

## Direct-Acting Antiviral Therapy for Hepatitis C: Attitudes Regarding Future Use

Paul J. Gaglio · Noah Moss ·  
Camille McGaw · John Reinus

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### Abstract

**Introduction** Response to current therapy of hepatitis C virus (HCV) is suboptimal. Direct-acting antiviral therapies (DAA) are expected to improve treatment outcomes. Additional treatments for HCV will invariably make therapeutic choices and patient management more complex. We hypothesize that current perceptions regarding the complexity of DAA therapy will influence attitudes towards future use by practitioners who are currently treating HCV.

**Methods** An Internet-based survey was sent to 10,082 AASLD and AGA members to determine if they treat HCV infection, their knowledge of DAA therapies, attitudes towards current and future HCV treatments, and if they participated in clinical trials using DAA agents.

**Results** Out of a total of 1,757 individuals responding to the survey, 75% treat HCV; 79% were MDs, 67% were

Gastroenterologists, and 24% were Hepatologists. Of the respondents, 77% indicated they were “very aware” or “aware” of DAA therapies, 20% participated in clinical trials, and 3% had minimal knowledge of DAA agents. Comparing treatment “today” versus in the future when DAAs were available, 85 vs. 81% would treat ( $p = 0.0054$ ), 6 vs. 10% would refer to an “HCV expert” ( $p = 0.016$ ), and 1% would refer to an ID specialist. Of respondents with “minimal knowledge” of DAA, 52% stated that they would use them in the future.

**Conclusions** Although the majority of respondents appear ready to utilize DAA agents in the future, referrals to “hepatitis C experts” will increase. More than half of respondents with “minimal knowledge” of DAA therapies also appear to be willing to utilize these compounds, raising concerns regarding their inappropriate use. Broad education of healthcare providers to prevent inappropriate use of these agents will be critical.

**Keywords** Hepatitis C · DAA · STAT C · Direct-acting antiviral therapy

### Introduction

Hepatitis C virus (HCV) represents the most common chronic blood-borne viral infection in the United States [1, 2]. At present, response to currently available therapy remains suboptimal as a significant number of patients fail to achieve a sustained virologic response to therapy [3–10]. Recent discoveries related to the life cycle and pathobiology of HCV have led to the development of novel therapies that directly inhibit viral replication. These compounds, characterized as “specifically targeted antiviral therapies against HCV” (STAT-C) or “direct-acting antiviral

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P. J. Gaglio · N. Moss · C. McGaw · J. Reinus  
Department of Medicine, Albert Einstein College of Medicine,  
Montefiore Medical Center, Bronx, NY, USA

P. J. Gaglio (✉)  
Montefiore Einstein Liver Center,  
111 East 210 Street, Bronx, NY 10467, USA  
e-mail: pgaglio@montefiore.org

agents” (DAA) have been investigated in naive as well as previously treated patients, and preliminary data from these studies have been encouraging [11–14]. Along with these encouraging results, these and other publications which describe experience with DAA agents have documented the emergence of HCV resistance [15, 16], as well as significant treatment-related adverse events including rash, gastrointestinal side-effects, and anemia [11–14].

As health care providers with interest and experience in treating HCV become aware of emerging data using novel therapeutic agents, we hypothesize that current perceptions regarding the complexity and side-effects of DAA therapies will influence decisions regarding the future use of these agents. To evaluate attitudes regarding the future use of these agents by individuals who are currently treating HCV, we sent an Internet-based survey to all United States-based members of the American Gastroenterology Association (AGA) and American Association for the Study of Liver Disease (AASLD). Members of these societies were chosen because they represent both the vast majority of HCV treaters in the United States, and a population of clinicians likely to have knowledge of DAA therapies. Recipients of the survey were queried regarding their primary professional affiliation and focus of practice, attitudes towards current and future HCV therapy, as well as participation in clinical trials using DAA agents. We determined if any of these parameters affected attitudes related to current and future treatment decisions regarding HCV.

## Methods

This study was reviewed and approved by the institutional review board at the Albert Einstein College of Medicine/Montefiore Medical Center. The e-mail addresses of the 10,082 US-based members of the AGA and AASLD were compiled from the 2009 member directories for both organizations. AGA and AASLD members were selected to be surveyed as they represent the majority of HCV treaters in the United States. Prescriber Profiler™ data provided to the authors by IMS Health Incorporated, reflecting a US-based database of retail pharmacies and total dispensed prescriptions of Copegus™, Intron-A™, Infergen™, Pegasys™, Peg-Intron™, Rebetol™, Rebetron™, Ribasphere™, and Ribavirin™ indicated that between December 2008 and November 2009, 177,300 prescriptions were written. Gastroenterologists or Hepatologists wrote approximately 94,000 or 55% of these, validating our hypothesis that the targeted survey recipients were a group which treated HCV most frequently. Internal medicine physicians (11%) and nurse practitioners (8%) were the next most common prescribers [17]. Using an Internet-based survey engine (“SurveyMonkey”

(surveymonkey.com)) a nine-question survey was sent to each AGA or AASLD member; only one questionnaire was sent to individuals who are members of both organizations. If an individual did not respond to the survey, the survey was re-sent with a second request to complete the survey. All results were tabulated, and statistical analysis was performed using Stata version 9.2, Statcorp LP, College Station, Texas.

## Results

Of the 10,082 surveys sent, 8,449 were deliverable. The most common reasons for inability to deliver a survey included use of an e-mail filter or vacation message by the intended recipient. A total 1,757 individuals responded to the survey, representing a 21% response rate. A recent analysis performed by supersurvey.com revealed a mean response rate of 18% to online surveys of similar question size and target audience ([www.supersurvey.com](http://www.supersurvey.com)). The survey questions and responses appear in Table 1. If a respondent stated that they did not treat HCV, their participation in the survey ended after question 1.

Of the respondents, 75% (1,320) stated that they treat HCV, and of these respondents, 79% were MDs, 10% were physician assistants or nurse practitioners, 8% MD-PhDs, 2% DO, and 1% PhD. Of the respondents, 32% graduated within the last 10 years, 25% 11–20 years ago, 21% 21–30 years ago, and 12% greater than 30 years ago.

When analyzing results based on focus of practice, 67% of respondents stated that gastroenterology was the primary focus of their clinical practice, 24% selected hepatology and/or liver transplantation, 2% infectious disease, and 7% stated “other” as the primary focus of their practice. The “other” respondents included primary care doctors, surgeons, as well as Gastroenterologists who considered hepato-biliary disease, oncology, or pancreatic disease their primary specialty. Forty-six percent of the respondents were in a private practice not associated with a medical school, 42% at a medical school or hospital associated with a medical school, 8% in a private practice associated with a medical school, and the remaining 4% of respondents practiced in a multispecialty group practice, Veterans Administration hospital, or hospital not associated with a medical school.

Professional affiliations were assessed; 55% of respondents considered the American Gastroenterological Association (AGA) their primary professional affiliation, 26% the American Association for the Study of Liver Disease (AASLD), 9% the American Society for Gastrointestinal Endoscopy (ASGE), and 10% “other” including the American College of Gastroenterology (ACG), American Medical Association (AMA), and the American Society for Transplantation (AST).

**Table 1** Responses to questions by respondents who treat HCV

Highest level of education	79% MD 10% PA 8% MD-PhDs 2% DO 1% PhD
Year of graduation from the last school you attended	32% within the last 10 years 25% 11–20 years ago 21% 21–30 years ago 12% > 30 years ago
Primary focus of practice	67% Gastroenterology 24% Hepatology and/or liver transplantation 2% Infectious disease 7% “other”
Location of primary practice	46% private practice not assoc with a medical school 42% medical school/hospital assoc with a medical school 8% private practice associated with a medical school 4% “other”
Primary professional affiliation	55% AGA 26% AASLD 10% “other” 9% ASGE
“If I saw a patient with HCV today”...	85% would treat 6% would refer them to a “hepatitis C expert” 4% would refer them to NP, PA in their practice 4% would refer to another MD in their practice 1% would refer them to an Infectious Disease specialist.
Awareness of DAA therapy	77% “aware” or “very aware” without participation in any clinical trials 20% were “very aware” and had experience using these agents in clinical trials 3% had “minimal knowledge” of STAT-C agents
If DAA therapies were available today	81% would evaluate and treat the patient 10% would refer to a “Hepatitis C expert” 5% would refer to another physician in their group 4% would refer the patient to NP, PA in their practice <1% would refer to an infectious disease specialist

When queried regarding what they would do when presented with an HCV-infected patient “today,” 85% of the respondents would treat them, 6% would refer them to a “hepatitis C expert,” 4% would refer them to a physician extender (PA, NP, or specially trained nurse) in their practice, 4% would refer to another MD in their practice, and 1% would refer them to an infectious disease specialist. Related to future therapies for HCV including DAAs in combination with interferon and ribavirin, 77% of the respondents were “aware” or “very aware” of this concept but had not participated in any clinical trials using DAA agents, 20% were “very aware” and had experience using these agents in clinical trials, and 3% had “minimal knowledge” of DAA agents.

When queried regarding treatment approaches if a DAA agent were available “today,” 81% of respondents would evaluate and treat the patient, 10% would refer the patient to a “hepatitis C expert,” 5% would refer the patient to another physician in their group, and 4% would refer the patient to a physician extender (PA, NP, or specially trained nurse) in their practice. Less than 1% of respondents reported that they would refer the patient to an infectious disease specialist.

Analysis of survey results (Table 2):

Overall, a significant number of respondents who treat HCV today with currently available therapies indicated that they would not prescribe DAA therapies when they became available; 85% of respondents to the survey would evaluate

**Table 2** Current and future therapy, and future referral to an HCV specialist

Respondent characteristic	Would treat HCV today	Would treat with DAA in the future	Future referral to HCV specialist	<i>p</i> value
Overall	85 (%)	81 (%)	10 (%)	0.0054
AASLD member	<sup>A</sup> 91	<sup>B</sup> 91	<sup>C</sup> 3	<sup>A</sup> 0.002
AGA member	<sup>A</sup> 84	<sup>B</sup> 79	<sup>C</sup> 12	<sup>B,C</sup> 0.001
Hepatologist	<sup>D</sup> 93	<sup>E</sup> 90	<sup>F</sup> 1	<sup>D</sup> .0034
Gastroenterologist	<sup>D</sup> 86	<sup>E</sup> 81	<sup>F</sup> 8	<sup>E,F</sup> 0.001
Private practice	<sup>G</sup> 91	<sup>H</sup> 89	<sup>I</sup> 12	<sup>G,H</sup> 0.001
Academic practice	<sup>G</sup> 81	<sup>H</sup> 75	<sup>I</sup> 15	<sup>I</sup> NS
Participated in DAA Clinical trial	<sup>J</sup> 91	<sup>K</sup> 90	<sup>L</sup> 4	<sup>J,K,L</sup> 0.0001
Minimal knowledge of DAA	<sup>J</sup> 59	<sup>K</sup> 52	<sup>L</sup> 22	

The *p* value related to the statistical significance of the comparisons of groups A to A, B to B, C to C, etc are reported

and treat an HCV-infected patient “today” versus 81% when DAA agents became available ( $p = 0.0054$ ). Similarly, more respondents indicated that they would refer their patients to a “hepatitis C specialist” after DAA agents became available (6% current, 10% after DAA availability ( $p = 0.016$ )).

Significant differences existed based on primary professional affiliation in attitudes and experience of survey respondents related to present and future HCV therapy. Ninety-one percent of respondents who considered the AASLD their primary affiliation compared to 84% of AGA members would treat their HCV-infected patient today ( $p = 0.002$ ), 48% of AASLD members versus 9% of AGA members participated in clinical trials with a DAA agent ( $p = 0.001$ ), and 91% of AASLD members versus 79% of AGA members would use a DAA agent to treat their HCV-infected patient in the future ( $p = 0.001$ ). A greater percentage of AGA members (12%) stated that they would refer their patient to an “HCV expert” when DAA agents became available compared to AASLD members (3%) ( $p = 0.001$ ). When analyzing attitudes related to current and future therapy of HCV based on focus of clinical practice, a comparison of Hepatologists/liver transplantation physicians to Gastroenterologists revealed that 93% versus 86% would treat their HCV-infected patient today ( $p = 0.0034$ ), 48% compared to 8% participated in clinical trials using DAA agents ( $p = 0.001$ ), 90% versus 81% would treat their patient with a DAA agent ( $p = 0.001$ ), and 1% versus 8% would refer their patient to an “HCV expert” when DAA therapies became available ( $p = 0.001$ ).

Practice type was also associated with differences in attitudes related to current and future therapy of HCV. Comparison of respondents in private practice versus those who practiced at a medical school or hospital associated with a medical school revealed that respectively, 91% versus 81% would treat their HCV-infected patient today ( $p = 0.001$ ), 9% versus 30% participated in a clinical trial

with a DAA agent ( $p = 0.001$ ), 89% versus 75% would use DAA therapies when they became available ( $p = 0.001$ ), and 12% compared to 15% would refer to an “HCV expert” when DAA therapies became available ( $P = NS$ ).

Current awareness and participation in clinical trials with DAA agents influenced attitudes regarding future use of these therapies, as 90% of respondents who participated in clinical trials with DAAs, 81% of those who were “very aware” or “aware” of DAA agents but did not participate in clinical trials, and 59% of those with minimal knowledge of DAA therapies would prescribe these agents in the future ( $p = 0.0001$  clinical trial participant/very aware or aware of DAA agents vs. minimal knowledge). Respondents with “minimal knowledge” of DAA agents also reported that when these compounds were available in the future, 25% would refer their HCV-infected patient to a PA, NP, or other MD in their practice, 22% would refer to an “HCV expert,” and 1% would refer to an ID specialist. Respondents who reported “minimal knowledge of DAA agents” were more likely to consider the AMA their primary professional organization (20 vs. 1% AGA/AASLD ( $p = 0.001$ )), or be in a private practice not associated with a medical school (83 vs. 17% practice or hospital associated with a medical school  $p = 0.0001$ ).

## Discussion

Emerging data suggest that direct-acting antiviral therapies against HCV (DAA) will provide improved response rates when given in combination with currently available therapies. The enthusiasm for these new treatments must be tempered by realistic concerns including side-effects as well as the threat of viral resistance induced by these agents. We hypothesized that concern regarding these issues might affect attitudes of future use of DAA therapies by health care providers who currently treat HCV. The goal of the current study was to query a group of experienced

HCV treaters using an Internet-based survey to assess attitudes regarding current and future treatment of HCV and correlate these responses related to focus of clinical practice, academic versus private practice, professional affiliation, and experience with DAA agents in clinical trials. US-based members of the AGA and AASLD were targeted for the survey as they represent the majority of HCV treaters in the US and a group most likely to have knowledge of DAA therapy. This manuscript represents the first description of attitudes regarding future use of DAA agents in a large group of experienced HCV treaters.

Based on responses to this survey, although the majority of current HCV treaters would prescribe a DAA agent, a significant number of respondents who treat HCV today (85%) would not initiate therapy when these agents became available in the future (81%). The decreased use of DAA therapies may be offset somewhat by an increase in referrals to a more experienced HCV treater, as more respondents would refer their patients to a “hepatitis C expert” after DAA agents became available in the future compared to referring patients if they were diagnosed with HCV today (10% versus 6%). Not surprisingly, future use of DAA therapy appears to be significant in treaters who identify themselves as Hepatologists, and those with experience using these agents in clinical trials. Moreover, direct clinical experience with DAAs did not appear to dampen the enthusiasm for future use of these agents, as 90% of respondents who participated in clinical trials with a DAA agent would utilize these agents to treat an HCV-infected patient when these agents became available.

We hypothesized that as infectious disease specialists have extensive experience prescribing oral antiviral agents for HIV, referrals to these providers would increase when DAA agents became available for HCV. Our hypothesis was clearly inaccurate as respondents to the survey were unlikely to refer their HCV-infected patients to an infectious disease specialist when faced with an HCV-infected patient today (1%) and when DAA agents were available in the future (0.8%). This trend was maintained even in respondents with minimal knowledge of DAA agents. Finally, a concerning observation was identified when assessing responses to the survey stratified by past experience with DAA therapy. Although a significant percentage of respondents who participated in clinical trials with a DAA (90%) or who were “aware or very aware” of these agents but did not participate in a clinical trial (81%) would use these agents in the future, more than half of respondents (52%) who reported minimal knowledge of DAA agents stated that they would also use them in the future. Although providers with minimal knowledge of DAA agents represented a small percentage of respondents to the survey, concern exists regarding the inappropriate use of DAAs in the future including inexperience with side-effect

management, and lack of recognition of both treatment failure as well as the emergence of viral resistance [11–16]. It is therefore apparent to the authors of this manuscript that extensive education of all future prescribers of DAA agents will be required to ensure successful use of these therapies.

There are limitations of this study that are unfortunately shared by other surveys utilizing similar data collection and analyses techniques. Any Internet-based survey is limited by response rate, which is affected both by the ability to deliver the survey and the willingness of the survey recipient to accurately respond to the queries posed to them. Although 21% of recipients of the survey responded, it is possible that the identified results would have been different if more individuals completed the survey. Unfortunately, the large volume of unsolicited e-mail has induced the use of blockers and filters, thus potentially limiting the response rates to the survey. However, we believe that these limitations were balanced by several strengths including the overall brevity of the survey (nine questions) increasing the likelihood that those who received and opened the survey fully completed it, and by the target audience which represented a significant number of current HCV treaters with the highest likelihood of having knowledge regarding DAA agents.

In summary, the responses to this Internet-based survey of more than 1,000 current HCV treaters indicated that although the majority of respondents appear ready to utilize DAA agents in the future, referrals to “hepatitis C experts” will increase when these agents become available. In addition, future referrals to ID specialists appear to be limited. Finally, as more than half of respondents to the survey with “minimal knowledge” of DAA therapies also appear to be willing to utilize these compounds in the future, significant provider education will be required to minimize inappropriate use of these agents.

**Conflict of interest** Paul J. Gaglio, MD, Speakers Bureau, Merck; has received study support from Schering Plough (now Merck) and Vertex Pharmaceuticals. Noah Moss, MD: No Disclosures Camille Baugh, MD: No Disclosures Noah Moss, MD: No Disclosures John Reinus, MD has received study support from Vertex Pharmaceuticals.

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## Appendix: HCV Survey

Question 1. Do you treat patients with hepatitis C? Yes/No  
Question 2. What is your highest level of education?

- MD
- DO

- PhD
- MD/PhD
- PA/NP

Question 3: What year did you graduate medical school (or osteopathic or graduate school)?

Question 4: What is the primary focus of your clinical practice? (please select one)

- General gastroenterology
- Hepatology
- Hepatology and liver transplantation
- Primary care
- Infectious disease
- Research
- Other

Question 5: What is the location of your primary practice?

- Medical school or hospital associated with a medical school
- Hospital not associated with a medical school
- V.A.
- Private practice associated with a medical school
- Private practice not associated with a medical school
- Other

Question 6: What is your primary professional affiliation?

- AASLD
- AGA
- AMA
- ASGE
- Other

Question 7: If I saw a patient with hepatitis C today I would (choose one answer):

- Evaluate and treat the patient
- Refer the patient to a hepatitis C expert
- Refer the patient to another physician in my practice
- Refer the patient to an RN,PA or other physician extender in my practice
- Refer the patient to an infectious disease specialist

Question 8: In the near future, hepatitis C therapy will likely include an interferon-like agent, a medication like ribavirin and direct-acting antiviral therapies such as protease and polymerase inhibitors. How aware are you of this concept?

- Very aware, have participated in trials using these new therapies
- Very aware, have not participated in trials using these new therapies
- Aware
- Minimal knowledge

Question 9: When direct-acting antiviral therapies (e.g., protease and polymerase inhibitors) become available and you see a patient who would require them you would:

- Evaluate and treat the patient
- Refer the patient to a hepatitis C expert
- Refer the patient to another physician in my practice
- Refer the patient to an RN,PA or other physician extender in my practice
- Refer the patient to an infectious disease specialist

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