

## **Rapid Progression to Decompensated Cirrhosis, Liver Transplantation, and Death in HIV-infected Men after Primary HCV Infection**

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Brief summary:

Four men from a cohort of HIV-infected men who were not cured after primary HCV infection developed decompensated cirrhosis within 17 months to six years after primary hepatitis C infection, with subsequent rapid progression to liver transplantation and death.

*Abstract*

**Background:** We and others have shown that primary hepatitis C (HCV) infection of HIV-infected men causes early onset liver fibrosis. Little is known about the long-term natural history of the liver disease in these HIV-infected men, however.

**Methods:** We followed a cohort of HIV-infected men with primary HCV infection in New York City. Four men who were not cured after their primary HCV infection rapidly developed decompensated cirrhosis and were followed longitudinally.

**Results:** Three of the four men had AIDS at the time of primary HCV infection. Decompensated cirrhosis subsequently occurred in all four within 17 months to six years after primary HCV infection. Three died within eight years of primary HCV infection and one survived after liver transplantation done two years after primary HCV infection. The most rapid progression occurred in the two men with the lowest CD4 counts at the time of HCV infection. Liver histopathology was most consistent with HCV-induced damage even though some had exposures to other potential hepatotoxins.

Conclusions: Primary HCV infection resulted in decompensated cirrhosis and death within two to eight years in four HIV-infected men. The rapid-onset of fibrosis due to primary HCV infection in HIV-infected men cannot therefore be considered benign. The rate of continued progression to liver failure may be proportional to the degree of underlying immunocompromise caused by HIV infection. More research is needed to better define the mechanisms behind accelerated liver damage.

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Liver failure due to hepatitis C virus (HCV) infection is among the leading causes of death in HIV-infected patients [1]. Nevertheless, HCV infection leads to cirrhosis in a minority of patients and only over a period of decades, even in those co-infected with HIV [2]. Historically, most co-infected patients acquired both HCV and HIV parenterally, and due to the higher infectivity of HCV parenterally, that infection was acquired first [3]. These co-infected patients have a modestly accelerated course of fibrosis progression compared to patients with HCV alone, with a mean time to stage 4 fibrosis (histological cirrhosis) of 26 years, compared to 34 years in non-HIV infected patients [4]. Once histological cirrhosis develops, liver failure and death does not typically occur for another five to 10 years, resulting in an HCV disease course of three to four decades or longer.

Recently, an international epidemic of HCV infection among HIV-infected men-who-have-sex-with-men (MSM) has occurred [5, 6]. These men acquired both HIV and HCV sexually, and partly due to the higher infectivity of HIV through a sexual route, that infection was acquired first. As fibrosis does progress rapidly after primary HCV infection in patients without underlying HIV infection [7, 8], we were surprised to find that nine of 11 HIV-infected men with newly-acquired HCV had developed moderate liver fibrosis (stage 2 of 4 [9]) shortly after diagnosis of their primary HCV infection [10]. We therefore proposed that there is a rapid onset of HCV-induced fibrosis due to the immunocompromise that results from an established HIV infection. Our findings were corroborated by a group in Belgium who found that 22 (59%) of 37 HIV-infected men who underwent liver biopsy a median of seven months after the diagnosis of primary

HCV infection had stage 2 or 3 fibrosis [11]. We then expanded our biopsy series to 29 men with longer follow-up (up to two years after primary HCV infection) and found significantly higher stages of fibrosis in men who underwent liver biopsy later in their HCV course [12], demonstrating that fibrosis is progressive and does not spontaneously resolve after the primary HCV infection period.

Neither we nor others [13], however, were able to determine the long-term natural history of the liver disease as the follow-up time was short and most men in these studies were subsequently cured of their HCV infection. So even with corroboration of our findings by Bottieau et al, some continued to suggest that early-onset fibrosis might not progress further at a clinically important rate [13]. We have continued to follow a cohort of HIV-infected men with subsequent primary HCV infection that was not cured and now report the cases of four men who progressed to decompensated cirrhosis in 17 months to six years after primary HCV infection. These cases demonstrate that the early-onset fibrosis due to primary HCV infection in HIV-infected men cannot be considered benign, and can continue to progress rapidly to cirrhosis, liver failure, and death in some men.

### *Methods*

Written informed consent was obtained with approval of the Institutional Review Boards in accordance with the Helsinki Declaration of 1975, as revised in 2000. Three patients (1-3) were enrolled at Mount Sinai School of Medicine and were part of a cohort that included 15 HIV-infected men who were not cured of HCV infection and who had at

least two years of follow-up after primary HCV infection. The initial liver biopsy result of patient 2 was previously reported [10]. One patient (4) was enrolled at the VA Medical Center, San Diego. As all patients were initially asymptomatic from their primary HCV infections, the clinical onset of HCV infection was considered to be the date of the first-noted elevation of liver transaminases.

### *Case reports*

Case 1: A 39 year old man with AIDS underwent routine laboratory testing in February 2008, which showed new elevations of liver transaminases [alanine aminotransferase (ALT) 529 U/L, aspartate aminotransferase (AST) 306 U/L] and a normal total bilirubin. Hepatitis B serology was negative and the diagnosis of HCV infection was not considered at that time. He was asymptomatic. His CD4 count and HIV viral load (VL) are in Figure 1. His antiretroviral treatment (ART) regimen, started just a few months prior, was tenofovir (TDF), emtricitabine (FTC), and efavirenz (EFV). HCV antibody (Ab) testing was negative twice within the prior 12 months when his liver transaminases were normal. He reported having unprotected receptive anal intercourse with multiple men over the prior year but never ingested illicit drugs and he drank no alcohol.

Three months later he became jaundiced and had tan-colored stool. ART was held. Evaluation for acute viral hepatitis, including HCV Ab, was negative.

Seven months after onset of primary HCV infection his liver transaminases (ALT 331 U/L, AST 540 U/L) and total bilirubin (4.3 mg/dL) remained elevated; HCV

VL was 6,144,372 IU/mL (genotype 1a) but HCV Ab testing was again negative. Percutaneous liver biopsy was performed eight months after onset of primary HCV infection, which showed stage 3 fibrosis [9] but no steatohepatitis or other types of liver injury. His prior ART regimen was restarted. HCV treatment with pegylated interferon (peg-IFN) plus ribavirin (RBV) was initiated but discontinued after five months because there was no significant drop in HCV VL. Within a month after stopping treatment he had new mild gynecomastia and hepatomegaly, and laboratory testing showed an albumin of 2.9 mg/dL, international normalized ratio (INR) of 1.6, platelet count of 138,000 cells/ $\mu$ L, and persistently elevated liver transaminases (ALT 120 U/L, AST 204 U/L). HCV Ab was now positive. Four months later, 17 months after onset of primary HCV infection, he had decompensated cirrhosis manifest by pedal edema, and small esophageal varices. His albumin was 1.8 g/dL, total bilirubin 11.6 mg/dL, INR 3.5, and platelet count 85,000 cells/ $\mu$ L, Model for End-stage Liver Disease (MELD) score of 30. Over the next few months he developed ascites, his MELD score rose to 34, and he underwent liver transplantation, seven months after onset of decompensated cirrhosis (Figure 1). At surgery he had a small cirrhotic liver. He recovered slowly from surgery but has remained clinically well over the subsequent 2 ½ years.

Case 2: A 55 year old man with AIDS underwent routine laboratory testing in January 2006, which showed elevation of his liver transaminases (ALT 436 U/mL, AST 220 U/mL), a normal total bilirubin, seroconversion to HCV Ab

positivity, and HCV VL of 26,600,000 IU/mL (genotype 1a). Testing for other causes of hepatitis including other acute viral hepatitis infections was negative. He was asymptomatic. His CD4 count and HIV VL are in Figure 1. His ART regimen was TDF, FTC, and ritonavir-boosted lopinavir (LPV/r). HCV Ab testing had been negative 3 ¼ years earlier and HCV VL was undetectable (< 600 IU/mL) 2 ½ years earlier at the time that his liver transaminases had first been mildly elevated (range 49 to 107 U/L). He reported receiving intravenous vitamin preparations on multiple occasions from an “alternative” practitioner in the prior year, but denied ever using illicit drugs. He had a history of significant (but unquantified) alcohol use but had stopped drinking alcohol completely a few years prior.

Four months after his diagnosis with primary HCV infection he underwent percutaneous liver biopsy that showed grade 2 inflammation and stage 2 fibrosis, with concomitant grade 2 steatohepatitis ([10], patient 4). He refused treatment for HCV. His liver transaminases peaked at the time of liver biopsy (ALT 622 U/L, AST 343 U/L) and subsequently remained in the 200 to 300 U/L range. He interrupted ART for three months and his CD4 count dropped to 92 (4%) cells/μL; he restarted ART [substituting ritonavir-boosted atazanavir (ATV/r) for LPV/r] with subsequent re-suppression of HIV viremia but his CD4 count never improved beyond 187 (5%) cells/μL. Nineteen months after diagnosis of primary HCV infection an abdominal computerized tomography (CT) scan showed mild to moderate hepatosplenomegaly; and 10 months later he presented with ascites

and esophageal varices. He underwent initial evaluation for liver transplantation and had a MELD score of 19. He did not return for further evaluation and died two months later from liver failure (Figure 1).

Case 3: A 40 year old man with AIDS underwent routine laboratory testing in August 2004, which showed new elevation of liver transaminases (ALT 114 U/L, AST 78 U/L), a normal total bilirubin, a negative HCV Ab test, and an HCV VL of 10,700,000 IU/mL (genotype 1a). Testing for other causes of hepatitis including other acute viral hepatitis infections was negative. He was asymptomatic. His CD4 count and HIV VL are in Figure 1. His ART regimen was TDF, nevirapine (NVP), and LPV/r. Liver transaminases had been normal and HCV Ab test negative two years earlier. He reported having had unprotected receptive anal intercourse with multiple men over the prior year but never injected drugs. He had ingested methamphetamine in the past but not around the time of his HCV infection. He denied any significant alcohol use.

He refused HCV treatment. HCV serology was repeated 28 months later and was positive. He tolerated ART poorly and his CD4 count fell to 114 (7%) cells/ $\mu$ L. Forty months after diagnosis with primary HCV infection he underwent cholecystectomy and an intra-operative liver biopsy showed grade 4 inflammation and stage 3 fibrosis but was not compatible with toxicity due to his prior d4T or ddI use [17, 18]. After a single dose of peg-IFN he discontinued further treatment due to multiple side effects. Soon after he developed

decompensated liver disease with massive ascites requiring hospital admission and had small esophageal varices. A repeat liver biopsy showed grade 3 inflammation and stage 4 fibrosis characteristic of HCV-induced liver disease. He continued to tolerate his ART poorly and his CD4 count never increased beyond 200 cells/ $\mu$ L. He was ineligible for liver transplant due to his low CD4 count and lack of control of HIV infection. He died from liver failure eight years after diagnosis of primary HCV infection (Figure 1).

Case 4: A 54 year old man with asymptomatic HIV infection underwent routine laboratory testing in June 2002, which showed new elevation of liver transaminases (AST 332 IU/L, ALT 367 IU/L), a normal total bilirubin, and a negative HCV Ab test. Testing for other causes of hepatitis including other acute viral hepatitis infections was negative. He was asymptomatic. His CD4 count and HIV VL are in Figure 1. His ART regimen was zidovudine (AZT), lamivudine (3TC), and abacavir (ABC). He reported having had unprotected receptive anal intercourse with multiple men during the prior year and had injected crystal methamphetamine on multiple occasions and shared injection equipment once in the prior month. He reported moderate (50 grams/day) alcohol use intermittently for many years.

Four weeks later he became jaundiced at which time his HCV VL was 2,410 IU/mL. Three weeks later his HCV Ab was positive and HCV VL was > 500,000 IU/mL. He did not continue in regular medical care for either his chronic HIV or

his primary HCV infections presumably due to his addiction to crystal methamphetamine and to some extent to his intermittent alcohol use, although he did continue to take the same ART. He underwent percutaneous liver biopsy 3 ½ years after diagnosis of primary HCV infection, which showed grade 2 inflammation and stage 3 fibrosis, with concomitant grade 1 steatohepatitis. Repeat liver biopsy one year later showed grade 3 inflammation and stage 4 fibrosis, but no change in grade 1 steatohepatitis. He returned for medical care 6 ½ years after diagnosis of primary HCV infection due to new onset of peripheral edema and ascites. His health declined quickly and he died of liver failure seven months later (Figure 1).

### ***Discussion***

In this report we describe four HIV-infected men who progressed from primary HCV infection to decompensated cirrhosis far more rapidly than expected (Figure 1 shows time course). Three died of liver failure and one survived through liver transplantation.

We do not know the precise mechanism(s) that caused HCV to take such a rapid course in these four men but we hypothesize that they fit into a model of highly accelerated progression to liver failure after HCV infection previously suggested by clinical experience with other immunocompromised patient cohorts. Examples include patients who acquired HCV infection after immunocompromise due to hematological malignancies [19], common variable immunodeficiency [20, 21], and renal [22, 23] and orthotopic liver transplantation [24, 25]. In addition, earlier case reports showed that

acquiring “non-A, non-B hepatitis” and HIV simultaneously through blood transfusion resulted in particularly bad outcomes, with decompensated cirrhosis and death occurring within three years of the infections [26, 27]. Our cases are much more similar, then, to these patients who acquired HCV when they were already immunocompromised than to the “usual” patients with co-infection as described by Benhamou et al [4], who were healthy young adults at the time of HCV infection [3]. Further, even in this small series of four men there is a suggestion that the lower the CD4 count at the time of primary HCV infection, the higher the rate of progression to liver failure. Patients 1 and 2 who had the fastest progression had AIDS and the lowest CD4 counts at the time of HCV infection of any men in our cohort. Patient 3 had a somewhat higher CD4 count but a recent clinical AIDS diagnosis (Kaposi sarcoma) that persisted during his HCV course. Patient 4 had the longest time to decompensated cirrhosis of the four men (Figure 1), and his case demonstrates that having a higher CD4 count does not preclude this rapid progression. Taken together with the prior literature, these observations suggest that the rate of progression of HCV-induced liver disease is greatly accelerated if patients are immunocompromised, including by HIV infection, at the time of acquisition of HCV infection.

Our study has a number strengths as well as weaknesses. Our study endpoint, decompensated cirrhosis, is easy to recognize and incontrovertible, although by using it, we probably underestimate the prevalence of advanced liver disease in our cohort. We were able to prove that none of the four men had pre-existing sub-clinical cirrhosis from some unknown cause as all four underwent liver biopsy early in their course and they

did not have histological evidence of cirrhosis or any other advanced liver disease such as non-cirrhotic portal hypertension from hepatoportal sclerosis [18]. Further, all biopsies were re-read by a single liver pathologist (M.I.F.), eliminating inter-observer variation. Not all causes of liver injury can be histologically distinguished from those caused by HCV infection but fibrosis from the other likely causes of liver disease in our case patients (i.e. alcoholic and non-alcoholic steatohepatitis and di-deoxy nucleoside use) can be distinguished histologically and those changes were not present. Specifically, patient 4, and possibly patient 2, drank alcohol to a degree that was probably unhealthy and both of their early biopsies showed steatohepatitis, which could have been due to alcohol. But the large majority of their actual fibrosis was portal in location, which is the distribution from HCV infection, and not perivenular, which is the distribution from alcohol. Drug use in general and methamphetamine use specifically is common in men in the HCV epidemic in New York [6], but although there have been rare deaths from fulminant hepatitis after overdose of methamphetamine, to our knowledge there are no published reports in the medical literature that methamphetamine use causes portal fibrosis in humans (and only patients 3 and 4 reported such drug use and the other two men denied such use). Pre-existing but seronegative chronic HCV infection must be considered, but that is rare, especially in patients with normal ALT, even in those with low CD4 counts [28]. We note that these four men were also much older (39 to 55 years old at the time of HCV infection) compared to the typical age at HCV infection in parenterally-acquired HCV (~20 to 30), and they were all men. Both older age and male sex are risk factors for faster fibrosis progression, although neither the age of these men nor their sex could on their own

explain this large an effect. Since three patients lived in New York, we cannot absolutely exclude that there is an unknown, yet to be recognized co-factor that these men share. However, one patient was from San Diego, so the syndrome is not geographically limited. Finally, the total number of cases we report is low and we cannot accurately assess the prevalence of this syndrome. Qualitatively, however, patient 2 was one of the original 11 patients we reported with rapid-onset fibrosis after primary HCV infection ([10], patient 4) and he was one of only two of these 11 men who were not cured of HCV, and patients 1-3 were part of our well-characterized cohort at Mount Sinai that included 15 HIV-infected men who were not cured of HCV infection and who had at least two years of follow-up after primary HCV infection (the time frame of the disease course for patient 1). Nonetheless, we believe we will need to follow more men with this syndrome before we can determine the precise risk of developing liver failure and the clinical and immunological parameters that affect that risk.

In conclusion, four HIV-infected men with primary HCV infection developed rapid onset of fibrosis with continued rapid progression to decompensated cirrhosis, and death within two to eight years. While other risk factors for liver damage may have been present, we suggest that the rapidity of progression was due primarily to the degree of underlying immunocompromise caused by HIV infection. Clearly, more research is needed to better define the mechanisms behind this devastating rate of liver damage.

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Figure 1. Baseline Demographics, Liver Biopsy Results, and Clinical Outcomes of Four HIV-infected Men after Primary HCV Infection Compared to Typical Course of HCV Infection in HIV-infected Patients

Figure legend:

\*[4, 14-16]; pIFN/RBV Rx = pegylated interferon plus ribavirin treatment

