Impact of New Hepatitis C Treatments in Different Regions of the World

The rapid development of new antiviral drugs for hepatitis C (HCV) and the availability of interferon (IFN)-free and soon ribavirin-free treatment regimens of ≤12 weeks duration with sustained virologic response (SVR) rates of >90% has stimulated predictions that HCV will be eradicated. This commentary discusses the impact of these new treatments in different regions of the world and the barriers to HCV eradication.

Prevalence of HCV and Disease Burden in Different Regions of the World

The World Health Organization (WHO) estimates that >185 million people worldwide or 2.8% of the human population have been infected with HCV; of these 130–170 million are chronically infected and 350,000 deaths occur each year as a result of HCV-related cirrhosis and liver cancer.[1] The prevalence of HCV varies from 1.2% to 3.8% in different regions of the world (Figure 1). Although HCV is recognized as the most common cause of hepatocellular carcinoma (HCC) and the most frequent indication for liver transplantation in North America, Western Europe, and Japan (Supplementary Table 1), the disease burden from HCV is much higher in many regions of the world where HCV receives little attention. When countries are grouped into Global Burden of Disease regions, the estimated prevalence of HCV infection is highest in Central Asia, East Asia, and North Africa/Middle East regions. Egypt has the highest prevalence of approximately 15%. It is estimated that 2 densely populated regions in Asia—East Asia and South Asia—each has >50 million people chronically infected with HCV compared with 15 million in North Africa/Middle East, 10 million in Western Europe, and 4.4 million in North America.[1] Within each country, the prevalence of HCV varies according to risk of exposure. In the United States, the overall prevalence is 1.6% with an higher prevalence among blacks, people born between 1945 and 1965, and those with a history of injection drug use.[2] In China, the overall prevalence is estimated to be 2.2% with a range of 2.1% in Fujian province to 9.6% in Henan province, with an higher prevalence in injection drug users and hemodialysis patients.[3]

HCV is grouped into seven genotypes (1-7) and a number of subtypes. The distribution of HCV genotypes varies in different regions of the world (Figure 2).[4] Worldwide, genotype 1b is most common. In the United States, however, genotype 1a is most prevalent, and in India and Pakistan, genotype 3 is predominant. In Egypt, it is almost exclusively genotype 4. HCV genotype has major bearing on response to IFN-based treatment and antiviral activity of some direct-acting antiviral agents (DAAs). HCV genotype may also play a role in liver disease progression, for example, genotype 3 is more commonly associated with hepatic steatosis and accelerated progression to cirrhosis.[5]

Left untreated, chronic HCV infection can cause liver cirrhosis, liver failure, and HCC. The risk of cirrhosis is 5%–30% within 20 years of infection and the risk of HCC in patients with cirrhosis is 2%–4% per year. In addition to liver damage, HCV also contributes to a wide range of extrahepatic diseases, including insulin resistance and diabetes, mixed cryoglobulinemia, glomerulonephritis, and B-cell lymphomas. Sustained virological response

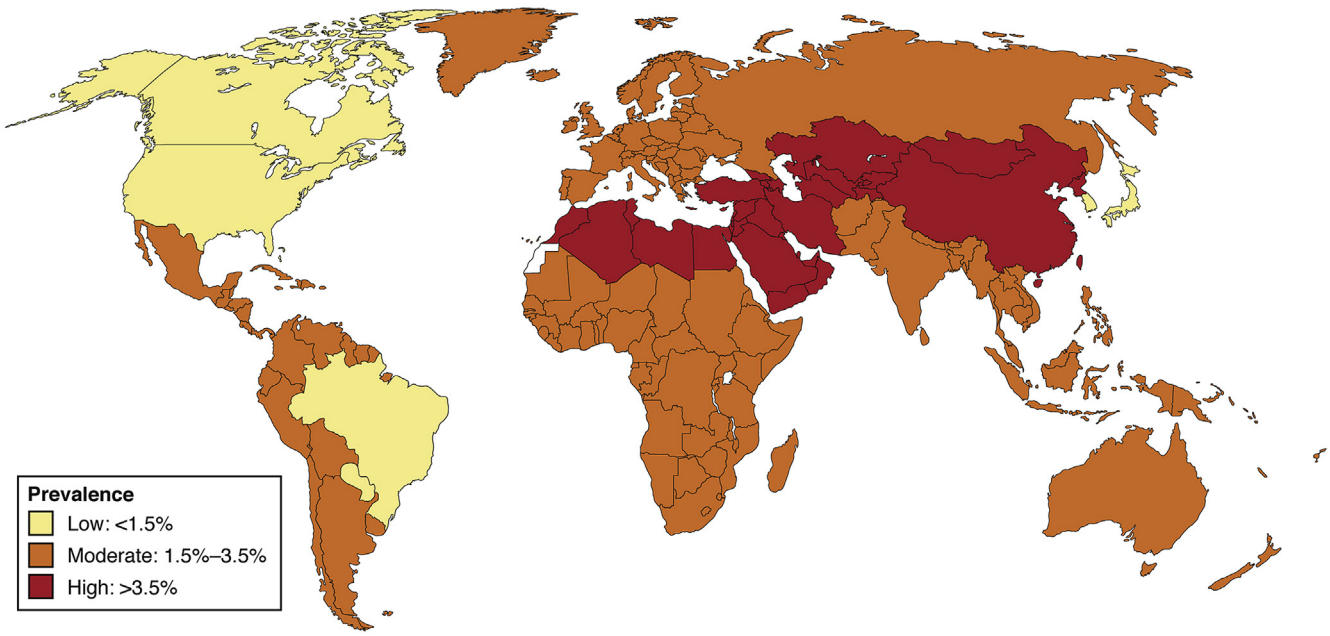

Figure 1. Global prevalence of anti-hepatitis C, with data derived from Mohd Hanafiah et al.[1]

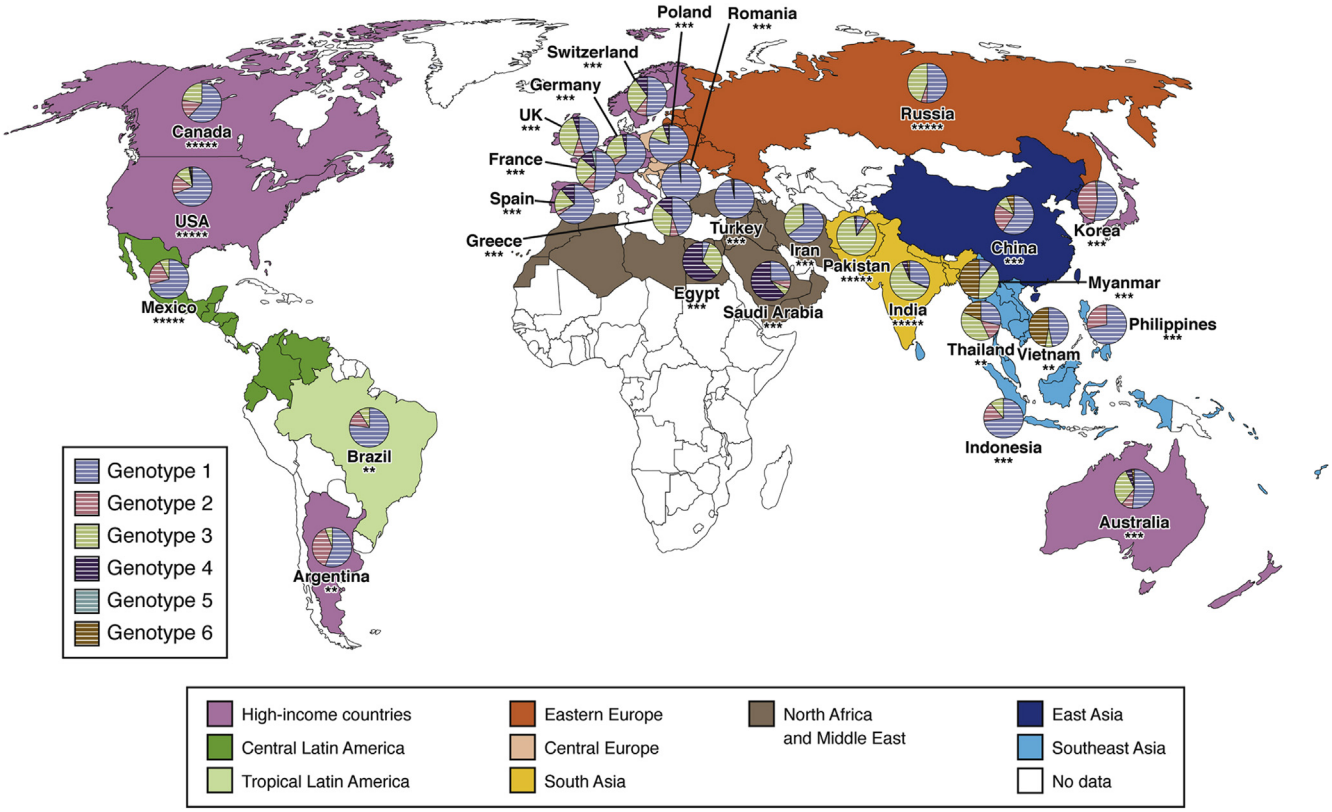

Figure 2. Distribution of hepatitis C virus genotypes by country. World Health Organization Global Burden of Disease Regions are shown in different colors; data derived from Wartelle-Bladou et al[4] and literature review (see Supplementary Materials). Studies were reviewed and scored as follows: *Estimates without a formal study; **small study in a select population (<100) or study in blood donors only; ***large study in a select population (>100); ****small study in the general population (<100); and *****large study in the general population (>100).

(SVR) to HCV treatment had been shown to improve quality of life, reverse liver fibrosis including cirrhosis, decrease HCC, and reduce liver-related as well as overall mortality.[6–8]

Standard-of-Care HCV Treatment

Until recently, standard-of-care HCV treatment has utilized a combination of pegylated (PEG)-IFN and ribavirin. SVR rates of 65%–75% can be achieved with a 24-week course of PEG-IFN and ribavirin in patients with HCV genotypes 2 or 3, but SVR rates are lower (~45%), even with a 48-week course of treatment in those with HCV genotype 1. SVR rates are intermediate in patients with HCV genotypes 4, 5, or 6.

Several host, viral, and disease factors have been found to modulate the response to PEG-IFN and ribavirin treatment. Of these, polymorphism in the interleukin (IL)28B or IFNλ3 promoter region stimulated the greatest interest. A favorable IL28B genotype—rs12979860 CC (vs CT or TT) or rs8099917 TT (vs GT or GG)—is associated with 2- to 3-fold greater SVR rate to PEG-IFN and ribavirin therapy for HCV genotype 1, regardless of the race of the patient.[9,10] The marked difference in prevalence of favorable IL28B genotype in different regions of the world (Figure 3; Supplementary Table 2), approximately 30% in North America and Western Europe compared with 70% in East Asia accounts for the higher SVR rates reported in Japan and Taiwan.[11] Indeed, studies in Taiwan found that SVR rates as high as 58% can be achieved in patients with HCV genotype 1 with a 24-week course of PEG-IFN and ribavirin.[12] These findings suggest that the incremental benefit of DAAs would be lower in countries with a high prevalence of favorable IL28B genotype.

In 2011, 2 DAAs, telaprevir and boceprevir, were approved for treatment of HCV genotype 1. Triple therapy of telaprevir or boceprevir in combination with PEG-IFN and ribavirin increased SVR rates to 67%–75%, but the treatment regimens are complicated and adverse reactions are frequent and sometimes serious.[13,14] Indeed, preliminary data from the French Early Access Programme found that 40% of patients had serious adverse events and 6.4% had severe complications (severe infections, hepatic decompensation, or death).[15]

New Era of HCV Treatment

After 2 decades of intense research, we now enter an exciting era when new drugs for HCV are expected to be approved every year in Western countries for the next 4–5 years. The availability of multiple DAAs with distinct viral targets promises highly efficacious, well-tolerated, IFN-free combinations with short treatment duration.

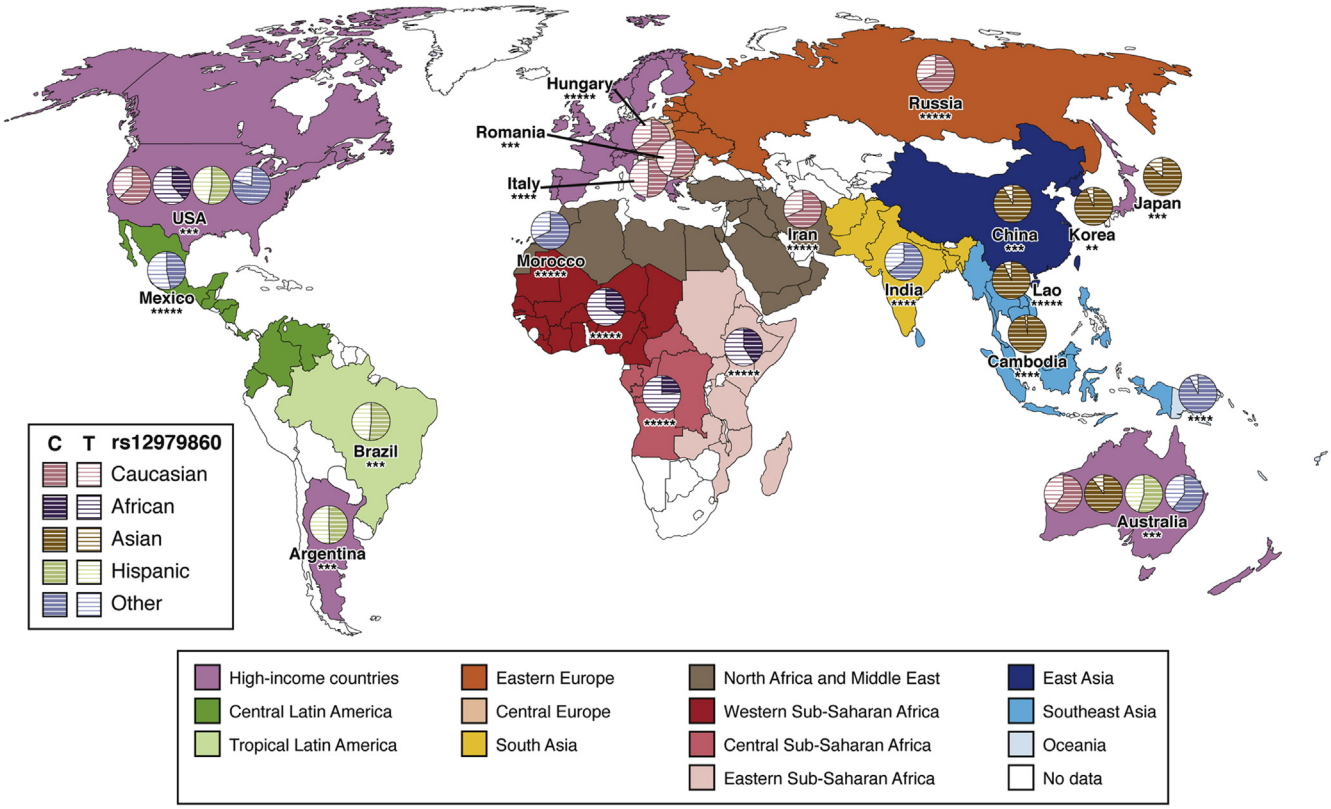

Figure 3. Global distribution of interleukin (IL)28B genotypes; data derived from Huang et al[12] and literature review (see Supplementary Materials). Studies were reviewed and scored as in Figure 2.

In late 2013, 2 additional DAAs—simeprevir, a protease inhibitor and sofosbuvir, a nucleotide polymerase inhibitor—were approved by the US Food and Drug Administration. Sofosbuvir was approved by the European Medicines Agency in January 2014. Approval of these new DAAs in many countries where no DAA has yet been approved may not occur for ≥1 years. Within the next year, additional DAAs—notably faldaprevir, a protease inhibitor, and daclatasvir, an NS5A inhibitor, in combination with PEG-IFN and ribavirin, along with several IFN-free regimens—are expected to be approved in the United States and Europe. Preliminary results of phase 3 clinical trials in patients with HCV genotype 1 showed SVR rate of 96% after a 12-week course of sofosbuvir and ledipasvir (NS5A inhibitor) with or without ribavirin in treatment-naïve as well as treatment-experienced patients, including patients with compensated cirrhosis. An equally high SVR rate was reported after a 12-week course of ABT-450/r (protease inhibitor with ritonavir boost), ABT-267 (NS5A inhibitor), ABT-333 (non-nucleoside polymerase inhibitor), and ribavirin in treatment naïve as well as treatment experienced patients with no cirrhosis. For details regarding efficacy of these new DAAs, please refer to the accompanying review by Pawlotsky in this issue of *Gastroenterology*.[16]

Thus, there is reasonable optimism that within the next 5 years, multiple IFN-free well-tolerated regimens administered for 8–12 weeks can result in SVR rates of >95% in a broad spectrum of HCV patients. Contrary to IFN-based regimens, IFN-free regimens are expected to have similar efficacies in patients with the same HCV genotype, stage of liver disease, and treatment status regardless of which region of the world they are in. The simplicity of these regimens and the infrequent occurrence of adverse events greatly improve adherence and ease of monitoring; however, drug–drug interactions and adverse events can occur with some regimens and the knowledge and experience of treating physicians can make a difference in the safety and effectiveness of these regimens.

Limitations of New HCV Treatment

The availability of IFN-free regimens permits many patients who could not be treated previously because of medical or psychiatric contraindications or an inability to tolerate IFN to receive treatment. Nonetheless, SVR rates remain lower in some patient populations, for example, those with cirrhosis and HCV genotypes 3 and 1a (for some DAAs). More important, many patient groups have been largely neglected because drug development and clinical trials are driven by market needs in developed countries. Patient populations for which limited or no data are available include patients with genotypes 5, 6, or 7; decompensated cirrhosis; renal failure; and liver or other organ transplantations. Although off-label use can be attempted in these patients, the lack of data on safety, efficacy, and appropriate dosing exposes patients and prescribing physicians to risks and the high cost of these drugs makes it unlikely that they will be covered by

health insurance or national health policies. Another group that has been forgotten is children. It has been estimated that, worldwide, ≥5 million infants each year will acquire HCV from infected mothers, with the vast majority unnoticed until they present with advanced liver disease in adult life. This problem is more serious in countries where the prevalence of HCV is high and a large proportion of HCV-infected mothers are coinfected with HIV.

Implementation of New HCV Treatments in Different Regions of the World

The rapid pace of HCV drug development has led to the optimistic prediction that eradication of HCV is feasible. This would be the first chronic viral infection that can be eradicated in the absence of a prophylactic vaccine. Although HCV eradication is potentially feasible, that time is not imminent; there remain many barriers that need to be overcome (Table 1). Such barriers include the development of simplified and highly effective drug regimens, improving the rates of detection of infection, and the availability of resources (including financial and medical expertise).

The easiest barrier to overcome is the development of drugs that are more potent than current ones, truly pangenotypic, active against variants associated with resistance to first-generation DAAs, with minimal drug–drug interactions, and safe to use in patients with hepatic and renal impairment. Ten years ago, this scenario would have been considered an impossible dream, even by optimists; however, with >30 DAAs in phase 2 or 3 clinical trials, including some second-generation protease inhibitors and NS5A inhibitors with activity against resistance variants to first-generation drugs of the same class, this goal can be realistically accomplished in the next 5–10 years.[17] Nevertheless, the availability of treatment regimens that can result in higher SVR rates alone will have very little impact on global burden of HCV. A modeling study performed in 2009 showed that improving rates of diagnosis and treatment has a greater impact on reducing disease burden than improving efficacy of treatment.[18] Indeed, even treatments of 100% efficacy will have no impact on patients with undiagnosed infection.

Thus, the first barrier to overcome is to improve the detection of those who are infected. Worldwide, it is estimated that <15% of persons infected with HCV are aware of their infection. In the United States, <50% of those infected with HCV had been diagnosed, 32%–38% had been referred to care, and only 7%–11% had received treatment.[19] In Europe, up to 90% in parts of the European Union are unaware of their infection[20] and as of 2006, <16% of the HCV-infected persons in any country had received HCV treatment.[21] In China, it is estimated that <3% of those infected had been diagnosed and as of 2012, only half of those diagnosed had been treated.

To improve diagnosis, each country needs to have information on national prevalence and characteristics of those groups with higher prevalence so that screening programs can target high-risk or high prevalence groups; sensitive, specific, and affordable tests for screening and confirmation of HCV infection must be available. In Western countries, reliable HCV assays are readily available and risk groups are known, but risk-based screening has not been effective because most infected persons do not recognize or acknowledge that they are at risk and primary care physicians seldom assess HCV risks owing to competing demands on their time. In August 2012, the US Centers for Disease Control and Prevention recommended 1-time testing of all individuals born between 1945 and 1965 because this cohort is estimated to comprise two thirds of all HCV-infected persons in the United States.[22] The barriers to improving diagnosis are greater in resource-limited countries, where epidemiologic data are lacking. Even if the high-risk groups are known, many of these countries do not have the resources or the availability of reliable tests for HCV testing. It was not until 2010 that the WHO passed a resolution to include hepatitis among major public health priorities. In 2014, the first ever WHO guidelines on HCV screening, care and treatment will be released. These guidelines will help local governments to develop HCV screening and care programs tailored for their country but the success of these programs will require commitment of resources, marketing, and education to raise public awareness.

The benefit of increased diagnosis can be materialized only if infected

Table 1. Barriers That Need to Be Overcome to Achieve HCV Eradication

Detect persons who are infected
Identification of high-risk/high-prevalence groups
Availability of sensitive, specific, and affordable tests for screening and for confirmation of infection
Screening programs that are practical and tailored to individual countries or settings
Public awareness of risk groups, sequelae, and treatment options
Link infected persons to care
Access to care for all infected persons
Availability of trained health care providers and resources to manage infected persons
Eradicate HCV with safe and effective drugs
Development of drugs that are potent, safe, and have pangenotype activity
Development of treatment regimens that are simple and effective against all HCV genotypes and all stages of liver disease
Availability of safe and efficacious drugs at affordable price

persons have access to care so that they can be counseled, evaluated for liver damage, and considered for treatment. Even in developed countries, only a small fraction of those diagnosed had received treatment. The reluctance of providers to recommend and patients to accept treatment had been attributed to low efficacy and frequent adverse reactions of PEG-IFN and ribavirin. These concerns are rapidly eliminated with the new HCV drugs, but a major barrier to implementing these new treatments is cost. The wholesale price of 1 tablet of sofosbuvir in the United States is estimated to be US$1,000 putting the price tag of a-12 week course of sofosbuvir alone at US$84,000.[23] Although studies of telaprevir- or boceprevir-based regimens showed that HCV treatment is cost effective in the United States,[24] the cost of DAAs will be prohibitive in low-income countries where resources are limited and there are many competing health priorities. As of 2013, none of the drugs used for treatment of HCV is included in the WHO List of Essential Medications. Concerted efforts of the WHO, government authorities, nongovernment organizations, and patient advocacy groups are needed to negotiate agreements with the pharmaceutical companies that will make these new DAAs accessible and affordable. These measures have proven successful for HIV, and Gilead recently announced that generic sofosbuvir will be produced in India.[25] Egypt has shown that commitment from the government and tough negotiations can pay off. In 2006, Egypt established a highly specialized network of treatment centers and brought the price of 48 weeks of PEG-IFN and ribavirin to <US$2,000 (<10% of that in the United States).[26] Within 6 years of the program, 300,000 Egyptians have been treated.

While waiting for the price of new DAAs to become more affordable, an alternative strategy is to determine the incremental value and cost effectiveness of DAAs in countries with a high prevalence of favorable IL28B genotype in patients who do not have contraindications to the use of IFN. This strategy is particularly relevant in East Asian countries. Another strategy is to use combination DAA regimens with high SVR rate for genotype 1b in countries where it is predominant. These "second-line" regimens with limited utility in countries where genotype 1a is common might be priced lower. One example is the combination of asunaprevir, a protease inhibitor, and dacalatasvir, an NS5A inhibitor,[27] which is under consideration for approval in Japan, where genotype 1b predominates.

Beyond drugs, there are other issues, such as medical expertise to evaluate liver disease and to monitor treatment. Thus, training of health care providers must go hand in hand with the implementation of screening and treatment programs. Having an adequately prepared work force is necessary not only in low-income countries, but also in developed countries, because the availability of simpler, safer, and more efficacious treatment will encourage patients to seek testing and treatment. In both low- and high-income countries efforts to raise public awareness such that persons at risk are informed of the potential sequelae of HCV infection and the ever-improving treatment options are essential if HCV is to be eradicated.

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Supplementary Materials

Note: To access supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2014.03.008.

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Conflicts of interest

The authors disclose the following: Lai Wei has served on advisory boards of Gilead and GSK and receives research grants from Bristol-Myers Squibb and Roche. Anna S.F. Lok has served on advisory boards of Gilead and Janssen and receives research grants from AbbVie, Bristol-Myers Squibb, Gilead, Idenix, and Merck.

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Supplementary Materials

Literature Search and References for Figures 2 and 3

A search of PubMed and Google was performed with MeSH terms or key words ('Hepatitis C') AND ('genotype') AND ('human') for Figure 2 and ('Hepatitis C') AND ('IL28B' OR 'IFNλ3' OR 'rs12979860') AND ('human') for Figure 3. In addition, the reference lists of all original articles and previous reviews were hand searched for other relevant papers. No restrictions were placed on the time period, sample size, population, or language. When multiple reports were available for a single unique study population, we included only the most recent or largest report. Studies were reviewed and scored according to the following scale[1,2]:

* Estimates without a formal study

** Small study in a select population (<100) or study in blood donors only

*** Large study in a select population (>100)

**** Small study in the general population (<100)

***** Large study in the general population (>100)

Data from countries were grouped according to the WHO Global Burden of Disease classifications.[3] Eligible studies[4] met the following criteria: 1) Studies with a score that is >1*; 2) the highest ranking study was selected for each region.

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Supplementary Table 1. Detailed Data Showing Distribution of HCV Genotypes by Country and World Health Organization Global Burden Disease Regions for Figure 2, Percent With Mixed or Unknown Genotypes Not Shown

Country	Level of Evidence	Genotype1 (%)	Genotype 2 (%)	Genotype 3 (%)	Genotype 4 (%)	Genotype 5 (%)	Genotype 6 (%)	Ref.
USA	*****	70.00	16.00	12.00	1.00	<1	<1	[4]
Canada	*****	60.00	15.40	22.30	NR	NR	NR	[5]
Germany	***	61.70	6.90	28.00	3.20	NR	NR	[6]
United Kingdom	***	45.00	10.00	40.00	5.00	NR	NR	[7]
Switzerland	***	51.00	9.00	30.00	10.00	NR	NR	[8]
France	***	56.00	9.00	21.00	9.00	3.00	NR	[9]
Greece	***	45.10	7.00	34.00	13.90	NR	NR	[10]
Spain	***	65.40	3.10	19.60	11.60	0.30	NR	[11]
Poland	***	79.40	0.10	13.80	4.90	NR	0.09	[12]
Romania	***	98.00	NR	0.8	1.2	NR	NR	[13]
Russia	*****	50.30	4.70	44.80	NR	NR	NR	[14]
Korea	***	51.60	45.80	1.10	0.10	NR	NR	[15]
China	***	58.40	24.10	9.10	NR	NR	6.30	[16]
Viet Nam	**	47.10	NR	5.80	NR	NR	47.10	[17]
Philippines	***	67.30	26.30	NR	0.20	NR	0.20	[18]
Thailand	**	29.00	14.00	39.00	NR	NR	18.00	[19]
Indonesia	***	72.70	16.00	11.40	NR	NR	NR	[20]
Myanmar	***	11.00	0.70	39.30	NR	NR	49.00	[21]
India	*****	31.20	0.50	61.80	4.50	0.04	1.90	[22]
Pakistan	*****	7.03	3.81	78.96	1.59	0.1	0.13	[23]
Australia	***	52.00	9.30	32.00	5.50	NR	1.70	[24]
Iran	***	63.70	0.20	33.40	0.90	NR	NR	[25]
Saudi Arabia	***	24.10	7.40	5.90	62.00	0.30	NR	[26]
Turkey	***	97.10	0.90	1.40	0.60	NR	NR	[27]
Egypt	***	6.00	NR	31.00	63.00	NR	NR	[28]
Mexico	*****	70.20	21.80	7.20	NR	NR	NR	[29]
Brazil	**	77.20	13.60	9.00	NR	NR	NR	[30]
Argentina	**	50.00	35.00	5.00	NR	NR	NR	[31]

*Estimates without a formal study.
****Small study in the general population (<100).
**Small study in a select population (<100) or study in blood donors only.
***Large study in a select population (>100).
*****Large study in the general population (>100).

Supplementary Table 2. Detailed Data Showing Distribution of Interleukin-28B Genotypes by Race, Ethnicity, and World Health Organization (WHO) Global Burden of Disease Regions for Figure 3

WHO Global Burden of Disease Region	Country	Level of Evidence	Race/Ethnicity	rs12979860, Allele C (%)	Ref.
High-income North America	USA	***	Caucasian	62.50	[32]
			African	38.50	
			Hispanics	53.00	
			Other	79.00	
High-income Western Europe	Italy	****	Caucasian	51.00	[33]
Central Europe	Romania	***	Caucasian	55.60	[34]
Central Europe	Hungary	*****	Caucasian	65.10	[35]
Eastern Europe	Russia	*****	Caucasian	68.50	[35]
High-income Asia Pacific	Japan	***	Asian	87.45	[36]
High-income Asia Pacific	Korea	**	Asian	93.85	[37]
East Asia	China	***	Asian	91.75	[16]
Southeast Asia	Lao	*****	Asian	93.60	[35]
Southeast Asia	Cambodia	****	Asian	97.90	[35]
South Asia	India	****	Other	65.50	[35]
Oceania	NR	****	Other	92.50	[35]
High-income Australia	Australia	***	Caucasian	59.50	[38]
			Asian	90.00	
			Hispanic	55.00	
			Other	60.50	
North Africa and Middle East	Iran	*****	Caucasian	68.00	[25]
North Africa and Middle East	Morocco	*****	Other	67.80	[39]
Central sub-Saharan Africa	NR	*****	African	23.50	[35]
Eastern sub-Saharan Africa	NR	*****	African	40.70	[35]
Western sub-Saharan Africa	NR	*****	African	33.40	[35]
Central Latin America	Mexico	*****	Other	46.60	[35]
Tropical Latin America	Brazil	***	Hispanics	51.50	[40]
Southern Latin America	Argentina	***	Hispanics	49.50	[41]

*Estimates without a formal study.
**Small study in a select population (<100) or study in blood donors only.
***Large study in a select population (>100).
****Small study in the general population (<100).
*****Large study in the general population (>100).