HIV and Liver Disease

K Kothari*, P Rijhwani, R Choudhary****

*Professor and Head, **Assistant Professor,
Department of Medicine, Mahatma Gandhi National Institute of Medical Sciences, Sitapura,
Jaipur, Rajasthan.

145

A B S T R A C T

In HIV positive patients liver disease is one of the leading causes of morbidity and mortality nowadays, which reflects several nonexclusive pathogenic processes that include drug-related hepatotoxicities; chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection; other liver diseases, such as steatosis or nonalcoholic steatohepatitis (NASH); and diseases that are common among patients who abuse alcohol or drugs. The development of HAART has completely modified the pattern of hepatic events in HIV infection, and the liver is now one of the most important organs to consider when treating HIV-infected patients as approximately one-third of the deaths of patients with HIV infection are in some way related to liver disease.

HCV and HIV coinfection is common due to the shared route of transmission of these viruses. Patients with HIV infection should therefore be evaluated for the presence of HCV. HIV coinfection may enhance the sexual and vertical transmission of HCV. HCV therapy in the HIV-infected individual appears to be effective and the goals of HCV treatment in the setting of HIV include decreasing rate of liver disease progression and better tolerance of anti-HIV medications. HBV or HCV co infection is frequent in HIV-infected patients (10% and 30%, respectively) because of similar routes of transmission. In early studies, hepatotropic HBV or HCV infections did not appear to change the natural course of HIV infection. By contrast, HIV significantly modifies the natural history of HBV or HCV infection. HIV infection increases the levels of HBV / HCV viremia, especially at the time of HIV seroconversion. Treatment of HBV with lamivudine is effective but drug-resistant mutants occur in a proportion of patients. Development of lamivudine-resistant HBV or discontinuation of lamivudine can be associated with a flare of hepatitis.

INTRODUCTION

Hepatic events have emerged as a key issue in the management of HIV-infected patients. At the beginning of the AIDS era, liver dysfunction in HIV-infected patients mainly corresponded with opportunistic infections (OIs). These may have included cytomegalovirus [CMV] or mycobacteria and leishmaniasis, including AIDS-related cholangitis associated with parasitic infections (cryptosporidiosis and microsporidiosis), viral infections (e.g., with CMV), or mycobacterial infections; tumors (lymphoma and Kaposi sarcoma); and drug-related hepatitis (caused by trimetoprim-sulfamethoxazole and other antibiotics). All of these events reflected the severe immunodeficiency state of patients who, at that time, had a very poor prognosis.

Treatments were restricted to symptomatic therapies and/or anti-infective or anticancer therapies that had their own hepatic side effects. The development of HAART has completely modified the pattern of hepatic events in HIV infection, and the liver is now one of the most important organs to consider when treating HIV-infected patients as approximately one-third of the deaths of patients with HIV infection are in some way related to liver disease.
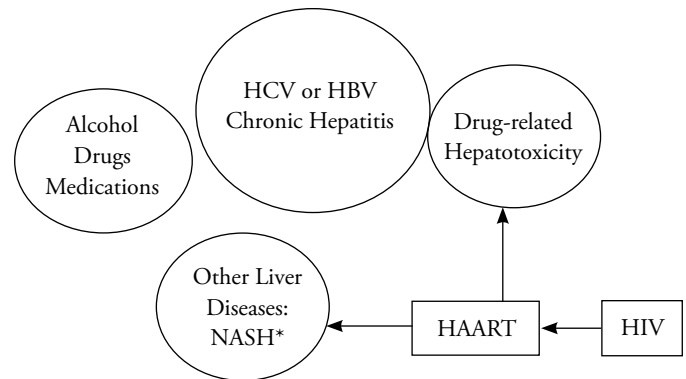

Fig. 1: Potential causes of liver enzyme elevations in HIV-infected patients. HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis.

Liver disease is one of the leading causes of morbidity and mortality nowadays, which reflects several nonexclusive pathogenic processes (Fig. 1) that include drug-related hepatotoxicities; chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection; malignancies and liver diseases, such as steatosis or nonalcoholic steatohepatitis (NASH); and diseases that are

common among patients who abuse alcohol or drugs. The early recognition and diagnosis of hepatic events will facilitate the safe and effective use of HAART and enhance the survival of HIV-infected patients.

Nevertheless, the intricacies of the various pathogenic mechanisms may result in difficulties in the diagnosis, as well as in the management, of such patients with liver abnormalities.

Hepatotoxicity is characterized by biochemical liver abnormalities, but there are pitfalls in the definition. Liver enzyme elevations of 1.25-2.5, 2.6-5, 5.1-10, or >10 times the upper limit of normal (ULN) value or their increase to 1.25-2.5-, 2.6-3.5-, 3.6-5-, or >5-fold the baseline value usually define hepatotoxicity of grades 1, 2, 3, and 4, respectively.

The lack of a homogenous definition for hepatotoxicity prevents reproducible comparisons among studies dealing with the issue of drug-related toxicity. It is better to adjust the level of liver biochemical abnormalities with respect to the baseline value than to use the ULN value, to avoid selection bias, which favors the exclusion of persons with chronic viral hepatitis or other liver disease (i.e., NASH). Moreover, "hepatotoxicity", as defined by these liver enzyme elevations, is a general term that supposes that abnormalities are related to drug therapy: this is not always the case, and the causality of the drug in liver enzyme elevations is rarely ascertained.

Although reports of liver enzyme elevations with HAART are frequent, the analysis of these events is limited, because HIV-infected patients have several risk factors for biochemical abnormalities, and a precise etiology is rarely clearly defined.

OPPORTUNISTIC INFECTIONS

Opportunistic infections of the liver are seriously under-recognized. Studies have found that 40 % of the livers from deceased people with AIDS contain undiagnosed opportunistic infections, and many of the same pathogens also were found in the bile ducts and gall bladder.

The most frequent opportunistic infections of the liver are *Mycobacterium tuberculosis* (TB), *Mycobacterium avium* (MAC) and cytomegalovirus (CMV). Less often, *Pneumocystis carinii* (which causes PCP in the lungs) and *Leishmania* (parasitic protozoa common in Asia) are present. Some of these conditions are treatable, with prognosis directly tied to how early diagnosis is made. In the case of extrapulmonary tuberculosis, response to treatment in HIV-positive patients has been shown to be similar to that of HIV-negative patients if diagnosed early. However, if untreated, disease progression is rapid and nearly always fatal.

Also, various unexpected pathogens (such as fungi, parasites, and bacteria) may be found in the liver following diagnosis of a viral hepatitis. Since these often respond to antibiotic treatments, doctors must carefully watch for such infections. Among the fungal opportunistic infections *C. immitis* and *Histoplasma capsulatum* are those most likely to involve the liver.

LIVER CANCERS

The most commonly found malignancies in the liver of AIDS patients are non-Hodgkin's B cell lymphoma and Kaposi's sarcoma (KS). Up to one third of people with KS will have some involvement in the liver, but this generally remains asymptomatic,

being found only at autopsy. Lymphoma, which affects five to nine percent of people with AIDS, the gastrointestinal tract and liver, are the most common sites of involvement outside of the lymph nodes. For non- Hodgkin's lymphoma, treatment with intensive chemotherapy can be beneficial, with a 52 percent response rate found in one series.

HEPATITIS C AND HIV COINFECTION

Epidemiology

There are about 150 million chronic hepatitis C (HCV) carriers throughout the world with an estimated global prevalence of 3% (range 0.1-5%). Symptomatic acute infection occurs in an estimated 1-3 cases/100,000 persons annually but the actual incidence of new HCV infection is higher as the majority of cases are asymptomatic. Following exposure to hepatitis C, approximately 85% of patients develop chronic infection. Chronic HCV infection can lead to cirrhosis and hepatocellular carcinoma. Coinfection with HCV in HIV-infected individuals is common, presumably due to the shared route of transmission of these viruses. The prevalence of HCV infection among all HIV-infected individuals can be as high as 40% but this prevalence varies substantially among different risk groups. Although the rate of sexual transmission of HCV is low (<5%), this rate may be increased in the setting of coinfection with HIV. Similarly the rate of mother-to-infant transmission of HCV increases in the presence of HIV, presumably due to high levels of HCV viremia observed in these individuals. Interestingly, there is an increased rate of vertical transmission of HIV in the presence of HCV.

HCV Diagnosis

Hepatitis C viremia (HCV RNA by PCR) is present in 60-90% of coinfected HCV-antibody-positive patients. However, a single negative antibody assay may not sufficiently exclude HCV in HIV-infected individuals. The first generation EIA tests (sensitivity 70-80%) can result in a significant rate of false negativity in HIV-infected individuals, underreporting the incidence of HCV infection by as much as 10-30%. This increased rate of false-negative antibody testing in the presence of HIV has been attributed to several factors, including a possible lack of HCV antibody production with immunosuppression, more rapid decline in HCV antibody titer, possible interaction between the two viruses, and an anti-HCV seroreversion into a negative state. Also the hypergammaglobulinemia reported in HIV infection can lead to false-positive EIA anti-HCV results.

Impact of HIV on the Course of HCV Infection

HCV-induced liver disease can be progressive with cirrhosis developing in up to 20-30% of individuals over a 10-20 year follow-up. HIV coinfection has been associated with a more rapid progression of liver disease as well as a higher prevalence of cirrhosis. A recent study compared a cohort of 122 HIV/HCV coinfected individuals with 122 HIV-negative, HCV-infected patients. HIV seropositivity, alcohol consumption of >50g/d, age at infection greater than 25 years and CD4 T-lymphocyte counts less than 200 cells/mm^3 were associated with an increased rate of liver fibrosis progression. Among the coinfected individuals, alcohol consumption, low CD4 counts, and higher age at HCV infection were independent predictors of fibrosis progression.

Some have found a higher rate of mortality from liver-related diseases in the coinfected patients, yet others have not shown any effect on survival.

HCV Viral Levels and HCV Heterogeneity

HCV replication is enhanced in the presence of HIV, resulting in higher serum and liver HCV RNA levels. While some studies have shown a further increase in HCV RNA levels as immunodeficiency progresses, others have failed to find a correlation between the CD4 count and hepatitis C viral load. Similarly, while a decrease in HCV viremia has been reported with successful antiretroviral therapy and immune restoration, other investigators have noted no change or a transient increase in HCV replication in this setting. HIV coinfection may also affect hepatitis C viral heterogeneity.

Antiretroviral Therapy for HIV and Hepatotoxicity: Role of HCV

Treatment of HIV with combination antiretroviral therapy (ART) may result in severe hepatotoxicity in a proportion of patients. Coinfection with HCV may result in a higher rate of ART-induced hepatotoxicity. Therefore, ART should be administered cautiously and LFTs must be followed in all patients, especially those coinfected with HCV/HBV.

Impact of HCV Infection on the Course of HIV Disease

The influence of HCV infection on the natural history of HIV disease is disputed. Most studies fail to show a direct alteration of the course of HIV and progression to AIDS in the presence of HCV coinfection. Although in one study patients with HCV genotype 1 experienced a more rapid progression to AIDS, another study did not reveal this HCV genotype effect.

Management of HCV in HIV-Coinfected Individuals

Patients with adequately controlled HIV disease (CD4 >150-200 cells/mm^3), compensated liver disease, and chronic hepatitis C on liver biopsy should be evaluated for HCV treatment. Liver biopsy will aid in establishing the diagnosis of chronic HCV as well as identifying individuals at risk of progression of liver disease. These individuals must have no evidence of active opportunistic infection and must be stable on antiretroviral therapy. The studies assessing the role of interferon monotherapy in HIV/HCV coinfection are predominantly non-randomized and uncontrolled. In these studies, the dose of interferon has ranged from 1 million units thrice weekly to 9 million units daily as induction therapy for 6-18 months. The end-of-therapy and sustained (6 months following end of therapy) biochemical and/or virologic response rates are similar to those of treated individuals with chronic HCV alone (23-55% & 0-29%, respectively).

Presently, the combination of interferon and ribavirin is the standard of care for the treatment of chronic HCV. The overall sustained hepatitis C virologic response to combination therapy is approximately 40%. There are only limited reports on the use of interferon and ribavirin combination therapy in patients with HIV coinfection. Studies of this combination to date in subjects who are either interferon-naive or who have relapsed or failed to respond to interferon alone have shown 28-31% end-

of-treatment and 14-19% sustained virologic response rates. Although these results are encouraging, further information from ongoing larger clinical trials will be required to assess the long-term HCV response with combination therapy in the setting of coinfection. Additionally, there are concerns about potential antagonism between ribavirin and pyrimidine nucleoside analogues. Conjugation of interferon with polyethylene glycol ("pegylation") delays the clearance of the drug, permitting once-weekly dosing. Recent studies with pegylated interferon ("peginterferon") in individuals with HCV infection alone have been encouraging. The role of pegylated interferon therapy in coinfected individuals is currently being evaluated. Peginterferon alfa-2a alone has resulted in either the loss of HCV RNA or at least 2 log drop in the HCV RNA levels in 39% of coinfected patients at 3 months of therapy, and 59% of those who responded at 3 months also had undetectable HCV RNA by 6 months of therapy. Preliminary data suggest a better treatment response to peginterferon and ribavirin compared to standard interferon and ribavirin combination therapy. Currently, it is recommended to treat HIV infection before tackling HCV infection. Boosting the immune system with HIV medications helps the body fight HCV more effectively. Also, HCV treatment is not recommended until there is at least minimal fibrosis, and there are many HIV/HCV coinfected patients whose HCV infection will never progress.

HEPATITIS B AND HIV COINFECTION

Epidemiology

Coinfection with hepatitis B virus (HBV) and HIV is common, with 70-90% of HIV-infected individuals having evidence of past or active infection with HBV. The prevalence of hepatitis B surface antigen (HBsAg) chronic carriage among HIV-infected individuals is 1.9-9%.

Influence of HBV on the Course of HIV Disease

There are conflicting data with respect to the impact of HBV on the course of HIV infection. While some studies have shown an increased rate of HIV progression to AIDS among individuals with markers of exposure to HBV (anti-HBc), others have not shown any change in the progression of HIV disease or survival. In the largest prospective cohort of 3,040 HIV-seronegative homosexual men, 296 underwent HIV seroconversion during the 4-year follow-up period. The likelihood of HIV infection was associated with serologic markers of HBV (RR 2.03 for HBV carriers, and 2.22 for HBV immune), an association that remained even after adjustment for sexual behavior or sexually transmitted disease over time. However, there was no significant increase in the rate of progression to AIDS in these individuals over a 2.5-year follow-up. Therefore, HBV does not appear to significantly influence the progression of HIV infection but may correlate with risk for HIV infection in some populations.

Influence of HIV on the Course of HBV Infection

The course of acute hepatitis B may be modified in the presence of HIV with lower incidence of icteric illness and a higher HBV carriage rate of about 25% compared to about 5% in those uninfected with HIV. In chronic infection, markers of HBV replication appear to be influenced by HIV infection. There is a trend towards lower rate of clearance of HBeAg and HBV DNA as well as a significant increase in the serum HBV DNA viral

Table 1: Probable Mechanisms of Antiretroviral-Induced Hepatotoxicity

Drug Class	Mechanism	Manifestations
NRTIs	Impaired mitochondrial polymerase gamma function	Lactic acidosis, steatosis
PIs	? Inhibition of retinoic binding protein	Hepatocellular injury, steatosis
	UDP-glucuronyl transferase competition	Unconjugated hyperbilirubinemia
NNRTIs	? Impaired mitochondrial polymerase gamma	Lactic acidosis, steatosis
	? Immune-mediated hypersensitivity	Eosinophilic hepatic injury

Table 2: Patterns of Hepatic Injury

	Cholestatic	Mixed	Hepatocellular
Alanine amonotransferase (ALT)	↑	↑↑	↑↑↑
Aspartate aminotransferase (AST)	↑	↑↑	↑↑↑
Alkaline phosphatase	↑↑↑	↑↑	↑
Gamma glutamyl transpeptidase (GGT)	↑↑↑	↑↑	↑

Table 3: Common Etiologies in HIV-Infected Patients

	Cholestatic	Mixed	Hepatocellular
Hepatitis A		•	
Hepatitis B			•
Hepatitis C			•
Cytomegalovirus			•
Epstein-Barr virus			•
Bacteria	•		
Fungi	•		
Lymphoma	•		
Kaposi's sarcoma	•		
Nonspecific granulomas	•		
Co-trimoxazole, erythromycin, azithromycin, amoxicillin + clavulinic acid	•		
Zidovudine, didanosine, isoniazid, ritonavir, nevirapine, dilantin			•
Steatosis	•	•	
Bacillary angiomatosis	•	•	

load. Additionally, HIV-induced immunosuppression may result in lower serum transaminases possibly due to a reduction in the severity of liver disease. However, immunosuppression may also be associated with reactivation of HBV infection in persons who have lost detectable HBsAg, or HBeAg. Although in HIV-infected individuals, symptomatic reactivation and loss of anti-HBs is uncommon, asymptomatic reactivation or reinfection occurs frequently in patients who develop AIDS, leading to a significantly higher prevalence of HBsAg. A prospective cohort study of 152 untreated homosexual male HBV carriers and 212 HBsAg-negative controls, of which 41% and 70%, respectively, were seropositive for HIV, assessed the effect of HIV on the natural history of HBV. After a mean follow-up of 2.8 years, serum HBV DNA levels were higher, ALT levels were lower and loss of serum HBsAg occurred at a lower rate in HIV carriers compared with HIV uninfected carriers. Therefore, HIV seropositivity has been associated with significantly lower ALT levels, higher serum HBV DNA levels, lower rate of serum HBeAg and serum DNA clearance, decreased liver injury, and an increased loss of anti-HBs.

Management of HBV in HIV-Coinfected Individuals

Interferon Therapy

HIV coinfection may result in poor response to interferon due to high level of HBV DNA, low transaminase levels, and HIV-induced immunosuppression.

Lamivudine

Lamivudine, a nucleoside analogue, inhibits both RNA- and DNA-dependent DNA polymerase activities of both HBV and HIV reverse transcriptase. In HBV-infected individuals, a 1-year course of lamivudine results in a 16-18% rate of HBeAg seroconversion (loss of HBeAg with detection of anti-HBe), an efficacy that is similar to a 4-month course of interferon. Although the antiviral response is durable in most patients, very few patients actually clear HBsAg and most have detectable serum HBV DNA by PCR. Lamivudine therapy can result in drug-resistant HBV mutants (YMDD motif mutation) leading to an increase in serum ALT and HBV DNA levels in about 15-25% of cases after 1 year of therapy and at about 49% after 3 years of treatment. In the HIV-coinfected population the development of lamivudine resistance may be more frequent and can be associated with hepatitis flares. Additionally, severe hepatitis flares have been observed with the discontinuation of lamivudine. Dose of Lamivudine in coinfected patients is 150 mg BID.

Adefovir Dipivoxil

Adefovir, a nucleotide analogue and potent inhibitor of HBV infection has recently been approved by the FDA for treatment of chronic HBV. Adverse effects associated with use of adefovir include renal failure and acute worsening of hepatitis B after discontinuation of therapy. Adefovir may be effective for the treatment of lamivudine-resistant HBV in individuals coinfected with HIV.

Tenofovir Disoproxil Fumarate

Tenofovir Disoproxil Fumarate (TDF) is an acyclic nucleotide reverse transcriptase inhibitor that is effective against wild type and most nucleoside-resistant HIV. Additionally, TDF has shown activity against wild type and lamivudine-resistant HBV. Combination of TDF with lamivudine also appeared to be more effective in suppressing development of lamivudine resistance. However, further results are required in order to evaluate the efficacy and safety of TDF in patients with HBV/HIV coinfection.

ANTIRETROVIRAL THERAPY AND HEPATOTOXICITY

Prevention and management of antiretroviral therapy-related toxicity has emerged as a major issue for HIV/AIDS treatment

Table 4: Treatment Regimens for Viral Hepatitis

Virus	Regimen	Dose	Duration	Results in HIV-Infected Patients
Hepatitis B	Interferon-alfa	30-35 MU/week	14 weeks	<5% seroconversion
	Lamivudine	100 mg/day	1 year	90%-100% initial DNA clearance
	Adefovir*	10 mg/day	1 year?	Unknown
Hepatitis C	Interferon-alfa + ribavirin	3 MU 3-times-weekly + 1000-1200 mg/day	6 months - 1 year (depends on genotype)	Limited data; sustained response in 18%-25%
	Pegylated interferons (PEG-Intron, PEGASYS*)	PEG-Intron: 1.0-1.5 mcg/kg PEGASYS: 180 mcg/day	1 year	Unknown
	Pegylated interferons + ribavirin*	As noted above	1 year	Unknown

*Investigational agents/regimens

Table 5: Factors Affecting Response to Treatment in HIV/HCV-Coinfected Patients

Factor	Effect
CD4+ cell count	Lower response rates at lower CD4+ cell counts
HCV genotype	Patients infected with HCV genotype 1 (84% of coinfected patients in the ACTG) least likely to respond to interferon-based regimens.
HCV quasispecies	Presence of multiple quasispecies associated with poorer response
HCV viral load	Lower response rates at higher HCV RNA levels
Cirrhosis	Presence of cirrhosis associated with poorer response
Alcohol	Response rarely seen in patients using more than 50 g/day

and care. Elevations in serum hepatic enzymes have been described in association with all major classes of antiretroviral therapy, with several underlying mechanisms proposed as shown in Table 1.

Transaminitis and hepatotoxicity are associated with most of the antiretroviral agents, although initially most concern focused on the Protease Inhibitors (PIs). The hepatotoxicity of this drug class varies with the specific drug: in a prospective cohort study, 30% of patients who initiated treatment with ritonavir but only 6% to 7% of those who initiated therapy with saquinavir, nelfinavir or indinavir experienced severe hepatotoxicity (defined as a grade 3 or 4 change in the serum levels of alanine aminotransferase and aspartate aminotransferase). The rate of severe hepatotoxicity associated with any PI among patients with hepatitis C infection was 12%, twice as high as among patients without hepatitis C infection. Den Brinker and colleagues have reported similar findings. The risk of liver enzyme elevation among patients with chronic hepatitis B or C was, respectively, 2.77- or 2.47-fold greater after initiation of a PI-containing regimen than among patients without evidence of viral hepatitis. In this context, it has been suggested that successful treatment of hepatitis C in dually infected patients may facilitate the introduction of PI-containing antiretroviral therapy. Coadministration of low-dose ritonavir with other PIs is now common; in fact, the newest member of the class represents a coformulation of lopinavir and low-dose ritonavir. The extent to which such combinations will affect the safety profiles of the individual agents remains to be fully characterized.

In addition, there have been recent attempts to understand the hepatic histologic changes, other than elevation of transaminases, which occur with PI-containing antiretroviral regimens. Benhamou and associates reviewed liver biopsy samples from 182 patients with both HIV and hepatitis C. The liver fibrosis stage was lower among patients receiving PIs than among those who had never received PI therapy. The authors concluded that long-term use of PIs might have a beneficial impact on progression of liver fibrosis in patients infected with HIV and hepatitis C.

The NNRTIs are also associated with transaminitis and hepatotoxicity. Reisler and colleagues found that the rate of hepatotoxicity was 8.9 % and 10.8%, respectively, among patients receiving nevirapine and efavirenz. These two drugs were significantly more likely to be associated with grade 3 or 4 elevation of transaminases than delavirdine. Others have observed similar rates of hepatotoxicity for nevirapine and efavirenz but found that elevation of CD4 cell count of more than 50/µL was most strongly linked to hepatotoxicity, perhaps due to adherence or immune reconstitution. The hypersensitivity reaction with nevirapine (characterized by rash and fever) can also include severe transaminitis. In a study in which nevirapine was used for post exposure prophylaxis, two patients experienced liver failure, and one of them required liver transplantation. Therefore, nevirapine is no longer used for post exposure prophylaxis and is used with caution in the setting of liver disease.

Finally, as discussed in the previous section, the NRTIs are associated with risk of mitochondrial toxicity and hepatic steatosis. While these may be particular problems with stavudine and didanosine, the overall rate of severe hepatotoxicity with NRTI therapy reported by Reisler and colleagues was 12%, which highlights the complexity and difficulty of evaluating and managing hepatotoxicity associated with antiretroviral therapy.

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