HIV and Hepatitis C Virus Coinfection: Approach to Management

Lindsey Reese, MD, Rachel Chasan, MD, MPH, and Dawn A. Fishbein, MD, MS

Abstract

- *Objective:* To review screening, diagnosis, and treatment in patients with HIV and hepatitis C virus (HCV) coinfection.
- *Methods:* Review of the literature in the context of a clinical case.
- *Results:* All persons with HIV should be routinely screened for HCV infection, as chronic hepatitis C has become a major source of mortality among HIV-infected persons. The course of liver disease is more rapid in HIV/HCV coinfected persons, and the risk for cirrhosis is nearly twice that in persons with HCV monoinfection. Prior to therapy, it is important to assess for contraindications to treatment, such as uncontrolled depression or pregnancy, and to obtain HCV genotype and quantitative HCV RNA. The standard treatment regimen is pegylated interferon alfa with weight-based ribavirin. During treatment, regular monitoring for bone marrow suppression and depression from pegylated interferon and hemolytic anemia from ribavirin is necessary. Certain antiretrovirals, such as zidovudine and didanosine, should be avoided during treatment for HCV as they may worsen treatment-related side effects. Treatment options are limited in relapsers and nonresponders but may include retreatment or even consensus interferon; for decompensated liver disease, referral for liver transplantation should not be delayed. Specifically targeted anti-HCV agents are under investigation and appear promising in monoinfected persons.
- *Conclusion:* Although much progress has been made in understanding HIV/HCV coinfection, an urgent need for further research remains.

Since the introduction of antiretroviral therapy (ART), persons living with human immunodeficiency virus (HIV) have experienced significantly prolonged survival and decreased morbidity [1,2]. The improvement in survival is largely due to the decrease in opportunistic infections that had complicated advanced HIV infection. As persons with HIV are living longer, there has been an increase in the morbidity and mortality associated with non–HIV-related comorbidities. Liver disease, often due to hepatitis C virus (HCV) infection, accounts for nearly 30% of non–HIV-related deaths among HIV-infected persons [1,3,4]. The prevalence of HCV in HIV-infected persons is estimated at 30% in urban areas, and in high-risk populations such as injection drug users, the prevalence is nearly 80% [5–7]. In addition, the progression of liver disease from HCV is accelerated in HIV-infected persons as compared to that in persons with HCV monoinfection [8–10]. One study showed a twofold increased risk of cirrhosis among HIV/HCV coinfected persons compared with HCV monoinfected persons [8]. Another study found significantly faster hepatic decompensation in coinfection than in HCV monoinfection: 50% versus 13% at 2 years and 70% versus 40% at 5 years [9]. As HCV infection is common and liver disease is often more severe in persons with HIV infection, it is important to understand the recommendations for screening, diagnosis, and treatment in coinfection.

CASE STUDY
Initial Presentation

A 61-year-old man with HIV infection presents for evaluation for chronic hepatitis C.

History

The patient was diagnosed with HIV in 1988, which he likely acquired from injection drug use (IDU); he last used heroin 5 months prior to his evaluation for chronic hepatitis C. His nadir CD_4 count was 190 cells/mm^3, and there is no history of opportunistic infections. He has intermittently been on ART since his diagnosis. In 2005 the patient had a CD_4 count of 334 cells/mm^3 and an HIV viral load of 690 copies/mL. The patient currently is off ART secondary to pancreatitis diagnosed 4 months earlier; his regimen had been zidovudine, lamivudine, and efavirenz.

The patient was diagnosed with HCV infection in 1996

From the Mount Sinai School of Medicine, New York, NY.

Table 1. Persons for Whom Hepatitis C Virus (HCV) Screening Is Recommended

Persons who have injected illicit drugs in the recent and remote past
Persons with conditions associated with a high prevalence of HCV infection, including:
Persons with HIV infection
Persons with hemophilia who received clotting factor concentrates before 1987
Persons who were ever on hemodialysis
Persons with unexplained abnormal aminotransferase levels
Prior recipients of transfusions or organ transplants, including:
Persons who were notified that they had received blood from a donor who later tested positive for HCV infection
Persons who received a transfusion of blood or blood products before July 1992
Persons who received an organ transplant before July 1992
Health care, emergency medical, and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood
Current sexual partners of HCV-infected persons; although the prevalence of infection is low, a negative test in the partner provides reassurance

Adapted from reference 14.

and has never received therapy for this infection. He reports that he was told previously that his "liver was fine" and that he did not need additional workup or treatment. His past medical history is significant for iron deficiency anemia, infective endocarditis, a renal cyst, osteoarthritis, and osteopenia. Review of systems is positive for early satiety, but he denies abdominal pain, back pain, nausea, vomiting, or diarrhea. He reports no change in his bowel habits and denies melena or hematochezia. He denies cardiac or pulmonary symptoms, including chest pain, shortness of breath, orthopnea, or dyspnea on exertion. He denies a history of depression or other mental illness. His social history is significant for a history of IDU, last IDU 20 years prior, but no current tobacco or alcohol use. As previously stated, last use of intranasal heroin was 5 months prior to evaluation.

Physical Examination

The patient is pleasant, noncachectic, and well-appearing and has normal vital signs; his weight is 65 kg. Head and neck examination are significant for anicteric sclera and no evidence of thyroidmegaly or lymphadenopathy. His heart rate and rhythm are regular and lungs are clear to auscultation. He has an old right-sided posterior scar on his chest from a rib resection he underwent as a child for "pleurisy." His abdomen is nontender and nondistended with a palpable liver edge 3 cm below the costal margin. He has no edema, spider angiomas, palmar erythema, or asterixis.

Laboratory Evaluation

Laboratory tests are significant for anemia with a hemoglobin level of 10.6 g/dL, elevated aminotransferases with an aspartate aminotransferase (AST) level of 95 U/L and an alanine aminotransferase (ALT) level of 125 U/L, and a normal bilirubin level of 0.8 mg/dL. Albumin is slightly low at 3.6 g/dL, but his international normalized ratio (INR) is normal at 1.1. Other biochemistry results are within normal limits.

- **What risk factors warrant screening for HCV?**
- **Which diagnostic tests are recommended?**

HCV is a single-stranded ribonucleic acid (RNA) virus categorized into 6 major genotypes that are important in predicting the likelihood of a treatment response. Genotype 1 occurs most commonly in the Unites States (70%) and in coinfection [11]. Genotypes 2 and 3 are the other main genotypes and, as will be discussed below, are associated with improved treatment outcomes. Genotype 4 is common in the Middle East and North Africa, and genotypes 5 and 6 are rarely seen outside of South Africa and Southeast Asia, respectively [12].

Persons at Risk for HCV

The virus is predominantly transmitted via infected blood or blood products. In the United States, IDU is the predominant mode of transmission, and all persons with a history of IDU should be screened for HCV [13]. Other groups that should be screened include persons who received blood or organ transplants prior to 1992, persons with unexplained elevations in aminotransferases, persons who have been on hemodialysis, and persons infected with HIV, especially if acquired via IDU [14] (**Table 1**). Sexual transmission of HCV in low-risk heterosexual persons occurs at a very low frequency, with an estimated 0.2% to 0.3% risk annually [15]. Sexual transmission may occur more frequently in persons with concurrent sexually transmitted diseases or those who engage in sexual contact that traumatizes the anal or genital mucosa leading to contact with blood; thus, it is reasonable to screen this group of persons for HCV as well. Recent data have suggested an increased risk of sexually transmitted HCV among HIV-positive men who have sex with men in association with high-risk sexual behaviors or sexually transmitted diseases [16–19].

Routine screening of the above groups is indicated as HCV infection most frequently presents as a chronic disease with few symptoms until progressing to end-stage liver disease. Between 55% and 85% of people who are infected with HCV will develop chronic hepatitis C, and in HIV-positive persons spontaneous viral clearance occurs less frequently than it does in monoinfected persons [18]. Spontaneous clearance of HCV

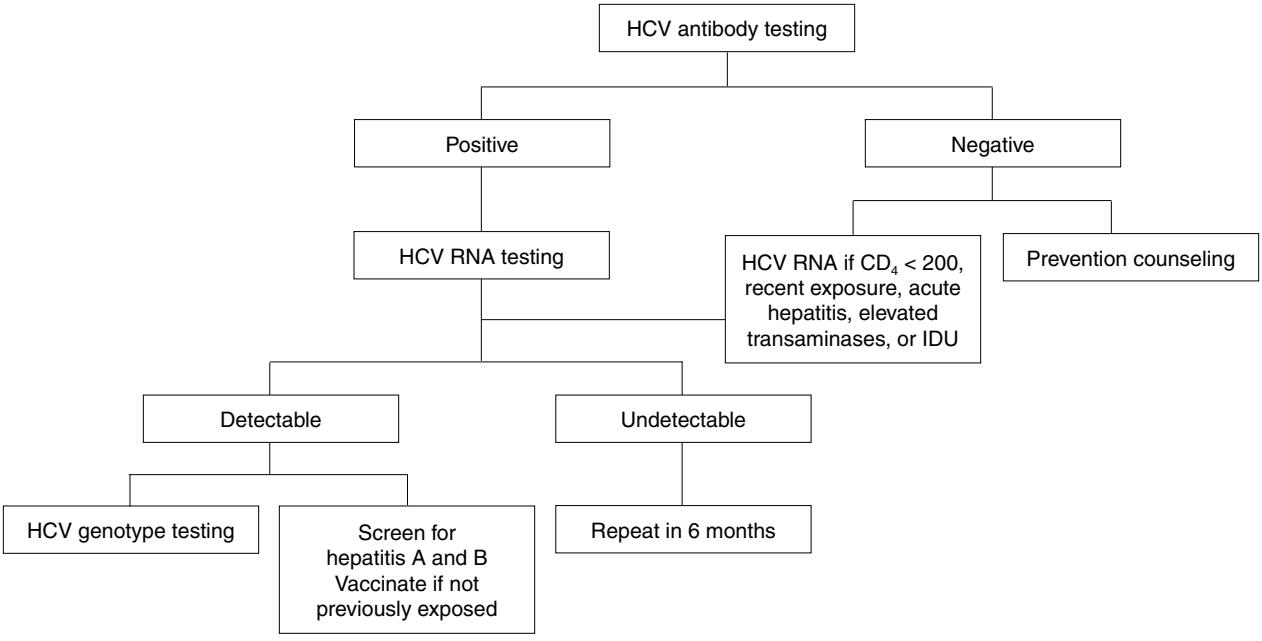

Figure 1. Diagnostic algorithm for hepatitis C virus (HCV) infection. IDU = injection drug use. (Adapted from reference 24.)

can occur in nearly one third of HIV-negative persons but occurs in only 5% to 9% of persons infected with HIV [20,21]. Thus, nearly 80% of persons with HCV develop chronic infection with some degree of fibrosis; 20% to 30% will develop cirrhosis from 15 to 50 years after infection, and each year 1% to 5% of persons with cirrhosis will develop hepatocellular carcinoma [22,23]. As mentioned, persons with coinfection have an accelerated course of liver disease; they are twice as likely to develop cirrhosis in as little as 10 years after infection and are at greater risk for hepatic decompensation and carcinoma [1,4,8–10].

HCV Assays

Screening begins with an enzyme-linked immunoassay (EIA) that detects antibodies to viral antigens [24] (**Figure 1**). All positive results should be followed by quantification of HCV RNA to detect active viral replication. Supplemental immunoblot antibody testing is used in some settings to confirm a positive EIA but is used less frequently in HIV-positive persons as they have a higher frequency of indeterminate immunoblot results [25]. If HCV RNA is detectable, the HCV genotype should be evaluated for prognostic value and to determine treatment duration. Vaccinations for hepatitis A and B should also be administered if the person is not found to be immune. If the HCV RNA is undetectable, the test should be repeated in 6 months to rule out HCV infection. If confirmed negative, the person should receive prevention counseling, emphasizing avoidance of exposure to contaminated blood products and IDU. If the initial HCV antibody test (EIA) is negative in those with HIV, quantitative HCV RNA testing should also be performed if there is a possibility of recent exposure to HCV, if the person has symptoms of acute HCV infection, or if the CD_4 count is less than 200 cells/mm^3 [26]. HCV RNA is usually detectable within 2 weeks after infection, while HCV antibodies develop from 6 weeks to 6 months after infection [18].

- **Should this patient be treated? What other tests are necessary prior to treatment?**

Twenty percent of those with acute HCV infection will experience symptoms, including fever, fatigue, loss of appetite, abdominal pain, nausea, vomiting, and jaundice [23]. In cases of symptomatic acute HCV, early detection of HCV is important as early treatment during the acute phase is highly efficacious; one study reported a sustained virologic response (SVR) of 89% to 94% in HCV monoinfected persons [27]. The response rate is lower for early treatment of acute HCV in HIV-positive persons, but studies have reported a SVR of 71% to 89%, which is much higher than the SVR in treatment for HCV in coinfection [28,29].

In asymptomatic persons, when the diagnosis of HCV is established the decision of if and when to treat is multifaceted, based on genotype and degree of liver fibrosis, which

Table 2. Contraindications to Treatment for HCV

Major uncontrolled depressive illness
Renal, heart, or lung transplant recipient
Autoimmune hepatitis or other condition known to be exacerbated by interferon and ribavirin
Untreated hyperthyroidism
Pregnant or unwilling/unable to comply with adequate contraception
Severe concurrent disease such as severe hypertension, heart failure, significant coronary artery disease, poorly controlled diabetes, obstructive pulmonary disease
Age < 2 years
Known hypersensitivity to drugs used to treat HCV

Adapted from reference 35.

is often evaluated by liver biopsy, radiographic imaging, and laboratory indicators of inflammation. The primary therapeutic goal is viral eradication, or SVR. SVR is the absence of detectable HCV RNA 24 weeks after treatment completion [24]. The threshold for treating persons with coinfection is lower than for HCV monoinfected persons as progression of fibrosis is accelerated in coinfection.

Prior to treatment, a thorough history should include an assessment of the likely duration of infection, route of transmission, current alcohol and drug use, and other comorbidities, especially psychiatric diagnoses. Laboratory values, such as a complete blood count (CBC), chemistry profile, liver function tests, thyroid-stimulating hormone (TSH) level, and prothrombin time should be measured to document baseline values for monitoring during treatment. HCV genotype and quantitative HCV RNA should be measured initially as they direct prognosis and treatment duration [24]. The patient should also undergo pretreatment counseling to advise avoidance of alcohol, IDU, and hepatotoxic medications, and referral to drug and alcohol treatment programs should be made if needed. The patient should be tested for exposure to hepatitis A and B and vaccinated if necessary. Also, a thorough medication history should be elicited in HIV-positive persons as modification of ART may be necessary to avoid adverse reactions during treatment for HCV.

It is not clear to what extent HIV infection itself decreases the rate of a SVR, and there are conflicting data about the role of ART in the progression of liver disease. Some studies have shown that immune restoration, as evidenced by higher CD_4 cell counts and undetectable HIV viral loads, are associated with slower progression of liver disease in coinfected persons and subsequent lower rates of death from liver disease [30]. Conversely, the hepatotoxic effects of ART are more likely to develop in patients with chronic heptitis C [31]. Despite the risk of hepatotoxicity from therapy, data indicate that initiating ART prior to HCV treatment, especially with CD_4 cell counts below 200 cells/mm^3, may improve response rates [32]. Furthermore, recent data from the SMART trial indicate that interruption of ART is particularly unsafe in persons with coinfection [33]. The risk of nonopportunistic disease death was increased in the drug conservation group (ART was interrupted until the CD_4 cell count was < 250 cells/mm^3) compared with the viral suppression group (continued ART use) irrespective of viral hepatitis status, but the risk was greater in the coinfected patients than in the HIV monoinfected patients. In the coinfected patients, there were 1.6 more nonopportunistic disease deaths per 100 person-years in the drug conservation group compared with the viral suppression group; in the monoinfected patients, there were 0.4 more deaths in the drug conservation group compared with the viral suppression group. Thus, it is currently recommended by the International AIDS Society to consider initiating ART in coinfected persons, irrespective of CD_4 cell count, and maintaining ART in persons throughout treatment for HCV [34]. However, some ART should be avoided in the treatment of patients with chronic hepatitis C, and these will be discussed later.

There are a few contraindications to treatment for HCV [35] (**Table 2**). The major contraindications are (1) uncontrolled depression, which includes hospitalization for depression or a suicide attempt within the prior year, as disease can worsen during treatment; (2) pregnancy, as ribavirin is teratogenic; (3) solid organ transplant or autoimmune disease that may be exacerbated by the medications used to treat HCV infection; and (4) severe concurrent medical disease such as significant coronary disease, chronic obstructive pulmonary disease, or uncontrolled diabetes [35]. Treatment is not contraindicated but should be individualized for persons with current illicit drug use or alcohol use as well as those with psychiatric comorbidities, persons who have failed prior treatment for HCV, and persons with chronic renal disease, prior liver transplant, or decompensated cirrhosis [14,35]. Compensated cirrhotics may benefit from a course of treatment, and data on HCV monoinfected persons indicates that treatment can induce the regression of cirrhosis, decreasing liver-related complications and death from liver disease [32]. Persons who are cirrhotic and may be awaiting treatment should be monitored regularly for hepatocellular carcinoma. Current recommendations include an ultrasound of the liver every 6 months in persons who are cirrhotic; measurement of serum alfa-fetoprotein (AFP) can be added to ultrasound screening or be used exclusively for persons who cannot obtain high-quality ultrasounds due to size or body habitus [36,37]. A follow-up computed tomography scan or magnetic resonance imaging of the liver should be pursued if the AFP level is greater than 20 ng/mL or if there is an abnormality detected on ultrasound.

Zidovudine should not be administered with ribavirin due to the added risk of anemia [35]. In HIV-positive persons, ribavirin-associated anemia is often more severe, especially in persons taking zidovudine. Anemia is not currently listed as a contraindication to treatment, but treatment should be individualized in this group and should include more frequent monitoring with dose reductions if needed as discussed below.

There are other prognostic indicators that should be considered prior to treatment. The single most important predictor of a SVR is HCV genotype. Factors positively associated with a SVR are genotype non–1 and baseline HCV RNA level less than 800,000 IU/mL. Conversely, factors associated with a poor treatment response include genotype 1, pretreatment HCV RNA levels greater than 800,000 IU/mL, HIV coinfection, cirrhosis, older age at time of treatment, obesity, diabetes or insulin resistance, and alcohol intake during treatment [38,39]. There are also racial and ethnic differences in treatment response as African Americans and Latinos have been found to have poorer treatment responses [40,41]. These prognostic factors are important as some are modifiable, such as obesity, insulin resistance, or alcohol use, and once corrected could positively affect treatment outcomes. In addition, persons with the above positive prognostic indicators, HCV genotype 2 or 3, or genotype 1 and a low baseline viral load (< 800,000 IU/mL) can be considered for early treatment, often without biopsy, as their rate of SVR is higher, as noted below [14,35]. Although the likelihood for a SVR is lower in persons with coinfection, many of the factors associated with a poor treatment response are disproportionately represented in the coinfected population.

Indications for treatment in persons with HCV are based on genotype and degree of liver fibrosis, often necessitating a liver biopsy. In persons with genotype 1, a liver biopsy is needed to gauge the severity of fibrosis. In patients with HCV monoinfection only and little or no fibrosis, treatment can be deferred, but repeated biopsy for monitoring is associated with morbidity and has not been found to be cost-effective [14,42]. In HIV-infected persons with chronic hepatitis C, the threshold for treatment is much lower as progression of liver disease is accelerated; thus, any evidence of fibrosis on liver biopsy justifies treatment [8–10]. Moreover, although fibrosis tends to be worse in persons with elevated aminotransferases, persons can have normal aminotransferases with significant fibrosis; therefore, persons with genotype 1, even with normal liver function by serology, should be referred for biopsy to determine the necessity of treatment [14]. As liver biopsy is not without risk, both monoinfected and coinfected persons with genotype 2 or 3 may forgo biopsy prior to treatment as their rates of SVR are much higher [14,35].

While liver biopsy has been considered the gold standard for fibrosis assessment, there is known sampling error and risk with this invasive procedure [43]. Consequently, there has been increased investigation into alternative, noninvasive indices to measure the degree of liver fibrosis. Indices that use serologic markers of liver inflammation and fibrogenesis, such as the Forn's index [44] or the aspartate aminotransferase/platelet ratio (APRI) [45], or the Fib-4, which have been validated in coinfection [46] and found to be useful in identifying persons in either extreme of fibrosis (lack of significant fibrosis versus advanced fibrosis). Persons at either end of these indices may avoid biopsy, but persons with moderate levels of fibrosis would still need a biopsy to confirm the need for treatment. Another recent innovation in assessing liver fibrosis is the Fibroscan, an ultrasound-based technique that assesses liver stiffness as a measure of fibrosis [47]. Liver stiffness is correlated to stage of fibrosis, and recent data suggests that this imaging modality may be more accurate than the serologic noninvasive indices. This test remains under investigation and has not yet received U.S. Food and Drug Administration approval.

Follow-up

The patient agrees to undergo treatment for chronic hepatitis C infection and is counseled to avoid exposure to alcohol and other drugs and hepatotoxic medications. The patient is not sexually active and was already counseled about practicing protected sex due to his HIV infection. He is informed of the small risk of sexual transmission of HCV and is again encouraged to practice protected sex. He is screened for hepatitis A and B and is not found to be immune to either virus, so he is vaccinated for both. The patient is infected with HCV genotype 1 and has a viral load of 1,450,000 IU/mL. His biopsy shows grade 2 inflammation and stage 3 fibrosis. Utrasound also shows hepatomegaly and no masses or evidence of cirrhosis. He is restarted on ART based on genotypic resistance testing; his regimen consists of emtricitabine, tenofovir, atazanavir, and norvir. Zidovudine is not used given his history of anemia and likely future treatment of his HCV. The patient is adherent with this regimen.

The patient is referred to gastroenterology for evaluation of his early satiety and iron deficiency anemia; upper endoscopy and colonoscopy are negative for malignancy and active bleeding. The patient is pretreated with darbepoetin for his anemia. The patient is also evaluated by a cardiologist given his age and remote history of endocarditis; a transesophageal echocardiogram is performed and results are within normal limits.

- **What is treatment for chronic hepatitis C?**

Table 3. Major Trials for Treatment of Hepatitis C Virus Infection in HIV Coinfection

Study	Treatment	Duration	Sustained Virologic Response, %		
			Overall	Genotype 1	Genotype 2, 3
Adult AIDS Clinical Trial Group A5071 (2004) [48]	Peginterferon alfa-2a (180 µg/wk) plus ribavirin (600 mg/day x 4 wk, 800 mg/day x 4 wk, 1000 mg/day for the remainder)	48 wk	27	14	73
APRICOT (2004) [38]	Peginterferon alfa-2a (180 µg/wk) plus ribavirin (800 mg/day)	48 wk	40	29	62
RIBAVIC (2004) [49]	Peginteferon alfa-2b (1.5 µg/kg/wk) plus ribavirin (800 mg/day)	48 wk	27	17	44

The treatment of chronic hepatitis C in coinfection closely mirrors that for HCV monoinfection with pegylated interferon alfa and weight-based ribavirin, but the SVR in coinfection is significantly lower. SVR for coinfected persons ranges from 27% to 40% overall; 14% to 29% in genotype 1, and 44% to 73% in genotypes 2 or 3, based on the major trials in HCV treatment in coinfection [38,48,49] (**Table 3**). These SVRs are compared to an overall rate of 54% to 56% in monoinfected persons; 40% to 50% in genotype 1, and 73% to 78% in genotypes 2 or 3 [39,50]. The standard treatment regimen consists of subcutaneous pegylated interferon alfa-2a (180 µg/wk) or pegylated interferon alfa-2b (1.5 mg/kg/week) with weight-based ribavirin [48,49]. Pegylated interferon became the standard of care over interferon due to significantly higher SVR, and there has been no difference in efficacy between pegylated interferon alfa-2a and -2b in either the monoinfected or coinfected groups [48,49,51,52]. Consensus interferon, also known as interferon alfacon-1, has been studied as an alternative to pegylated interferon. It is a synthetically derived interferon that has exhibited high antiviral activities in vitro, but requires daily dosing. One study has shown it to be as efficacious as pegylated interferon and ribavirin with activity against HCV genotype 1 and high viral loads [53]. It will be discussed further in the section on alternative treatment options. In HCV monoinfection, dosing of ribavirin for genotype 1 is 1000 mg per day if the patients weighs less than 75 kg or 1200 mg per day if the weight is greater than 75 kg; for genotype 2 or 3, dosing is 800 mg per day. In previous coinfection treatment trials, ribavirin was dosed at 800 mg per day, likely contributing to the lower SVR [38,48,49]. Recent trials have demonstrated higher rates of SVR using pegylated interferon with weight-based ribavirin in coinfection. The PRESCO trial showed an overall SVR of 49.6% (35% in genotype 1 and 72.4% in genotypes 2 or 3) using pegylated interferon and weight-based ribavirin in coinfection [54]. Rates comparable to those for HCV monoinfection were also demonstrated in a recent abstract that showed an overall SVR of 51% (40% in genotype 1 and 83% in genotypes 2 or 3) using pegylated interferon and weight-based ribavirin in coinfection [55].

Treatment Duration

Duration of treatment for HCV monoinfected persons depends on genotype. In persons with genotype 2 or 3 infection, treatment with pegylated interferon plus ribavirin at a dose of 800 mg daily should be administered for 24 weeks. As discussed below, this does not hold for coinfection. An SVR should be verified by undetectable HCV RNA 24 weeks after completion of treatment [14,35]. In genotype 1, treatment with pegylated interferon and weight-based ribavirin should be administered for 12 weeks, at which time an early virologic response (EVR) should be assessed with an HCV RNA. A complete EVR is defined at week 12 as an undetectable HCV RNA, while a partial EVR is a 2-log decline in HCV RNA level compared with baseline. Among persons who have evidence of an EVR, nearly 70% will go on to achieve SVR, but among those who do not have a complete or partial EVR, the chances of an SVR are negligible and treatment should be discontinued [35,56]. For persons who achieve a complete EVR, treatment should be continued for a total of 48 weeks, and if the HCV RNA is undetectable at that time, the person has attained an end-of-treatment response (ETR). If HCV RNA remains undetectable at 24 weeks posttreatment, they are considered to have an SVR. Those with an ETR but who fail to achieve an SVR are considered relapsers and can be considered for retreatment. Alternatively, for persons who have a partial EVR, treatment should be continued and HCV RNA should be drawn at week 24. If viral load is undetectable at this time, these persons are termed slow or partial responders. These persons may benefit from individualization of treatment, often extended to 60 or 72 weeks, or 48 weeks postundetectability [57].

Recent data has demonstrated the utility of assessing a rapid virologic response (RVR) at 4 weeks with an HCV RNA. An RVR is defined as undetectable HCV RNA at 4 weeks and has been found to have a good positive predictive value (PPV) toward achieving a SVR, reported as 87% in a recent study [58]. If an RVR is achieved in persons with HCV monoinfection with genotype 2 or 3, recent data suggests treatment may be shortened to 12 to 16 weeks [59,60]. In persons with genotype 1 and a low baseline viral load who achieve an RVR,

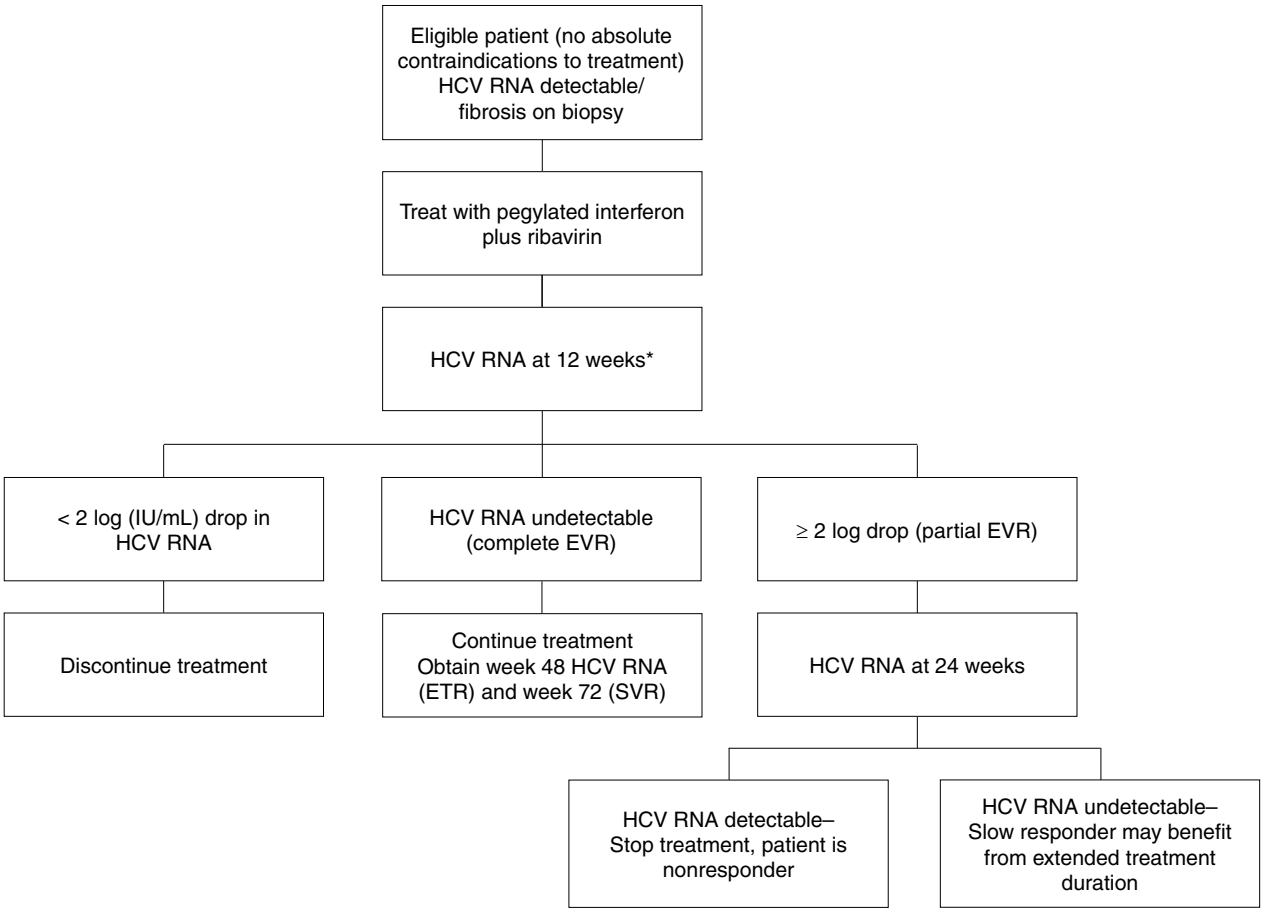

Figure 2. Treatment algorithm in coinfection. ETR = end-of-treatment response; EVR = early virologic response; SVR = sustained virologic response. *Rapid virologic response can be assessed at week 4, but shortened treatment duration is not well studied in coinfection. (Adapted from reference 24.)

SVR rates were similar for both the 24-week and the 48-week regimen, indicating that truncated therapy may be acceptable for this group as well [61]. As discussed below, this does not hold for coinfection. In contrast, persons who have detectable viremia at week 4 may benefit from an extended duration of treatment; one study showed significantly higher SVRs in persons treated for 72 weeks if they had detectable viremia at week 4 [62].

In coinfected persons, most of the existing studies have used treatment durations of at least 48 weeks [35,38,48,49]. Abbreviated courses of treatment, even for genotypes 2 or 3, have not been adequately studied in coinfected persons. An EVR should be assessed at 12 weeks, and treatment should be continued if there is an undetectable viral load or if there is a 2-log decline in baseline HCV RNA. Treatment should be discontinued if there is a lack of response at 12 weeks. For those with a complete EVR, HCV RNA is assessed at end of treatment, 48 weeks, and again 24 weeks after treatment end to document a SVR [14, 35] (**Figure 2**). As with HCV monoinfected persons, for coinfected persons with a partial EVR, viral load should be established at 24 weeks to identify slow or partial responders who may benefit from extended treatment regimens. An RVR also appears to be important in monitoring treatment in coinfected persons [63,64]. In recent studies, an RVR was shown to be a positive predictor of SVR in coinfection. In persons with genotype 1 who achieved an RVR, the PPV of attaining an SVR was 69%, while in persons with non-genotype 1 virus the PPV for an SVR was 80% to 90% [63,64]. Coinfected persons with genotype 2 or 3 virus and an RVR may be candidates for abbreviated therapy of 24 weeks, but further research is needed and this is not currently recommended.

Initiation of HCV Treatment

The patient is initially started on pegylated interferon alfa-2a at 180 μg/week and ribavirin 800 mg

Table 4. Laboratory Monitoring During Treatment of Hepatitis C Virus (HCV) Infection

Laboratory Evaluation	During Therapy, wk*												Post Therapy, wk			
	4	8	12	16	20	24	28	32	36	40	44	48	4	8	12	24
CBC†	X		X			X			X			X				X
ALT	X		X			X			X			X				X
Creatinine	X		X			X			X			X				X
TSH			X			X			X			X				
HCV RNA	X		X			X						X				X
CD_4 cell count			X			X						X			X	X

ALT = alanine aminotransferase; CBC = complete blood count; TSH = thyroid-stimulating hormone. (Adapted from reference 35.)

*Body weight measurement and assessment for depression should be done monthly during HCV therapy

†Weekly monitoring for the first 4 weeks has been recommended due to increased risk of anemia in coinfection (*see* Koziel MJ, Peters MG. Viral hepatitis in HIV infection. N Engl J Med 2007;356:1445–54).

daily. His HIV viral load is undetectable at the time of treatment initiation and his hemoglobin is over 12 g/dL. After 2 weeks, the dose of ribavirin is decreased to 600 mg daily because the patient's hemoglobin has fallen by 2 g/dL to 10 g/dL due to hemolytic anemia. The patient is restarted on darbepoetin and the hemoglobin recovers to 12 g/dL after 4 weeks. At this time, as data was emerging on the improved efficacy of weight-based ribavirin in coinfection, the patient is started on ribavirin 1000 mg daily in divided doses, as he weighs 65 kg; he is maintained on darbepoetin at this time. After this, he has a detectable HCV RNA at week 4 (no RVR) but has an undetectable HCV RNA at week 12 (complete EVR). Treatment is individualized for this patient and a team decision is made to give a total treatment course of 54 weeks. This gives the patient a full 48 weeks of weight-based ribavirin, especially since the patient has stage 3 fibrosis, which is advanced and could be stage 4 considering sampling error. The patient's side effects during treatment include anemia, clinically significant weight loss of 5 kg (> 5% of his baseline weight), insomnia, facial skin eruption, and hair loss.

- **What are common adverse effects of HCV treatment and how often should we monitor for these adverse effects?**

After initiating therapy, frequent monitoring is necessary to address treatment-related side effects (**Table 4**). Many patients report flu-like symptoms such as fatigue, headaches, and myalgias, which can be treated with low doses of acetaminophen or nonsteroidal anti-inflammatory medications. More serious side effects include depression and bone marrow suppression from pegylated interferon and hemolytic anemia from ribavirin.

Depression from pegylated interferon can occur in up to 50% of persons and usually manifests over the first months of treatment [65]. Severe, uncontrolled depression, including hospitalization or suicide attempt within the prior year, is currently a contraindication for HCV treatment. Therapy with selective serotonin reuptake inhibitors in persons with interferon-associated depression has been shown to alleviate depressive symptoms, allowing treatment to continue [66]. In a recent study, depression scores declined significantly in patients taking citalopram for interferon-associated depression compared to placebo. Moreover, all subjects taking citalopram were able to complete interferon therapy; the study was terminated prematurely due to the positive results [66].

The bone marrow suppression from pegylated interferon can result in neutropenia, thrombocytopenia, or anemia. Although pegylated interferon use has not been correlated with increased rates of infection, granulocyte colony-stimulating factor (GCSF) can be considered for severe neutropenia, such as absolute neutrophil counts (ANCs) of 500 to 750 cells/μL, to avoid dose reduction [67]. If dose reduction of pegylated interferon is necessary, it should be reduced by 50% for an ANC of less than 750 cells/μL and discontinued for an ANC of less than 500 cells/μL. In coinfected persons, monitoring of CD_4 lymphocytes is recommended. The absolute CD_4 lymphocytes usually decrease, yet the percentage of CD_4 to total lymphocytes often remains the same or may even increase. Opportunistic infection prophylaxis may be indicated if the CD_4 lymphocytes fall below 200 cells/mm^3, but HCV treatment is continued.

Thrombocytopenia is also an adverse side effect of treatment with pegylated interferon. Persons should be monitored closely if their platelet count falls to less than 50,000/μL of blood, and treatment should be held for platelet counts of less than 25,000/μL. Recent data suggests that the use of eltrombopag for thrombocytopenia may allow persons with cirrhosis to

complete treatment without dose reduction, but this medication has not been FDA approved for this indication [68].

Other adverse effects of pegylated interferon include autoimmune thyroiditis, necessitating monitoring of TSH at baseline and periodically throughout treatment, gastrointestinal effects such as nausea or vomiting, various cutaneous reactions, and opthalmologic disorders such as ischemic retinopathy [69]. Serious cardiac or pulmonary side effects are rare. Weight loss, as mentioned in the current case, is also a significant side effect from both pegylated interferon and ribavirin and may be more severe in coinfection. A recent cohort study compared 3 groups: 1 group had HCV monoinfection receiving standard treatment, 1 group had coinfection receiving ART and standard treatment for HCV, and 1 group was HIV-positive receiving only ART. They found that clinically significant weight loss (≥ 5% of baseline weight) was found in 76% of the subjects with coinfection versus 39% of the subjects with HCV monoinfection and only 3% of the subjects with HIV receiving ART alone [70]. Thus, weight loss from treatment may be a significantly greater problem in coinfection than in HCV monoinfection, as is the anemia induced by both pegylated interferon and ribavirin.

Bone marrow suppression from pegylated interferon is a less common cause of anemia than the hemolytic anemia that may result from ribavirin. The hemolytic anemia is reversible in 4 to 8 weeks with dose reduction of the ribavirin to 600 mg/day. The ribavirin should be discontinued if the hemoglobin falls below 8.5 g/dL [71]. Maintaining ribavirin dosage, though, is critical to achieving a SVR, and dose reduction should be avoided if possible. To avoid dose reduction, therapy with epoetin or darbepoetin alfa should be initiated when the hemoglobin drops 2 to 3 g/dL from baseline or when it is less than 10 gm/dL [72]. Ribavirin is also teratogenic and pregnancy should be avoided using 2 forms of contraception for up to 6 months after cessation of treatment. Contraception needs to be addressed in men having sex with women of childbearing age.

Besides the above-mentioned adverse affects from pegylated interferon and ribavirin, there are certain ARTs that should be avoided when treating HCV. Ribavirin and interferon should not be administered with zidovudine when possible because of the added risk of anemia. Ribavirin and didanosine have an increased risk of mitochondrial toxicity and resulting lactic acidosis [73,74]. Some studies have shown trends toward lower SVRs in persons treated with ART that included abacavir, especially persons treated with lower ribavirin doses [75,76]. However, the data is inconclusive, and one recent study showed that abacavir did not influence the rate of virologic response in coinfected persons treated with pegylated interferon and weight-based ribavirin [77].

Response to Treatment

The patient finishes the 56 weeks of treatment and had an undetectable HCV RNA at that time (ETR). Follow-up at 6 months' posttreatment reveals continued undetectable HCV RNA, and he is considered to have a SVR.

- **What are some alternative treatment options if this patient had failed treatment?**

After treatment is completed, a SVR should be verified with an undetectable HCV RNA 6 months following treatment end, or week 72; if HCV RNA is again detectable at this time, this person is a relapser. If an EVR is not achieved by week 12 or 24 and treatment is discontinued, the person is a nonresponder. Options for both relapsers and nonresponders are limited, with very low efficacy. Retreatment as well as increased treatment duration can be considered in both relapsers and nonresonders, especially if dose reduction was necessary in the initial treatment. There is limited data that higher doses of ribavirin (1600 mg/day) may be more efficacious, although higher doses of pegylated interferon has no increased efficacy and has increased adverse effects [78]. In HCV monoinfection, consensus interferon has been shown to be effective in retreatment in previous nonresponders [79]. A recent study reported SVRs of 11% to 13% in persons with HCV monoinfection who failed treatment with pegylated interferon and ribavirin and were retreated with consensus interferon and ribavirin [80]. Data for consensus interferon is lacking in coinfection, however. Interferon maintenance therapy, one half the standard dose, given to persons that do not achieve SVRs has been hypothesized to slow progression of liver fibrosis and reduce the progression to end-stage liver disease. This practice is controversial, however, as recent data (HALT-C) has questioned the efficacy of maintenance therapy in reducing the rate of disease progression in those with advanced fibrosis [81]. In persons with minimal fibrosis or low risk for progression to cirrhosis, retreatment can be postponed and they may be observed with sequential liver biopsies. In contrast, persons with decompensated cirrhosis should be referred for liver transplant and they should not be treated. Mortality among HIV-infected liver transplant recipients appears to be similar to HIV-negative recipients [82].

Treatment for HCV infection is less than ideal due to its poor efficacy, severe treatment-related side effects, and intensive monitoring, especially in persons with coinfection. Thus, there are several new specifically targeted agents against hepatitis C (STAT-C) that are under investigation. Due to the high potential for resistance, these agents are

used in combination with standard treatment with pegylated interferon and ribavirin, and none have been studied in persons with coinfection.

In preliminary studies, the nucleoside polymerase inhibitors, of which valopicitabine has been most extensively studied, have been associated with a greater decline in HCV viral load in combination with pegylated interferon when compared to standard therapy alone [83,84]. Due to gastrointestinal side effects, development of valopicitabine has been halted. Other nucleoside polymerase inhibitors, R-1626 and R-7128, and non-nucleoside polymerase inhibitors, GS-9190 and VCH-759, are in early trials [85]. The non-nucleoside polymerase inhibitor HCV-796 was shown to have HCV antiviral activity, but development of this agent was halted due to hepatotoxicity [86].

Other specifically targeted agents include the protease inhibitors telaprevir and boceprevir. The PROVE 1 trial divided patients with HCV genotype 1 monoinfection into a control group that received pegylated interferon and weight-based ribavirin for 48 weeks (called PR48) or into 1 of 3 telaprevir groups: each received telaprevir for 12 weeks and 1 group received pegylated interferon and ribavirin for 12 weeks (T12PR12), one for 24 weeks (T12PR24), and one for 48 weeks (T12PR48) [87]. The rate of SVR was 41% in the PR48 group as compared with 35% in the T12PR12 group, 61% in the T12PR24 group, and 67% in the T12PR48 group. The groups receiving telaprevir had a higher rate of discontinuation due to rash. It was concluded that treatment with a telaprevir-based regimen for 24 or 48 weeks significantly improved SVR rates over standard of care in HCV monoinfected patients with genotype 1. In a subsequent trial, the PROVE 2 trial, patients monoinfected with HCV genotype 1 were divided similarly into a standard of care group (PR48) and 3 telaprevir groups: similar T12PR12 and T12PR24 groups and a third group that received telaprevir and pegylated interferon without ribavirin for 12 weeks (T12P12) [88]. The rate of SVR was 46% in the PR48 group, compared with 60% in the T12PR12 group, 69% in the T12PR24 group, and only 36% in the T12P12 (no ribavirin) group. In HCV monoinfected patients with genotype 1, the group receiving telaprevir with pegylated interferon and ribavirin for 24 weeks had significantly higher SVR rates than the standard of care group, and response rates were lowest in the group that did not contain ribavirin.

Boceprevir began in phase 3 trials in 2008, and preliminary data from the SPRINT-1 trial reported SVR rates of 56% in whites and 45% in blacks when boceprevir was added to standard of care in treatment-naive persons [89]. Other protease inhibitors, ITMN-191 and TMC-435350, are in early trials in HCV monoinfected persons [85]. As seen in ART, in HIV there is potential to develop rapid resistance to monotherapy with these protease inhibitors [90]. Thus, there is current interest in using combinations of STAT-C agents in an attempt to overcome resistance as well as eventually to avoid pegylated interferon or ribavirin and the adverse effects that accompany those medications. In addition, it has been strongly recommended that studies be initiated in coinfected persons as they have accelerated rates of liver fibrosis and an abbreviated time to end-stage liver disease when compared HCV monoinfected persons [91].

Cyclophilin inhibitors, such as DEBIO-025 and NIM-811 are being investigated as specifically targeted agents, based on observations of the anti-HCV activity of cyclosporine in vitro. The combination of DEBIO-025 with pegylated interferon led to greater decreases in HCV viral load [92]. Both agents are being further studied in current clinical trials. Another drug, nitazoxanide, is currently being investigated with reported data from phase 2 trials that have examined the added benefit of nitazoxanide to standard therapy with pegylated interferon and ribavirin. Nitazoxanide is an antiparasitic agent used primarily to treat *Cryptosporidia parva* diarrhea and was found to recently have efficacy for *Clostridium difficile* infection. In the STEALTH C-1 trial, nitazoxanide plus pegylated interferon (dual regimen) or nitazoxanide plus pegylated interferon and ribavirin (triple regimen) was compared to standard of care in treatment-naive persons with HCV monoinfection, genotype 4 [93]. A SVR occurred in 50%, 61%, and 79% of persons receiving the standard of care, dual regimen, and triple regimen, respectively. A second study examined nitazoxanide with pegylated interferon without ribavirin and reported a SVR of 80%, raising the possibility of using nitazoxanide without ribavirin, which requires further study but may limit toxicity [94].

SUMMARY

All persons with HIV should be routinely screened for HCV infection as chronic hepatitis C has become a major source of mortality among HIV-infected persons, accounting for nearly 30% of non–HIV-related deaths. Moreover, the progression of liver disease is accelerated in coinfection compared with HCV monoinfection, so the threshold for treatment is lower in coinfected persons.

Prior to therapy, it is important to assess for contraindications to treatment, such as uncontrolled depression or pregnancy, and to obtain HCV genotype and quantitative HCV RNA to direct prognosis and treatment duration. Assessment of liver fibrosis via liver biopsy or noninvasive indices of fibrosis is also recommended prior to treatment in genotype 1 or 4, and any evidence of fibrosis justifies treatment in coinfected persons.

The standard treatment regimen consists of subcutaneous pegylated interferon alfa-2a (180 μg/week) or pegylated interferon alfa-2b (1.5 mg/kg/week) with weight-based

ribavirin. The likelihood for a SVR is lower in persons with coinfection compared to persons with HCV mono-infection and the duration of treatment differs between the groups. In coinfection, most of the existing studies have used a treatment duration of at least 48 weeks; abbreviated courses of treatment, even for genotypes 2 or 3 have not been adequately studied. An RVR should be assessed at week 4 to aid in positively predicting a SVR, and an EVR should be assessed at 12 weeks to determine if treatment should be continued. For those with an EVR, HCV RNA is assessed at end of treatment, and again 24 weeks after treatment end to document a SVR.

During treatment, regular monitoring for bone marrow suppression and depression from pegylated interferon and hemolytic anemia from ribavirin is necessary. In addition, certain antiretrovirals, such as zidovudine and didanosine, should be avoided during treatment for HCV as they may worsen treatment-related side effects. Adverse effects may necessitate dose reduction or utilization of growth factors.

Treatment options are limited in relapsers and nonresponders but may include retreatment or even consensus interferon; for decompensated liver disease, referral for liver transplantation should not be delayed. STAT-C agents appear promising in HCV monoinfected persons, both as initial therapy and after failed treatment, but studies are lacking in those with coinfection. Studies of alternative agents are urgently needed, especially in coinfected persons, as liver disease is accelerated in coinfection, progressing often to cirrhosis and hepatocellular carcinoma.

Corresponding author: Lindsey Reese, MD, Mount Sinai Hospital, One Gustave L. Levy Place, New York, NY 10029, lindsey.reese@mssm.edu.

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