



A Global View of Hepatitis C: Physician Knowledge, Opinions, and Perceived Barriers to Care

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Chronic infection with the hepatitis C virus (HCV) is a leading cause of global morbidity and mortality. Although recent advances in antiviral therapy have led to significant improvements in treatment response rates, only a minority of infected patients are treated. Multiple barriers may impede the delivery of HCV therapy. The aim of this study was to identify perceived barriers to care, knowledge, and opinions among a global sample of HCV treatment providers. An international, multidisciplinary survey of HCV treatment providers was conducted. Each physician responded to a series of 214 questions concerning his or her practice characteristics, opinions regarding the state of HCV care, knowledge regarding HCV treatment, and perception of treatment barriers. A total of 697 physicians from 29 countries completed the survey. Overall, physicians viewed patient-level barriers as most significant, including fear of side effects and concerns regarding treatment duration and cost. There were distinct regional variations, with Central and Eastern European physicians citing government barriers as most important. In Latin America, the Middle East, and Africa, payer-level barriers, including lack of treatment coverage, were prominent. Overall, the perception of barriers was strongly associated with physician knowledge, experience, and region of origin, with the fewest barriers reported by Nordic physicians and the most reported by Middle Eastern and African physicians. Globally, physicians demonstrated deficits in basic treatment principles, including the role of viral kinetics and the management of treatment nonresponders. Two thirds of surveyed physicians believed that patients do not have adequate access to providers in their community. Conclusion: Barriers to HCV treatment vary globally, though patient-level factors are viewed as most significant by treating physicians. Efforts to improve awareness, education, and specialist availability are needed. (Hepatology 2013;57:1325-1332)

epatitis C virus (HCV) infection affects between 130 and 170 million persons worldwide, is a leading indication for liver transplantation, and contributes to 350,000 deaths each year. HCV is a potentially curable disease, with the majority of treated patients currently afforded the promise of a sustained virologic response (SVR). Unfortunately, less than half of HCV-infected persons are aware of their diagnosis, and among those with known infection, only 1%-30% will receive treatment. 6-11

Multiple factors serve as impediments to the delivery of antiviral therapy. These barriers may arise at the patient, provider, payer, and/or government level. Patients cite fear of treatment-related side effects, lack of symptoms, financial constraints, and social stigmatization as primary reasons for declining therapy. Physicians may fail to refer patients for subspecialty evaluation or may place undue emphasis on purported contraindications. As a result, more than 70% of patients are deemed ineligible for treatment based on

Abbreviations: ANOVA, analysis of variance; EVR, early virologic response; GI, gastroenterology; HCV, hepatitis C virus; IDs, infectious diseases; IFN, interferon; Peg-IFN, pegylated interferon; RBV, ribavirin; SD, standard deviation; SVR, sustained virologic response.

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psychiatric disease, substance use, or medical comorbidities,^{6,7} despite evidence that these factors are not absolute.^{18,19} A lack of available and competent specialists may further interfere.^{20,21} Finally, limitations in funding, medical coverage, and office staffing may prevent treatment.^{11,22}

Increasingly, hepatitis C is recognized as a global health crisis, demanding an international, coordinated emphasis on promotion, prevention, and treatment.²³ To inform these initiatives, we surveyed an international sample of HCV treatment providers, with an aim of assessing knowledge, opinions toward HCV therapy, and perceived barriers to care.

Materials and Methods

An international, mixed-mode survey study of HCV treatment providers was conducted in December 2010 with an aim to identify physician and practice characteristics, opinions regarding HCV care, knowledge of treatment principles, and perceived barriers to care. A 214-item questionnaire was developed by the International Conquer C Coalition (I-C3; see Appendix), an organization of hepatitis C experts formed with the goal of optimizing global HCV care. The questionnaire was piloted by a 67-member focus group of I-C3 members. Physicians were considered eligible for the study if they treated a minimum of 10 HCV patients each month and if they resided in one of the eight predetermined global regions: United States; Canada; Latin America; Western Europe; Central/Eastern Europe; Nordic; Asia/Pacific; and Middle East/Africa. Target respondents included hepatologists, gastroenterologists, infectious disease (ID) physicians, internists, and general practitioners. The survey was distributed

to a sample of 1,400 physicians identified by an international market research database²⁴ and was administered by 25-minute phone interview or internet-based format by a professional survey company (Phoenix Marketing International, Rhinebeck, NY). Participants were asked a series of open-ended, multiple-response, and Likert-scale questions. Translation was provided for non-English-speaking participants. Each participant received a modest honorarium for completing the survey. All responses were anonymous.

Physician/Practice Characteristics and Opinions Regarding HCV Care. Each physician was asked about his or her medical specialty, practice location, patient volume, and patient characteristics. Opinions regarding the current state of HCV care were assessed according to level of agreement with the following statements: (1) national treatment guidelines are available in my country; (2) treatment guidelines and policies are consistent among professional societies, payers, and government; (3) government and/or payers recognize national or international treatment guidelines; (4) healthcare providers have knowledge of screening and treatment guidelines; (5) the general public is aware of HCV; (6) patients understand the consequences of HCV if it is not treated; (7) most patients are aware that HCV is curable; and (8) patients have adequate access to HCV providers in their community; responses were rated on a 10-point Likert scale, with 0 representing "strongly disagree," 5 "neither agree nor disagree," and 10 "strongly agree."

Knowledge. Physician knowledge was assessed according to level of agreement with the following eight statements: (1) the addition of ribavirin (RBV) to pegylated interferon (Peg-IFN) improves the likelihood of SVR; (2) maintaining an optimal dose of RBV with interferon (IFN) is necessary to achieve an

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Additional Supporting Information may be found in the online version of this article

Table 1. Perceived Barriers to HCV Treatment

Patient Related	Provider Related
Fear of side effects	Treatment limited to government-mandated centers
Medication expense	 Lack of office infrastructure to treat patients
Laboratory expense	 Insufficient reimbursement for physicians
Low success rate of treatment	 Unable to obtain necessary labs for treatment
 Fear of stigma related to HCV 	 Limited access to medications or labs
Preference for alternative therapy	 Insufficient training for HCV management
Desire to wait for newer therapies	 Lack of referral to HCV providers by other physicians
Difficulty with administration	 Lack of proper storage for medications
Treatment duration	Payer Related
Patient declines liver biopsy	 Insurance plan does not cover treatment
 Inaccessibility of experienced providers 	 High out-of-pocket expense for patients
Government Related	 Restricted insurance coverage for patients with HCV
Government restricts treatment	 Insurance plans will not cover RNA/genotyping
 Insufficient funds allocated to HCV 	 Excessive paperwork requirements
 Lack of promotion for HCV treatment 	 Insurance plans limit which physicians treat HCV
	 Insurer does not cover serum markers of fibrosis
	 Insurance plans do not cover medications for side effects
	 Liver biopsy required for treatment

All barriers scored on a 10-point Likert scale, with 0 representing "not a barrier to treatment," 5 representing "somewhat of a barrier to treatment," and 10 representing "large barrier to treatment."

SVR; (3) different viral genotypes require different treatment durations; (4) treatment should be discontinued for patients who fail to achieve a 2-log decrease in HCV RNA by treatment week 12; (5) treatment should be discontinued for patients who have detectable HCV RNA at treatment week 4; (6) patients with stage 1 fibrosis have worse treatment outcomes than patients with stage 4 fibrosis; (7) level of HCV RNA has no correlation with severity of liver disease; and (8) maintenance therapy should be prescribed for treatment nonresponders. Each response was rated on a 10-point Likert scale, with 0 representing "strongly disagree," 5 representing "neither agree nor disagree," and 10 representing "strongly agree."

Barriers to Care. The main focus of this study was to assess perceived barriers to HCV care. Each respondent was presented with 31 potential barriers categorized

by patient-, provider-, government-, and payer-related categories (Table 1). Responses were based on a 10-point Likert scale, with 0 representing "not a barrier to treatment," 5 representing "somewhat of a barrier to treatment," and 10 representing "large barrier to treatment."

Statistical Analysis. Mean, range, standard deviation (SD), and shape of the distribution were examined for each continuous variable, with frequencies tabulated for each categorical variable. Physician and practice characteristics were compared across global regions using Pearson's chi-square test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. Bivariable analysis was used to examine the relationship between physician and practice characteristics and perceived barriers to care using Pearson's correlation analysis for continuous independent variables and one-way ANOVA for each categorical independent variable.

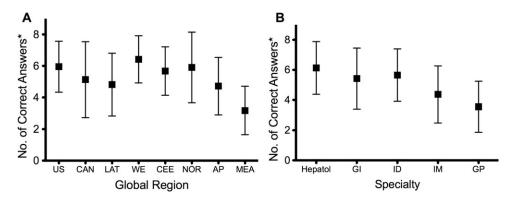


Fig. 1. Knowledge of HCV treatment principles. Physician knowledge by global region (A) and medical specialty (B). US, United States; CAN, Canada; LAT, Latin America; WE, Western Europe; CEE, Central/Eastern Europe; NOR, Nordic; AP, Asia/Pacific; MEA, Middle East/Africa; Hepatol, hepatology; IM, internal medicine; GP, general practice. *Correct responses indicated by a Likert rating of 6 or higher on the 10-point scale for each of eight knowledge questions.

Table 2. Physician and Practice Characteristics By Global Region

Characteristic Mean (SD) or %	United States (n = 102)	Canada (n = 30)	Latin America (n = 100)	Western Europe (n = 103)	Central/Eastern Europe (n = 101)	Nordic (n = 52)	Asia/Pacific (n = 108)	Middle East/Africa (n = 101)	Overall
Years in practice	12 (8)	17 (10)	18 (9)	16 (8)	21 (8)	20 (8)	13 (8)	13 (6)	16 (8)
Specialty									
Hepatology	18	10	9	43	10	17	26	8	19
GI	35	23	32	32	20	19	19	18	25
ID	24	33	17	15	58	40	25	21	28
IM/GP	23	33	42	10	12	24	30	53	28
Practice location									
Urban	68	87	98	90	88	96	86	80	86
Rural/suburban	32	13	2	10	12	4	14	20	14
Practice type									
Private	57	56	63	19	21	21	48	56	43
University	36	40	5	49	25	35	25	9	26
Government	2	0	26	29	43	40	25	32	26
Other	5	3	6	3	11	4	2	3	5
Dedicated HCV nurses/assistants	47	53	40	70	67	76	40	47	53
HCV patients seen monthly	64 (79)	36 (39)	35 (61)	58 (54)	55 (69)	24 (19)	35 (36)	44 (43)	46 (57)
Patient coverage									
Public	42	71	52	83	85	86	60	25	61
Private	46	24	33	6	4	7	21	38	23
Uninsured	12	5	15	11	11	7	19	37	16
Patients declining therapy	25	29	23	14	14	13	37	23	22
Patients stopping therapy after initiation	25	19	19	14	10	14	24	13	17

Abbreviations: IM/GP, internal medicine/general practitioner; RN, registered nurse.

Multiple linear regression was used to identify characteristics independently associated with perceived barriers to care. All analyses were performed using Stata 11 (Stata-Corp LP, College Station, TX).

Results

A total of 697 physicians were surveyed across eight global regions, representing 29 individual countries (Supporting Fig. 1). Overall response rate was 50%. Physician and practice characteristics are summarized in Table 2. Overall, physicians were in practice for a mean of 16 years and treated an average of 46 HCV patients each month (range, 5-500). Physician specialty

varied by region, with HCV care more commonly provided by hepatologists and gastroenterologists in the United States and Western Europe, by infectious disease specialists in Central/Eastern Europe, and by internists or general practitioners in remaining regions. Physicians most frequently worked in a private, urban facility, though a government-affiliated practice was most common in Central/Eastern Europe and Nordic regions. Dedicated treatment nurses and/or assistants were more frequently employed in European countries. Source of medical coverage varied significantly, with patients in Europe, Canada, and Asia/Pacific regions covered primarily by public insurance. A mix of public and private coverage was noted in the United States

Table 3. Physician Opinions Regarding Current HCV Care

	% of Respondents in Agreement With Statement*								
Statement	US	CAN	LAT	WE	CEE	NOR	AP	MEA	0verall
National treatment guidelines are available in my country.	57	60	46	85	81	86	57	31	62
Treatment guidelines/policies are consistent among professional societies, payers, and government.	30	23	28	59	58	75	44	28	43
Government/payer recognizes treatment guidelines.	36	37	37	71	70	83	46	38	52
Providers have knowledge of guidelines.	29	20	26	50	54	52	33	45	40
The general public is aware of HCV.	18	30	17	27	35	17	27	20	24
Patients understand the consequences of untreated HCV.	16	30	29	22	41	44	19	20	26
Patients are aware that HCV is curable.	7	10	20	20	32	39	22	23	22
Patients have adequate access to HCV providers in their community.	17	27	31	54	51	62	20	28	35

Abbreviations; US, United States; CAN, Canada; LAT, Latin America; WE, Western Europe; CEE, Central/Eastern Europe; NOR, Nordic; AP, Asia/Pacific; MEA, Middle East/Africa.

^{*}Response of 6 or higher on a 10-point Likert scale, where 0 represents "strongly disagree," 5 "neither agree nor disagree," and 10 "strongly agree."

Table 4. Physician Knowledge of HCV Treatment Principles

	% of Respondents in Agreement With Statement*								
Statement	US	CAN	LAT	WE	CEE	NOR	AP	MEA	Overall
The addition of RBV to Peg-IFN improves likelihood of SVR.	91	87	83	93	92	85	77	39	80
Maintaining an optimal dose of RBV is necessary to achieve SVR.	93	90	89	90	82	85	81	46	81
Different viral genotypes require different treatment durations.	92	77	79	92	96	88	73	57	82
Treatment should be stopped if patient does not achieve EVR.	75	57	37	72	61	77	42	50	58
Treatment should be stopped if patient does not achieve RVR.	44	43	34	31	31	33	37	66	40
Patients with stage 1 fibrosis have worse outcomes than patients with stage 4 fibrosis.	28	33	42	19	29	27	41	72	38
The level of HCV RNA has no correlation with liver disease severity.	53	30	33	66	51	54	52	36	48
Maintenance therapy should be prescribed for treatment nonresponders.	37	50	63	21	55	38	74	70	52

Abbreviations: US, United States; CAN, Canada; LAT, Latin America; WE, Western Europe; CEE, Central/Eastern Europe; NOR, Nordic; AP, Asia/Pacific; MEA, Middle East/Africa; RVR, rapid virologic response.

and Latin America. More than one third of patients in the Middle East and Africa were reportedly uninsured. Overall, approximately one quarter of patients were reported to refuse therapy, with the highest refusal rate in Asia/Pacific countries and the lowest in Nordic countries (37% versus 14%; P < 0.0001).

Opinions Regarding HCV Care. Physician opinions regarding the current state of HCV care are shown in Table 3. The majority of physicians indicated that national treatment guidelines existed in their country; however, less than half felt that guidelines were consistent across sources. Only 36%-38% of physicians in North America, Latin America, and Middle East/Africa believed that government and/or payers recognized treatment guidelines, compared to 71%-83% in European countries. Between 20% and 54% of respondents felt that healthcare providers have adequate knowledge of HCV guidelines, with higher levels of agreement across European countries. Globally, less than one quarter of physicians felt that the general public is aware of HCV and know that it is a curable disease. Only 35% of all surveyed physicians believed that patients have adequate access to HCV treatment providers, with the lowest percentage in the United States (17%) and the highest in Nordic countries (62%).

Knowledge. Knowledge of HCV treatment principles varied significantly by region, with physicians in Western Europe correctly answering the most knowledge questions, and those in Middle East and African countries correctly answering the fewest (6.4 versus 3.2; P < 0.001; Fig. 1A). Overall, physicians understood that RBV is a necessary component of treatment, treatment duration varies by genotype, and treatment should be discontinued for patients who fail to achieve an early virologic response (EVR). However, a majority of physicians incorrectly believed that HCV RNA level correlates with liver disease severity, and

that treatment nonresponders should receive maintenance therapy (Table 4). In Middle East/African countries, a majority of respondents also did not appreciate the importance of RBV, the role of HCV viral kinetics, and the significance of liver fibrosis stage. Globally, knowledge was highest among hepatologists and lowest among general practitioners (P < 0.001 for overall comparison; Fig. 1B). Source of treatment information varied by region, with national and government guidelines used most frequently in all regions except in the United States, where guidelines from the American Association for the Study of Liver Diseases were most commonly used (Supporting Fig. 2).

Barriers to Care. There was significant regional variation in perceived barriers to care, with the greatest barriers reported in Middle East/Africa and the fewest in Nordic countries (P < 0.0001 for overall comparison; Fig. 2A). Globally, patient-related barriers were viewed as most significant, representing the highest rated barrier category in five of eight regions, including the United States (Fig. 2B). Specific patient-related barriers included fear of side effects and concerns regarding treatment duration, cost, and effectiveness (Supporting Table 1). Payer-related barriers were most prominent in Latin American and Middle East/Africa and included lack of coverage leading to out-of-pocket expense and excessive paperwork requirements. Only one region (Central/Eastern Europe) cited government-related barriers (insufficient funding and lack of treatment promotion) as most significant.

Along with geographic region, perceived barriers were significantly associated with physician specialty, physician experience, practice setting, and physician knowledge (Table 5). Subspecialists (hepatology, gastroenterology [GI], and IDs) reported fewer perceived barriers than internists and general practitioners. Likewise, physicians with more experience and higher knowledge scores reported fewer barriers. In multivariable regression

^{*}Response of 6 or higher on a 10-point Likert scale, where 0 represents "strongly disagree," 5 "neither agree nor disagree," and 10 "strongly agree."

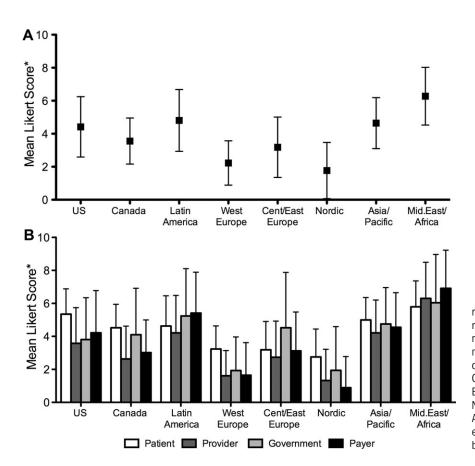


Fig. 2. Barriers to HCV treatment. (A) Barriers by global region: mean (SD) Likert response to each of 31 potential barriers, by region. (B) Regional barriers by category: mean (SD) Likert response to each barrier category, by region. US, United States; CAN, Canada; LAT, Latin America; WE, Western Europe; CEE, Central/Eastern Europe; NOR, Nordic; AP, Asia/Pacific; MEA, Middle East/Africa. *Each barrier rated on a 10-point Likert scale, from 0 "not a barrier" to 10 "large barrier"

analysis, only global region, years of experience, and knowledge were significantly associated with perceived barriers to care (Supporting Table 2).

Discussion

This international, multidisciplinary survey study provides insight into the current state of hepatitis C care, as viewed by treating physicians. Key findings of our study include marked regional variation in perceived barriers, the importance of patient-level obstacles, concerning deficits in provider knowledge, and the shared pessimism regarding the current state of HCV care.

Foremost, barriers to care were not perceived equally across global regions. Physicians from Nordic and Western European countries had remarkably low perceptions of treatment barriers (mean Likert responses of 1.7 and 2.1, respectively, on a 10-point scale). In contrast, Middle Eastern and African physicians perceived all barrier categories as problematic (mean Likert response: 6.1 of 10). Despite regional differences in the magnitude of perceived barriers, there was agreement regarding the nature of these barriers. Across all global regions, patient-level factors were viewed as the greatest obstacles to treatment. This is consistent with previous surveys of physicians and patients in the United States and United

Kingdom. 13,15,16,22 Specifically, fear of treatment-related side effects was the most frequently cited barrier in our study. This fear is not unfounded, because nearly all patients will experience at least one treatment-related side effect, and 10%-14% of patients will discontinue treatment as a result. Though side effects are common, appropriate pretreatment counseling, along with a structured plan for monitoring and management, may help alleviate such fears. 25

Further patient-level barriers included concerns regarding treatment duration and antiviral effectiveness. Fortunately, the recent introduction of direct-acting antivirals offers the potential for improved response rates and reduced treatment lengths. However, these benefits will need to be balanced against a greater incidence of treatment-related side effects. Avertheless, each of these patient-level barriers is addressable and, in many cases, modifiable.

To properly address patient fears, physicians must have a thorough understanding of antiviral therapy. This study identified concerning knowledge deficits, which were most apparent in Middle East/African countries. Physicians in this region often did not acknowledge important treatment principles, including the significance of RBV in HCV therapy, although the frequency of non-specialty physician respondents was also highest in this region.

Table 5. Bivariable Associations Between Physician/Practice
Characteristics and Perceived Barriers to Care

		Mean Barrier Score*	
Characteristic	n	or Correlation	P Value†
Global region			
United States	102	4.4	< 0.0001
Canada	30	3.6	
Latin America	100	4.8	
Western Europe	103	2.1	
Central/Eastern Europe	101	3.2	
Nordic	52	1.7	
Asia/Pacific	108	4.6	
Middle East/Africa	101	6.3	
Specialty			
Hepatology	129	3.4	< 0.0001
GI	176	3.8	
IDs	194	3.8	
Internal medicine	83	4.6	
General practice	115	5.1	
Years in practice	697	-0.26	< 0.0001
Patients seen monthly	697	0.02	0.67
Practice Location			
Urban	599	4.0	0.49
Rural/suburban	98	4.2	
Practice setting			
Private	298	4.5	< 0.0001
University/academic	183	3.4	
Government	182	3.9	
Other	34	4.1	
Knowledge score	697	-0.40	< 0.0001

^{*}Mean response to each of 31 barrier questions, rated on a 10-point Likert scale.

Interestingly, across all regions, more than half of physicians indicated that they would treat nonresponders with maintenance IFN therapy, despite its lack of efficacy.²⁶ Similarly, most physicians incorrectly believed that HCV RNA level reflects liver disease severity. Though previous studies of healthcare providers have demonstrated significant knowledge gaps related to HCV,²⁷ our study documented these deficits in experienced HCV treaters. This is concerning, because inadequate physician knowledge is a known barrier to care.²⁰ Furthermore, independent of geographic region, medical specialty, or experience level, physicians who scored lower on the knowledge assessment tended to perceive greater barriers to care. The implication here is 2-fold: Physicians with less knowledge may treat fewer patients as a result of incorrectly perceived barriers, and these perceived barriers may be overcome through improved education.

Recognizing the current deficits in physician knowledge, the Institute of Medicine recently recommended the development of HCV educational initiatives, emphasizing a need for increased awareness and improved adherence to guidelines.²⁸ In our study, only 40% of respondents believed that providers have adequate knowledge of treat-

ment guidelines, highlighting this need. Physicians held similar views regarding public awareness, with less than one quarter of respondents believing that the public is aware of HCV and its consequences. This view is supported by findings from the National Health and Nutrition Examination Survey, in which more than half of HCV-infected persons were unaware of their diagnosis.²⁹ Among injection drug users, this number is as high as 72%-90%. 30,31 Unfortunately, awareness does not guarantee treatment. In our study, only 35% of physicians believed that patients have adequate access to HCV providers. A lack of trained specialists, combined with their concentration at academic medical centers, may limit the widespread availability of treatment. Indeed, market surveys in the United States indicate that 80% of HCV patients are managed by 20% of gastroenterologists.²¹ Models of expanded HCV treatment, including the use of tele-health, have shown promise.³² These warrant broader exploration and implementation.

This is the first international study to examine barriers to care among HCV treatment providers. The findings are strengthened by a comprehensive questionnaire, developed and piloted by a panel of internationally recognized HCV experts. The survey achieved a 100% item response rate, eliminating the potential for nonresponse bias. However, as with any survey, the findings in our study may not be representative of the entire population. Likewise, it was not feasible to survey physicians within every country, leading to the potential for coverage error. By grouping our findings into global regions, we may not have adequately addressed the differences that exist between individual countries. Furthermore, the perceptions identified in this study may not be representative of less-experienced physicians. This may have led to an underestimation of treatment barriers. Finally, HCV treatment is frequently delivered by mid-level providers (i.e., nurse practitioners and physician assistants), particularly in the United States. This study did not address the perspective of these providers, which may differ from those of physicians.

Still, the findings of this study highlight the significant barriers that may impede the prompt, appropriate treatment of HCV infection. A focus on patient and provider education, increased awareness, and treatment promotion is necessary if progress is to be made in the global fight against HCV infection.

Recent advances in antiviral therapy have produced dramatic improvements in the treatment of HCV infection. Unfortunately, only a minority of HCV-infected persons will receive treatment as a result of multiple barriers to care. Globally, physicians cite patient-level factors, including fear of side effects and concerns regarding treatment duration and cost, as the greatest barriers to

 $[\]dagger$ Means and P values based on one-way ANOVA for categorical variables; correlations and P values based on Pearson's correlation.

treatment. Inadequate physician knowledge and limited specialist availability may further contribute. Efforts to improve patient and physician education, public awareness, and access to treatment providers are needed.

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Appendix: International Conquer C Coalition

This analysis was led by the International Conquer C Coalition (I-C3), an international, interdisciplinary group of physicians involved in the treatment and care of patients infected with HCV. Its goal was to increase the understanding of the epidemiology, diagnosis, side-effect management, and treatment options. The group sought to facilitate an exchange of knowledge, analyze trends, and share best practices. The I-C3 was formed in 2009 through an educational grant by Schering-Plough/Merck and was led by Drs. N. Afdhal and S. Zeuzem. Workgroups within I-C3 were responsible for the analysis and publication of key findings on a variety of topics, including barriers to care. The work presented here is the result of the Barriers-to-Care Workgroup.

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