

Hepatitis C and HIV co-infection: a review

Irena Maier, George Y. Wu

Irena Maier, **George Y. Wu**, Department of Medicine, Division of Gastroenterology-Hepatology University of Connecticut Health Center, Farmington, CT, USA

Correspondence to: George Y. Wu, M.D., Ph.D, Department of Medicine Division of Gastroenterology-Hepatology, University of Connecticut Health Center, Rm. AM-045,263 Farmington Avenue, Farmington, CT 06030-1845,USA. wu@nso.uconn.edu

Telephone: +1-860-679-3158 **Fax:** +1-860-679 3159

Received 2002-06-27 **Accepted** 2002-07-04

Abstract

Co-infection with hepatitis C virus and human immunodeficiency virus is common in certain populations. Among HCV (+) persons, 10 % are also HIV (+), and among HIV (+) persons, 25 % are also HCV (+). Many studies have shown that in intravenous drug users, co-infection prevalence can be as high as 90-95 %. There is increasing evidence supporting the concept that people infected with HIV have a much more rapid course of their hepatitis C infection. Treatment of co-infection is often challenging because highly active anti-retroviral therapy (HAART) therapy is frequently hepatotoxic, especially in the presence of HCV. The purpose of this review is to describe the effects that HIV has on hepatitis C, the effects that hepatitis C has on HIV, and the treatment options in this challenging population.

Maier I, Wu GY. Hepatitis C and HIV co-infection: a review. *World J Gastroenterol* 2002; 8(4):577-579

INTRODUCTION

Hepatitis C is an RNA flavivirus that infects 4 million people in the United States making up approximately 1.8 % of the population, and 150-200 million worldwide. In persons with HIV, its prevalence is estimated to be approximately 50 %^[1]. Main sources for transmission include IV drug use, transfusion of blood products prior to screening, and to a lesser extent sexual intercourse and needle sticks. It is almost universal among hemophiliacs who received transfusions prior to July 1992^[2]. HCV is the leading indication for liver transplantation in the U.S. today, and is responsible for approximately 10 000 deaths per year. It is estimated that by 2 015, HCV will be responsible for 40 000 deaths per year.

Seventy to eighty percent of acute HCV infections become chronic. Approximately 25 % of these patients develop end stage cirrhosis after 20 to 25 years, and 1 to 4 % of patients with cirrhosis develop hepatoma each year. The median time to cirrhosis is about 19 years. Once cirrhosis is present, the risk of hepatoma increases dramatically. The median time to develop hepatoma is about 29 years. Factors that promote progression of HCV include: alcohol intake, age over 45 at the time of infection, HIV co-infection, male gender, and co-infection with hepatitis B or other viruses. HIV infection and alcohol consumption are independently associated with accelerated progression of fibrosis^[3].

Potential mechanisms of HCV-induced liver disease include direct cellular toxicity, immune-mediated toxicity, viral replication, immune selection, and role of cryoglobulins. In patients that are immunosuppressed, there is an increased rate of viral replication and an increased progression rate of HCV.

The diagnosis of HCV is made by an ELISA test, which is sensitive and specific. In immunosuppressed persons, however, there may be a false negative test in the presence of hepatitis C viremia. Therefore, in a high risk HIV patient who has a negative antibody test, a quantitative PCR is also recommended^[2].

The standard treatment for persons who do not have HIV is combination therapy consisting of interferon alfa and ribavirin. Should this be the standard of care in HIV positive patients as well? The approach to the co-infected patient is somewhat more complicated.

HCV/HIV CO-INFECTION

Epidemiology

Not all HIV (+) persons are at risk for HIV. Of HCV (+) persons, approximately 10% are also HIV (+), and of HIV (+) persons, approximately 25% are also HCV (+)^[4-6]. Table 1^[7] shows the incidence of HCV and HIV infection by special population.

Table 1^[7] The incidence of HCV and HIV infection by special population

	% HCV Infection	% HIV
IV Drug Users	60%	31%
Homosexual Men	Unclear	47%
Heterosexual Men	20%	10%
Transfusion <1992	7-20%	2%
Occupational	<1%	<1%
Unknown	10%	9%

Table 2^[11] Similarities and differences of HCV and HIV

Statistics	HCV	HIV
U.S. Infected	4 million	1 million
Globally Infected	60-180 million	45 million
Primary transmission	Blood	Sex
Treatment Cure	Yes (40%)	No
T 1/2	2.3	6.4
Daily Replication	10 ¹² -10 ¹³	10 ⁹ -10 ¹⁰
Mutation Rates	10 ⁻³ -10 ⁻⁴	10 ⁻³ -10 ⁻⁴

In developed countries, the majority of HIV positive persons who acquired infection by IV drug use (IDU) are co-

infected with HCV^[8]. In many studies, more than 90-95 % of IV drug users are co-infected. Only 4-8 % of gay men who are HIV (+) are also HCV (+)^[9], since HCV is not as easily transmitted by sexual contact. If a patient has both HIV and HCV infection, that patient will be more likely to transmit HIV compared with HCV through heterosexual contact. The presence of HIV may increase the risk of acquiring HCV, as seen in some studies^[10]. Two to 10% of women co-infected with HIV/HCV transmitted HCV to their newborns. The risk of transmission was directly related to the degree of HCV viremia. Also, HIV transmission is more likely in mothers with high HCV-RNA levels. Table 2^[11] lists some statistics for HCV and HIV.

Natural history

In infections with HCV alone, the host cell-mediated immune response often determines the long term outcome. It has been evident that HIV makes the course of HCV infection more rapid and that end stage liver disease is the leading cause of death in HIV patients. It is thought that the more rapid progression of HCV in co-infected patients is due to a weakened cellular immune response. The estimated mean interval from HCV infection to development of cirrhosis is significantly shorter for patients co-infected with HIV (7 vs 30 years)^[12-15]. Co-infected patients have higher levels of HCV RNA than HCV-only infected patients. Titers usually correlate with the CD4 count^[16]. Viral load is considered to be a predictor of response to therapy, but HCV viral loads in HCV-only infected patients cannot be compared to HIV/HCV patients with any prediction to outcome of treatment. Patients with HIV/HCV infection may also have more severe liver damage (higher score of piecemeal necrosis and a higher stage of fibrosis) than those without HIV infection^[17-19].

However, the impact that HCV has upon HIV disease progression is less clear. Some studies have reported a significantly faster HIV progression (predominantly in hemophiliac patients infected with HCV genotype 1)^[20], while others showed no impact. IL-10 has been proposed to decrease inflammation in HCV patients. It also should be noted that patients that have HIV naturally have lower levels of IL-10, which may explain the observed accelerated liver disease in co-infected patients^[21].

Treatment options

HIV patients have been living longer making the HCV infection a pressing problem^[22]. Regarding treatment of HCV in co-infected patients, the main factor in deciding who should be treated is the CD4 count. Patients with CD4 counts greater than 500 have been found to have response rates not significantly different from patients without HIV. Patients with CD4 counts less than 200 have been shown to have no significant response. Hence, therapy in those cases is not recommended. Patients with CD4 counts less than 500, but greater than 200 have intermediate response rates^[17]. Accordingly, patients are generally treated with HAART first to optimize the immune system before initiating anti-HCV therapy.

Interferon

Interferon monotherapy for hepatitis C in patients with HIV, without AIDS, is similar to that observed in patients with HCV alone. Periodic monitoring of CD4 count is warranted since up to 80 % of the patients treated had significant reductions in the absolute CD4 count^[23].

Interferon plus ribavirin

Standard treatment in co-infected patients with satisfactory CD4 counts is to treat the HCV with interferon alfa plus ribavirin for 24 weeks^[24-27]. If the quantitative HCV RNA PCR is negative at the 24 week point, then treatment should be continued for an additional 24 weeks (for a total of 48 weeks). However, if the PCR is positive at 24 weeks, the risks of continuing treatment are likely to outweigh benefits of the regimen^[23].

Further treatment options

Pegylated interferon is an alternative to interferon plus ribavirin that seems to provide similar treatment efficacy without the ribavirin side effects^[28,29].

There are no definitive data on pegylated interferon and ribavirin in co-infected patients, but preliminary reports suggest a further increase in the sustained viral response rate compared to standard thrice weekly interferon plus ribavirin^[30]. It is likely that the dependence of response rates on CD4 counts will likely be similar to standard interferon-ribavirin.

Liver toxicity is a potential problem with all of the HAART medications^[1]. There is a higher rate of hepatotoxicity in co-infected patients who are being treated with HAART therapy. Of the protease inhibitors, several sources cite Ritonavir as the most liver toxic. Ritonavir trough levels are often twice as high in patients with HCV infection. Indinavir can cause severe hyperbilirubinemia in patients with HCV co-infection. Nelfinavir and Saquinavir are the safest among protease inhibitors in patients with compromised liver function. Among the NNRTIs, Nevirapine frequently causes elevation in transaminases, while Efavirenz is least likely to cause liver toxicity^[31].

Ribavirin may interact with selected nucleoside reverse transcriptase inhibitors (AZT, ddi, d4T) and reduce their anti-HIV activity due to interference with intracellular phosphorylation. If AZT is given concomitant with ribavirin, there is an increased incidence of anemia and complete blood counts should be carefully monitored^[32].

Future challenges

In order to maximize therapeutic efficacy, we will need to determine the immunological defect that is responsible for the diminished cellular immune response to HCV in HIV/HCV co-infected patients. It will be of value to determine the mechanism causing the defect that leads to an increase in hepatotoxicity in anti-retroviral drugs so that drug therapy can be better managed. Hepatotoxicity can possibly be decreased by manipulating the chemical structures of some of these medications. More studies need to be done on the interactions between HIV and HCV in man.

REFERENCES

- 1 **Dodig M.** Hepatitis C and human immunodeficiency virus co-infections. *J Clin Gastroenterol* 2001;**33**:367-374
- 2 **Troisi CL,** Hollinger FB, Hoots WK, Contant C, Gill J, Ragni M, Parmley R, Sexauer C, Gomperts E, Buchanan G. A multicenter study of viral hepatitis in a United States hemophilic population. *Blood* 1993;**81**:412-418
- 3 **Papaevangelou V,** Pollack H, Rochford G, Kokka R, Hou Z, Chernoff D, Hanna B, Krasinski K, Borkowsky W. Increased transmission of vertical hepatitis C virus (HCV) infection to human immunodeficiency virus (HIV) - infected infants of HIV - and HCV - co-infected women. *J Infect Dis* 1998;**178**:1047-1052
- 4 **Wright TL,** Hollander H, Pu X, Held MJ, Lipson P, Quan S, Polito A, Thaler MM, Bacchetti P, Schar Schmidt BF.

- Hepatitis C in HIV-infected patients with and without AIDS: Prevalence and relationship to patient survival. *Hepatology* 1994;**20**:1152-1155
- 5 **Bonacini M.** Hepatitis C in patients with human immunodeficiency virus infection: diagnosis, natural history, meta-analysis of sexual and vertical transmission, and therapeutic issues. *Arch Intern Med* 2000;**160**:3365-3373
 - 6 **Ockenga J.** Hepatitis B and C in HIV-infected patients. Prevalence and prognostic value. *J Hepatol* 1997;**27**:18-24.
 - 7 **Bower W.** The Epidemiology of Hepatitis C Virus and HIV. Report from Conference on HIV/HCV Co-infection: Part 1, Session2: Co-infection, October 11, 2001
 - 8 **Stark K,** Schreier E, Muller R, Wirth D, Driesel G, Bienzle U. Prevalence and determinants of anti-HCV seropositivity and of HCV genotype among intravenous drug users in Berlin. *Scand J Infect Dis* 1995;**27**:331-337
 - 9 **Bodsworth NJ,** Cunningham P, Kaldor J, Donovan B. Hepatitis C virus infection in a large cohort of homosexually active men: Independent associations with HIV-1 infection and injecting drug use but not sexual behavior. *Genitourin Med* 1996;**72**:118-122
 - 10 **Eyster ME,** Alter HJ, Aledort LM, Quan S, Hatzakis A, Goedert JJ. Heterosexual co-transmission of hepatitis C virus (HCV) and human immunodeficiency virus (HIV). *Ann Intern Med* 1991;**115**:764-768
 - 11 **Stapleton J.** Basic Virology of HIV and HCV: Parallels and Contrasts? Report from Conference on HIV/HCV Coinfection: Part 1, Session 5, October 11,2001
 - 12 **Pol S,** Lamorthe B, Thi NT, Thiers V, Carnot F, Zylberberg H, Berthelot P, Brechot C, Nalpas B. Retrospective analysis of the impact of HIV infection and alcohol use on chronic hepatitis C in a large cohort of drug users. *J Hepatol* 1998;**28**:945-950
 - 13 **Benhamou Y,** Di Martino V, Bochet M, Colombet G, Thibault V, Liou A, Katlama C, Poynard T. The MultivirC Group. Factors affecting liver fibrosis in human immunodeficiency virus – and hepatitis C virus – co-infected patients: Impact of protease inhibitor therapy. *Hepatology* 2001;**34**:283-287
 - 14 **Soto B,** Sanchez-Quijano A, Rodrigo L, del Olmo JA, Garcia-Bengochea M, Hernandez-Quero J, Rey C, Abad MA, Rodriguez M, Sales Gilabert M, Gonzalez F, Miron P, Caruz A, Relimpio F, Torronteras R, Leal M, Lissen E. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J Hepatol* 1997;**26**:1-5
 - 15 **Benhamou Y,** Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, Vidaud M, Bricaire F, Opolon P, Katlama C, Poynard T. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus co-infected patients. *Hepatology* 1999;**30**:1054-1058
 - 16 **Beld M,** Penning M, Lukashov V, McMorro M, Roos M, Pakker N, van den Hoek A, Goudsmit J. Evidence that both HIV and HIV-induced immunodeficiency enhance HCV replication among HCV seroconverters. *Virology* 1998;**244**:504-512
 - 17 **Garcia-Samaniego J,** Soriano Y, Castilla J, Bravo R, Moreno A, Carbo J, Iniguez A, Gonzalez J, Munoz F. Influence of hepatitis C virus genotypes and HIV infection on histological severity of chronic hepatitis C. The hepatitis/HIV Spanish Study Group. *Am J Gastroenterol* 1997;**92**:1130-1134
 - 18 **Allory Y,** Charlotte F, Benhamou Y, Opolon P, Le Charpentier Y, Poynard T. Impact of human immunodeficiency virus infection on the histological features of chronic hepatitis C: A case-control study. The MULTIVIRC group. *Hum Pathol* 2000;**31**:69-74
 - 19 **Causse X,** Payen JL, Izopet J, Babany G, Girardin MF. Does HIV-infection influence the response of chronic hepatitis C to interferon treatment? A French multicenter prospective study. *J Hepatol* 2000;**32**:1003-10
 - 20 **Dieterich DT.** Hepatitis C virus and human immunodeficiency virus: clinical issues in co-infection. *Am J Med* 1999;**107**:79S-84S
 - 21 **Koziel M.** Immune responses Against HIV and HCV: What Lessons Can We Learn From These Different Viruses? Report from Conference on HIV/HCV Coinfection: Part2, Session7, October11,2001
 - 22 **Poles MA.** Hepatitis C virus/human immunodeficiency virus co-infection: clinical management issues. *Clin Infect Dis* 2000;**31**:154-161
 - 23 **Soriano V,** Garcia-Samaniego J, Bravo R, Gonzalez J, Castro A, Castilla J, Martinez-Odriozola P, Colmenero M, Carballo E, Suarez D, Rodriguez-Pinero FJ, Moreno A, del Romero J, Pedreira J, Gonzalez-Lahoz J. Interferon alpha for the treatment of chronic hepatitis C in patients infected with human immunodeficiency virus. Hepatitis – HIV Spanish Study Group. *Clin Infect Dis* 1996;**23**:585-591
 - 24 **Landau A.** Efficacy and safety of combination therapy with interferon-alpha 2b and ribavirin for chronic hepatitis C in HIV-infected patients. *AIDS* 2000;**14**:839-844
 - 25 **Sherman KE.** Diagnosis and management of the HCV/HIV – co-infected patient. *AIDS Clin Care* 2002;**14**:39-48
 - 26 **Soriano V.** Interferon plus ribavirin for chronic hepatitis C in HIV-infected patients. *AIDS* 2000;**14**:2409-2410
 - 27 **Nasti G.** Chronic hepatitis C in HIV infection: feasibility and sustained efficacy of therapy with interferon alpha-2b and ribavirin. *AIDS* 2001;**15**:1783-1787
 - 28 **Schiffman M,** Pockros PJ, Reddy RK. A controlled, randomized, multicenter, descending dose phase II trial of pegylated interferon alfa-2A (PEG) vs standard interferon alfa-2A (IFN) for treatment of chronic hepatitis C. *Gastroenterology* 1999;**116**:A1275
 - 29 **Zeuzem S,** Feinman SV, Rasenack J, Heathcote EJ, Lai MY, Gane E, O'Grady J, Reichen J, Diago M, Lin A, Hoffman J, Brunda MJ. Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med* 2000;**343**:1666-1672
 - 30 **Sulkowski MS,** Reindollar R, Yu J. Pegylated interferon alfa-2A (Pegasys) and ribavirin combination therapy for chronic hepatitis C: A phase II open label study. *Gastroenterology* 2000;**118**:A950
 - 31 **Bonacini M.** Management issues in patients co-infected with hepatitis C and HIV. *AIDS Read* 2002;**12**:19-21
 - 32 **Sulkowski MS,** Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA* 2000;**283**:74-80

Edited by Zhang JZ