

Hepatitis C Virus Infection and Coinfection With Human Immunodeficiency Virus

Challenges and Advancements in Management

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CASE PRESENTATION

The patient was a 61-year-old African American man who was diagnosed with HIV in 1985 and HCV genotype 1a in 1993. His medical history was also significant for hypertension, depression, hyperglycemia, and previous alcohol and polysubstance abuse. He had been followed up at the National Institute of Allergy and Infectious Diseases HIV clinic since 1995.

He received zidovudine monotherapy for HIV from 1989 to 1991 and combination antiretroviral therapy beginning in 1996. He had cytomegalovirus colitis in 2000 and his nadir CD4 T-cell count was 94/ μ L in 1994. Since 2005, the patient's HIV regimen included lopinavir, ritonavir, tenofovir, and emtricitabine with excellent adherence and virologic suppression. His most recent immune profile in October 2010 was a CD4 T-cell count of 544/ μ L with an HIV viral load of less than 50 copies/mL.

With regard to his HCV, an initial liver biopsy performed in July 1997 revealed mild active hepatitis and bridging fibrosis. The patient received standard interferon monotherapy from July 1997 to December 1997. He later re-

Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) both emerged in the second half of the 20th century, and chronic infection with these agents is among the greatest challenges facing health care in the United States and worldwide. Despite tremendous advances in treatment and management of HIV and HCV, individuals with HIV/HCV coinfection experience a more complicated disease course and treatment. Recognition of the important role that host factors, such as IL28B genotype, have in response to HCV therapy and the emergence of new effective therapies for HCV are actively reshaping the standard of care. These advances may translate into more effective treatment and management of patients with chronic HCV and HIV coinfection in the years ahead.

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ceived standard interferon plus ribavirin from November 1999 to May 2000. The patient did not experience a significant decline in HCV viral load with either treatment course. His HCV viral load was more than 1 million copies/mL in June 2000, 1 month after stopping therapy. Between January 2002 and November 2002, the patient received pegylated interferon plus ribavirin. This treatment did not lead to HCV clearance and was also complicated by neutropenia, for which he received granulocyte colony-stimulating factor. A subsequent liver biopsy in December 2002 revealed moderate inflammation and bridging fibrosis separating regenerative nodules suggestive of cirrhosis (grade 4). More recently, the patient had IL28B genotyping performed to evaluate the single-nucleotide polymorphism in the interferon λ gene associated with favorable

response to interferon-based HCV treatment. IL28B genotyping had not yet been incorporated in standard HCV care, but the patient had the TT haplotype, which predicts poor response to interferon-based therapy.

In December 2008, a liver biopsy showed active inflammation, with grade 1 steatosis and bridging fibrosis (grade 3) (FIGURE 1). Magnetic resonance spectroscopy of the liver indicated 12% hepatic lipid content. The patient then entered a 48-week randomized, double-blind, placebo-controlled trial of pioglitazone, 45 mg

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daily followed by 48-week open-label treatment at the same dose. After the patient received open-label pioglitazone for 1 year, a posttreatment follow-up biopsy was performed in November 2010 and showed a reduction in inflammation, grade 0 steatosis, and bridging fibrosis (grade 3). Magnetic resonance spectroscopy of the liver showed 5% hepatic lipid content. Although there was no improvement in the patient's fibrosis grade at the end

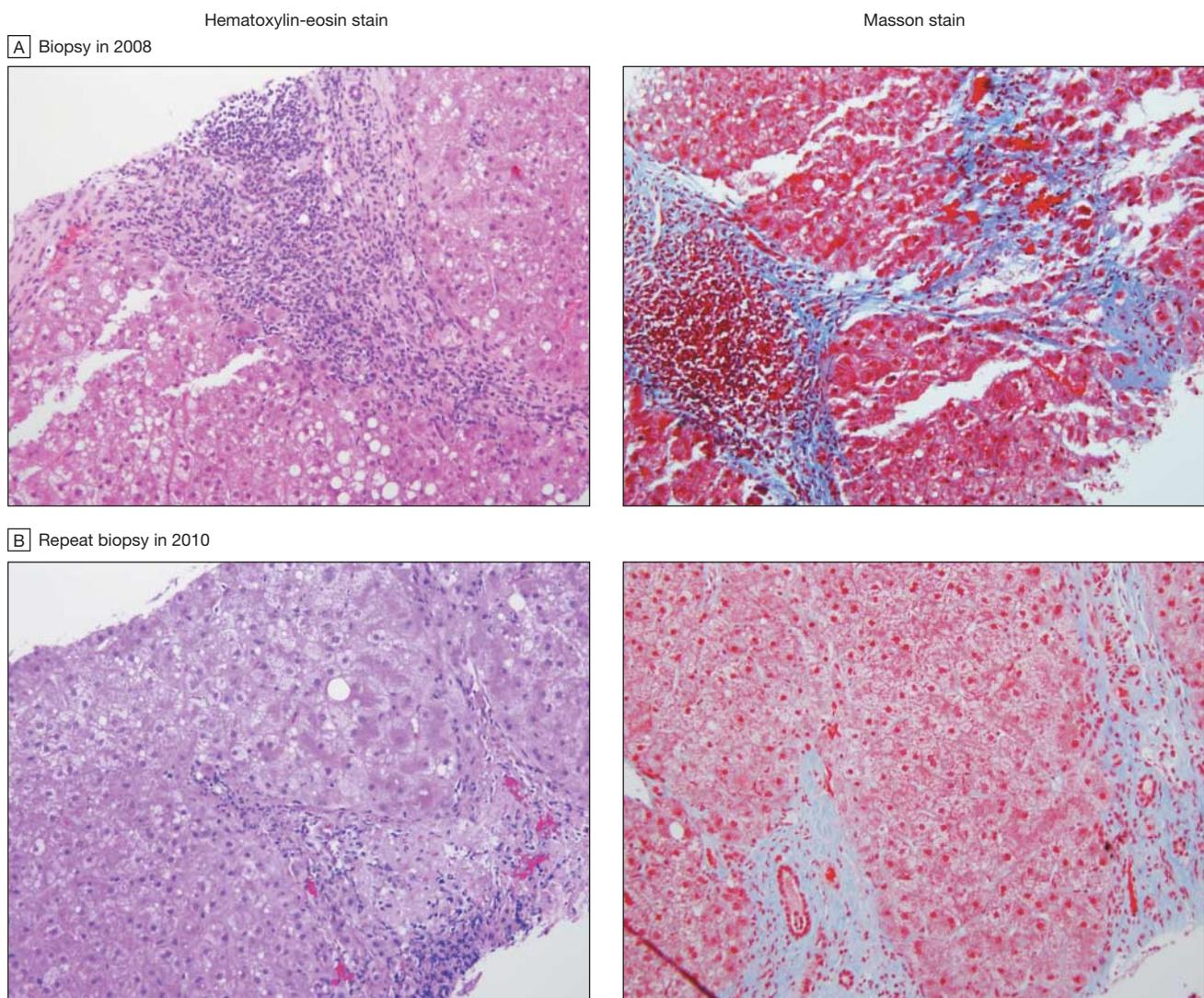
of this experimental treatment, there was notable improvement in inflammation, steatosis, and hepatic lipid content.

Epidemiology of HCV Infection

Hepatitis C and HIV are presently the leading chronic viral infections in the United States and worldwide, significantly affecting the morbidity and mortality of infected individuals. Currently, HCV infects 180 million people

worldwide and 4.1 million in the United States alone.¹ Infection with HCV is the leading indication for liver transplant and is approaching alcoholic liver disease as a leading cause of liver-related death in the United States.^{1,2} Between 1994 and 2001, health care utilization for HCV-related care increased annually by 25% to 35%.³ More recent data demonstrate 3-fold greater health care costs for HCV-infected patients compared with controls.⁴ Although the in-

Figure 1. Histopathology Results From Case Patient's Percutaneous Liver Biopsy Specimens



A, From a biopsy in 2008, hematoxylin-eosin stain demonstrates moderate portal inflammation, moderate interface hepatitis, and mild steatosis, and Masson stain shows bridging fibrosis (blue). B, Repeat biopsy in 2010 shows hematoxylin-eosin stain demonstrating decreased inflammation and decreased steatosis, and Masson stain showing fibrosis (blue), which is unchanged. Original magnification $\times 200$.

Box. Negative Prognostic Factors for Achieving Sustained Virologic Response to Interferon-Based Therapy for Hepatitis C Virus Infection

Host Factors

- Older age
- African American race
- IL28B TT haplotype
- Alcohol consumption
- Advanced liver fibrosis
- Human immunodeficiency virus coinfection
- Type 1 interferon response
- Low CD4 T-cell counts
- Increased body mass index
- Lack of ribavirin use
- Previous interferon use

Viral Factors

- Hepatitis C virus genotype 1
- High pretreatment hepatitis C viral load
- Chronicity of infection

idence of HCV infection is on the decline, rates of HCV-related cirrhosis and hepatocellular carcinoma are expected to peak in 2020.⁵ However, projected liver-related mortality over the next 10 years would be reduced by 34% to 68% if effective HCV treatment was successfully provided to half or all of HCV-infected patients, respectively.⁵ Of the 6 genotypes, genotype 1 is the most predominant in North America and also the least responsive to interferon alfa-based treatment.⁶

HCV Infection: Treatment Challenges

The single goal for initiation of HCV therapy today is to achieve enduring HCV viral clearance or a sustained virologic response (SVR). Large randomized controlled studies in HCV-infected and HIV/HCV-coinfected patients clearly demonstrate no clinical benefit in continued interferon-based treatment for those who do not

attain an SVR.^{7,8} Treatment for chronic HCV infection has evolved significantly since the initial development of interferon alfa-2b more than 20 years ago.⁹ The addition of ribavirin¹⁰; pegylation of interferon alfa¹¹; and the HCV serine protease inhibitors telaprevir and boceprevir, which were recently approved by the Food and Drug Administration, have increased the rates of HCV eradication in treatment-naive patients from 20% to approximately 65%.^{12,13} A combination of pegylated interferon alfa (weekly subcutaneous injections), twice-daily oral ribavirin, and 3-times-a-day HCV protease inhibitor (either boceprevir or telaprevir) is the present standard of care for HCV-infected individuals.

Despite advances in antiviral therapy, important host and viral factors influence treatment outcome to interferon-based therapy (BOX). Our patient had numerous negative predictors, including genotype 1, high baseline HCV viral load, older age, African American race, IL28B TT haplotype, advanced liver fibrosis, previous nonresponse to interferon, and HIV coinfection. Not surprisingly, most inner-city chronic hepatitis C clinics in the United States comprise patients like ours, making treatment and the prevention of morbidity associated with chronic liver disease difficult. Notably, African American race alone has been shown to be an independent risk factor for lower HCV viral load decline and poor response to pegylated interferon/ribavirin therapy in HIV-infected patients.¹⁴⁻¹⁶ Similarly, the recently described IL28B genotypes (TT/CT) that are associated with poor response to interferon-based treatment are observed at a higher rate among African American individuals.¹⁷ These host-derived negative predictors are based on therapeutic responses to interferon-containing regimens and may be determinants of how the host immune system responds to interferon alfa. However, their role in predicting a patient's response to HCV therapeutics without interferon is unknown. In this regard, anti-HCV therapeutics that do not rely on the host im-

mune system, such as direct-acting agents, may be more suitable to treat patients who have many of the poor prognostic factors described in the Box. Furthermore, it is promising that HCV, unlike hepatitis B virus and HIV, does not integrate into the host genome and has not yet been shown to have a clinically relevant extra-hepatic reservoir. This knowledge generates optimism regarding the potential for developing successful combination therapies that may result in SVR for most patients.

Unacceptable adverse effects and toxicities represent significant limitations to current therapy for HCV. Toxicities to interferon and ribavirin are often dose-limiting and contribute to overall treatment failure. In trials of pegylated interferon and ribavirin, early treatment discontinuation due to adverse effects occurred in 14% to 18% of participants; dose adjustment was required in up to 42% of participants; and more than half of patients experienced flu-like symptoms of fatigue, myalgias, and headache.^{11,18} Depression associated with interferon therapy poses another important barrier to HCV treatment. Emergence or exacerbation of depression occurs in up to one-third of patients receiving interferon for HCV and is associated with early termination and treatment failure.^{19,20} Recent data suggest that multidisciplinary support of psychiatric symptoms during interferon therapy decreases depressive adverse effects²¹; however, randomized controlled trials of prophylactic antidepressant therapy did not show benefit.^{22,23}

HIV/HCV Coinfection

HIV coinfection presents a unique challenge to the management of HCV. Worldwide, 4 million to 5 million people are estimated to be living with chronic HIV/HCV coinfection.⁶ The prevalence of HIV/HCV coinfection varies widely by mode of transmission. A 2002 study of an urban US HIV-infected cohort found that HCV prevalence was 89% among injection drug users, but as low as 14% among those whose HIV transmission risk factor was

heterosexual contact and 10% among men who have sex with men (MSM).²⁴ However, since 2000 an increase in the number of HCV outbreaks among HIV-infected MSM has been noted, particularly in Australia, Europe, and the United States.²⁵ In the era of combination antiretroviral therapy for HIV, liver-related morbidity and mortality, driven largely by chronic HCV coinfection, has increased as opportunistic infections and AIDS-related conditions have declined.^{26,27} Further, rates of health care utilization and disability related to HIV/HCV coinfection are estimated to be 70% higher than rates for HIV without HCV.²⁸

Management of HIV/HCV coinfection is characterized by decreased responsiveness to standard therapy and increased rates of disease progression. For example, the likelihood of achieving an SVR is lower among individuals with HIV/HCV coinfection than in HCV infection (TABLE). Effects of ongoing HIV replication and related chronic immune activation on HCV viral levels have been proposed as potential mechanisms for this disparity in treatment response rates.^{6,32}

HIV/HCV coinfection is associated with accelerated development of fibro-

sis, cirrhosis, hepatocellular carcinoma, and end-stage liver disease.^{24,33,34} Both HIV and HCV produce reactive oxygen species that are proinflammatory and may play a role in accelerated disease progression.³⁵ The risk of developing cirrhosis with chronic HCV is estimated at 5% to 25% over 25 to 30 years, and this risk increases with age, alcohol consumption, and immune suppression.¹ For example, HIV-infected individuals with lower CD4 T-cell counts are at increased risk of developing severe HCV-related events (eg, development of ascites, variceal bleeding, or hepatic encephalopathy) compared with those with CD4 counts above 200/ μ L.³⁶

The toxicities of interferon-based HCV therapy are seen in similar frequency in HIV/HCV coinfection.^{14,15} Treatment of coinfecting individuals is further complicated by drug interactions between ribavirin and HIV antiretroviral agents. For example, ribavirin-associated anemia is common and potentially exacerbated by zidovudine coadministration.³⁷ There are also case reports of severe mitochondrial toxicity with combination ribavirin and thymidine analogue use for HIV/HCV coinfection.³⁸

The management of chronic hepatitis C among HIV-infected patients is complex and treatment responses often suboptimal, as seen in our case patient. Alternative strategies for managing chronic liver disease and the emergence of new direct-acting agents for the treatment of HCV may hold benefit for our patient and others like him.

Strategies to Improve or Preserve Liver Function

Hepatic steatosis is an independent prognostic factor that may contribute to decreased responsiveness to HCV therapy and increased rates of liver disease progression in HIV/HCV coinfection. Individuals with HIV/HCV coinfection may experience more hepatic steatosis, which is associated with an increased risk of advanced fibrosis.³⁹⁻⁴³ Hepatitis C virus core protein may directly up-regulate hepatic fatty acid production and interfere with hepatic lipid processing.⁴⁴⁻⁴⁶

Both steatosis and insulin resistance are associated with decreased responsiveness to HCV therapy.⁴⁷ Insulin sensitizing agents such as the peroxisome proliferator-activated receptor (PPAR)- γ agonist pioglitazone are under investigation for the treat-

Table. Sustained Virologic Response Rates to Interferon-Ribavirin-Based Therapy for HCV and HIV Coinfection

Source	Treatment Groups	No. SVR/No. Treated (%)		Comments
		All Genotypes	Genotype 1	
HCV Treatment Trials				
Manns et al, ¹¹ 2001	Peginterferon alfa-2b and ribavirin	274/511 (54)	145/348 (42)	
	Interferon alfa-2b and ribavirin	235/505 (47)	114/343 (33)	
Fried et al, ¹⁶ 2002	Peginterferon alfa-2a and ribavirin	255/453 (56)	138/298 (46)	
	Interferon alfa-2b and ribavirin	197/444 (44)	103/285 (36)	
Jeffers et al, ²⁹ 2004	Peginterferon alfa-2a and ribavirin	20/78 (26)	20/78 (26)	All genotype 1, black
	Peginterferon alfa-2a and ribavirin	11/28 (39)	11/28 (39)	All genotype 1, white
Rodriguez-Torres et al, ³⁰ 2009	Peginterferon alfa-2a and ribavirin	90/269 (33)	90/269 (33)	All genotype 1, Latino
	Peginterferon alfa-2a and ribavirin	148/300 (49)	148/300 (49)	All genotype 1, Non-Latino
HIV/HCV Coinfection Treatment Trials				
Chung et al, ¹⁴ 2004	Peginterferon alfa-2a and ribavirin	18/66 (27)	7/51 (14)	
	Interferon alfa-2a and ribavirin	8/67 (12)	3/52 (6)	
Torriani et al, ¹⁵ 2004	Peginterferon alfa-2a and ribavirin	116/289 (40)	1/176 (29)	
	Interferon alfa-2a and ribavirin	33/285 (12)	12/171 (7)	
Carrat et al, ³¹ 2004	Peginterferon alfa-2b and ribavirin	56/205 (27)	21/125 (17) ^a	
	Interferon alfa-2b and ribavirin	41/207 (20)	8/129 (6) ^a	

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; SVR, sustained virologic response.
^aGenotypes 1 and 4.

ment of nonalcoholic steatohepatitis⁴⁸ and as adjuvant therapy to interferon/ribavirin treatment for HCV with some evidence indicating improved SVR in those with HCV genotype 4.⁴⁹ Our patient received pioglitazone under investigation for hepatic steatosis in HIV/HCV coinfection, and although biopsy results indicated decreased inflammation and resolution of steatosis, it is not clear these benefits will persist after therapy.⁵⁰ Use of pioglitazone for hepatic steatosis remains investigational, and there are no current recommendations for continued use or re-treatment in this setting.

Strategies Targeting HCV Replication

Recent progress in HCV treatment is focused on developing therapeutic agents that target multiple stages of the HCV life cycle (FIGURE 2). Following the lead of antituberculosis therapy and HIV antiretroviral therapy, development is ongoing for direct-acting antiviral agents that target multiple steps of the HCV life cycle and will lead to maximal and sustained viral suppression. Recent studies using 2 new HCV nonstructural 3/4A (NS3/4A) serine protease inhibitors (telaprevir and boceprevir) in combination with interferon/ribavirin have validated this approach by substantially improving SVR rates.^{12,13} The addition of 12 weeks of telaprevir to pegylated interferon alfa-2a and ribavirin resulted in higher SVR rates than treatment with pegylated interferon and ribavirin (70% vs 40%) in treatment-naïve patients with chronic HCV genotype 1.¹² Similarly, the addition of boceprevir was associated with higher rates of SVR than pegylated interferon alfa-2b and ribavirin alone in treatment-naïve, non-African American patients with chronic HCV genotype 1.¹³

The improved SVR rates achieved with the addition of these HCV protease inhibitors are encouraging, but there are important key points that should be noted. First, the use of ribavirin is critical; SVR rates were substantially reduced when ribavirin was not included with both telaprevir and

boceprevir.^{12,13,51} Second, concomitant use of pegylated interferon was necessary to limit the development of resistance to HCV protease inhibitors.⁵² As with interferon/ribavirin alone, response rates to interferon/ribavirin and boceprevir in African American individuals were reduced when compared with non-African American individuals.⁵³ Finally, both boceprevir and telaprevir are metabolized through CYP3A4 (p450 cytochrome) pathways with considerable potential for important drug interactions with HIV antiretroviral medications.⁵⁴

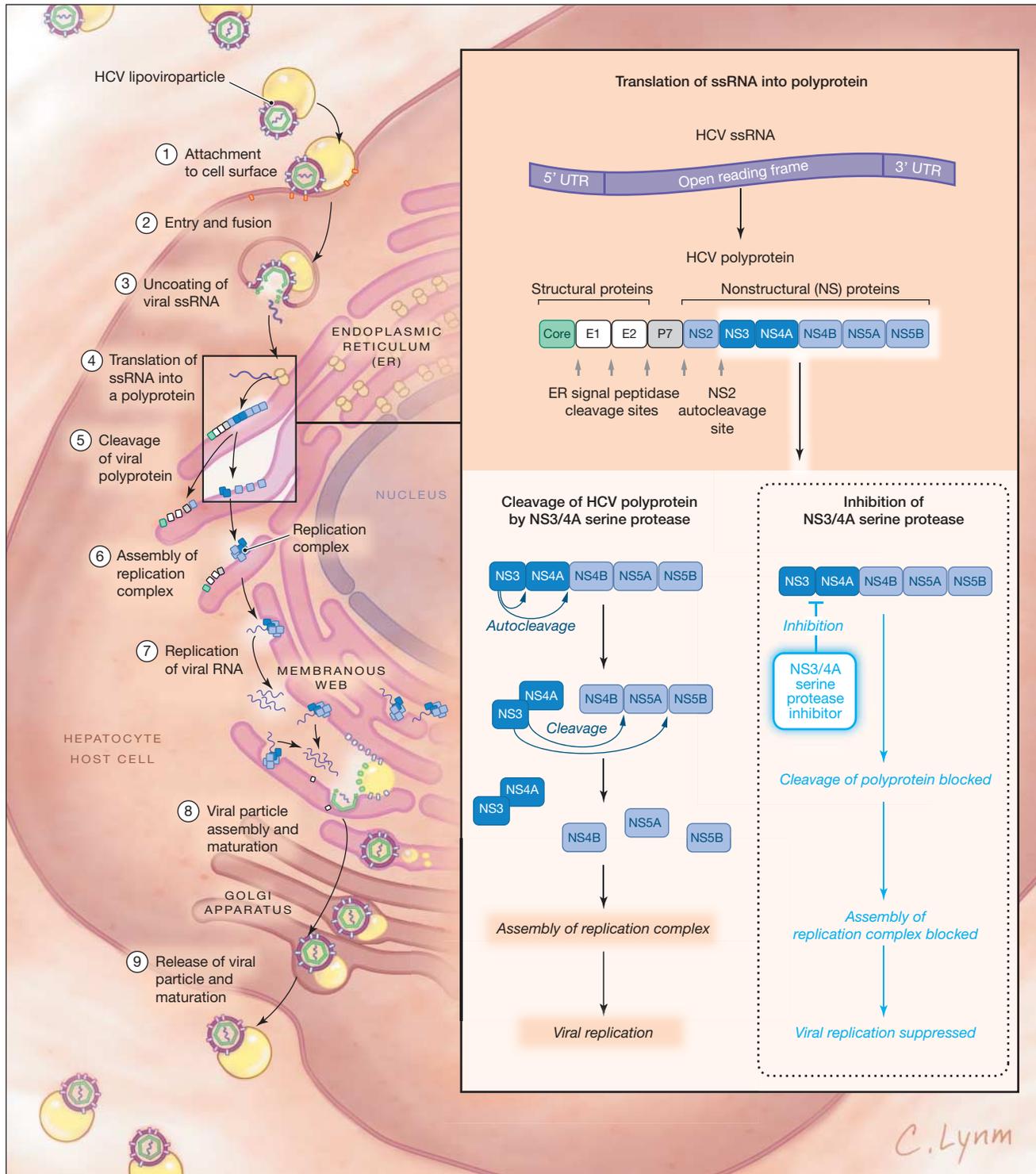
Several therapeutic approaches are under investigation to address cases like our patient for whom previous treatment with interferon and ribavirin has failed. Three large clinical trials re-treated nonresponders (ie, individuals who did not achieve an SVR) with interferon and ribavirin (the EPIC3, REPEAT, and DIRECT trials) with either higher doses or longer duration of both pegylated interferon and ribavirin.⁵⁵⁻⁵⁷ However, all 3 studies reported dismal SVR rates for previous nonresponders who received weekly pegylated interferon alfa-2b, pegylated interferon alfa-2a, or consensus interferon along with oral ribavirin for 48 weeks (6.3%, 8%, and 10.7%, respectively), suggesting this may not be an effective strategy for nonresponders. An alternative strategy tested whether increasing the pegylated interferon alfa-2a dose to biweekly for the first 4 weeks of treatment with ribavirin successfully enhanced the kinetics of HCV viral decline. Compared with standard weekly pegylated interferon alfa-2a, biweekly therapy significantly improved early HCV kinetics in HIV/HCV-coinfected patients, particularly African American patients.⁵⁸ However, this study was not large enough to look at differences in SVR and it did not include nonresponders. Larger clinical trials that include previous nonresponders are needed to fully evaluate whether this approach effectively increases SVR in this group.

Two clinical trials have provided preliminary data evaluating the addition of

HCV protease inhibitors to interferon/ribavirin for patients who experienced prior interferon/ribavirin treatment failures. The addition of telaprevir resulted in an SVR rate of 31% vs 5% among null responders (ie, individuals with <1-log decline in HCV viral load after 4 weeks of treatment),⁵⁹ while addition of boceprevir resulted in an SVR rate of 40% vs 7% among partial responders (individuals with >2-log decline in HCV viral load but who had detectable virus after 12 weeks of therapy).⁶⁰ These data indicate modest improvements in response rates. It is unclear whether these results will be applicable to patients with multiple poor prognostic factors such as HIV infection, African American race, advanced liver disease, and high HCV viral load.

As in the case of our patient, HIV-infected, African American patients with an unfavorable IL28B genotype and a high HCV viral load are less likely to respond to interferon-based regimens. Host genetic studies show that enhanced type 1 interferon response in the liver⁶¹ and in peripheral blood monocytes³² is a strong negative predictor of subsequent response to interferon therapy. Therapeutic strategies that do not rely on the host immune system may be optimal to treat HCV in these patients, provided they have demonstrated safety and efficacy. Interferon-sparing therapy including 1 or more direct-acting agents could play a major role in treating individuals who are not good candidates for interferon. Several early studies of interferon-sparing regimens have demonstrated early HCV viral decline in prior nonresponders. For example, 1 study treated 50 null responders with a combination of an HCV protease inhibitor and an NS5A inhibitor and demonstrated early virologic response in 46%. These preliminary data suggest that suppression of HCV viral load to below the level of detection in this difficult-to-treat population is possible using potent direct-acting agents.⁶² Larger long-term studies are needed before it can be determined whether this approach is an effective strategy for sustained HCV clearance.

Figure 2. Target of Nonstructural 3/4A Serine Protease Inhibitors in the HCV Life Cycle



Nonstructural 3/4A (NS3/4A) serine protease inhibitors are directly acting antiviral agents that interfere with viral NS3 serine protease and its cofactor, NS4A. In the hepatitis C virus (HCV) life cycle, viral NS3/4A serine protease cleaves the HCV polyprotein into small nonstructural proteins that are necessary for viral replication within the hepatocyte. Two drugs in this class, telaprevir and boceprevir, were recently approved by the US Food and Drug Administration. ssRNA indicates single-stranded RNA.

Further, the use of direct-acting agents is complicated by the emergence of resistance in patients with inadequate virologic suppression.⁶³ In this regard, recent studies show that treatment with 2 direct-acting agents without pegylated interferon, ribavirin, or either is associated with HCV viral breakthroughs,^{62,64} the mechanisms of which are not completely understood. Although interferon-sparing therapy is an ideal strategy for many patients, it is still to be determined whether such strategies will yield high SVR rates.

CONCLUSION

Patients with multiple poor prognostic factors for response to HCV therapy, like the patient we described with HIV/HCV coinfection, are representative of the HCV epidemic in the United States. To date, our patient is clinically stable and contemplating future therapy with direct-acting agents as they become available. Development of therapeutic strategies to improve SVR rates in this group is essential from both a patient management and a public health point of view. Existing data suggest that these patients would benefit from an HCV regimen that does not rely on the host immune system. Eradication of HCV or chronic suppression of HCV replication may be achievable with long-term interferon-sparing direct-acting agents, but concerns regarding viral breakthrough and emergence of viral resistance remain. Hepatitis C virus lacks the 2 major impediments to eradication seen in most chronic viral infections, namely a clinically relevant viral reservoir and integration into the host genome. Therefore, it is plausible that effective suppression of HCV replication with potent anti-HCV agents could result in a marked improvement in SVR rates achieved in this population.

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Study concept and design: Hadigan, Kottlilil.

Acquisition of data: Kottlilil.

Analysis and interpretation of data: Kottlilil.

Drafting of the manuscript: Hadigan, Kottlilil.

Critical revision of the manuscript for important intellectual content: Kottlilil.

Statistical analysis: Kottlilil.

Administrative, technical, or material support: Hadigan, Kottlilil.

Study supervision: Hadigan, Kottlilil.

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