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Clinical Presentation and Course of Acute Hepatitis C Infection in HIV-Infected Patients

Annie Luetkemeyer, MD[*,†], **Bradley Hare, MD**[*], **John Stansell, MD**[*], **Phyllis C. Tien, MD**[‡], **Edwin Charlesbois, MPH, PhD**[†], **Paula Lum, MD, MPH**[*], **Diane Havlir, MD**[*], and **Marion Peters, MD**[§]

[*]HIV/AIDS Division, San Francisco General Hospital, University of California at San Francisco, San Francisco, CA

[†]Center for AIDS Prevention Studies, University of California at San Francisco, San Francisco, CA

[‡]Department of Medicine, University of California at San Francisco, and Infectious Disease Section, San Francisco Veterans Affairs Medical Center, San Francisco, CA

[§]Division of Gastroenterology, University of California at San Francisco, CA

Abstract

Hepatitis C virus (HCV) has become a significant source of morbidity and mortality in HIV-infected patients. However, little is known about the clinical presentation and course of acute HCV infection in this population. This study reports the outcomes of acute HCV infection in 9 HIV-infected men. Sex with men was the only reported risk factor for HCV infection in 6 of the subjects. Clinical presentation of acute HCV ranged from incidentally discovered elevated transaminases to severe liver dysfunction requiring hospitalization. At the time of HCV diagnosis, 8 of 9 patients had $CD4^+$ counts >250 cells/mm^3, and 6 had HIV viral loads of ≤5000 copies/mL. Eight patients were receiving antiretroviral therapy. Outcome of these acute HCV infections varied. Five patients experienced virologic clearance, 2 in whom virus cleared spontaneously and 3 who were treated with pegylated interferon and ribavirin. Four patients developed chronic infection, one of whom had a relapse during HCV treatment and 3 of whom were untreated. All 4 patients to whom HCV therapy was administered experienced significant anemia or neutropenia, necessitating dose reduction or support with growth factors. Prompt recognition of acute HCV infection may minimize antiretroviral treatment interruption and will allow early treatment, which may improve virologic clearance. Unexplained transaminase elevations in HIV-infected patients, including men who have sex with men, should trigger an evaluation for acute HCV infection.

Keywords

acute hepatitis C; HIV; pegylated interferon; men who have sex with men

Reprints: Annie Luetkemeyer, HIV/AIDS Division, San Francisco General Hospital, University of California, San Francisco, Box 0874, Building 80, 995 Potrero Avenue, San Francisco, CA 94110 (aluetkemeyer@php.ucsf.edu).

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Hepatitis C virus (HCV) has emerged as a significant cause of morbidity and mortality in the HIV-infected population in the antiretroviral era. Coinfection with HCVis seen in 15%–30% of the HIV-infected population of the United States.[1,2] Compared with HIV-uninfected patients, HIV-infected patients have higher HCV viral loads,[3] lower rates of spontaneous HCV clearance, and sometimes accelerated liver disease.[4–6] Additionally, HIV-infected patients with chronic HCV respond less well to therapy; sustained virologic response (SVR) is achieved in only 27%–40% of patients treated with pegylated interferon and ribavirin and in as few as 14% of patients with genotype 1.[7–9] Treatment of acute HCV in HIV-infected persons may be a window of opportunity for improved response to therapy, as has been demonstrated in HIV-uninfected patients.[10,11] However, the presentation and clinical course of acute HCV infection have not been well described in patients with HIV infection. To better characterize acute HCV in the HIV-infected population, we report on 9 patients with acute HCV.

PATIENTS AND METHODS

Between 2002 and 2004, 9 patients with acute HCV were identified by hepatologists or primary HIV providers at the University of California, San Francisco. Institutional approval for a retrospective review of the cases was obtained. To meet the case definition of acute HCV, detectable serum HCV RNA was required in the setting of either documented seroconversion to HCV antibody positivity within the past 6 months or all of the following: alanine aminotransferase (ALT) >5 times the upper limit of normal with normal levels within the previous year, documented history of negative HCV antibody, and the exclusion of acute hepatitis A (HAV) and hepatitis B (HBV). Early virologic response (EVR) was defined as a >2 log reduction in or undetectable serum HCV RNA at 12 weeks of therapy compared with baseline. End-of-treatment response (ETR) was defined as undetectable serum HCV RNA at the cessation of therapy, and SVR was defined as undetectable serum HCV RNA 24 weeks after completion of therapy.

Medical charts were reviewed for history, physical examination, HCV therapy and risk factors for HCV, including injection drug use (IDU) status, blood transfusion, and surgeries within the past year. IDU and sexual practice were assessed by patient self-report to providers. Information on tattooing and acupuncture was not available in the medical record. Laboratory values extracted included ALT, aspartate aminotransferase (AST), bilirubin, and hepatic synthetic function, as assessed by serum albumin and prothrombin time. HCV antibody testing was performed with a third-generation enzyme immunoassay (Ortho Diagnostics, Rochester, NY). Quantitative HCV RNA was evaluated with either version 3.0 bDNA assay (Bayer Diagnostics, Berkeley, CA; lower limit of detection 615 IU/mL) or version 2.0 Cobas Amplicor (Roche Diagnostics, Indianapolis, IN; lower limit of detection 600 IU/mL). Qualitative HCV RNA was performed using version 2.0 Cobas Amplicor (Roche Diagnostics) or by polymerase chain reaction (Palo Alto VA Medical Center, Palo Alto, CA). HCV genotyping was performed using the INNO-LiPAassay (Bayer Diagnostics, Berkeley, CA).

CASES

The demographics and baseline characteristics of these patients are summarized in Table 1. HCV treatment regimens and outcomes for the 4 patients treated for HCV infection are shown in Table 2.

Patient 1

A 47-year-old Hispanic man had had HIV infection for 5 years and was on a stable antiretroviral therapy (ART) regimen. Routine laboratory work revealed serum ALT and AST of 178 and 378 IU/L, respectively, with normal bilirubin and hepatic synthetic function. ART was discontinued owing to concern for hepatotoxicity, and further evaluation revealed positive HCV antibodies and HCV RNA of 3.8 million IU/mL (genotype not obtained). Five years previously, HCV antibody had been negative, and positive HAV total antibody and positive hepatitis B surface antibody (HBsAb) had been documented. Three months prior to diagnosis, his AST and ALT were normal at 23 and 21 IU/L, respectively. During the month after HCV diagnosis, he developed scleral icterus and mild right upper quadrant (RUQ) pain for 1 week, with an ALT that peaked at 1473 IU/L and a total bilirubin peak of 8.5 mg/dL. Hepatic synthetic function remained normal. He reported sex with men as his only risk factor for HIV and HCV infection. He was offered therapy for acute HCV but declined. One month after his initial serum transaminase abnormalities were noted, serum HCV RNA had decreased to 1896 IU/mL, and at 5 months serum HCV RNA was <615 IU/mL with normal transaminases, indicating spontaneous clearance of HCV viremia.

Patient 2

A 26-year-old white man had HIV infection of unknown duration and took no ART. Of note, he had a history of chronic HBV infection with positive HBsAg at the time of HCV diagnosis, with baseline AST and ALT of 75 IU/L and 54 IU/L, respectively. He presented with 1 week of diarrhea, arthralgia, and dark urine. Physical examination revealed no jaundice or RUQ tenderness, and laboratory analysis demonstrated an elevation from his baseline transaminase values to an AST of 271 IU/L and ALT of 361 IU/L, with normal bilirubin and synthetic function. HCV antibody was negative but HCV RNA was detectable at 2.1 million IU/mL (genotype 1b). The patient was offered HCV therapy but declined. Three months after diagnosis, HCV RNA had fallen to 978 IU/mL, with AST and ALT of 54 IU/L and 54 IU/L, respectively; 6 months after diagnosis, serum HCV RNA had become undetectable at <615 IU/mL, indicating spontaneous clearance of HCV viremia. HCV antibody was not reevaluated.

Patient 3

A 56-year-old white man had been infected with HIV for >20 years and was on stable ART. On routine monitoring, he was found to have abnormal liver function. AST and ALT both peaked at >3000 IU/L, and his total bilirubin rose to 7.0 mg/dL, at which time the patient developed nausea, RUQ fullness, and jaundice. Hepatic synthetic function remained normal. Further testing revealed positive HCV antibody and detectable serum HCV RNA, with a recent positive HBsAb and negative HAV total antibody. Four years earlier, he had had a documented negative HCV antibody, and 7 months earlier, he had normal AST and ALT

values. He reported contracting HIV through sex with men and denied additional risk factors for HCV. Two months after diagnosis with HCV, he initiated a 48-week course of pegylated interferon and ribavirin, which resulted in SVR.

Patient 4

A 35-year-old Hispanic man had been infected with HIV for 5 years and had recently resumed ART after a treatment interruption. He was noted to have elevated serum transaminases on routine laboratory monitoring. AST and ALT were 230 and 426 U/L, respectively, with normal total bilirubin and hepatic synthetic function and no clinical symptoms. Elevated serum transaminases initially were attributed to the ART regimen of stavudine, lamivudine, and nevirapine, which was continued. However, the persistently elevated AST and ALT over the following 2 months prompted further laboratory evaluation that revealed positive HCV antibody and subsequent detectable serum HCV RNA. HCV antibody had been negative 4 months previously. Of note, 1 month prior to the diagnosis of HCV, he was treated for urethral gonorrhea. His only reported risk factor for HIV and HCV infection was sex with men. Eleven weeks after the first transaminase abnormalities were noted, he started a 48-week course of pegylated interferon and ribavirin, which resulted in an ETR; SVR data have not yet been obtained.

Patient 5

A 50-year-old white man had been infected with HIV for 20 years and was on a stable ART regimen. He presented to an outside hospital with acute onset of influenzalike symptoms and headache and was told he had evidence of acute HCV infection. Ten days later he was seen at our institution, at which time his HCV antibody was positive, with detectable serum HCV RNA. Transaminases were elevated with ASTof 55 IU/L and ALT of 95 IU/L, with normal bilirubin and hepatic synthetic function. HCV antibody had been negative 6 months prior to this presentation. On examination, he was anicteric with no RUQ discomfort. He reported a history of unprotected sex with women and remote IDU. Seven months prior to his presentation with HCV, urethral *Chlamydia* infection had been diagnosed. He initiated a 24-week course of therapy with pegylated interferon and ribavirin, which resulted in SVR.

Patient 6

A 55-year-old white man had had HIV infection for 7 years and was on stable ART. He presented with an acute influenza-like illness accompanied by jaundice, weight loss, and dark urine. Of note, he had chronic HBV infection, known for >30 years, with stable elevation of his AST and ALT in the range of 50–100 IU/L, and he was well compensated on lamivudine. His laboratory data prior to presentation were notable for positive HBsAg, negative hepatitis B e antigen, HBV DNA of <160 copies/mL, and AST and ALT of 68 and 105 IU/L, respectively. At presentation, physical examination was notable for scleral icterus and mild RUQ tenderness. Laboratory evaluation revealed an AST and ALT of 1295 and 2128 IU/L, respectively, total bilirubin of 9.1 mg/dL, normal hepatic synthetic function, negative hepatitis delta serology, negative total HAV antibody, and negative HAV IgM. Liver biopsy demonstrated an acute viral hepatitis superimposed on chronic disease, grade 2, stage II by Batts–Ludwig scoring system.[12] Quantitative serum HCV RNA was detectable,

and HCV antibody was now positive; HCV antibody had been negative 4 years previously in the setting of a CD4 count of >400 cells/mm^3. This patient's only reported risk factor for HIV and HCV was sex with men.

Three months after HCV diagnosis, he was treated with pegylated interferon and ribavirin. Serum HCV RNA at 12 weeks of therapy had decreased by >2 log to 84,000 IU/mL, indicating EVR, but rebounded to 7 million IU/mL at 24 weeks of therapy and was 3.5 million IU/mL at the completion of 48 weeks of therapy, indicating failure to attain ETR.

Patient 7

A 38-year-old white man had had HIV infection for 1 year and was currently on a stable ART regimen. On routine laboratory testing, he was noted to have elevated AST and ALT of 1105 and 1194 IU/L, respectively, and a total bilirubin of 4.4 mg/dL. He was asymptomatic and had benign findings on abdominal examination. ART was discontinued owing to concern for hepatotoxicity. Evaluation revealed positive HCV antibodies, with a negative HCV antibody test 3 months previously, and serum HCV RNA of 1.0 million IU/mL (HCV genotype 1a). He had been treated for rectal gonorrhea 1 month previously, and his only reported risk factor for HIV and HCV infection was sex with men. He was offered therapy for his acute hepatitis but declined. Three months after HCV diagnosis, transaminase elevation and mild hyperbilirubinemia persisted, and serum HCV RNA remained elevated at 1.1 million IU/mL.

Patient 8

A 45-year-old African American man had had HIV infection for 5 years, with intermittent ART use. On routine laboratory monitoring, he was noted to have AST of 276 IU/L and ALT of 256 IU/L, with a history of normal transaminases 4 months previously. HCV antibody and HAV total antibody were both negative. Elevated transaminases persisted for several months, at which time HCV RNA was evaluated and found to be >700,000 IU/mL. Two years previously, HCV qualitative RNA had been negative, and 5 years previously, HBsAb was positive. The patient was asymptomatic, and his only reported risk behavior was unprotected sex with multiple female partners. He was offered therapy for HCV but declined. Six months after HCV diagnosis, HCV RNA remained detectable at >700,000 IU/mL, with a persistently negative HCV antibody, in the setting of a CD4 count of 44 cells/mm^3.

Patient 9

A 33-year-old Hispanic man had had HIV infection for 6 years with intermittent ART use. Three weeks after starting ART with nevirapine, ritonavir-boosted lopinavir, and didanosine, he developed fatigue, diarrhea, and muscle pain and was found to have an ALT of 363 IU/L and an AST of 510 IU/L. HCV antibody was negative and the symptoms were initially attributed to ART, which was discontinued. The patient was admitted to the hospital for evaluation several days later when frank jaundice developed. He had a previously documented positive HAV total antibody and HBsAb. Over the next week, total bilirubin rose to a peak of 9.9 mg/dL; ALT and AST peaked at 4722 IU/L and 5429 IU/L, respectively; and acute HCV infection was diagnosed when HCV RNAwas found to be

162,000 IU/mL (genotype 1). He reported injecting speed with shared needles 2 weeks prior to presentation and denied sex with men. Given the patient's ongoing IDU, unstable living situation, and poor adherence with ART, he was considered a poor candidate for HCV therapy and not offered treatment at that time. His symptoms resolved over the next month and transaminases returned to normal. Chronic HCV infection developed, with seroconversion to HCV antibody positivity, and persistence of detectable HCV RNA at 300,000 IU/mL 20 months after initial presentation.

DISCUSSION

Acute HCV infection has been increasingly reported in HIV-infected individuals, including in men who have sex with men (MSM). Our cases illustrate the varying clinical presentations of acute HCV in HIV-infected patients. Two patients were asymptomatic and infection was diagnosed with serum transaminase elevations discovered on routine laboratory testing. The 7 symptomatic patients experienced influenza-like illness, nausea, and abdominal pain, and 5 of these patients developed jaundice. Two patients required hospitalization for severe symptoms and hepatic dysfunction. Of note, the majority of our patients had well-controlled HIV disease at the time of their diagnosis with HCV. Eight of 9 cases had CD4 values of >250 cells/mm^3 and were on ART therapy. Six patients had HIV viral loads of ≤5000 copies/mL.

The importance of men having sex with men as a risk factor for HCV acquisition has been controversial. Although several studies have demonstrated men having sex with men as a risk factor for HCV,[13–15] not all studies identify this association.[16] There is also evidence that sexual transmission of HCV may be facilitated by HIV infection,[6,16,17] as well as by concomitant sexually transmitted infections.[14,18,19] Our cases suggest that MSM sexual activity as well as sexually transmitted infections may play an important role in HCV transmission in HIV-infected patients. Six patients reported sex with other men as their only risk factor for HCV infection. Two patients reported unprotected sex with female partners. Three patients had had sexually transmitted infections diagnosed within the 7 months preceding acute HCV diagnosis. None of the patients had a recent history of surgery or blood transfusion. Given the retrospective nature of our chart review, we could not assess specific sexual behaviors or the use of barrier protection, nor could we exclude occult IDU as a potential source of HCV infection in the 8 patients who denied IDU.

Our findings are similar to several recent European case reports describing acute HCV infection in HIV-infected MSM, particularly in association with concurrent sexually transmitted diseases. A British sexually transmitted diseases clinic series reported on 27 patients who presented with acute HCV infection, 25 of whom were HIV-infected MSM.[20] In 21 patients (77%), the only identified exposure risk for HCV acquisition was unprotected sexual intercourse, and 9 (33%) had recent or concurrent syphilis. Only 3 (11%) presented with symptomatic acute HCV infection. In a similar report from France, 5 HIV-infected MSM with no risk factors for HCV other than sexual behavior were diagnosed with asymptomatic acute HCV infection in the setting of primary or secondary syphilis.[21] Chaix et al[22] reported on 12 HIV-infected men who developed acute HCV infection between the years 2001–2004, with MSM as their only risk factor for HCV acquisition. Phylogenetic

analysis demonstrated that 10 patients had infection with genotype 4d HCV, which clustered separately from other local sequences of 4d virus, suggesting a common source of infection, which in these cases appeared to be sexually transmitted. Finally, a recent report from the Netherlands describes 6 HIV-infected MSM men with no parenteral risk factors for hepatitis who contracted acute HCV in the setting of lymphogranuloma venereum infection.[23] Even in the absence of traditional risk factors such as IDU, surgery, and blood transfusions, HIV-infected MSM should be considered at risk for HCV acquisition, especially in conjunction with sexually transmitted infections that may facilitate HCV transmission.

After acute HCV infection, HCV antibody may remain negative for up to 6 months and occasionally for longer periods.[24,25] Consistent with this finding, 3 of our patients were HCV antibody negative at the time of diagnosis with positive serum HCV RNA. One subject never demonstrated HCV antibody seroconversion but had ongoing HCV viremia at 6 months of follow-up. His low CD4 count may have played a role in his failure to convert to HCV seropositivity, as has been reported in chronic HCV–HIV coinfection.[26,27] In HCV antibody–negative patients in whom acute HCV is clinically suspected, serum HCV RNA should be evaluated. Prompt diagnosis of HCV infection is important not only to allow for early treatment but also to establish that ART is not the cause of the hepatitis. As was seen in 3 of our patients, abnormal serum transaminase values may prompt discontinuation of ART due to concern for hepatotoxicity. Rapid and appropriate diagnosis of HCV with serum HCV RNA may minimize the need for or duration of these ART treatment interruptions.

In HIV-uninfected patients, standard-formulation interferon therapy without ribavirin for up to 24 weeks for acute HCV infection is successful, with studies demonstrating SVR rates of 70%–98%.[10,28–31] However, owing to a lack of prospective, randomized controlled trials, the type of interferon, the need for ribavirin, and the duration of therapy required for acute HCV treatment remain unclear. In comparison with acute HCV therapy, chronic HCV infection treated with 48 weeks of pegylated interferon and ribavirin has yielded an overall SVR of about 55% in HIV-uninfected patients,[32,33] compared with SVRs of 27%–40% in HIV-infected patients.[7,8] Ninety percent to 95% of HIV and HCV–coinfected patients develop chronic HCV infection without therapy.[34,35]

Data are limited on treatment of acute HCV infection in HIV-infected individuals. A recent series from Germany describes 11 HIV-infected patients with acute HCV infection who were treated with interferon for 11–48 weeks; 5 patients also received ribavirin.[36] Two patients received standard interferon and 9 received pegylated interferon. Ten of 11 patients had an SVR, the majority of whom had the less favorable HCV genotypes 1 or 4. Of note, 10 of these patients with acute HCV infection were believed to have contracted their HCV infection sexually. An additional 2004 case report describes a 17-year-old man with acute HIV–HCV coinfection, who initiated 24 weeks of therapy with pegylated interferon and ribavirin 2 months after diagnosis with HCV. Transaminases returned to normal and SVR was demonstrated 24 weeks after completion of therapy.[37]

In comparison, in our series, 8 of 9 patients were offered HCV therapy, and 4 underwent treatment with pegylated interferon and ribavirin for a minimum of 24 weeks, each within 3 months of HCV diagnosis. All 4 exhibited an EVR. Of these, 1 patient with chronic hepatitis

B infection had a virologic relapse at 24 weeks of therapy, 2 patients achieved SVR, and 1 had an ETR and is awaiting SVR data. Quantitative HCV RNA was used to evaluate response to therapy in most cases, which may have precluded detection of HCV viremia below the limit of assay detection. All 4 of the treated patients had clinically significant hematologic toxicity, requiring growth factors or dose reduction of interferon and ribavirin. However, no patients experienced new opportunistic infections while on therapy, despite transiently depressed leukocyte counts from interferon therapy. Given the retrospective, observational nature of this study and the small number of patients included, we cannot draw conclusions about efficacy of pegylated interferon and ribavirin therapy for acute HCV in coinfected patients. However, as HIV-infected patients have a poor response to treatment of chronic HCV infection and a low rate of spontaneous clearance, acute HCV therapy in HIV-infected patients should be further evaluated as a promising opportunity for enhanced clearance of HCV viremia.

In summary, cases of acute HCV in HIV-infected patients appear to be increasingly reported, especially among MSM and in association with other sexually transmitted infections. Presentation may vary from asymptomatic with elevated ALT values to severe symptomatic hepatitis requiring hospitalization. Acute HCV infection may occur in patients with well-controlled HIV viremia and relatively high CD4 counts. Even in the absence of traditional risk factors for HCV infection such as IDU or blood transfusion, HIV-infected MSM with unexplained elevated transaminase values should be evaluated for acute HCV infection. When serum HCV antibody is negative, serum HCV RNA is a useful diagnostic tool that may aid in prompt diagnosis of acute HCV infection, allowing for early HCV treatment and potentially reducing ART interruption. Therapy for acute HCV is feasible in HIV-infected patients but may be associated with significant side effects including neutropenia, anemia, and depression. Further investigation is warranted to evaluate the efficacy of acute HCV therapy in HIV-infected individuals and to elucidate the optimal components and duration of therapy.

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TABLE 1

Demographics and Baseline Data of 9 HIV-Infected Men With Acute Hepatitis C Infection

		HCV Exposure		At Time of HCV Diagnosis			
Patient	Age	MSM	Parenteral*	ARV	CD4 (cells/mm3)	Plasma HIV RNA (copies/mL)	HCV Antibody
1	47	Y	No	3TC, D4T, NFV	292	<50	Positive
2	26	Y	No	None	355	39,556	Negative
3	56	Y	No	3TC, TDF, EFV	350	<50	Positive
4	35	Y	No	3TC, D4T, NVP	435	5000	Positive
5	50	N	Prior IDU	3TC, ZDV, NFV	329	<50	Positive
6	55	Y	No	3TC, ABC, FOS/r	450	<50	Positive
7	38	Y	No	3TC, TDF, ATZ	283	<50	Positive
8	45	N	No	DDI, TDF, IDV/r	7	>100,000	Negative
9	33	N	Active IDU	DDI, NVP, LOP/r	312	30,000	Negative

Patient	Age	Clinical Presentation	Sexually Transmitted Infections	ALT Peak Value (IU/L)	HCV Therapy	Outcome
1	47	Jaundice, RUQ pain	—	1473	Declined therapy	Spontaneous clearance of HCV viremia
2	26	Diarrhea, Arthralgia	—	361	Declined therapy	Spontaneous clearance of HCV viremia
3	56	Jaundice, Nausea	—	>3000	PEG IFN + RBV	SVR
4	35	Jaundice, RUQ pain	Urethral GC 4 weeks prior to HCV diagnosis	426	PEG IFN + RBV	ETR
5	50	Flu-like illness, Headache	Urethral Chlamydia 7 months prior to HCV diagnosis	286†	PEG IFN + RBV	SVR
6	55	Jaundice, Flu-like illness, RUQ pain	—	2128	PEG IFN + RBV	Chronic HCV
7	38	Asymptomatic	Rectal GC 1 month prior to HCV diagnosis	1194	Declined therapy	Chronic HCV
8	45	Asymptomatic	—	334	Declined therapy	Chronic HCV
9	33	Jaundice, Diarrhea, Myalgia	—	4722	Therapy not offered	Chronic HCV

*Surgery within one year, history of blood tranfusion, reported IDU.

†Peak ALT from hospitalization not available.

3TC indicates lamivudine; ABC, abacavir; ATZ, atazanavir; D4T, stavudine; DDI, didanosine; EFV, efavirenz; ETR, end of treatment response; FOS/r, ritonivir-boosted fosamprenavir; GC, gonorrhea; IDV/r, ritonavir-boosted indinivir; LOP/r, ritonivir-boosted lopinivir; PEG IFN, pegylated infeferon; NVP, nevirapine; NFV, nelfinivir; RBV, ribavirin; SVR, sustained virologic response; TDF, tenofovir; ZDV, zidovudine; and MSM, men who have sex with men.

TABLE 2

Treatment Regimen, Duration and Outcome for Subjects Receiving HCV Therapy

Patient	Weight	HCV Genotype	HCV RNA (IU/mL)	First Abnormal ALT to Start of HCV Therapy	HCV Diagnosis to Start of HCV Therapy
3	88 kg	1a	2.0 million	2 wks	2 wks
4	71 kg	1b	140,000	11 wks	4 wks
5	87 kg	2	762	7 wks	7 wks
6	80 kg	1	6.0 million	12 wks	12 wks

Patient	HCV Treatment	Length of Therapy	Complications of HCV Therapy	Dose Reduction	Use of Growth Factors	Outcome
3	PEG IFN α-2a 180 mcg/wk +RBV 1000 mg/day	48 wks	Anemia, Neutropenia, Depression	IFN decreased to 135 mcg/wk	—	EVR, SVR
4	PEG IFN α-2a 180 mcg/wk +RBV 1000 mg/day	48 wks	Anemia, Neutropenia, Depression	IFN decreased to 135 mcg/wk	Epo, G-CSF	EVR, ETR*
5	PEG IFN α-2a 180 mcg/wk +RBV 1000 mg/day	24 wks	Anemia, Neutropenia, Depression	IFN decreased to 135 mcg/wk	Epo, G-CSF	EVR, SVR
6	PEG IFN α-2a 180 mcg/wk +RBV 1000 mg/day	48 wks	Anemia, Depression	—	Epo	EVR, No ETR

* SVR data not yet available.

Epo indicates erythropoetin; EVR, early virologic response; ETR, end treatment response; PEG IFN, pegylated interferon; RBV, ribavirin; and SVR, sustained virologic response.