

Hepatitis C Virus Treatment in HIV-Coinfected Patients: No Longer Different From Monoinfection Treatment

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Abstract: Between 15% and 30% of patients infected with HIV in the United States and Europe are coinfecting with hepatitis C virus (HCV), and rates of acute HCV infection have been increasing in some populations of HIV-positive patients. Liver disease is now a leading cause of death in HIV-infected patients. Patients with HIV/HCV coinfection have lower rates of spontaneous acute HCV clearance, poorer response to treatment of chronic HCV in the pre-direct-acting antiviral era, more rapid progression to cirrhosis, and increased risk of hepatocellular carcinoma. This article will summarize data on management of HIV/HCV coinfection, discuss the epidemic of acute HCV infection in HIV-infected patients, and examine the many new HCV treatment regimens on the horizon with data on coinfecting patients.

HIV and Hepatitis C Virus Coinfection

Between 15% and 30% of patients infected with HIV in the United States and Europe are coinfecting with hepatitis C virus (HCV).^{1,2} Coinfection rates are higher in patients with a history of injection drug use or high-risk sexual practices.³ Since the emergence of HIV antiretrovirals (ARVs) and the subsequent decreased incidence of opportunistic infections, HCV-related liver disease has been a major cause of death in HIV-infected persons. HIV infection adversely impacts all stages of HCV infection in a host. Coinfecting patients tend to progress to cirrhosis more quickly than monoinfected HCV patients,⁴ increasing the risk of liver-related complications such as ascites, spontaneous bacterial peritonitis, and esophageal varices.

The prevalence of positive HCV antibody status in the US population, according to National Health and Nutrition Examination Survey data, fell from 1.8% to 1.3% from 1988 to 2010.⁵⁻⁷ However, when estimates include the high-risk populations omitted from the survey data—such as the homeless, veteran, and incarcerated populations—it has been suggested that HCV prevalence could be closer to 2%.⁸

Acute Hepatitis C Virus Infection in HIV-Infected Persons

The incidence of acute HCV infection in the United States increased from 0.3 cases per 100,000 persons during 2007 to 2010 to 0.4 cases per 100,000 persons in 2011.⁹ Many of these infections (59.9%) were associated with the use of injection drugs, and 12.9% were associated with sexual exposures.

In the past decade, there has been an increased incidence of acute HCV infection among HIV-positive men who have sex with men (MSM).^{10,11} A Swiss HIV cohort study described a significant rise in the incidence of HCV among HIV-positive MSM from 0.23 per 100 person-years in 1998 to 4.09 per 100 person-years in 2011, nearly an 18-fold increase.¹² Over the same time period in the same study, the incidence of HCV in HIV-positive injection drug users (IDUs) fell dramatically and that of HIV-positive, non-IDU heterosexuals remained stable at very low rates (<0.5 per 100 person-years). MSM who are HIV-negative do not carry the same increased risk of HCV infection. A meta-analysis described rates of acute HCV infection as more than 4 times higher in HIV-positive MSM compared with HIV-negative MSM.¹³ Another Swiss study found the prevalence of HCV in HIV-negative MSM to be similar to the prevalence in the general population.¹⁴

The rising incidence of HCV in HIV-positive MSM described in Europe has been seen around the world. A Taiwanese prospective observational study of 892 HIV-positive, non-IDU patients, of whom nearly 75% were MSM, demonstrated a rise in HCV incidence from 0 per 1000 person-years between 1994 and 2000 to 10.13 per 1000 person-years between 2006 and 2010.¹⁵ Similar increases in HCV incidence among HIV-positive MSM have been observed in Australia and the United States.^{11,16-19}

High-risk sexual practices that are associated with acute HCV infection in HIV-positive MSM include group sex, fisting, use of sex toys, and unprotected anal intercourse with or without ejaculation.^{18,20} In a French study of HIV-positive MSM, men were aware of HIV transmission risk from high-risk behaviors, but there was a poor understanding of the transmission risk for other blood-borne viruses such as HCV.²¹ Other sexually transmitted infections, specifically syphilis, have also been associated with an increased risk of transmission among HIV-positive patients.¹⁵

Rates of spontaneous HCV clearance in HIV-positive patients are lower than those seen in patients with HCV monoinfection. A systematic review of 31 longitudinal studies including 675 non-HIV-infected subjects with acute HCV infection identified a spontaneous clearance rate of 26%.²² In contrast, a prospective UK longitudinal cohort of 112 HIV-positive patients with acute HCV infection demonstrated spontaneous clearance of the virus in 15% of patients.²³ Spontaneous clearance was

associated with a rapid fall in HCV RNA levels, elevated bilirubin and alanine aminotransferase levels, and a high baseline CD4 count.

Although acute HCV incidence rates are high in the MSM population, the rate in IDU patients is falling. A cohort study of 1276 IDU patients in Amsterdam demonstrated nearly a 15-fold reduction in HCV incidence from the 1980s to 2005, from 27.5 per 100 person-years to 2 per 100 person-years. Over the same time period, HIV incidence also fell 5-fold, from 8.52 per 100 person-years to 1.65 per 100 person-years.²⁴

Liver Disease in HIV Patients

Liver disease is the leading cause of non-AIDS-related deaths in HIV-positive individuals according to the Data Collection on Adverse Events of Anti-HIV Drugs study.²⁵ Among the types of liver disease, chronic HCV was the largest cause of cirrhosis (66%) and hepatocellular carcinoma (HCC; 80%).^{26,27} Increasingly, symbiosis must exist between the worlds of hepatology and HIV care.²⁸

The Pathology of Cirrhosis and HIV Screening

The chronicity of repeated insult and inflammation in liver parenchyma results in cirrhosis.²⁹ As tissues become increasingly fibrous, regenerative nodules coalesce around hepatocellular tracts, potentiating portal hypertension.³⁰ HCV ignites a cascade of cytokines, stellate cells, and oxidative reagents.²⁸ Dual infection with HIV increases cellular apoptosis and microbial translocation, accelerating the risk of cirrhosis, HCC, and other complications.^{4,28} Once cirrhosis develops, decompensation can take anywhere from years to decades.³¹ This progression is unpredictable and differs individually. Decompensated cirrhosis is manifested by variceal bleeding, encephalopathy, and ascites and carries a median survival time of 2 to 4 years.³¹ CD4 cell counts often decrease in the presence of cirrhosis.³²

Early detection of cirrhosis is, therefore, key to preventing HIV-associated mortality. Transaminase levels remain normal in more than 40% of patients with early cirrhosis.³³ Physical examination signs of palmar erythema, spider angiomas, ascites, and gynecomastia are late indicators of cirrhosis.³³ A more practical approach to detection was suggested by Parikh and colleagues, who developed an algorithm in which the marked presence of splenomegaly and thrombocytopenia (platelet counts <150 × 10³/μL) should trigger referral to a hepatologist for HIV patients.³⁴

Diagnosing Cirrhosis and Following Its Progression

The tests utilized to diagnose and manage cirrhosis in monoinfected HCV patients are also used in HIV/HCV-coinfected patients. The gold standard for diagnosing cirrhosis is liver biopsy. However, biopsy is not without risk of

complications, sampling error, and interobserver variability.³⁵ METAVIR and Ishak nomenclature are used to gauge degrees of liver fibrosis. A METAVIR score of 3 (Ishak score of 4) suggests bridging fibrosis, whereas a METAVIR score of 4 (Ishak score of 5-6) highlights cirrhosis.³³

The aspartate aminotransferase-to-platelet ratio index (APRI) test is an inexpensive assay comparing aspartate aminotransferase levels to platelet levels. Cirrhosis is positively predicted in 51% of cases, but concordance decreases with advancing fibrosis.^{35,36} Further discordance is noted with CD4 counts of less than 250 cells/ μ L.³³ The Fibrosis 4 (FIB-4) test is another inexpensive measure designed for coinfection and is better able to distinguish more advanced cases of fibrosis regardless of CD4 counts.³⁷

FibroTest (or FibroSure), HepaScore, and FibroMeter are commercially available assays that are more accurate than APRI or FIB-4 for coinfection.^{33,38} APRI and FIB-4 were accurate in less than 53% of cases in a comparison study, whereas the assays were able to classify 62%, 68%, and 71% of patients, respectively.³⁸ FibroTest and HepaScore incorporate bilirubin and γ -glutamyltransferase.³⁹ This can lead to false estimations of fibrosis in patients receiving atazanavir- or nevirapine-based ARV therapy.³³

In summary, the diagnostic value of serum tests is limited by their tendency to overestimate fibrosis.⁴⁰ One study revealed a lack of fibrosis in up to 77% of coinfecting patients who had been diagnosed as having cirrhosis using these tests when compared with liver biopsy.³⁹

In 2013, the US Food and Drug Administration (FDA) approved yet another noninvasive measure of fibrosis: transient elastography (FibroScan).³³ The FibroScan probe emits low-frequency vibrations that create shear waves to measure stiffness.⁴¹ These waves travel 2 to 4 times faster in abnormal tissue, and scores range from 0 to 75 kPa. Cirrhosis has been defined by a score of greater than 12.3 kPa in coinfecting patients.⁴² FibroScan has consistently demonstrated the ability to correctly classify 83% of cases of actual cirrhosis and distinguish cirrhosis from mild fibrosis.^{41,42} Limiting factors include the presence of ascites, narrowed intercostal spaces, obesity, and pregnancy.³³

Assessing Risks of Morbidity and Mortality in Cirrhosis

The Child-Turcotte-Pugh score is a helpful tool for assessing the risk of morbidity and mortality in cirrhosis in both HCV-monoinfected and -coinfecting patients.⁴³ Interobserver variability, however, limits the use of this score with regard to interpretations of ascites and encephalopathy. As such, the Model for End-Stage Liver Disease scoring system is the preferred way of prioritizing candidates for organ transplantation.⁴³ Accuracy of this model has been validated in numerous cohorts²⁸; however, its utility has also been questioned for failing to predict many pretransplant deaths among those with low scores.⁴³

Hepatocellular Carcinoma Screening and Surveillance

Screening for HCC is cost-effective when the index of suspicion for HCC exceeds 1.5% per year in HCV patients and 0.2% in hepatitis B virus patients.⁴⁴ HIV is known to magnify the risk for Kaposi sarcoma, lymphoma, and cervical and anorectal cancers.²⁸ Subsequently, HIV also increases the risk of HCC 7-fold.⁴⁵ Although the use of α -fetoprotein has fallen out of favor due to its low sensitivity and specificity, experts still use it along with magnetic resonance imaging or biphasic or triphasic computed tomography in the presence of F3-bridging fibrosis.^{28,33} Early HCCs are often curable, and such patients should be referred promptly to hepatologists or liver transplant specialists.³³

Managing Cirrhosis

As in non-HIV-infected patients, coinfecting patients with cirrhosis need to be screened for esophageal varices and counseled about minimizing the use of hepatotoxic agents, including over-the-counter medications, herbs, and supplements. Acetaminophen use should be limited to 2 g daily, and the use of nonsteroidal anti-inflammatory drugs should be minimized to reduce potential renal injury and bleeding.³³ Other drugs such as benzodiazepines are potentiated and require dose adjustment. Patients should minimize or refrain from alcohol consumption.³³ The development of alcohol-related lesions was closely correlated with moderate (1-19 g/d) alcohol consumption in HCV patients, and, thus, alcohol use should be avoided.⁴⁶ Nutritionally, sodium should also be restricted to 2000 mg daily to prevent fluid retention. Shellfish should be avoided, given concern for improper preparation and the risk of disease.

Hepatitis C Virus Treatment Regimens for HIV-Coinfecting Patients

When planning to initiate HCV treatment for a coinfecting patient, the patient's HIV ARV regimen should be examined because there are many drug-drug interactions with medications used to treat HCV. Several studies suggest that ARVs are protective against HIV exacerbating HCV-related liver disease^{47,48}; however, transaminitis and hepatotoxicity can occur with ARV treatment (particularly with nonnucleoside reverse transcriptase inhibitors and some protease inhibitors) in patients with chronic liver disease.⁴⁹ The risk of hepatotoxicity with some ARVs, such as nevirapine, appears to be increased in the coinfecting patient.^{50,51}

Coinfecting patients have lower rates of spontaneous acute HCV clearance, poorer response to treatment of chronic HCV in the pre-direct-acting antiviral era, more rapid progression to cirrhosis, and a greater risk of HCC, all of which suggest that treatment should be considered for acute infection. Rates of sustained virologic response (SVR) are higher when treating acute HCV infection than when

treating chronic HCV infection in coinfecting patients. An Australian trial examined 24 weeks of pegylated interferon alfa-2a (PEG-IFN- α 2a) and ribavirin treatment for acute HCV infection in 20 HIV-coinfecting patients and found an 80% SVR rate at week 24 (SVR24).⁵² A study from Mount Sinai School of Medicine assessed 12 weeks of treatment with telaprevir (Incivek, Vertex), PEG-IFN, and ribavirin in 19 HIV-positive MSM with acute HCV genotype 1 infection and found an 84% SVR12 rate.⁵³

Despite successful treatment of acute HCV infection, reinfection is possible. A cumulative incidence of acute HCV infection of 33% over 2 years was found in a Dutch HIV clinic population of patients who were previously successfully treated for acute HCV infection.⁵⁴

Interferon and Ribavirin

Interferon and ribavirin, the traditional agents of choice in the treatment of HCV-monoinfecting patients, have also been employed in the past few decades for treatment of the coinfecting population. In the largest published study (APRICOT), participants were randomly assigned to 1 of 3 arms with different doses of PEG-IFN and either ribavirin or placebo for varying time periods of 12 to 36 weeks.⁵⁵ SVR24 rates in coinfecting patients were 29% for genotype 1-infected patients and 62% in genotype 2/3-infected patients. This study and others have historically shown lower rates of success in treating HCV in an HIV-infected population.^{56,57} Many side effects are associated with interferon use in patients with decompensated liver disease, solid organ transplants other than the liver, autoimmune disease, severe uncontrolled psychiatric illnesses, or severe cytopenias. Ribavirin is teratogenic and contraindicated in female patients who are pregnant or wish to become pregnant. As such, some of the newer anti-HCV medications offer new hope to coinfecting patients.

Direct-Acting Antivirals

In 2011, 2 direct-acting antiviral NS3/NS4 protease inhibitors, telaprevir and boceprevir (Vicitrelis, Merck), were approved for HCV treatment. When these drugs were used in combination with PEG-IFN/ribavirin, SVR rates increased in all patients: the success rates for coinfecting patients increased from approximately 45% with PEG-IFN plus ribavirin to 60% to 70% with the addition of telaprevir or boceprevir, showing that treatment with direct-acting antivirals in the coinfecting population yields SVR rates similar to those in monoinfecting patients.^{56,61}

Telaprevir SVR rates for coinfecting patients receiving telaprevir/PEG-IFN/ribavirin in a phase 2a double-blind trial of treatment-naïve patients were 74% vs 45% in the control group receiving PEG-IFN/ribavirin with placebo.⁵⁹ In studies including prior PEG-IFN/ribavirin

treatment failure in patients who had fibrosis or compensated cirrhosis, 45% of the population achieved SVR12.⁶² Telaprevir is metabolized by the cytochrome P450 3A system, causing numerous drug-drug interactions. Harmful interactions can occur with the ARVs fosamprenavir, lopinavir, and darunavir, and these medications should not be used with telaprevir.^{63,64} ARVs that can be used safely with telaprevir include, but are not limited to, tenofovir, emtricitabine, efavirenz, rilpivirine, etravirine, raltegravir, and ritonavir-boosted atazanavir.^{65,66} If patients are taking telaprevir and efavirenz, the dose of telaprevir needs to be increased because of the drug-drug interaction that reduces the concentration of telaprevir.

For the first 12 weeks of therapy, telaprevir is combined with PEG-IFN and ribavirin, and telaprevir use is then stopped to solely continue using PEG-IFN and ribavirin for the duration of therapy. The duration is dependent on the patient's virologic response and whether he or she is eligible for response-guided therapy. Significant side effects associated with telaprevir/PEG-IFN/ribavirin triple therapy are rapid anemia and rash. In a study of coinfecting patients on this regimen, 87.8% experienced anemia and 45% experienced significant anemia, defined as a hemoglobin level less than 9 g/dL or a drop in hemoglobin level of greater than 4.5 g/dL.⁶² As a result of anemia, dose reduction of PEG-IFN and ribavirin may be needed, in addition to the use of erythropoietin and blood transfusions. The FDA recommends that blood work be done at week 2 of therapy to monitor hemoglobin levels.⁶⁷

Boceprevir In a randomized, double-blind, controlled phase 2 trial comparing boceprevir to placebo in combination with PEG-IFN/ribavirin, 63% of patients in the boceprevir arm achieved SVR24 as opposed to 29% in the placebo arm.⁶⁸ Similar SVR rates were seen in HCV-monoinfecting treatment-naïve patients.⁶⁹

In terms of drug-drug interactions, boceprevir is an inhibitor of the CYP3A4 system and is a substrate of the P-glycoprotein pathway. Boceprevir can decrease the levels of HIV protease inhibitors.⁷⁰ Although the actual clinical impact of this type of drug interaction remains unclear, the FDA has recommended against combining these agents in coinfecting patients due to the risk of HIV breakthrough viremia.⁷¹ Although boceprevir use in combination with efavirenz remains controversial, use of boceprevir with rilpivirine appears to be safe.⁷² Boceprevir has been used safely with tenofovir, emtricitabine, abacavir, lamivudine, raltegravir, and dolutegravir.^{73,74}

The first 4 weeks of treatment consist of a lead-in phase with PEG-IFN/ribavirin, and boceprevir is added at week 5. The duration of treatment is 24 or 48 weeks based on treatment history, presence of cirrhosis, and response to the current therapy.⁷¹ The most common side effects

are anemia and dysgeusia. In the ANRS-HC27 study, erythropoietin use was reported in 38 of 62 patients, and grade 4 anemia, described as a hemoglobin level of less than 7 g/dL, was seen in 3 patients.⁷⁵

New Treatments for Hepatitis C Virus

Two new direct-acting antivirals for HCV, simeprevir (Olysio, Janssen) and sofosbuvir (Sovaldi, Gilead), were approved by the FDA in late 2013, and a fixed-dose combination of ledipasvir and sofosbuvir (Harvoni, Gilead) was approved by the FDA in October 2014. Several other new drugs are in the late stages of investigational clinical trials with FDA review expected by late 2014. The new classes of medications include HCV NS5A replication complex inhibitors (daclatasvir, ledipasvir, ombitasvir, and MK-8742), a nucleotide analogue (HCV NS5B), a polymerase inhibitor (sofosbuvir), a nonnucleoside NS5B polymerase inhibitor (dasabuvir), and NS3/4A protease inhibitors (simeprevir, ABT-450, and MK-5172). Several studies have examined the efficacy of these new medications in HIV/HCV coinfection as detailed below with highlighted trials shown in Table 1.

Sofosbuvir Sofosbuvir was approved by the FDA for treating HIV/HCV coinfection based on data from the PHOTON-1 trial, in which patients were treated with sofosbuvir and ribavirin.⁷⁶ Subjects in PHOTON-1 had well-controlled HIV with a suppressed HIV viral load of less than 50 copies/mL; patients with CD4 counts greater than 200 cells/ μ L were taking ARVs at the time of enrollment and those with CD4 counts greater than 500 cells/ μ L were not taking ARVs. Treatment-naïve patients with HCV genotype 1, and both treatment-naïve and previously treated patients with genotype 2 or 3, were enrolled. Genotype 1 patients had a 76% SVR12 rate with a 22% relapse rate after 24 weeks of sofosbuvir/ribavirin treatment. By subtype, SVR12 was achieved in 82% of genotype 1a patients and 54% of genotype 1b patients. Genotype 2 patients received sofosbuvir/ribavirin for 12 weeks, with 88% achieving SVR12 and 0 relapses. Patients with genotype 3 disease who were treated for 24 weeks with sofosbuvir/ribavirin had a 92% SVR12 rate with an 8% relapse rate. Of those patients with genotype 3 who were treated for 12 weeks, 67% achieved SVR12 with a 29% relapse rate. Rates of SVR24 remained high in treatment-naïve patients with 75% in genotype 1, 88% in genotype 2, and 67% in genotype 3.⁷⁷

In PHOTON-1, median CD4 counts decreased by 85 cells/ μ L and 84 cells/ μ L at the end of sofosbuvir/ribavirin treatment for 12 weeks and 24 weeks, respectively.⁷⁶ This was thought to be consistent with known ribavirin-mediated decreases in lymphocyte counts. There was no change in the percentage of CD4 cells compared with other lymphocyte types during treatment. In patients who had HCV relapse after treatment with sofosbuvir, there was

no evidence of virologic resistance (S282T mutation) to sofosbuvir with deep sequence analysis.⁷⁷ This suggests that another treatment regimen containing sofosbuvir could be utilized for patients who were previously treated with this medication without fear of resistance. The study medications were very well tolerated, and minimal side effects were reported. Furthermore, sofosbuvir does not appear to have any clinically significant drug interactions with ARVs.⁷⁸

Simeprevir Simeprevir in combination with PEG-IFN/ribavirin was evaluated in HIV/HCV genotype 1 coinfecting patients in study C212.⁷⁹ Study C212 enrolled 106 patients; these included patients with prior PEG-IFN/ribavirin treatment who had relapsed, had partially responded, or were null responders and HCV treatment-naïve patients. Subjects had well-controlled HIV, with 88% of patients taking ARVs with a mean baseline CD4 count of 561 cells/ μ L. Patients not taking ARVs had a mean baseline CD4 count of 677 cells/ μ L. Baseline HIV viral loads were less than 50 copies/mL in 88% of patients taking ARVs and in 15% of those not taking ARVs. Most subjects had HCV genotype 1a (82%), and fibrosis was absent to moderate (METAVIR score, F0-F2) in 42% and was advanced to cirrhotic (METAVIR score, F3-F4) in 21%. At baseline, the NS3 Q80K polymorphism was seen in 28% of patients.

In study C212, subjects all received 12 weeks of simeprevir treatment with PEG-IFN/ribavirin, and those in the treatment-naïve and prior relapse groups were eligible for response-guided therapy if they achieved an HCV RNA level of less than 25 IU/mL at week 4, did not have cirrhosis, and had undetectable HCV RNA at week 12.⁸⁰ Those who received response-guided therapy (89% of those eligible) received PEG-IFN/ribavirin for an additional 12 weeks, for a total of 24 weeks of treatment. Subjects who were not receiving response-guided therapy received an additional 36 weeks of PEG-IFN/ribavirin therapy for a total treatment duration of 48 weeks. In the intention-to-treat analysis, SVR12 was seen in 79% of treatment-naïve patients, 87% of prior relapsers, 70% of partial responders, and 57% of null responders.⁸¹ In patients who met criteria for response-guided therapy, SVR12 was achieved in 88% of treatment-naïve patients and 85% of prior relapsers. Patients with F0 to F2 scores had an overall higher rate of SVR12, 80% vs 64% in those with F3 to F4 scores. Subjects taking ARVs had an overall higher rate of SVR12, 75% vs 62% in those not taking ARVs.⁸¹

A total of 18 patients had on-treatment failure, and 9 had viral relapse. HIV virologic failure was seen in 2 patients after they completed the HCV study therapy and achieved SVR12.⁸¹ All 29 patients with treatment failure (100%) had emerging mutations, mostly R155K mutation alone or in combination with other mutations at the NS3 position 80 and/or 168.

Table 1. Summary of Select Clinical Trial Data for HIV/HCV Coinfection Treatment

HCV Trial and Therapy	Year and Authors	Study Purpose	Baseline HIV Characteristics	Baseline HCV Characteristics	Length of Treatment	Outcome
APRICOT: PEG-IFN- α 2a \pm RBV	2004; Torriani et al ⁵⁵	Compare SVR24 rates among coinfecting patients taking different doses of PEG-IFN \pm RBV	Mean CD4 count: >500 cells/ μ L Patients did not necessarily need to be on HAART regimen.	HCV genotypes 1, 2, 3, 4; tx-naive; few cirrhotic patients ^a	12-36 weeks ^b	SVR24 rates highest in PEG-IFN- α -2a + RBV group: 29% for genotype 1 62% for genotypes 2/3 PEG-IFN alone: 14% for genotype 1 36% for genotypes 2/3
Telaprevir + PEG-IFN- α 2a + RBV	2013; Sulkowski et al ⁵⁹	Assess safety and efficacy of telaprevir in HIV/HCV patients	Mean CD4 count: >500 cells/ μ L 78% (47/60) of patients were on HAART regimen and had undetectable HIV viral loads.	HCV genotypes 1a/1b; tx-naive; 3% cirrhotic	12 weeks of telaprevir or placebo + PEG-IFN + RBV, then 36 more weeks of PEG-IFN + RBV	SVR12: 74% in telaprevir group 45% in placebo group
Boceprevir + PEG-IFN- α 2b + RBV	2013; Sulkowski et al ⁶⁸	Assess safety and efficacy of boceprevir with PEG-IFN + RBV	97% of patients were on HAART regimen and had undetectable HIV viral loads.	HCV genotypes 1a/1b; tx-naive; 3% cirrhotic	Lead-in period for all groups: 4 weeks of PEG-IFN + RBV followed by 44 weeks of boceprevir vs placebo + PEG-IFN + RBV	SVR24: 63% in boceprevir group 29% in placebo group
PHOTON-1: Sofosbuvir + RBV	2013; Sulkowski et al ⁷⁶ 2014; Naggie et al ⁷⁷	Assess SVR12 rates with an all-oral regimen	Patients on and off HAART regimen were enrolled. AIDS patients were excluded.	HCV genotype 1 patients were tx-naive; 4% cirrhotic HCV genotype 2/3 patients were tx-naive or tx-experienced; 16% cirrhotic	Genotype 1, 24 weeks Genotypes 2/3 ^c	SVR12: Genotype 1: 76% Genotype 2 (total): 90% Tx-naive: 88% (23/26) Tx-experienced: 92% (22/24) Genotype 3 (total): 75% Tx-naive: 67% (28/42) Tx-experienced: 94% (16/17)
C-WORTHY: MK-5172 + MK-8742 \pm RBV	2014; Sulkowski et al ⁸³	Assess SVR12 rates with an all-oral regimen	Patients had to be on HAART regimen with CD4 counts >300 cells/ μ L and undetectable HIV viral loads.	HCV genotype 1; tx-naive; 0% cirrhotic	12 weeks	SVR4 ^d : 97% with RBV 90% without RBV
ERADICATE: Ledipasvir + sofosbuvir	2014; Osinusi et al ⁸⁴	Assess safety and efficacy of an all-oral regimen	Patients both on and off HAART regimen were enrolled. AIDS patients not on HAART regimen were excluded.	HCV genotype 1; tx-naive; 0% cirrhotic	12 weeks	SVR12: 100% (13/13) patients not on HAART regimen SVR12 data for patients on HAART regimen will be presented at the 2014 AASLD meeting. Known SVR4 rates are 97% (36/37).

AASLD, American Association for the Study of Liver Diseases; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; PEG-IFN, pegylated interferon; RBV, ribavirin; SVR, sustained virologic response; tx, treatment.

^a Study design excluded cirrhotic patients, but a few patients with compensated cirrhosis diagnosed by imaging were included (3/860).

^b Dependent on treatment arm.

^c Treatment-naïve patients were placed on 12 weeks of therapy, and treatment-experienced patients were placed on 24 weeks of therapy.

^d SVR4 data are all that are available at the time of this publication.

Simeprevir has multiple drug interactions with ARVs because it is a mild inhibitor of intestinal CYP3A enzymes, a substrate for the CYP3A pathway, and also an inhibitor of the hepatic CYP1A29 enzymes. A summary of its interactions with HIV drugs is shown in Table 2. Administration of simeprevir with HIV protease inhibitors, elvitegravir, efavirenz, etravirine, nevirapine, or delavirdine is contraindicated. Simeprevir can be safely administered with tenofovir, rilpivirine, and raltegravir without modifying any of the medication doses.⁸²

MK-5172 and MK-8742 The combination of MK-5172 and MK-8742 with or without ribavirin was studied in HCV genotype 1 HIV/HCV-coinfected patients in the C-WORTHY study. The trial enrolled 59 noncirrhotic patients who were treated with MK-5172/MK-8742 for 12 weeks either with or without ribavirin.⁸³ Prior to study enrollment, subjects had well-controlled HIV and had had an undetectable HIV viral load for at least 24 weeks, and they had been on a stable ARV regimen for at least 8 weeks with a CD4 count of greater than 300 cells/ μ L. Only 7% of patients in the MK-5172/MK-8742/ribavirin arm and 10% in the MK-5172/MK-8742 arm had F3 fibrosis; all others were in stages F0 to F2.

This study is ongoing, and, at the time of this article's publication, only study data from 4 weeks after the end of treatment were available. In the MK-5172/MK-8742/ribavirin arm, 97% of patients achieved SVR4, and in the ribavirin-sparing arm (treatment with MK-5172/MK-8742 alone), the SVR4 rate was 90%.⁸³ Two patients in the MK-5172/MK-8742 arm experienced virologic breakthrough, and 1 patient in the MK-5172/MK-8742/ribavirin arm had virologic relapse. No patients experienced HIV breakthrough, and the rate of severe adverse events in each arm was less than 10%. MK-5172 and MK-8742 can be safely given with the ARVs raltegravir, tenofovir, emtricitabine, abacavir, and lamivudine without dose adjustment.

Ledipasvir The fixed-dose combination of ledipasvir and sofosbuvir was approved by the FDA in October 2014 based on the data discussed below. Ledipasvir in combination with sofosbuvir was studied in HIV/HCV genotype 1 patients in the ERADICATE trial. The study enrolled 50 noncirrhotic, treatment-naive patients to receive 12 weeks of ledipasvir/sofosbuvir to evaluate safety and efficacy in coinfecting patients.⁸⁴ Prior to enrollment, 13 patients were not taking HIV ARVs but had stable CD4 counts with an HIV viral load of less than 50 copies/mL or a CD4 count of greater than 500 cells/ μ L. The 37 other subjects were on a stable regimen of ARVs for at least 8 weeks with CD4 counts of greater than 100 cells/ μ L and an HIV viral load of less than 40 copies/mL. This study is ongoing, and, at the time of this article's publication, data for subjects taking ARVs at the time of enrollment

Table 2. Simeprevir and HIV Antiretroviral Drug Interactions

HIV Drugs	Simeprevir Drug Interactions
NRTIs	All are compatible.
NNRTIs	Rilpivirine is compatible. All others (including efavirenz, nevirapine, delavirdine, and etravirine) are contraindicated.
Integrase inhibitors	Raltegravir and dolutegravir are compatible. Elvitegravir is contraindicated. ^a
Protease inhibitors	All are contraindicated.
Entry inhibitor	Maraviroc is compatible.

NNRTIs, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors.

^aElvitegravir is only available coformulated with tenofovir, emtricitabine, and cobicistat in a combination pill. Cobicistat (not elvitegravir) increases simeprevir drug levels, thereby making administration contraindicated.

showed that 100% of patients achieved SVR4.⁸⁴ Subjects who had not been taking ARVs achieved a 100% SVR12 rate. Ledipasvir/sofosbuvir was found to increase levels of tenofovir in ARV regimens containing this medication, and caution is advised when using these drugs in combination.⁸⁵ No significant interactions were found between ledipasvir/sofosbuvir and the ARVs emtricitabine, efavirenz, raltegravir, or rilpivirine. The regimen was well tolerated.

The use of ledipasvir with sofosbuvir has been studied in several trials of HCV genotype 1—monoinfected patients. The ELECTRON trial studied ledipasvir with sofosbuvir and ribavirin in noncirrhotic patients who were treatment-naive or prior null responders.⁸⁶ After 12 weeks of therapy, 100% of patients reached SVR12 regardless of prior treatment history. When ledipasvir/sofosbuvir with ribavirin or the nonnucleoside polymerase inhibitor GS-9669 was taken for 12 weeks in patients with cirrhosis or advanced liver fibrosis, results were equally promising, with 100% achieving SVR12.⁸⁷ The ION trials evaluated combinations of ledipasvir and sofosbuvir with or without ribavirin for 8, 12, or 24 weeks and found SVR12 rates of more than 90% in patients treated for 8 or 12 weeks regardless of prior treatment history and cirrhosis status.^{88,89} Similarly, LONESTAR found SVR12 rates of 95% to 100% in patients treated with the combination of ledipasvir and sofosbuvir with or without ribavirin for 8 or 12 weeks.⁹⁰

Medications Studied in Hepatitis C Virus Mono-infection

Additional studies of sofosbuvir with daclatasvir, sofosbuvir with ledipasvir, MK-5172/MK-8742, and ABT-450/ritonavir, ombitasvir, and dasabuvir with ribavirin in coinfecting patients are planned. Because there are limited studies directly evaluating new HCV therapies in coin-

fecting patients, data from trials in mono-infected patients are being extrapolated for consideration in coinfected patients. The following investigational studies were conducted in mono-infected patients and show the promising SVR results of additional new investigative therapies.

Combination of Simeprevir and Sofosbuvir Treatment with simeprevir and sofosbuvir with or without ribavirin was evaluated in genotype 1 patients in the COSMOS trial. The trial included 1 group of prior PEG-IFN/ribavirin null responders with fibrosis stages F0 to F2 and another group of treatment-naïve patients and prior null responders in stages F3 to F4.⁸⁰ Among patients treated for 12 weeks in group 1, 93% treated with simeprevir/sofosbuvir and 96% taking simeprevir/sofosbuvir/ribavirin achieved SVR12.⁹¹ Among patients with advanced fibrosis (group 2) treated for 12 weeks, all achieved an SVR12 rate of 93% regardless of inclusion or exclusion of ribavirin from the simeprevir/sofosbuvir combination.⁹² Of the group 2 patients who received 24 weeks of simeprevir/sofosbuvir therapy, 100% achieved SVR12, and the SVR12 rate was 93% when ribavirin was included for 24 weeks.⁹² Overall, 96% of patients with a baseline Q80K polymorphism achieved SVR12 compared with 97% of those without this polymorphism,⁹² suggesting that the Q80K polymorphism may not be a significant factor in determining treatment response.

Daclatasvir The combination of daclatasvir and sofosbuvir has been studied with or without ribavirin in patients with HCV genotypes 1, 2, and 3 with promising results. In the AI444040 study, treatment-naïve genotype 1 patients received daclatasvir/sofosbuvir with or without ribavirin for 12 or 24 weeks, and SVR12 rates were 95% to 100%.⁹³ Genotype 1 patients whose disease previously failed to respond to telaprevir or boceprevir with PEG-IFN/ribavirin treatment achieved SVR12 in 98% after 24 weeks of therapy. Genotype 2 and 3 patients were treated for 24 weeks with daclatasvir/sofosbuvir with or without ribavirin, with SVR12 rates of 92% in genotype 2 patients and 89% in genotype 3 subjects.⁹³ Daclatasvir is a substrate of the CYP3A4 pathway, and there are limited data thus far regarding daclatasvir interactions with ARVs. When used with HIV protease inhibitors such as atazanavir and ritonavir, daclatasvir requires dose reduction, and coadministration with efavirenz requires an increased dose of daclatasvir.⁹⁴

ABT-450/Ritonavir, Ombitasvir, and Dasabuvir Regimens of ABT-450 boosted with ritonavir, ombitasvir, and dasabuvir with or without ribavirin were evaluated in genotype 1 patients in the SAPPHERE studies. In the SAPPHERE-II study of noncirrhotic, treatment-experienced patients, subjects received 12 weeks of combination therapy with ribavirin and achieved an SVR12 of 96%

despite prior treatment failure with PEG-IFN/ribavirin.⁹⁵ Because this regimen contains ritonavir, many CYP3A4 drug interactions are likely; however, studies are in progress.

Conclusion

HIV/HCV coinfection is no longer considered a special treatment population, given the remarkable improvements seen in SVR rates with direct-acting antivirals. Coinfected patients now have the same treatment outcomes and rates of adverse events as those seen in patients with HCV mono-infection. There is great urgency to treat HIV/HCV-coinfected patients because of the higher rates of all-cause and liver-related mortality in these patients as well as high rates of mortality for HIV patients awaiting liver transplant.

We recommend treating patients with HCV genotypes 2, 3, 4, 5, and 6 now with currently available direct-acting antiviral treatment regimens. Patients with genotype 1 who are well compensated with low fibrosis scores may benefit from waiting for the investigational drugs discussed above to become available, likely in late 2014 or early 2015, as they spare ribavirin and PEG-IFN. As new antiviral medications become available, practitioners will need to continue to be wary of drug interactions in their coinfected patients. Overall, however, the future is bright for patients afflicted with HCV regardless of HIV coinfection, as newer and better agents become available year after year.

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