

# Hepatobiliary diseases in patients with human immunodeficiency virus (HIV) treated with non highly active anti-retroviral therapy: frequency and clinical manifestations

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## Abstract

**Objective:** To evaluate the frequency of hepatobiliary diseases and the clinical manifestations in patients with HIV treated with non highly active anti-retroviral therapy. **Methods:** Seven hundred clinical records of patients with HIV infection who entered the Instituto Nacional de Ciencias Médicas y de la Nutrición Salvador Zubirán from January 1987 to December 1996 were reviewed. All patients with alterations associated to hepatobiliary disease and/or liver function tests derangement throughout the clinical development of their disease were included. Demographic variables, date of diagnosis and clinical stage of the disease, as well as the presentation forms, diagnostic approach and image studies were analyzed. **Results:** One hundred and sixty-one patients (22.8%) with hepatobiliary manifestations were found. The average time between the HIV diagnosis and the presentation of hepatic manifestations was 2-12 years. The majority of patients 124/161 (77%) did not show clinical signs of liver damage. The diagnostic suspicion was established by the presence of alkaline phosphatase above normal in 29% and alkaline phosphatase plus aminotransferases above normal in 45%. Hepatomegaly and jaundice were present in 18% and 4% of the patients, respectively. The most frequent ul-

trasonographic diagnosis were hepatomegaly (40%) and steatosis (30%). Liver biopsies were performed in 85 (51%) of the patients. The main histologic diagnoses were granulomatous hepatitis (29%), steatosis plus granulomatous hepatitis (19.5%), and steatosis alone (14.6%). Microorganisms were isolated in 27.9% being the most frequent *Mycobacterium tuberculosis* (26.6%), *Histoplasma capsulatum* (20%), *Cytomegalovirus* (13.3%), and *Mycobacterium avium intracellulare* (11%). The HBsAg was positive in 21 of the 69 patients (30.4%). **Conclusions:** The clinical presentation was asymptomatic in most of cases and the main etiology could be explained by the presence of associated infections, granulomatoses and liver steatosis.

**Key words:** Acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus (HIV), liver, hepatomegaly, granuloma, steatosis, cholangitis, hepatitis, infection.

## Introduction

In many cases, the diagnosis of hepatic or biliary affection establishes or suggests the diagnosis for AIDS in a patient infected by the Human Immunodeficiency Virus (HIV). This affection may be determined by specific pathogenic microorganisms and conditioned to the degree of immunosuppression, in early stage (CD4 > 500 cells/mm<sup>3</sup>) liver complications normally show specific processes such as hepatotoxicity associated to drugs, primary neoplasm, or hepatotropic virus infection. As immunodeficiency progresses (CD4 < 200 cells/mm<sup>3</sup>), the liver is involved by systemic opportunistic infection such as atypical mycobacteriosis, deep mycosis, or cytomegalovirus (CMV), including other. It is worth noticing that, in most cases, the liver disease *per se* is not the primary cause of death in this group of patients.<sup>1-3</sup>

Hepatobiliary disease may vary from its asymptomatic form associated to biochemical alterations (increased alkaline phosphatase and aminotransferases), discomfort in the right hypochondrium, with hepatomegaly, jaundice, encephalopathy, or non-specific symptoms such as general discom-

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fort and anorexia. In more advanced stages, the disease may show common symptoms to other extrahepatic illnesses.<sup>4-9</sup>

The aim of this study was to retrospectively evaluate the clinical, biochemical, and anatomopathological characteristics in HIV patients (treated with non highly active anti-retroviral therapy) and associated hepatobiliary disease.

## Methods

### Criteria for selecting patients

We reviewed the clinical records of all patients diagnosed with HIV that were admitted to the Instituto Nacional de Ciencias Médicas y de la Nutrición Salvador Zubirán during the period from January 1987 through December 1996 all patients were treated with non highly active anti-retroviral therapy. The search was performed based on the diagnosis at the time of discharge from hospital. All patients diagnosed with HIV infection and associated hepatobiliary affection and/or with liver function tests derangement throughout the clinical development of their disease were included.

### Clinical Assessment

The variable demographics that were analyzed included age, gender, use of alcohol, history of transfusions, date of diagnosis and stage of disease, history of liver problems, type of hepatic and/or biliary manifestation at the time of diagnosis, as well as the final diagnosis at the time of discharge or decease, use of medication, time infected by HIV, and the start of hepatobiliary manifestations.

### b) Biochemical Assessment

We investigated the presence of liver function tests (LFT) derangement. These included levels of bilirubin (total, direct and indirect), aminotransferases (AST and ALT), alkaline phosphate, albumin, globulins, gammaglutamyltranspeptidase (GGT), prothrombin time, viral markers for Hepatitis A Virus (HAV) (IgG and IgM), Hepatitis B Virus (HBV) [Hepatitis B surface antigen(HBsAg), Hepatitis B core antibody (Anti-HBc) Hepatitis B e particle antibody, (AntiHBe), cytomegalovirus (CMV) and other hepatotropic viruses.

### c) Assessment by Imaging and Endoscopy

Main alterations were reported by ultrasound and/or computerized tomography. In cases where an endoscopic retrograde cholangiopancreatography (ERCP) was performed, the findings were recorded.

### Histopathological Assessment

In cases where a hepatic biopsy was performed, was determined the type and degree of hepatic and/or biliary affection.

### e) Microbiological Assessment

The main microorganisms that may have a direct effect on the hepatobiliary manifestations were searched.

### Statistical Analysis

Results are shown as mean  $\pm$  standard deviation, percentages, and intervals.

## Results

A total of 700 clinical records of patients with HIV infection who entered at the Instituto Nacional de Ciencias Médicas y de la Nutrición "Salvador Zubirán" from January 1987 to December 1996 were reviewed, 161 patients (22.8%) showed hepatobiliary manifestations, 135 (84%) males and 26 (16%) females. The male:female ratio was 5.1:1. The interval between the HIV infection was diagnosed and the hepatic derangement appeared was 2-12 years. The use of alcohol was present in 105 (66%) of the cases and a previous history of liver disease in 7 (4%) of the cases. A majority of 124 patients (77%) showed no symptoms of liver disease at the time of the diagnosis. Hepatomegaly and jaundice were present in 30 (18%) and 6 (4%) of the patients, respectively.

The diagnosis suspicion was supported by the presence of altered LFT, with high alkaline phosphatase in 46 (29%), and high alkaline phosphatase plus high aminotransferases in 73 (45%) of the patients.

The findings in the biochemical tests performed on HIV patients included total bilirubin of  $1 \pm 0.5$  mg/dL, direct bilirubin of  $1 \pm 2$  mg/dL, alkaline phosphate of  $346 \pm 30$  UI/L, AST  $113 \pm 10$  UI/dL and ALT  $92 \pm 8$  UI/dL. The HBsAg was positive in 21 out of 69 patients (30.4%). Positive serology for cytomegalovirus was found in 22 out of 33 patients (66%).

Hepatobiliary ultrasounds were performed on 60 patients. The most frequent diagnosis were hepatomegaly in 24 (40%), steatosis in 18 (30%).

A computerized axial tomography performed on 42 (26%) patients revealed hepatomegaly in 8 (36%), focal lesions in 6 (27%), steatosis in 5 (23%), and bile duct dilatation in 3 (14%). In 12 (35%) of the cases, the computerized tomography showed normal results.

An ERCP performed on 4 patients with jaundice reported the followings results: normal (1 patient), distal choledochal obstruction (1 patient), biliary fistula (1 patient), and non-specific derangement (1 patient). In this series we found no patient with sclerosing cholangitis associated to HIV.

Liver biopsies were performed in 85 (51%) of the patients as part of their diagnostic assessment. The main diagnosis in order of frequency were: granulomatous hepatitis in 24 (29.2%), steatosis + granulomatous hepatitis in 16 (19.5%), and steatosis in 12 (14.2%). Other diagnoses are displayed in *table I*.

Microorganisms were isolated in 27.9% of the patients. The most frequent one was *Mycobacterium tuberculosis*, found in 12 (26.6%) of the patients. *Histoplasma capsulatum* was found in 9 (20%), *cytomegalovirus* in 6 (13.3%), *Mycobacterium avium intracellulare* in 5 (11.1%), *Cryptococcus neoformans* and pathogenic bacteria in 4 (8.8%) patients. Two patients were infected by *Pseudomonas sp.*, one by *Salmonella typhi*, and another by *Escherichia coli* (Table II).

## Discussion

Although in other series have been reported that two thirds of AIDS patients have some kind of liver derangement manifested as hepatomegaly or altered LFT at some time of their disease, we could only demonstrated hepatobiliary disease in 22.8%. It is possible we identified some patients in early stages of HIV infection. The time of appearance of liver damage since the time HIV infection was acquired to the diagnosis of liver derangement ranges greatly from 2 to 12 years and it is most of the times asymptomatic (77%),<sup>10</sup> probably the derangements of LFT in initial phases are associated to viral replication and in more advanced disease could be associated to the immunosuppression state, because 27.9% of patients had opportunistic infections, common findings in patients with immunosuppression. Hepatomegaly and jaundice were present in 18% and 4% of the patients, respectively. Some retrospective studies have shown that hepatomegaly, as well as other alterations in the LFT in the form of high alkaline phosphatase and/or ami-

notransferases –which in our series resulted in 29% and 45%, respectively– are explained by some subjacent intraparenchymatous disease.<sup>11,12</sup>

The LFT may help establish a diagnosis. Hepatocellular affection (hypertransaminasemia 3 or 4 times greater than normal values) may be considered to be due to viral hepatitis, drug toxicity, ischemic hepatitis, and other. In the other hand, the high serum levels of alkaline phosphatase (cholestatic pattern) may indicate an obstruction in the bile flow or a granulomatous illness (*Mycobacterium tuberculosis*, mycosis, etc.).

As in other series reported,<sup>4</sup> there was an outstanding elevation in the levels of alkaline phosphatase (alone or associated to hypertransaminasemia) and it was associated to granulomatosis and steatosis. These affections may be manifested as cholestasis in the LFT.<sup>13</sup> The cases of reported hypertransaminasemia may be associated to viral hepatitis episodes or drug toxicity. In this study, the association between HIV and the HBsAg was 30.4% and could explain the elevation of the LFT, but the design of this study and the lack of HCV marker in most of our patients, it is not possible to establish a specific cause of the derangements of the LFT.

In most cases hepatomegaly is related to the presence of steatosis or granuloma, Kaposi's sarcoma or lymphoma.<sup>14</sup> Hepatic biopsy results show steatosis and granuloma in 29.2% and 14.6%, respectively, and a combination of both pathologies in 19.5% of the samples. Lymphoma and active chronic hepatitis were found in 3.6% of the patients.

Some isolated intrahepatic infections may be found in this group of patients. In our study we found tuberculosis and histoplasmosis as one of the causes for the altered results of the liver function tests manifested by the presence of granulomas in the hepatic tissue biopsy.

In general, patients who develop hepatic histoplasmosis also present a systemic illness, patients with AIDS develop a minimal granulomatous response and the isolation of the microorganisms requires of at least six weeks.<sup>15-17</sup>

Hepatic granulomatosis is the main pathology found and in most cases, these are caused by *Mycobacterium avium intracellulare* (MAI). A noticeable fact is that previously reported studies demonstrate that MAI may be found in 57% of the cases,<sup>18</sup> in our study we found it in only 11.1% of the samples, according with more recent data.<sup>19</sup>

Steatosis was found to be associated to the presence of granuloma in 19.5% of the cases and it was the second cause for the altered hepatic function tests found in the hepatic biopsy. In most cases, fatty liver infiltration was found to be macrovesicular, which may be diffuse or lobular. The pathogenesis of this condition is very complex and it is thought to be related to the effects of circulating cytokines such as the tumor necrosis factor, interleukin and interferon.<sup>21</sup>

The biliary affection was found in the 8.8% of the patients. Hepatic cholestasis diseases caused by polymicrobial infections including CMV, *criptosporidium* and *mi-*

**Table I.** Main histological findings in the hepatic biopsy in patients infected with HIV.

Histological diagnosis	N = 82	%
Granuloma	24	29.2
Steatosis + Granuloma	16	19.5
Steatosis	12	14.6
Lymphoma	3	3.6
Cholangitis	3	3.6
Active Chronic Hepatitis	3	3.6
Other	15	17

**Table II.** Main microorganisms found in HIV patients during the hepatic biopsy.

Isolated Microorganisms	N = 45	%
<i>Mycobacterium tuberculosis</i>	12	26.6
<i>Histoplasma capsulatum</i>	9	20
<i>Cytomegalovirus</i> *	6	13.3
<i>Mycobacterium avium intracellulare</i>	5	11.1
<i>Cryptococcus neoformans</i>	4	8.8
Pyogenic Bacteria	4	8.8
Other	5	11

\* Inclusions present.

*crosporidium* are currently recognized as an important cause of cholangitis and may be similar to primary sclerosing cholangitis, thus, being named as HIV-related cholangiopathy.<sup>20</sup> ERCP may show alterations to the hepatic ducts. However, we found no evidential data of biliary obstruction or cholangitis in this study.

The percentage of patients with HIV and the HBsAg was of 30.4%, the presence of active chronic hepatitis was confirmed in three cases (3.6%). The frequency of viral markers is higher in HIV patients.<sup>21</sup> Other studies have reported a 9% to 90% of HBsAg carriers, which places this group of patients in an intermediate position as to the prevalence of HBsAg. However, this figure is still higher than the reported for non-HIV infected patients.

In conclusion, in this series of patients with HIV infection the hepatobiliary affection was demonstrated in 22.8%. The clinical presentation was asymptomatic in most of cases and the main etiology could be explained by the presence of associated infections, granulomatoses and liver steatosis.

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