Clinical Challenges and Controversies in the Management of HIV/ HCV-Coinfected Individuals

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The natural history of HIV infection has been dramatically changed by the highly active antiretroviral therapies, reducing complications, morbidity and mortality of the disease. Approximately 25% of persons infected with HIV are co-infected with hepatitis C, and some high risk populations have a prevalence of HCV of more than 75%. Liver disease has become one of the principal causes of morbidity and mortality in this population.

Co-infection increases viremia of hepatitis C, with increase in fibrosis progression, cirrhosis and death related to hepatitis C. The permanent state of chronic immune activation related to the persistent hepatitis C virus favors transcription of HIV in infected cells and causes a more rapid destruction of T4 and absolute lymphocytes. In addition, the immunologic response after the start of highly active antiretroviral therapy for HIV is less than in mono-infected patients.

The role of liver biopsy in the management of co-infected patients is controversial. Many of these patients, even with normal transaminases, show fibrosis in liver biopsy. Predictive factors for advanced fibrosis include male sex, alcohol consumption in excess of 50 grams per day, age over 35, and HIV infection of more than 15 years with CD4 lymphocytes less than 400/ mm^3.

The treatment of hepatitis C is limited and sustained viral response is less than 30% for genotypes 1 and 4. This response is even less in the more advanced stages of HIV and hepatitis C. The determination of when to start treatment and the increased toxicity when combining pegylated interferon plus ribavirin and antiretroviral medications makes the management of these patients more difficult.

The development of more potent, safe and tolerated medications is required. Management strategies for patients unresponsive to conventional therapy are geared towards improving liver histology and delaying progression to cirrhosis, hepatocellular cancer and liver transplantation.

Key words: HAART, HIV, HCV, HCC

The advent of potent antiretroviral therapy (ART) has dramatically reduced AIDS-related complications and death (1, 2). In addition, there has been an increase in the recognition of concomitant co-morbidities, such as hepatitis C virus (HCV) infection. There are many similarities between hepatitis C virus (HCV) and the human immunodeficiency virus (HIV) (see Table 1). Because there are shared routes of transmission, HIV/ HCV-coinfection is common. Approximately 25% of persons infected with human immunodeficiency virus (HIV) are infected with HCV, and the prevalence of coinfection can be >75% in selected at-risk populations, such as injection drug users (IDU) and those who have received contaminated blood products (3, 4).

Table 1. Similarities Between HCV and HIV

Parameter	HCV	HIV
Type of virus	RNA virus-flavivirus	RNA virus-retrovirus
RNA Sequence	Single-stranded	Single-stranded
Prevalence	Worldwide	Worldwide
Replication	10^{12} virions/day	10^{9}-10^{10} virions/day
Genotypes	6+ genotypes	11+clades
Clinical manifestations	Sub-clinical	Sub-clinical

HIV infection is an important cofactor in HCV disease progression. Coinfection with HIV increases HCV viral loads, the rate of progression to fibrosis and cirrhosis and liver-related mortality in HCV-infected patients (5). The natural history of HCV infection is quite variable in immunocompetent patients: one third of patients develop liver cirrhosis 15-20 years after infection, and another one-third develops it 20-30 years after infection (6, 7).

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Furthermore, end-stage liver disease currently represents the leading cause of death among HIV-infected IDUs and hemophiliacs.

The United States Public Health Service and the Infectious Disease Society of America have issued a set of guidelines for the prevention of opportunistic infections among patients who are infected with HIV (8). With regard to HCV infection, the guidelines recommend the following:

- HIV-infected persons should be screened for HCV by enzyme-linked immunosorbent assay
- Patients should be advised on alcohol use
- Patients should be screened for hepatitis A virus IgG
- Patients should be screened for hepatitis B virus (If negative, they should be vaccinated)
- Patients should be evaluated for liver disease and possible need for treatment
- Liver enzymes should be monitored after initiation of HAART

Management controversies. In patients with persistent HCV infection, HIV-coinfection, heavy alcohol use, and hepatic steatosis are associated with accelerated and more-severe progression to cirrhosis and related complications (9). HCV-induced liver failure may occur more rapidly in HCV/HIV-coinfection than in HCV alone. This accelerated progression may be caused by the effect of HIV on the immune system. This may effect or impair how the immune system responds to HCV or the therapy for HCV.

The state of permanent immune activation provided by chronic HCV infection might act deleteriously in HIV-positive individuals through several mechanisms (3, 10). First, unspecific immune stimulation driven by chronic HCV infection might enhance HIV replication. Second, the infection of immune cells by HCV could favor CD4+ cell depletion and partly blunt the immune recovery. Third, HCV could compromise the benefit of antiretroviral drugs as a result of a higher incidence of liver toxicity and treatment discontinuation. In addition to the HIV-mediated effects on liver disease progression, plasma and hepatic HCV RNA levels are higher in HIV/HCV-coinfected persons than in those infected singly with HCV (11). On the other hand, the immune recovery seen after beginning effective antiretroviral therapy could be partly blunted in individuals with HCV infection as a result of similar mechanisms, or through the infection of immune cells by HCV (12). Thus, the management of HCV infection in HIV-infected patients should include the following general measures:

- Education regarding the prevention of liver damage
- Advise to avoid consumption of alcohol and, if necessary, referral for alcohol treatment and relapse-prevention programs
- Vaccination against hepatitis A and B viruses in susceptible patients
- Caution against initiating new medications, including over-the-counter, herbal, or alternative medications, without consulting a healthcare provider
- Monitoring of serum liver enzyme levels if the patient is taking concomitant ART for treatment of HIV infection, as these drugs may result in hepatotoxicity
- Information about other support resources that are available, such as educational materials (including self-help books and videos), patient newsletters, and national organizations
- Vigilant monitoring of serum lactic acid level for nucleoside analogue toxicity

Role of liver biopsy. The value of liver biopsy before prescribing anti-HCV therapy is under debate. A liver biopsy may not always be necessary, but is usually very important. It reveals the degree of liver inflammation and fibrosis, which helps predict when cirrhosis may develop. This controversy may be less justified in HIV/HCV-coinfected patients, in whom the rate of significant liver fibrosis is much higher than in HCV monoinfected individuals (see Table 2). Nearly half of HIV/HCV-coinfected patients showed unexpected cirrhosis or pre-cirrhosis even in the presence of normal ALT levels. The main predictor of advanced fibrosis stages seems to be the estimated duration of HCV infection (16). In a recent study that reviewed 914 liver biopsies in Europe, the following parameters were significantly associated with severe liver fibrosis, independent of HCV genotype or HCV load: male sex, high alcohol intake (>50gm/day) age >35 year, estimated duration of HCV infection >15 years, low CD4 count <500 cells/mm^3. ALT levels were not associated with severe liver fibrosis (17), thus liver biopsy should be performed before prescribing therapy in HIV/HCV-coinfected patients.

Table 2. Stage of Liver Fibrosis in Patients with Chronic Hepatitis C According to HIV Status

Study	No. of Patients	HIV	F0 %	F1 %	F2 %	F3 %	F4 %
Quereda et al. (18)	99	Pos	6	38	18	26	12
Martin-Carbonero et al. (19)	492	Pos	13	35	19	21	12
Foros et al. (20)	476	Neg	51	24	10	10	5

Standard of care and treatment. HCV infection appears to be a curable disease in a significant proportion

of non-HIV+ patients. The primary goal for treatment of HCV infection is to eradicate the virus. Secondary goals are to reduce HCV RNA titer (in the absence of viral eradication). Interim analysis of large ongoing clinical trials and from a few studies already completed, show that response rates to anti-HCV therapy are lower in HIV/HCV-coinfected patients, even using the new peg-IFN formulations with ribavirin. Sustained response rates of 40%-60% are seen in patients with HCV genotypes 2 or 3, but lower than 25% in those with HCV genotypes 1 or 4. Both early virological response and relapses are less and more frequent, respectively, in HIV/HCV-coinfected patients compared with HCV-monoinfected individuals (13).

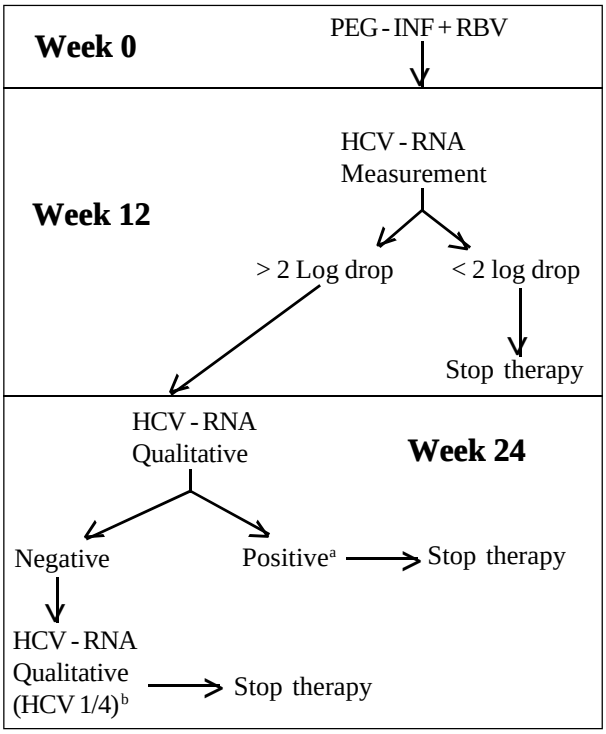
Viral genotype is the single most powerful predictor of sustained response. Other predictors of good response to treatment include age <40 years at infection and female gender (14). The duration of treatment for HCV infection should therefore be customized according to HCV genotype and other prognostic factors. Some of the factors contributing to the low response rates to anti-HCV therapy in HIV/HCV-coinfected individuals are the following:

- HIV-related immune dysfunction
- Advanced liver fibrosis grade
- Higher rate of steatosis
- Higher HCV-RNA viral loads
- Lower initial HCV-RNA clearance on treatment
- More frequent relapses after treatment discontinuation
- Higher rate of treatment discontinuation as a result of side-effects
- Lower drug compliance

Patients infected with HCV genotype 1 and high viral loads should be treated for 48 weeks even if the detection of HCV RNA is negative at 24 weeks. For genotype non-1 infections, 24 weeks of interferon/ribavirin is sufficient for most patients regardless of initial viral load. There is no evidence that prolonging therapy beyond that time increases efficiency. For non-responders to interferon/ribavirin, several lines of evidence are creating interest in maintenance therapy with the goal of retarding the progression of disease and preventing cirrhosis and hepatocellular carcinoma. Figure 1 shows the most current treatment algorithm for the treatment of HCV in HIV/HCV-coinfected individuals.

Treatment initiation. In most cases, when treatment for both infections is indicated, treatment of HIV infection should be initiated first, particularly when liver disease is mild. This strategy is used because HIV infection is generally a more rapidly progressive disease, and a good response to ART is more likely when it is initiated early

Figure 1. Hepatitis C Virus (HCV) Treatment Algorithm



(a) Patients with high baseline (HCV) loads prolonged treatment beyond 6 months (b) continue therapy to avoid relapse beyond 6 months (HCV 2-3) 12 months (HCV 1-4) *Adapted from Soriano V. AIDS 2004; 18: p4.*

(i.e. when CD4+ cell counts are high). If CD4+ cells are <200/mm^3, the goals are to foster tolerance of anti-HIV medication, reduce fibrosis, ALT, HCV viral load, risk of cirrhosis, and improve the quality of life (20). Select cases in which treatment of HCV infection may need to precede treatment of HIV infection are extremely debatable and should be individualized accordingly.

Treatment associated adverse effects and toxicity. This is an area of challenge and frustration both for the patient and the clinician. The lack of expertise in the management of side effects and interaction of drugs as well as insufficient information given to the patient about therapy expectations contribute to the inappropriate discontinuation and limited success of therapy. Some of the side effects observed in mono-infected (HCV) patients may be augmented in coinfected patients in the presence of some antiretroviral drugs. The side effects of anti-HCV medications are common, and may be grouped into (1) hematological abnormalities (mainly anemia), (2) influenza-like symptoms (headache, fever, asthenia, myalgias, and decreased appetite), (3) gastrointestinal symptoms (nausea, diarrhea), and (4) neuropsychiatric disorders (depression, irritability, and insomnia).

In the case of hematological abnormalities that may be caused either by peg-IFN or ribavirin, recombinant

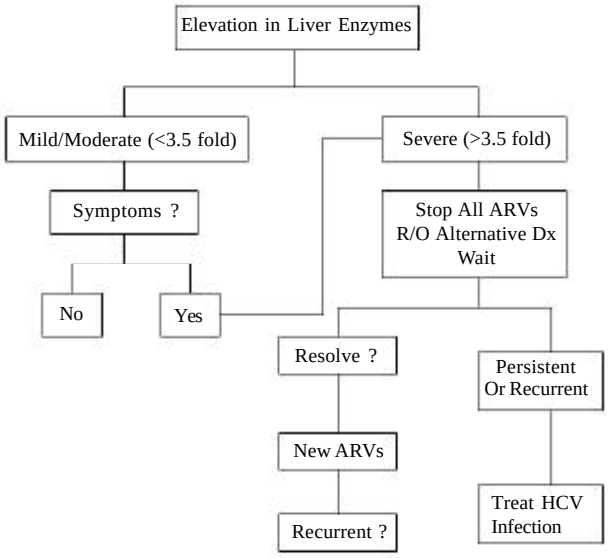
erythropoietin and supplements of folic acid are advisable. The dose of ribavirin should be reduced to half when the hemoglobin level drops below 10 g/dl, and it should be discontinued if it falls below 8.5 g/dl. Leukopenia especially neutropenia may develop with peg-IFN. In most instances they affect the absolute CD4+ cell number but not the percentage of these cells. The use of therapeutic growth factors, such as granulocyte colony-stimulating factor may be considered and eventually preferred over reducing peg-IFN doses.

Cumulative toxicity of antiretroviral agents has been extensively described in the last three years. Interaction between antiretroviral drugs and ribavirin may be harmful by causing mitochondrial damage manifesting conditions such as pancreatitis, hepatic steatosis, lactic acidosis, and hepatitis. Drugs like zidovudine, didanosine, stavudine, nevirapine, and ritonavir should be used cautiously in HIV/HCV-coinfected patients treated with ribavirin. Interestingly the majority of cases documented thus far have been seen with combinations of 2 or more of these antiretroviral drugs in obese women in the 35 – 45 age range (15). Recent data has suggested a potential *in vitro* interaction between pharmacokinetics of ribavirin and other antiretroviral drugs, in particular nucleosides and proteases. The clinical significance of this *in vivo* interaction has not been established. Ongoing clinical trials, including one at the University of Puerto Rico-Medical Sciences Campus, are looking very closely at this issue.

When significant hepatotoxicity develops in HIV/HCV-coinfected patients, the following issues should be considered: (1) the potential cause(s) of the abnormality, (2) the possibility of changing antiviral medications in an effort to decrease toxicity while maintaining antiretroviral effect, (3) the prevention of additional hepatotoxicity from other sources, and (4) the necessity of treating the underlying viral hepatitis. Figure 2 shows the options for the management of ART associated hepatotoxicities in HIV/HCV-coinfected patients (16).

Liver transplantation issues. All HIV infected patients with end-stage liver disease as a result of HCV should be considered as candidates for liver transplantation as long as they do not have advanced HIV disease. Since the introduction of ART, HIV-infected liver transplant recipients have improved their short and mid-term survival. Presently, close to 70 liver transplants in different medical centers around the world have been reported, (21-24), with an approximate 2 years survival follow-up (see Table 3). HCV recurrence is very frequent after liver transplantion and leads to cirrhosis in nearly 20% of cases within 5 years. Standard anti-HCV therapy must therefore be prescribed as early as possible (1-3 months after liver transplant).

Figure 2. Management of HAART-Associated Hepatotoxicity *



ARVs = Antiretrovirals; R/O = rule out; Dx = diagnosis

**Courtesy of Mark Sulkowski, MD*

Future trends. Evolution of HCV therapy resembles that of HIV 10 years ago, in that there is currently only one accepted therapy. Although research on HIV/HCV-coinfection is expected to flourish within the next few years, there are 2 important areas in which significant progress has been achieved with long-term maintenance in HCV monoinfected patients (non-responders and cirrhosis). Many physicians who treat HCV infection are considering long-term maintenance therapy with interferon for patients who did not achieve a sustained response to initial treatment. The goals of maintenance therapy are to:

- Improve hepatic histology
- Delay progression to cirrhosis
- Decrease the risk of hepatocellular carcinoma (HCC)
- Avoid the need for liver transplantation
- Improve life expectancy

Table 3. Liver Transplantation in HIV/HCV-coinfected Patients

Author	Year	Cases	Follow-up (months)	Status
Gow and Mutiner	2001	1	12	All alive
Praschalias et. al.	2001	4	3-25 (range)	All died
Neff et. al.	2002	3	12, 19, 20	All alive
Ragni et. al.	2003	23	36	5 deaths, 18 alive

In the single published study examining long-term maintenance therapy, Shiffman et al. randomized 53 virologic non-responders who demonstrated histologic improvement post- treatment to 30 months of interferon maintenance therapy (n = 26) vs. non-maintenance (n = 27) (17). In the maintenance therapy group, fibrosis score remained stable, whereas in the non-maintenance group, fibrosis score increased ultimately reaching pretreatment levels.

The most important determinant of outcome in patients with cirrhosis is Child-Pugh class, which is based on clinical and laboratory parameters. Patients classified as Child-Pugh class A (compensated cirrhosis) have a good prognosis and unless there is a major contraindication should be treated with pharmacologic therapy. Patients who do not respond to initial treatment may be candidates for maintenance therapy, as interferon has been shown to significantly reduce the risk of HCC and decompensation and to improve survival. However, clinical studies are needed to answer this question in the HIV/HCV-coinfected population.

Resumen

El curso natural de la enfermedad de VIH ha sido dramáticamente impactado por las terapias activas antiretrovirales reduciendo complicaciones, morbilidad y tasas de muertes. Aproximadamente 25% de las personas infectadas con el VIH están co-infectadas con el virus de hepatitis C, y en algunas poblaciones de riesgo la prevalencia sobrepasa el 75%. La enfermedad hepática se ha convertido en una de las causas principales de morbilidad y mortalidad en esta población. La co-infección aumenta la cantidad de viremia de hepatitis C con un aumento en progresión de fibrosis y cirrosis y mortalidad relacionada al virus. El estado permanente de activación crónica inmune relacionada al virus persistente de hepatitis C favorece la trascripción del virus de VIH dentro de las células infectadas y causa una destrucción más rápida de los linfocitos T4 y linfocitos absolutos. Por otro lado, la respuesta inmunológica luego del comienzo de terapia activa antiretroviral para el VIH es menor que en los pacientes mono-infectados. El rol de la biopsia hepática en el manejo del paciente co-infectado es controversial. Muchos de los pacientes con infección mixta, aún cuando sus transaminasas son normales, tienen fibrosis en la biopsia. Algunos de los factores predictivos de fibrosis avanzada son sexo masculino, ingesta de alcohol de más de 50 gramos al día, edad mayor de 35 años y duración de la infección por VIH por más de 15 años conjuntamente con linfocitos CD4 menores de 400/mm^3 .

El tratamiento de la hepatitis C es limitado y la respuesta sostenida de supresión viral es menor de 30% en los genotipos 1 y 4. Esta respuesta se compromete aún más en los estadíos más avanzados de VIH y de hepatitis C. El momento de comenzar tratamiento y la toxicidad potenciada de interferón peguilado con ribavirina y los medicamentos antiretrovirales dificultan el manejo de estos pacientes.

El desarrollo de medicamentos más potentes, seguros y tolerables es necesario. Las estrategias de manejo para el paciente que no responde a terapia convencional van encaminadas hacia mejorar la histología hepática y retardar el progreso a cirrosis, cáncer hepatocelular y trasplante de hígado.

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