm 4 – 0137, D 91, 1996) and ALP was analysed using reverse passive haemagglutination test (R.P.H.A) method.

HIV test was done using ELISA method with a sensitivity and specificity of 99.9% and 98.9%

respectively; HBsAg was analysed using Microelisa system, hepanostika (HBsAg Uni-FormII).

The presence of cholecystitis/ cholangiopathy was defined as elevated AST, ALT and/or ALP and clinical presentation of right upper quadrant pain/ tenderness, jaundice, fever and ultrasound description of cholecystitis/ biliary tree abnormality.

The raw data were cleaned, entered into a computer and analysed using SPSS package. The results were expressed as mean ± SD, tables and bar charts.

Intervention: All the patients in the study were appropriately managed conservatively as inpatients on intravenous antibiotics/analgesics fluids or surgery (Cholecystectomy). Seven patients with severe pruritus and sepsis had cholecystectomy done, given antibiotics and did well post-operatively and recovered. Highly active anti-retroviral therapy (HAART) was given to the patients who consented and could afford. The study was carried out during the period when the national ART access programme by Ministry of health had not been rolled out.

RESULTS

The results were expressed as mean ± SD, figures, tables and bar charts.

Seventy nine (32 males and 47 females) were included in the study. The mean age was 38.8 ± 11.5 years (17-70). All the 79 patients were HIV positive and had right upper quadrant tenderness, sixty nine were jaundiced and fifty had fever.

The four major clinical signs were jaundice, fever, diarrhoea and right upper quadrant abdominal pain present in 40, 63.3, 8 and 90% of patients respectively.

The mean CD4+ cell count was 122.4 ± 85.8 cells/μl (range, 3.0-380). Abnormal liver functions tests were present in all the patients. The serum level of Alkaline phosphatase was most persistently elevated feature (95% of patients) with a mean elevation of 678.8 ± 535.9 IU/L, (range 55-2790) (12xULN).

Serum AST and ALT was raised in 90 and 96% of patients respectively. Mean AST was 340.5 ± 113.3 (92-562) IU/L (4-20XULN) and ALT was 413.4 ± 126.4 (160-800) IU/L (3-13XULN). Mean white blood cell count was 12.8 ± 4.5 $X10^3$/ml (2.2-20.1 $X10^3$). Fifty patients had mean leucocytosis and neutrophilia of 12.8 X 10^3/ml and 81.2 ± 3% respectively. Fifty four (68.4%) patients were able to afford, consented and were initiated on HAART.

Thirty two (40.5%) patients had no co-infection or other morbidity and 47 (59.5%) patients had co-infection, Table 3.

Abdominal ultrasound features were varied and included: dilated intrahepatic and common bile duct (ten patients), isolated dilatation of intraheptic bile ducts (eight patients), enlarged gall bladder with thickened wall (cholecystitis) (thirty one patients), thickened common bile duct wall and cholecystitis ten, cholecystitis and gall stones in eleven patients and normal ultrasound scan in nine. Seven of the eleven patients with gallstones also had sepsis and severe pruritus and had cholecystectomy done. Seventy two (91.1%) patients had contracted or thickened gall bladder wall with sludge/abnormal biliary tree and were managed conservatively on antibiotics, iv fluids and analgesics as hospitalised patients.

However, nine patients (11%) had normal abdominal ultrasound scan and were diagnosed to have cholangiopathy/cholangitis by the presence of jaundice, diffuse abdominal pains and abnormal biochemical features.

Table 1

Patient flow through
The study

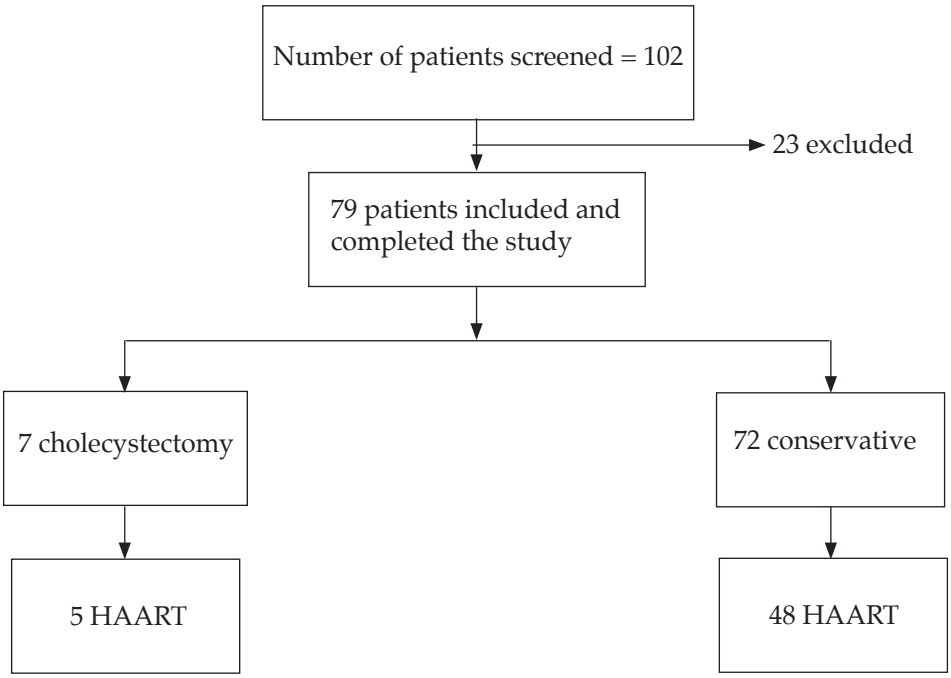

Figure 1

Age distribution of HIV patients who had cholecytitis.

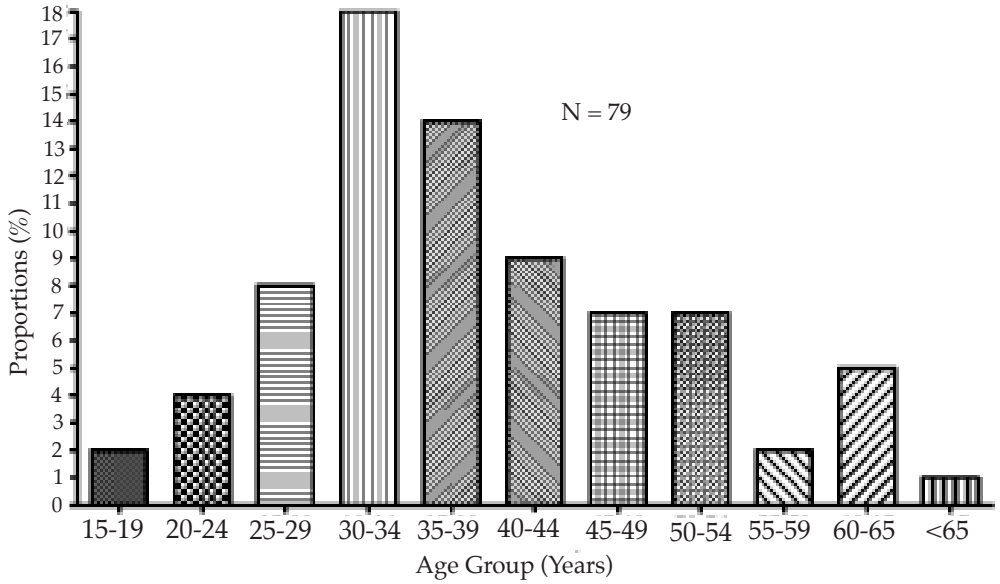

Figure 2

Age and gender distribution of HIV patients who had cholecytitis

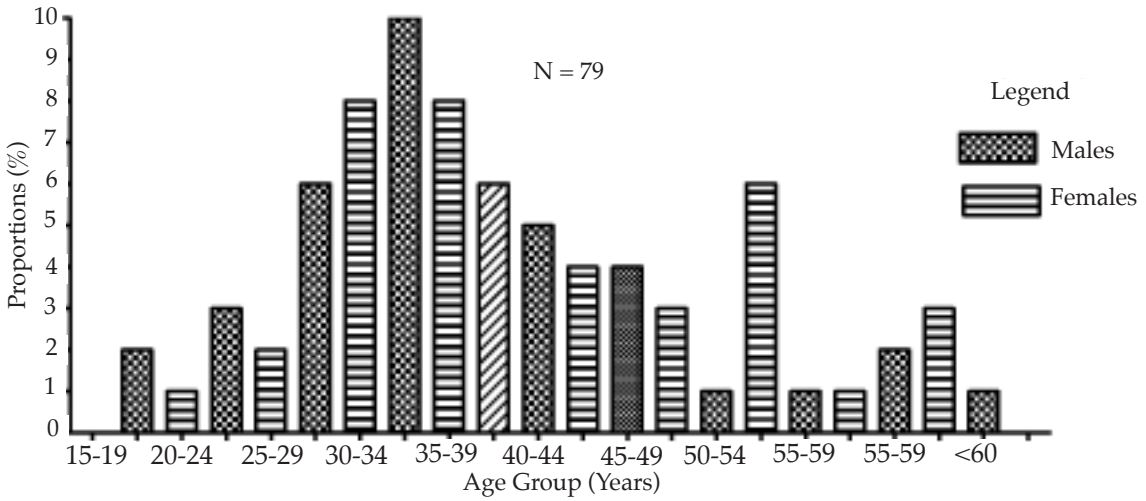

Table 2

Laboratory Features of the 79 patients with HIV/AIDS and Cholangiopathy.

Feature	Range	Mean	± SD
ALP (IU/L)	55-2790	678.8	± 535.9
AST (5-40 IU/L)	92-562	340.5	± 113.3
ALT (5-37 IU/L)	160-800	413.4	± 126.4
Bilirubin (1-17μmol/L)			
CD4+ cell count (cells/ml)	3.0-380	122.4	± 85.8
White blood cell count	2.2-20.1	12.8	± 4.5 X 10^3
Neutrophil (45-70%)		81.2	± 3

ALP - Alkaline phosphatase
Ast - Aspartate transaminase
ALT - Alanine transaminase

Table 3

Baseline characteristics and CDC-staging of the 79 HIV positive patients with cholangiopathy/cholecystitis.

Parameter	Value
M:F ratio	42:60 (1:1.4)
Mean age (years)	38.8 ± 11.5 (17-70)
CD4+ cell count (cells/μl)	
Mean	122.4 ± 85.8 (3.0-380)
> 500	1(1.3%)
350-499	1(1.3%)
200-349	11(13.9%)
< 200	66(83.5%)
***CDC clinical staging**	
A	4(5.0)
B	10(12.7%)
C	65(82.3%)
ALP (64-306 IU/L)	678.8 ±535.9 (55-2790)
AST (5-40 IU/L)	340.5 ±113.3 (92-562)
ALT (5-37 IU/L)	413.4 ± 126.4 (160-800)
Bilirubin(1-17μmol/L)	
White blood cell count(4-10.3 X 10^3/μl)	12.8 ± 4.5 (2.2-20.1)
Neutrophil count (40-70%)	81.2± 3
Ultrasound features:	
Cholangitis/cholangiopathy	70
Normal	9

*CDC-Centres for Disease Control. Source, Morb. Mort. Week. Rep. 42 (No. RR-17), Dec. 18.1992 (A-asymptomatic PGL, B-symptomatic, not A or C conditions, C-AIDS defining illness). ALP-alkaline phosphatese, ALT-alanine transaminase, AST-aspartate transaminase.

Table 4

Opportunistic infections in the 79 patients with HIV and cholangiopathy/Cholecystitis.

No. of patients	0.Is
4	PTB (pulmonary tuberculosis)
6	PJP (pneumocystis jiroveci pneumonia))
2	Cryptococcous
3	Cryptosporidium/microsporidium
10	Oral candidiasis
4	Kaposi's Sarcoma
7	Herpes Zoster Virus
11	Bronchopneumonia
10	Diarrhoea 10
32	No co-infection

Table 4
Ultrasound features in the 79 patients with HIV and cholangiopathy/cholecystitis.

Anatomy/Event	Number
Dilated intrahepatic and common bile duct	10
Isolated dilation of intrahepatic bile duct	8
Enlarged gall bladder with thickened wall, (cholecystitis)	31
Thickened common bile duct wall and cholecystitis	10
Cholecystitis and gall stones	11
Normal ultrasound	9

DISCUSSION

This series included 79 patients with AIDS-related cholangitis/cholangiopathy. The diagnosis was based on the four clinical signs; Jaundice, fever, diarrhoea and right upper quadrant abdominal pain and tenderness respectively, ultrasound findings and biochemical results. Thirty two (40.5%) patients had no co-morbidity while 47(59.5%) patients had co-infection or other morbidity (pulmonary tuberculosis, pneumocystis jiroveci pneumonia Cryptococcus meningitis, Kaposi's sarcoma (skin, buccal), herpes zoster virus, chronic diarrhoea and cryptosporidium). The co-morbidities usually occur at low CD4+ cell counts, which was evident in these patients. Other studies have also demonstrated that HIV-related cholangiopathy complicates severe immuno-suppression. Patients are generally in poor condition and often have co-existing infections and or malignancies like Kaposi's sarcoma and non Hodgkin's lymphoma (15).

These patients had very low CD4+ cell counts, with a mean of 122.4± 85.8 cells/μl which signifies severe immuno-suppression. Research has shown that higher CD4+ cell and absolute lymphocyte counts and a shorter duration of HIV infection prior cholongitis are factors associated with better prognosis. The disturbance of liver function tests did not influence survival of patients (4, 5, 13, 14).

Worse outcome measures are associated with high ALP levels, underlying immuno-suppression with a history of any opportunistic infections (9). HAART administration accounts for the recent dramatic improvement in survival of patients with AIDS cholangiopathy/cholangitis (9). Other major prognostic factors include CD4+ cell counts, duration of HIV sero-positivity and the patient's age (4, 5). In this cohort 47 patients had opportunistic infections and had poor prognosis and 32 patients had no opportunistic infection

Ultrasound defines the morphological study and anatomy of the billiary system and even in advanced centres, is performed prior endoscopic retrograde cholangiopancreatography (ERCP) (4). In 2-3% of cases, ultrasound may miss gall bladder wall and bile duct thickening, which is demonstrable by computerised tomographic (C-T) scan (4). ERCP is both diagnostic and therapeutic and precisely defines the location of the billiary tree abnormality. In cases of papillary stenosis defined as a common bile duct dilatation of >10 mm, ERCP-guided endoscopic sphincterotomy can then be performed (4,13). Sphincterotomy relieves pain and the patient's quality of life improves.

ERCP is not available in our primary and secondary healthcare facilities and patients are managed conservatively. ECRP, if available allows for collection of bile for polymerase chain reaction (PCR) and micro-biological analysis for opportunistic infections (Cytomegalovirus, microsporidium, cryptosporidium and cyclospora), papillary biopsy if a tumour (primary or secondary) is suspected and endoscopic sphincterotomy. ECRP also enables dilatation of the papilla and insertion of a stent when indicated (6, 12).

Bile duct dilatation and wall thickening on abdominal ultrasound are suggestive of cholangiopathy. Nevertheless, in this series, abdominal ultrasound was normal in nine(11%) patients. Ultra sound has low specifity for diagnosing ischaemic acalculuous cholecystitis, which may be due to HIV vasculitis (14).

Seven patients (8.9%) had cholecystectomy done. They had choledocholithiasis, cholecystitis, sepsis and marked skin pruritus. They improved post-operatively and were discharged. Eleven patients

(14%) had cholelithiasis and 68 patients (86%) had no cholelithiasis but abnormal liver function tests and right upper quadrant tenderness and are described as acalculous cholecystitis. This is usually suspected in HIV / AIDS patients presenting with vague abdominal pains and or diarrhoea with or without jaundice and fever. Causes of acalculous cholecystitis include cytomegalovirus (CMV), cryptosporidium, Kaposi's sarcoma, mycobacterium avium intracellulare complex (MAC), isospora belli, pneumocystis jiroveci pneumonia and HIV itself (9,14,16-18). Suffice it to note that some studies have demonstrated multiple causes of acalculuous cholecystis, that is, CMV and cryptosporidium, and PJP and isospora belli (15). These infections are thought to cause ductal strictures in HIV / AIDS cholangiopathy (19, 20).

Patients with HIV / AIDS with vague abdominal symptoms, right upper quadrant pain and tenderness should be evaluated for AIDS related cholangiopathy.

REFERENCES

1. Margulis S.I., Honig S.L., Soave R., *et al*. Biliary tract obstruction in the acquired Immunodeficiency syndrome. *Ann. Intern. Med.* 1986; **105**; 207 – 210.
2. Cello P.J. Acquired immunodeficiency syndrome cholangiopathy; spectrum of disease. *Am. J. Med* 1989; **86**; 539 – 546.
3. Wilcox C.M., and Monkemuller K.E. Hepatobiliary disease in patients with AIDS: Focus on AIDS cholangiopathy and gall bladder disease. *Dig Dis*. 1998; **16**: 205 – 213.
4. Ducreux M., Buffet C., Lamy P. *et al*. Diagnosis and prognosis of AIDS – related cholangitis. *AIDS* 1995; **9**; 875 – 878.
5. Forbes A., Blanshard C., and Gazzard B. Natural history of AIDS related sclerosing cholangitis: A study of 20 cases. *Gutt*. 1993: **34**: 116 – 121.
6. Beuche H., Housset C, Dumont J.L. *et al*. AIDS related cholangitis: Diagnostic features and course in 15 patients. *J. Hepatol.* 1993; **17**; 34 – 39.
7. Vakil N.B., Schwartz S.M., Buggy B.P, *et al*. Biliary crytosporidosis in HIV-infected people after the waterborne outbreak of cryptosporidosis in Milwaukee. *N. Engl. J. Med* 1996; **334**: 19 – 23.
8. Osmond D., Charlebois E., Lang W. *et al*. Changes in AIDS survival time in Two San Francisco Cohorts of homosexual men, 1983 – 1993. *JAMA* 1994; **271**: 1081–1087.
9. Wei-Fang Ko, Cello J.P., Rogers S.J. and Lecours A. Prognostic factors for the survival of patients with AIDS cholangiopathy. *Am. J. Gastro*. 2003; **98**: (10); 2176 – 2181.
10. Cappell M.S. Hepatobiliary manifestations of the acquired immune deficiency syndrome. *Am. J. Gastro*.1991; **86**, : 1 – 15.
11. Lowy A.M. and Barie P.S. Laparatomy in patients infected with human immunodeficiency virus: Indications and outcome. *Br J. Surg*.1994: **81**: 912 – 5.
12. Das C.J and Sharma R. Hepatobiliary and pancreatic: AIDS cholangiopathy. *J. Gastronterol. Hepatol*. 2006; **21**: 744.
13. Mercey D.E., Loveday C., Miller R.F. Sclerosing cholangitis rapidly following anti- HIV-1 seroconversion. *Genitourin. Med*. 1991; **67**: 239 – 243.
14. Vibert E. and Azoulay D. Alithiasic cholecystitis in the Adult: Etiologies, diagnosis and treatment. *Annals de chirugie* 2002; **127**; 330 – 336.
15. Benhamou Y., Caumes E., Gerosa Y., *et al*. AIDS related cholangiopathy. Critical analysis of a prospective series of 26 patients. *Dig. Dis. Sci*. 1993: **38**; 1113 – 1118.
16. Walden D.T. Biliary problems in people with HIV Disease. Curr. Treat. Options. *Gastroenterol*. 1999; **2**: 147 – 153.
17. French A.L., Beaudet L.M., Benator D.A., Levy C.S., Kass M., and Orenstein J.M. Cholecystectomy in patients with AIDS: Clinicopathological correlations in 107 cases. *Clin. Infect. Dis*. 1995: **4**: 852 – 858.
18. Fantry L.E. and Sun C.C. Mycobacterium avium complex- associated Cholecystitis in an HIV – infected woman. AIDS patient. Care. STDs. 2002; **16**; 201 –204.
19. Reiter G.S. Abdominal pain in an HIV – Infected man. *AIDS Clin. Care*. 1995; **7**; 92 – 96.
20. Lefkowitch J.H. The liver in AIDS. Semin. *Liver Dis*. 1997; **17**: 335 – 344.