Published in final edited form as:

J Clin Gastroenterol. 2013 October ; 47(9): 800–806. doi:10.1097/MCG.0b013e31828a37c0.

A Survey of Hepatitis C Treatment Clinical Practice Patterns Using the Newly-Approved Protease Inhibitors

Emerson Y. Chen, BA¹, William M. Lee, MD¹, Linda S. Hynan, PhD^{2,3}, and Amit G. Singal^{1,2}

¹Department of Internal Medicine, Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center and Parkland Health and Hospital System, Dallas, TX

²Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, TX

³Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX

Abstract

Goals—To describe current HCV treatment practices in the United States and identify physician characteristics associated with the use of first generation DAAs.

Background—Hepatitis C virus (HCV) treatment practice patterns have not been assessed after the introduction of direct-acting antivirals (DAA), which are now considered standard of care for most HCV genotype 1 patients.

Study—We sampled nationally representative physicians treating HCV patients with DAAs through a web-based survey. Stepwise multivariate logistic regression was performed to identify physician characteristics associated with the use of DAAs in four clinical vignettes (early stage fibrosis, prior null response, HIV co-infection, and post-liver transplantation).

Results—Of 1658 deliverable emails, 337 (20.3%) clinicians responded. Fifty percent of providers recommended DAA therapy for treatment-naïve patients with early stage fibrosis, whereas 49% of providers would await new therapies. For prior null responders with significant fibrosis, 74% would attempt re-treatment using DAAs and 26% would await new therapies. Off-label use of DAAs was recommended by 69% of providers for patients with HIV infection and 48% of providers for post-liver transplant patients. Academic affiliation was significantly associated with higher rates of off-label use in both HIV and post-liver transplant patients.

Conclusions—Despite more potent and less toxic therapies on the horizon, many physicians recommended DAAs in treatment naïve patients with early stage fibrosis. Providers also frequently recommended DAAs for off-label uses, such as treating post-liver transplant patients and those co-infected with HIV.

Keywords

direct-acting antiviral; protease inhibitors; HCV; survey; therapy

Correspondence: Amit G. Singal, M.D., M.S. Dedman Scholar of Clinical Care Division of Gastroenterology University of Texas Southwestern 5959 Harry Hines Blvd, POB 1, Suite 420 Dallas TX 75390-8887 Tel: 214-645-6029 Fax: 214-645-6294 amit.singal@utsouthwestern.edu.

Conflicts of Interest: None of the authors have any financial conflicts of interest related to this manuscript.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

INTRODUCTION

Approximately 2.2–3.0% of the world's population is infected with hepatitis C virus (HCV), including 3.2 million people in the United States.^{1, 2} HCV infection remains the leading cause of decompensated cirrhosis, hepatocellular carcinoma (HCC), liver transplantation, and liver-related mortality in the United States. Given the slow progression of HCV infection to advanced fibrosis, HCV-related morbidity and mortality rates are projected to peak near 2030 despite a decreasing incidence of new infections.³ These deaths could be prevented if HCV-infected patients were successfully treated. In fact, liver-related mortality rates and the incidence of HCC and liver decompensation could be reduced by 70–80%.⁴

Treatment with pegylated interferon (PEG-IFN) and ribavirin (RBV) therapy demonstrated sustained virological response (SVR) rates of 38–46% among HCV genotype 1 patients, with even lower rates among subgroups, such as African Americans and patients with cirrhosis.^{5, 6} Introduction of the direct-acting antivirals (DAAs) in May 2011 has led to improved SVR rates and abbreviated therapy for many treatment candidates. The first two DAAs, telaprevir and boceprevir, both protease inhibitors, achieved SVR rates of 67–73% among treatment-naïve patients when used in combination with PEG-IFN and RBV.^{7, 8} Nevertheless, these HCV treatments are expensive, lengthy, and not without serious side effects. Although the American Association for the Study of Liver Diseases (AASLD) released guidelines about the use of DAAs, details of patient selection for treatment have yet to be addressed.⁹

A survey prior to the approval of these protease inhibitors suggested that many gastroenterologists would be uncomfortable prescribing DAA therapy.¹⁰ Providers who participated in clinical trials or were astutely aware of DAA therapy development reported being significantly more likely to prescribe DAA agents when available. However, HCV treatment practice patterns have not been subsequently re-evaluated after the introduction of DAAs. The aim of this study was to describe current HCV treatment practices of physicians and to identify physician characteristics associated with the use of the first generation DAAs.

MATERIALS AND METHODS

Study Population

This study sampled nationally representative physicians treating HCV using the 2009 AASLD membership list and a list of clinicians practicing hepatology in U.S. academic centers. Eligible respondents included only clinicians who reported having treated at least one patient with HCV. Clinicians who did not have access to protease inhibitor-based therapy were excluded. This study was approved by the Institutional Review Board at the University of Texas Southwestern Medical Center.

Survey Methodology

A web-based survey was distributed in March 2012 to eligible clinicians through Research Electronic Data Capture (REDCap).¹¹ Clinicians who did not respond to the initial survey were sent two reminder invitations to complete the survey. All respondents were entered into a lottery for one of two \$50 gift cards and provided a summary of survey results.

The survey required approximately five minutes to complete and was organized into the following five sections: A) HCV treatment use, B) HCV treatment initiation clinical vignettes, C) pre-treatment evaluation, D) on-treatment management, and E) clinician and practice characteristics. Questions were adapted from earlier validated surveys when available.^{10, 12, 13} After initial development, the survey was pretested among seven

physicians with hepatology expertise and experience with HCV treatment, with each provider completing a cognitive interview about the survey.

Measures

The first section aimed at documenting current HCV treatment practices, including physician involvement in HCV treatment trials and the number of HCV patients treated using protease inhibitor-based therapy. Twelve clinical vignettes in the second section were used to assess treatment choices for hypothetical patients: treatment naïve patients with varying levels of fibrosis, relapsed patient to PEG-IFN/RBV with significant fibrosis, and non-responders to PEG-IFN/RBV with significant fibrosis. We also assessed HCV treatment choices for patients who underwent liver transplantation and those with HIV co-infection. Potential treatment choices for each clinical vignette were boceprevir-based therapy, telaprevir-based therapy, therapy with either protease inhibitor, PEG-IFN/RBV alone, or await new therapies. The section focusing on pre-therapy evaluation included questions regarding baseline cytopenias, psychiatric issues, and medical comorbid conditions. The section devoted to on-therapy management included questions regarding viral load monitoring, treatment duration, and management of cytopenias. Clinician and physician characteristics of interest included age, gender, race and ethnicity, residence, medical subspecialty, medical practice type (academic affiliation vs. private practice), and number of years in practice.

Statistical Analysis

Descriptive statistics are reported for physician characteristics, patient case scenarios, pre-therapy management and on-treatment management practices. Internal consistency was examined using Cronbach's coefficient α on the 12 clinical vignettes, with response categories as protease inhibitor-based therapy vs. PEG-IFN/RBV vs. no treatment. Comparison of treatment choices in the 12 clinical vignettes was analyzed with Chi Square and Fisher Exact tests, as appropriate. Treatment choice among four specific clinical vignettes of interest was defined as the following dichotomous outcomes: early liver disease (treatment vs. no treatment), prior null response (treatment vs. no treatment), HIV co-infection (protease inhibitor-based therapy vs. conventional management), and post-liver transplant (protease inhibitor-based therapy vs. conventional management). Conventional management was defined as either PEG-IFN/RBV or await new therapies. Bivariate analysis using Chi Square and Fisher Exact tests was performed to identify clinician demographic variables associated with the outcome variables in each of the four clinical vignettes. Stepwise multivariate logistic regression was then performed to identify clinician demographic predictors for the four clinical vignettes. Statistical significance was defined as a p -value < 0.05 for all analyses. All data analysis was performed using SAS Version 9.2 (SAS Institute, Inc., Cary, NC, 2008).

RESULTS

Patient Characteristics

Of 1658 deliverable emails, 337 (20.3%) clinicians responded. Of the 337 respondents, 57 did not treat HCV patients or did not have access to protease inhibitors. One hundred eighty-eight respondents practiced in the United States, and sixty-one outside of the United States, who practiced primarily in Europe and Australia. Demographics are shown in Table 1. One-third of all respondents were between ages 51–60, 75% were male, and 70% were non-Hispanic white. Over 90% reported hepatology and/or gastroenterology as their primary medical specialty and 87% had an academic affiliation. There was a wide range of experience with protease inhibitors; one-fifth of the providers had used protease inhibitor-based therapies in less than five patients, while 27% had treated over 30 patients. Physicians

in the United States had higher rates of experience with protease inhibitors than those practicing in other countries ($p<0.001$). Nearly 50% of respondents from the United States had treated over 20 patients with protease inhibitors, compared to only 11% of providers outside the United States.

Hepatitis C Treatment Practices in the United States

The majority of providers reported that they currently prefer using protease inhibitors among treatment naïve patients (Table 2). Indeed, for treatment-naïve patients with advanced fibrosis (stage 3–4 fibrosis), 98% of providers reported using protease inhibitor-based therapy. However, protease inhibitor-based therapy use was significantly less common among treatment-naïve patients with early stage fibrosis ($p<0.001$) and those with *IL28B* CC genotype ($p<0.001$), a well-recognized host DNA marker associated with marked treatment response to PEG-IFN even without DAA. Only 50% of providers would start protease inhibitor-based therapy in patients with early stage fibrosis, while 49% would await new therapies (Figure 1). Similarly, 10% of the providers would use PEG-IFN/RBV therapy in patients with *IL28B* CC genotype whereas 88% would use protease inhibitor-based therapy.

In patients with significant fibrosis and relapse from prior treatment, patient tolerance was important for determining HCV treatment practice pattern. In patients with an uneventful course during prior HCV treatment, 97% of providers would use protease inhibitors, compared to 79% of providers in those with a difficult course during prior treatment ($p<0.001$). Over one-fifth of providers would await new therapies among patients with significant fibrosis who had poor tolerance of previous HCV treatment. Similarly, 26% of providers would await new therapies among patients with significant fibrosis and null response to previous HCV treatment.

Use of protease inhibitors was common among patients in whom there is not a Food and Drug Administration (FDA) indication for protease inhibitor-based therapy use. Sixty-nine percent of providers reported using protease inhibitor-based therapy in HIV co-infected patients with significant fibrosis, and 48% reported using protease inhibitors in patients who underwent liver transplantation. In contrast, only 4% of the providers reported using protease inhibitor-based therapy among patients with HCV genotype 2 infection.

Across all twelve clinical vignettes, there was a consistent pattern of providers preferring telaprevir over boceprevir. Of those who preferentially used one protease inhibitor, 77–94% of providers reported using telaprevir over boceprevir in both treatment-naïve and treatment-experienced patients. Although telaprevir was still used more often than boceprevir in liver transplant patients, boceprevir use was higher than in other patient scenarios ($p=0.002$). Overall, there was acceptable reliability among the clinical vignettes (Cronbach $\alpha = 0.72$).

Pre-treatment and On-treatment Management of HCV in the United States

Liver biopsy was the most common pre-treatment evaluation, utilized by 78% of providers prior to protease inhibitor-based therapy (Table 3). Degree of liver fibrosis was assessed by alternate means in 25% of providers –14% Fibrosure, 6% use Fibroscan (approved for use only in Europe), and 5% reported using magnetic resonance elastography. *IL28B* genotype testing was performed by 45% of providers prior to protease inhibitor-based therapy. Providers reported encountering several common contraindications to therapy. Ten percent of providers did not use protease inhibitor-based therapy due to anemia and thrombocytopenia at least 40% of the time. Similarly, 20% of providers felt protease inhibitor-based therapy was not possible due to psychiatric disease and/or medical comorbidities in at least 40% of patients.

The majority of physicians continued using growth factors during protease inhibitor-based therapy. Neupogen was used for neutropenia by 75% of providers, erythropoietin was used for anemia by 89% of providers, and platelet growth factors were used for thrombocytopenia by 15% of providers, though platelet growth factors have yet to receive FDA approval for use in HCV treatment. Dose reductions of PEG-IFN and RBV were also common, although providers reported RBV dose reductions at significantly higher frequencies than PEG-IFN dose reductions ($p<0.001$). PEG-IFN dose was reduced by 69% of providers in the setting of neutropenia and 67% of providers in setting of thrombocytopenia, whereas 96% of providers reported RBV dose reductions for anemia. Blood product transfusions were also used for cytopenias by some providers – 61% of providers for anemia and 5% of providers for thrombocytopenia.

Close to one third of the physicians routinely equate unquantifiable as undetectable during the follow-up of patients being treated with protease inhibitors. Similarly, nearly one-fourth of providers would often terminate protease inhibitor-based therapy earlier than recommended by guidelines.

Predictors of HCV Treatment Practices

Early Stage Fibrosis—For treatment-naïve patients with early stage fibrosis, 49% providers would await new therapies, 50% would treat with protease inhibitors, and 1% would treat with PEG-IFN and RBV alone. On univariate analysis, 56% of male physicians recommended HCV treatment among this subgroup of patients, compared to 38% of female physicians ($p=0.03$). Similarly, 68% of physicians in private practice recommended HCV treatment, compared to 49% of physicians with an academic affiliation ($p=0.09$). Prior experience with protease inhibitor also predicted treatment recommendation in this subgroup, with rates of 39% for physicians who started protease inhibitors in 10 or fewer patients, 53% in 11–20 patients, and 57% if they had experience in more than 20 patients ($p=0.12$). On multivariate analysis, only male gender (OR 2.1, 95% CI 1.1 – 4.1) was significantly associated with HCV treatment initiation (Table 4).

Null Response to PEG-IFN and RBV—For patients with null response to prior therapy in the setting of significant fibrosis, 26% of providers would await new therapies whereas 74% would attempt re-treatment with protease inhibitors. On univariate analysis, academic affiliation (77% vs. 57% in private practice, $p=0.04$), medical practice location (Northeast 87%, Southeast 78%, Midwest 67%, West 59%, $p=0.03$) and more experience with protease inhibitor-based therapy (56% in those with 10 patients, 85% in those with 11–20 patients and 79% in those with >20 patients, $p=0.003$) were all significantly associated with HCV treatment initiation. On multivariate analysis, academic affiliation (OR 3.4, 95% CI 1.2 – 9.6) and protease inhibitor experience (OR 1.7, 95% CI 1.1 – 2.6) were significant predictors of HCV treatment initiation. Compared to providers in the Southeast, providers on the West Coast were significantly less likely to initiate HCV treatment (OR 0.3, 95% CI 0.1 – 0.9). Providers in the Northeast had a trend toward being more likely to initiate HCV treatment (OR 2.2, 95% CI 0.7 – 6.4) and those in the Midwest had a trend toward being less likely to initiate HCV treatment (OR 0.5, 95% CI 0.2 – 1.2) but neither was statistically significant.

HIV Co-infection—For patients with HIV infection, 15.5% of the providers would await new therapies, 69% would treat with protease inhibitors, and 15.5% would treat with PEG-IFN/RBV alone. On univariate analysis, 82% of providers with more than 20 years of experience would recommend treatment with protease inhibitors, compared to only 60% of providers with 11–20 years of experience and 61% of those with 10 years or less ($p=0.02$). Additionally, 73% of those with academic affiliation would recommend protease inhibitor-based therapy compared to only 39% in private practice ($p=0.004$). On multivariate analysis,

academic affiliation (OR 4.8, 95% CI 1.6 – 13.9) and practicing medicine for more than ten years (OR 1.8, 95% CI 1.1 – 3.0) were significantly associated with protease inhibitor-based therapy initiation.

Post-liver Transplant—For post-liver transplant patients, 22% of providers would await new therapies, 48% would treat with protease inhibitors, and 30% would treat with PEG-IFN/ RBV alone. On univariate analysis, hepatology subspecialty (53% vs. 14% non-hepatology, $p<0.001$), academic affiliation (51% vs. 7.7% private practice, $p=0.003$), medical practice location (Northeast 37%, Southeast 44%, Midwest 44%, West 69%, $p=0.07$), years in practice (43% of providers with more than 10 years in practice vs. 60% of providers with 10 or less, $p=0.07$), and experience with protease inhibitor-based therapy (22% of providers with 10 patients, 54% of providers with 11–20 patients and 56% of those with >20 patients, $p=0.002$) were associated with recommending protease inhibitor-based therapy. On multivariate analysis, hepatology subspecialty (OR 6.7, 95% CI 1.7 – 27), academic affiliation (OR 14.5, 95% CI 1.7 – 121), experience with protease inhibitor-based therapy (OR 2.2, 1.4 – 3.5), and medical practice location were significantly associated with initiation of protease inhibitor-based therapy.

DISCUSSION

The introduction of the direct-acting antiviral agents has led to the potential for improved outcomes for patients with hepatitis C. Our study assessed current HCV treatment practices in the United States after the introduction of protease inhibitor-based therapy approximately one year ago. We found that the majority of providers reported using protease inhibitors in both treatment naïve and treatment experienced patients, including off-label uses such as HIV co-infected patients and post-liver transplant patients. There was a consistent pattern of telaprevir preference over boceprevir among providers using protease inhibitor-based therapies.

Protease inhibitor-based therapy was recommended in treatment-naïve patients with early stage fibrosis by 50% of respondents. Although the AASLD guidelines, released prior to this study, have yet to address issues of specific patient selection, guidelines from the European Association for the Study of the Liver (EASL) currently stratify treatment recommendations based on the degree of underlying fibrosis.¹⁴ Prompt treatment should be strongly considered in patients with stage F2–F4 disease; however, treatment is less urgent among those with less severe fibrosis. Given the slow progression of HCV, patients with early stage fibrosis can safely await more potent and less toxic therapies, which will likely be approved in the next 3 years.¹⁵

We found that use of protease inhibitor-based therapy was prevalent among post-liver transplant patients and those with HIV co-infection, despite limited data on efficacy or safety. Protease inhibitors were reported to be prescribed by 69% of providers for HIV co-infected patients and 48% of providers for post-liver transplant patients, with significantly higher rates among providers with an academic affiliation. HCV is a growing cause of morbidity and mortality in patients with HIV, and traditional PEG-IFN/RBV therapy have been associated with low SVR rates nearing 29%¹⁶. Similarly, HCV infection is associated with decreased post-transplant graft and patient survival, given its universal recurrence and the poor efficacy of PEG-IFN/RBV therapy¹⁷. Although preliminary data suggests improved outcomes in these subgroups^{18, 19}, safety concerns such as drug-drug interactions still need be better studied.

Interestingly, few providers reported treating HCV genotype 2 with protease inhibitors despite phase II data suggesting its efficacy.²⁰ Although we could not determine why

providers did not recommend protease inhibitors more frequently in these patients, the generally high expectation of success with only PEG-IFN/RBV therapy likely explains this trend. Furthermore, only 2% of providers are awaiting new therapies despite the fast-track development of sofosbuvir, formerly PSI-7977, for HCV genotypes 2 and 3, which has been reported to have SVR rates near 100% among treatment naïve patients with these genotypes.²¹

Although the majority of providers would re-treat HCV genotype 1 prior null responders and relapsers with protease inhibitors, over one-fourth would await new therapies. Our data suggest that this decision is related to a perception of treatment efficacy as well as tolerance. Providers were significantly more likely to attempt re-treatment among relapsers if prior treatment with PEG-IFN and RBV was well tolerated. Although protease inhibitors have been associated with higher efficacy rates, they continue to be limited by toxicities and the need for accompanied use of PEG-IFN and RBV. In fact, providers reported that cytopenias, psychiatric disease, and medical comorbidities continue to preclude HCV treatment in a substantial number of previously treated patients. Interferon-free regimens, with substantially improved side effect profiles and high efficacy rates may be on the horizon and would offer hope to non-responders who tolerated prior therapy poorly.²²

Providers report continued use of both *IL28B* genotype testing and liver biopsy when evaluating potential treatment candidates. Although the association between *IL28B* genotypes and treatment response is attenuated in the setting of protease inhibitor-based therapy, there are increased SVR rates with telaprevir and boceprevir-based triple therapy in patients with *IL28B* CC genotype, so knowledge of *IL28B* status may still help guide duration of therapy.²³ Liver biopsy is not only helpful for determining length of therapy but can also help determine the urgency of treatment, particularly with the promise of IFN-free therapies on the horizon. Patients with early stage disease can likely safely wait for IFN-free regimens, whereas those with significant fibrosis and/or cirrhosis will likely need to be treated now – either with protease inhibitor-based therapy or through HCV trials, if eligible. However, with improving SVR rates and tolerability of DAAs on the horizon, patient selection may become more liberalized with less in-depth and invasive pre-treatment evaluation.

With regards to on-treatment management, close to one third of respondents equated unquantifiable viral RNA level during treatment as undetectable. Subsequent analysis of both boceprevir and telaprevir phase III trials have demonstrated that unquantifiable level at recommended time points had lower SVR in the end compared to those who achieved undetectable level at respective time points,²⁴ thus suggesting future HCV treatment guidelines should not only address patient selection but also fine details of treatment management. With regards to management of anemia while on therapy, over 85% of providers used erythropoietin and over 50% used red blood cell (RBC) transfusions, despite current data suggesting these strategies were not superior to RBV dose reduction alone. However, our survey did not characterize the frequency of RBC transfusions per patient nor the surrounding circumstances, so it is unclear if this was primarily isolated to patients hospitalized for severe anemia or if RBC transfusions were being used to prevent RBV dose reductions. Additional studies are needed to further assess the frequency of RBC transfusions and erythropoietin use among patients on HCV treatment, as well as the associated potential benefits and harms (including health care costs).

Currently there are no studies that compare the efficacy and safety between telaprevir and boceprevir-based therapies, as they were licensed through different phase III trials. However, marketing trends over the past year suggest that, at least initially, telaprevir prescriptions have accounted for a larger market share.²⁵ Factors favoring telaprevir include

slightly higher SVR rates in its phase III trials, shorter duration of protease inhibitor use (first 12 weeks), simpler viral load management, and inclusion of patients with prior null-response in its clinical trials. Further conclusions comparing these two protease inhibitors may be available from phase IV studies currently underway, such as HCV-TARGET (NCT01474811).

It is important to note that this study had several limitations. Respondent bias could have affected the results; however our response rate of 20% is similar to that of other provider surveys.¹⁰ The sampling strategy likely oversampled providers in academic practices, although this bias was likely toward physicians who see and treat patients with HCV. Results from this study were not verified by chart review and are limited by recall bias. It is well known that providers often over-report actual practices. For example, HCC surveillance rates were reported at 84% in a prior survey among AASLD members but then found to be substantially lower at 18% in chart review studies.^{26, 27}

In summary, the majority of providers report routine use of protease inhibitors in both treatment naïve and treatment experienced patients at this time. Despite more potent and less toxic therapies on the horizon, a majority of physicians are using protease inhibitors in treatment naïve patients with early stage fibrosis. There are also a substantial portion of physicians using protease inhibitor-based therapy for off-label uses, such as treating post-liver transplant patients and those co-infected with HIV. Continued assessment of treatment practice patterns in the setting of a changing landscape of available treatments is necessary, particularly given the lack of consensus guideline recommendations on which patients warrant treatment.

Acknowledgments

Robert Rahimi, Prathima Guntipalli, and Don Rockey were instrumental in obtaining email addresses. We again thank the Doris Duke Charitable Foundation for providing funding for this research study.

Financial Disclosures: This work was conducted with support from UT-STAR, NIH/NCATS Grant Number KL2 RR024983-05, CTSA NIH Grant UL1-RR024982, and the ACG Junior Faculty Development Award awarded to Dr. Singal. The content is solely the responsibility of the authors and does not necessarily represent the official views of UT-STAR, the University of Texas Southwestern Medical Center at Dallas and its affiliated academic and health care centers, the National Center for Advancing Translational Sciences, or the National Institutes of Health.

This work was also supported by a grant from the Doris Duke Charitable Foundation to UT Southwestern Medical Center to fund clinical research fellow Emerson Y. Chen. Additional funding was supplied by the Rollin and Mary Ella King Fund in the Southwestern Medical Foundation.

References

1. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med.* 2006; 144(10):705–14. [PubMed: 16702586]
2. Lavanchy D. The global burden of hepatitis C. *Liver Int.* 2009; 29(Suppl 1):74–81. [PubMed: 19207969]
3. Deuffic-Burban S, Poynard T, Sulkowski MS, et al. Estimating the future health burden of chronic hepatitis C and human immunodeficiency virus infections in the United States. *J Viral Hepat.* 2007; 14(2):107–15. [PubMed: 17244250]
4. Singal AG, Volk ML, Jensen D, et al. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. *Clin Gastroenterol Hepatol.* 2010; 8(3):280–8. 288, e1. [PubMed: 19948249]
5. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med.* 2002; 347(13):975–82. [PubMed: 12324553]

6. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet*. 2001; 358(9286):958–65. [PubMed: 11583749]
7. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med*. 2011; 364(25):2405–16. [PubMed: 21696307]
8. Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med*. 2011; 364(13):1195–206. [PubMed: 21449783]
9. Ghany MG, Nelson DR, Strader DB, et al. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011; 54(4):1433–44. [PubMed: 21898493]
10. Gaglio PJ, Moss N, McGaw C, et al. Direct-acting antiviral therapy for hepatitis C: attitudes regarding future use. *Dig Dis Sci*. 2011; 56(5):1509–15. [PubMed: 21336604]
11. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009; 42(2):377–81. [PubMed: 18929686]
12. Heller JC, Prochazka AV, Everson GT, et al. Long-term management after liver transplantation: primary care physician versus hepatologist. *Liver Transpl*. 2009; 15(10):1330–5. [PubMed: 19790168]
13. Shehab TM, Sonnad SS, Lok AS. Management of hepatitis C patients by primary care physicians in the USA: results of a national survey. *J Viral Hepat*. 2001; 8(5):377–83. [PubMed: 11555196]
14. Craxi A, Pawlotsky J-M, Wedemeyer H, et al. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol*. 2011; 55(2):245–64. [PubMed: 21371579]
15. Chung RT. A watershed moment in the treatment of hepatitis C. *N Engl J Med*. 2012; 366(3):273–5. [PubMed: 22256811]
16. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med*. 2004; 351(5):438–50. [PubMed: 15282351]
17. Yilmaz N, Shiffman ML, Stravitz RT, et al. A prospective evaluation of fibrosis progression in patients with recurrent hepatitis C virus following liver transplantation. *Liver Transpl*. 2007; 13(7):975–83. [PubMed: 17600360]
18. Ingiliz P, Rockstroh JK. HIV-HCV co-infection facing HCV protease inhibitor licensing: implications for clinicians. *Liver Int*. 2012
19. Roche B, Samuel D. Hepatitis C virus treatment pre- and post-liver transplantation. *Liver Int*. 2012; 32(Suppl 1):120–8. [PubMed: 22212582]
20. Foster GR, Hezode C, Bronowicki JP, et al. Telaprevir alone or with peginterferon and ribavirin reduces HCV RNA in patients with chronic genotype 2 but not genotype 3 infections. *Gastroenterology*. 2011; 141(3):881–889. e1. [PubMed: 21699786]
21. Mangia A, Mottola L. What's new in HCV genotype 2 treatment. *Liver Int*. 2012; 32(Suppl 1):135–40. [PubMed: 22212584]
22. Lok AS, Gardiner DF, Lawitz E, et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. *N Engl J Med*. 2012; 366(3):216–24. [PubMed: 22256805]
23. Holmes JA, Desmond PV, Thompson AJ. Does IL28B genotyping still have a role in the era of direct-acting antiviral therapy for chronic hepatitis C infection? *J Viral Hepat*. 2012; 19(10):677–684. [PubMed: 22967098]
24. Harrington PR, Zeng W, Naeger LK. Clinical relevance of detectable but not quantifiable hepatitis C virus RNA during boceprevir or telaprevir treatment. *Hepatology*. 2012; 55(4):1048–1057. [PubMed: 22095516]
25. [Accessed July 30, 2012] One Year Post-Launch, The Protease Inhibitors, Incivek and Victrelis have Collectively Penetrated Over Three-Quarters of the US Genotype 1 HCV Market [Marketwatch, Inc. Web site]. Jun 6. 2012 Available at: <http://www.marketwatch.com/story/one-year-post-launch-the-protease-inhibitors-incivek-and-victrelis-have-collectively-penetrated-over-three-quarters-of-the-us-genotype-1-hcv-market-2012-06-06>.

26. Chalasani N, Said A, Ness R, et al. Screening for hepatocellular carcinoma in patients with cirrhosis in the United States: results of a national survey. *Am J Gastroenterol.* 1999; 94(8):2224–9. [PubMed: 10445554]
27. Singal AG, Yopp A, C SS, Packer M, et al. Utilization of Hepatocellular Carcinoma Surveillance Among American Patients: A Systematic Review. *J Gen Intern Med.* 2012; 27(7):861–867. [PubMed: 22215266]

Figure 1.
Treatment choices for four clinical vignettes

Table 1

Provider Demographics

Clinician characteristics	U.S. Clinicians N=188		Non-U.S. Clinicians N=61
Age *	50 (27–77)		53 (32–72)
Gender (% male)	134 (71.3%)		53 (86.9%)
Race/Ethnicity			
Non-Hispanic White	132 (70.6%)		42 (68.9%)
Hispanic White	12 (6.4%)		7 (11.5%)
Asian	24 (12.8%)		8 (13.1%)
Black	7 (3.8%)		1 (1.6%)
Other	12 (6.4%)		3 (4.9%)
Medical Specialty			
Hepatology	147 (78.2%)		51 (83.6%)
Gastroenterology	20 (10.6%)		5 (8.2%)
Infectious Disease	10 (5.3%)		2 (3.3%)
Medical Practice (% academic affiliation)	164 (87.2%)		53 (86.9%)
Years in Practice			
<10 yrs	46 (24.7%)		4 (6.7%)
11–20 yrs	64 (34.4%)		11 (18.3%)
>20 yrs	76 (40.9%)		45 (75.0%)
Prior involvement with HCV clinical trials	147 (78.2%)		55 (90.2%)
# Patients started on protease inhibitor			
1 – 5	22 (11.7%)		28 (45.9%)
6 – 10	28 (14.9%)		14 (23.0%)
11 – 20	47 (25.0%)		12 (19.7%)
21– 30	31 (16.5%)		1 (1.6%)
> 30	60 (31.9%)		6 (9.8%)
Region			
Southeast	55 (29.3%)	Europe	34 (55.7%)
Northeast	52 (27.7%)	Australia	12 (19.7%)
Midwest	42 (22.3%)	Asia	8 (13.1%)
West	27 (14.4%)	South America	5 (8.2%)
Not specified	12 (6.3%)	Other	2 (3.3%)

* Age is expressed as median and range

Table 2

Clinical Vignette HCV Treatment Practices

Clinical Vignettes (N=188)	Boceprevir	Telaprevir	Either Protease Inhibitor	PEG-IFN/RBV alone	No treatment
Treatment-naïve					
Fibrosis stage 0–2	3 (1.6%)	47 (25.6%)	42 (22.8%)	2 (1.1%)	90 (48.9%)*
Fibrosis stage 3	13 (7.0%)	78 (42.2%)	90 (48.7%)*	1 (0.5%)	3 (1.6%)
Cirrhosis	23 (12.7%)	76 (42.0%)	78 (43.1%)*	0	4 (2.2%)
<i>IL28B</i> CC genotype	19 (10.2%)	69 (37.1%)	76 (40.9%)*	19 (10.2%)	3 (1.6%)
African American patient	18 (9.7%)	87 (46.5%)*	76 (40.6%)	0	6 (3.2%)
BMI>35	18 (9.7%)	71 (38.2%)	90 (48.4%)*	1 (0.5%)	6 (3.2%)
Prior PEG-IFN/ RBV therapy					
Relapser prior uneventful course	10 (5.3%)	94 (50.3%)*	78 (41.7%)	0	5 (2.7%)
Relapser prior difficult course	19 (10.7%)	67 (37.9%)*	53 (29.9%)	1 (0.6%)	37 (20.9%)
Null-responder	11 (6.0%)	84 (45.7%)*	42 (22.8%)	0	47 (25.5%)
Off-label use					
HIV co-infection	11 (7.4%)	55 (37.2%)*	36 (24.4%)	23 (15.5%)	23 (15.5%)
Post-liver transplant	24 (15.1%)	48 (30.2%)*	4 (2.5%)	48 (30.2%)*	35 (22.0%)
HCV genotype 2	0	6 (3.3%)	2 (1.1%)	172 (94.0%)*	3 (1.6%)

* Preferred practice pattern in each clinical vignette

Table 3

Pre-therapy evaluation and on-treatment HCV management practices

Experience with hepatitis C treatment	N (%)
Type of PEG-IFN used with protease inhibitor-based therapy	
Primarily PEG-IFN 2a (Pegasys)	170 (90.4%)
Primarily PEG-IFN 2b (Pegintron)	4 (2.1%)
No preference between either PEG-IFN	11 (5.9%)
Depends on the protease inhibitor	3 (1.6%)
Tests routinely done before protease inhibitor-based therapy	
<i>IL28B</i> genotype testing	84 (44.7%)
Liver biopsy	147 (78.2%)
Fibroscan	12 (6.4%)
Fibrosure	27 (14.4%)
Magnetic Resonance Elastography	9 (4.8%)
Contraindications to protease inhibitor-based therapy in > 40% of patients	
Baseline anemia	20 (10.6%)
Baseline thrombocytopenia	19 (10.1%)
Psychiatric illness	40 (21.3%)
Medical co-morbidities	37 (19.7%)
On therapy management performed in at least 50% of patients	
Order week 2 viral load	37 (19.7%)
Assume unquantifiable is equivalent to undetectable viral load	61 (32.4%)
Terminate therapy earlier than the recommended duration if patient achieved good virological response early in therapy	42 (22.3%)
Reduce PEG-IFN dose for neutropenia	130 (69.1%)
Use filgrastim (Neupogen) for neutropenia	141 (75.0%)
Reduce ribavirin dose for anemia	180 (95.7%)
Use erythropoietin (Procrit) for anemia	168 (89.4%)
Use blood products for anemia	114 (60.6%)
Reduce PEG-IFN dose for thrombocytopenia	126 (67.0%)
Use platelet growth factor (Eltrombopag) for thrombocytopenia	28 (14.9%)
Use platelet infusion for thrombocytopenia	9 (4.8%)

Table 4

Predictors of Protease Inhibitor-based Therapy Use

	Early Stage Fibrosis (0–2)	Prior Null Response	HIV co-infection	Post-liver transplant
Gender				
Male physicians	2.1 (1.1 – 4.1)		0.5 (0.2 – 1.2) *	
Medical Specialty				
Hepatologists				6.7 (1.7 – 27.0)
Medical Practice				
Academic affiliation	0.4 (0.1 – 1.0) *	3.4 (1.2 – 9.6)	4.8 (1.6 – 13.9)	14.5 (1.7 – 121)
Region				
Southeast		Reference		Reference
Northeast		2.2 (0.7 – 6.4)		1.1 (0.4 – 2.8)
Midwest		0.5 (0.2 – 1.2)		1.0 (0.4 – 2.7)
West		0.3 (0.1 – 0.9)		3.2 (1.0 – 9.9)
Year in Practice				
10 years			Reference	
>10 years			1.8 (1.1 – 3.0)	
Protease Inhibitor Experience				
1–10 patients	Reference	Reference		Reference
>10 patients	1.4 (0.96 – 2.0) *	1.7 (1.1 – 2.6)		2.2 (1.4 – 3.5)

* Not statistically significant in the final model