



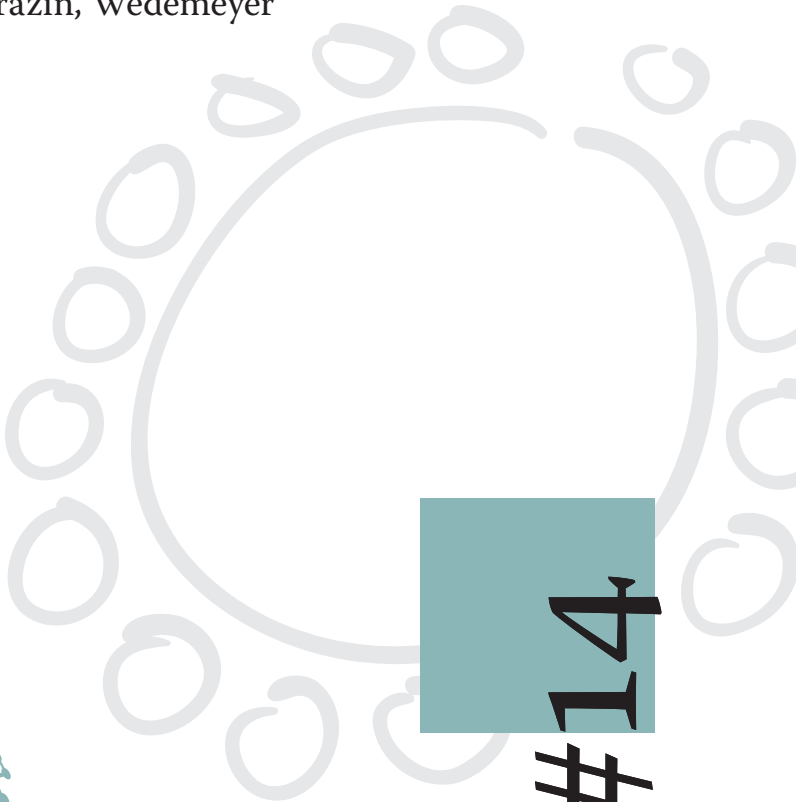
Download Free PDF

*the  
Flying Publisher*

# Short Guide to Hepatitis C

2014

*edited by*  
Mauss, Berg, Rockstroh,  
Sarrazin, Wedemeyer



#14



FLYING PUBLISHER

Mauss - Berg - Rockstroh - Sarrazin - Wedemeyer

Short Guide to Hepatitis C

2014 Edition

This PDF of the  
2014 *Flying Publisher Short Guide to Hepatitis C*  
is freely available from [www.FlyingPublisher.com](http://www.FlyingPublisher.com)  
**thanks to the financial support provided by**



Stefan Mauss  
Thomas Berg  
Jürgen Rockstroh  
Christoph Sarrazin  
Heiner Wedemeyer

*The Flying Publisher*  
**Short Guide to  
Hepatitis C**  
*2014 Edition*

Flying Publisher

Copy Editor:

**Rob Camp**

camporama@gmail.com

### **Disclaimer**

Hepatitis C management is an ever-changing field. The publishers and author of *The Flying Publisher Short Guide to Hepatitis C* have made every effort to provide information that is accurate and complete as of the date of publication. However, in view of the rapid changes occurring in hepatitis C management, as well as the possibility of human error, this guide may contain technical inaccuracies, typographical or other errors. It is the responsibility of the physician to rely on experience and knowledge about the patient to determine the most adequate treatment. The information contained herein is provided “as is” and without warranty of any kind. The contributors to this book, including Flying Publisher & Kamps, can not be held responsible for any errors or omissions or for results obtained from the use of information contained herein.

This work is protected by copyright both as a whole and in part.

© 2014 by Flying Publisher & Kamps

Design: Attilio Baghino, [www.baghino.com](http://www.baghino.com)

ISBN: 978-3-942687-15-7

Printed in Germany by Druckhaus Süd, [www.druckhaus-sued.de](http://www.druckhaus-sued.de)

## Preface

Hepatitis C is a rapidly developing area of medicine – diagnostic tools are ever more refined, and entirely new treatments and treatment strategies are arriving, with more on the horizon. And because the virus affects such a large and varying population – up to 170 million at last count – we think it is important to have a pocket reference especially devoted to hepatitis C. We look forward to your comments on the usefulness of our **2014 Short Guide to Hepatitis C**, which is an expansion and update of the HCV chapters in **Hepatology – A Clinical Textbook** (2014), also published by Flying Publisher. As always, we invite qualified people everywhere to translate this book into other languages, and make them available widely. This web-based free-of-charge concept is made possible by unrestricted educational grants from the pharmaceutical industry and has allowed the material to reach countries usually not covered by print media. We are convinced that this new pocket guide concept, focusing here on hepatitis C, will become a valuable source of information for our readers.

Stefan Mauss  
Thomas Berg  
Jürgen Rockstroh  
Christoph Sarrazin  
Heiner Wedemeyer

The Editors  
January 2014

## Contributing Authors

### **Thomas Berg**

Sektion Hepatologie  
Klinik und Poliklinik für  
Gastroenterologie &  
Rheumatologie  
Universitätsklinikum Leipzig  
Liebigstr. 20  
04103 Leipzig, Germany

Leber- und Studienzentrum am  
Checkpoint  
Charlottenstrasse 81  
10969 Berlin

### **Christoph Boesecke**

Department of Medicine I  
University Hospital Bonn  
Sigmund-Freud-Strasse 25  
53105 Bonn, Germany

### **Albrecht Böhlig**

Sektion Hepatologie  
Klinik und Poliklinik für  
Gastroenterologie &  
Rheumatologie  
Universitätsklinikum Leipzig  
Liebigstr. 20  
04103 Leipzig, Germany

### **Markus Cornberg**

Dept. of Gastroenterology,  
Hepatology  
and Endocrinology  
Medical School of Hannover  
Carl-Neuberg-Str. 1  
30625 Hannover, Germany

### **Katja Deterding**

Dept. of Gastroenterology,  
Hepatology and Endocrinology  
Medical School of Hannover  
Carl-Neuberg-Str. 1  
30625 Hannover, Germany

### **Svenja Hardtke**

Dept. of Gastroenterology,  
Hepatology and Endocrinology  
Medical School of Hannover  
Carl-Neuberg-Str. 1  
30625 Hannover, Germany

### **Christoph Höner zu Siederdisen**

Dept. of Gastroenterology,  
Hepatology and Endocrinology  
Medical School of Hannover  
Carl-Neuberg-Str. 1  
30625 Hannover, Germany

### **Bernd Kupfer**

Bonn University Hospital  
Department of Medicine I  
Sigmund-Freud-Strasse 25  
53015 Bonn, Germany

### **Christian Lange**

J. W. Goethe University  
Hospital  
Medical Department I  
Theodor-Stern-Kai 7  
60590 Frankfurt/Main,  
Germany

**Michael P. Manns**

Dept. of Gastroenterology,  
Hepatology  
and Endocrinology  
Medical School of Hannover  
Carl-Neuberg-Str. 1  
30625 Hannover, Germany

**Benjamin Maasoumy**

Dept. of Gastroenterology,  
Hepatology and Endocrinology  
Medical School of Hannover  
Carl-Neuberg-Str. 1  
30625 Hannover, Germany

**Stefan Mauss**

Center for HIV and  
Hepatogastroenterology  
Grafenberger Allee 128a  
40237 Duesseldorf, Germany

**Kerstin Port**

Dept. of Gastroenterology,  
Hepatology and Endocrinology  
Medical School of Hannover  
Carl-Neuberg-Str. 1  
30625 Hannover, Germany

**Karl-Philipp Puchner**

Charité, Campus Virchow-  
Klinikum,  
Universitätsmedizin  
Medizinische Klinik m. S.  
Hepatology und  
Gastroenterologie  
Augustenburger Platz 1  
13353 Berlin, Germany

**J. K. Rockstroh**

Department of Medicine I  
University Hospital Bonn  
Sigmund-Freud-Strasse 25  
53105 Bonn, Germany

**Christoph Sarrazin**

J. W. Goethe University  
Hospital  
Medical Department I  
Theodor-Stern-Kai 7  
60590 Frankfurt/Main,  
Germany

**Martin Schäfer**

Department of Psychiatry  
and Psychotherapy  
Kliniken Essen-Mitte  
Ev. Huyssenstift  
Henricistraße 92  
45136 Essen, Germany

**Carolynne Schwarze-Zander**

Department of Medicine I  
University Hospital Bonn  
Sigmund-Freud-Strasse 25  
53105 Bonn, Germany

**Jan-Christian Wasmuth**

Department of Medicine I  
University Hospital Bonn  
Sigmund-Freud-Strasse 25  
53105 Bonn, Germany

**Heiner Wedemeyer**

Dept. of Gastroenterology,  
Hepatology  
and Endocrinology  
Medical School of Hannover  
Carl-Neuberg-Str. 1  
30625 Hannover, Germany





## Abbreviations

<b>ADV:</b> adefovir dipivoxil	<b>NHL:</b> non-Hodgkin lymphoma
<b>AHA:</b> autoimmune haemolytic anaemia	<b>NPV:</b> negative predictive value
<b>ALT:</b> alanine aminotransferase	<b>NTR:</b> non-translated regions
<b>AST:</b> aspartate aminotransferase	<b>PCR:</b> polymerase chain reaction
<b>BID:</b> twice a day	<b>PCT:</b> porphyria cutanea tarda
<b>BOC:</b> boceprevir	<b>PEG-IFN:</b> pegylated interferon
<b>cccDNA:</b> covalently closed circular DNA	<b>PT:</b> prothrombin time
<b>CP:</b> Child-Pugh	<b>QD:</b> once a day
<b>EHM:</b> extrahepatic manifestation	<b>QW:</b> once a week
<b>ER:</b> endoplasmic reticulum	<b>RF:</b> rheumatoid factor
<b>EVR:</b> early virologic response	<b>RVR:</b> rapid virologic response
<b>GH:</b> growth hormone	<b>SSRI:</b> selective serotonin reuptake inhibitor
<b>GM-CSF:</b> granulocyte macrophage colony-stimulating factor	<b>SVR:</b> sustained virologic response
<b>GN:</b> glomerulonephritis	<b>TGF:</b> transforming growth factor
<b>HBsAg:</b> hepatitis B surface antigen	<b>RBV:</b> ribavirin
<b>HBV:</b> hepatitis B virus	<b>TID:</b> three times a day
<b>HCV:</b> hepatitis C virus	<b>TLP:</b> telaprevir
<b>HCV RNA:</b> ribonucleic acid of hepatitis C virus	<b>TSH:</b> thyroid stimulating hormone
<b>HCC:</b> hepatocellular carcinoma	
<b>IFN alfa:</b> interferon alfa	
<b>IGF-1:</b> insulin growth factor-1	
<b>INR:</b> international normalised ratio	
<b>IPF:</b> idiopathic pulmonary fibrosis	
<b>ITP:</b> immune thrombocytopenic purpura	
<b>LDL:</b> low density lipoproteins	
<b>MELD:</b> Model for End-Stage Liver Disease	



# Table of Contents

1. Epidemiology, Transmission and Natural History.....	17
<i>Christoph Boesecke and Jan-Christian Wasmuth</i> .....	17
Epidemiology .....	17
Transmission.....	18
Acute hepatitis.....	19
Chronic hepatitis.....	19
Natural history.....	20
Cirrhosis and hepatic decompensation .....	20
Disease progression.....	20
2. HCV Structure and Viral Replication .....	23
<i>Bernd Kupfer</i> .....	23
Taxonomy and genotypes .....	23
Viral structure .....	23
Genome organization.....	24
HCV proteins .....	25
Viral lifecycle.....	26
Adsorption and viral entry.....	26
Translation and post-translational processes .....	27
HCV RNA replication.....	28
Assembly and release .....	28
Model systems for research .....	29
3. Diagnostic Tests in Acute and Chronic Hepatitis C .....	30
<i>Christian Lange and Christoph Sarrazin</i> .....	30
Serologic assays .....	30
Nucleic acid testing for HCV .....	31
HCV genotyping .....	33

Implications for diagnosis and management .....	34
Diagnosing acute hepatitis C.....	34
Diagnosing chronic hepatitis C.....	35
Diagnostics in the management of therapy .....	35
Outlook .....	36
4. Standard Therapy of Chronic Hepatitis C Virus Infection.....	37
<i>Markus Cornberg, Christoph Höner zu Siederdissen, Benjamin Maasoumy, Svenja Hardtke, Katja Deterding, Kerstin Port, Michael P. Manns, Heiner Wedemeyer</i> .....	37
Goal of antiviral therapy .....	37
Basic therapeutic concepts and medication .....	38
Predictors of treatment response .....	44
Antiviral resistance.....	48
Treatment of HCV genotype 1 .....	50
Treatment of naïve patients.....	50
Treatment of patients with prior antiviral treatment failure.....	65
PEG-IFN maintenance therapy.....	70
Treatment of HCV genotypes 2 and 3 .....	71
Naïve patients .....	71
Treatment of HCV GT2/3 patients with prior antiviral treatment failure .....	75
Treatment of HCV genotypes 4, 5, and 6 .....	77
Optimisation of HCV treatment .....	80
Adherence to therapy .....	80
Management of side effects and complications.....	81
Drug interactions.....	82
Treatment of hepatitis C in special populations .....	84
Patients with acute hepatitis C .....	84
Patients with normal aminotransferase levels.....	86
Patients with compensated liver cirrhosis.....	87
Patients after liver transplantation .....	88
Hemodialysis patients.....	89

Drug abuse and patients on stable maintenance substitution .....	90
Patients with coinfections .....	90
Patients with hemophilia .....	90
Patients with extrahepatic manifestations .....	91
5. Hepatitis C: New Drugs.....	92
<i>Christian Lange, Christoph Sarrazin</i> .....	92
Introduction.....	92
HCV life cycle and treatment targets .....	95
NS3/4A protease inhibitors .....	96
Molecular biology .....	97
Other NS3 protease inhibitors .....	99
Resistance to NS3/4A inhibitors.....	101
NS5B polymerase inhibitors .....	104
Molecular biology .....	104
Nucleoside analogs .....	107
Non-nucleoside analogs.....	108
NS5A inhibitors .....	108
Compounds targeting viral attachment and entry.....	110
Host factors as targets for treatment .....	110
Cyclophilin B inhibitors.....	110
Nitazoxanide .....	112
Silibinin.....	112
Miravirsen .....	112
Newer combination therapies .....	113
PEG-IFN $\alpha$ -based quadruple therapy.....	116
All-oral therapy with or without ribavirin .....	118
Combinations of nucleoside analog NS5B inhibitors and NS3/4A protease inhibitors with or without ribavirin.....	119
Combinations of nucleoside analog NS5B inhibitors plus NS5A inhibitors with or without ribavirin.....	120

	Combinations of NS3/4A inhibitors and NS5A inhibitors.....	123
	Combinations of multiple DAAs with or without ribavirin .....	124
	Cyclophilin inhibitor-based therapies.....	125
	Novel interferons .....	126
	Conclusions .....	126
6.	Adverse Events and Drug Interactions.....	128
	<i>Martin Schaefer and Stefan Mauss</i> .....	128
	Interferon-based therapies.....	129
	Systemic symptoms.....	129
	Psychiatric adverse events.....	129
	Hematologic and immunologic effects .....	131
	Skin disorders .....	131
	Direct acting antiviral agents (DAAs) .....	133
	Telaprevir and boceprevir.....	133
	Simeprevir and faldaprevir .....	136
	Sofosbuvir.....	137
	Conclusion.....	137
7.	Extrahepatic Manifestations .....	139
	<i>Albrecht Böhmig, Karl-Philipp Puchner and Thomas Berg</i> .....	139
	Lymphoproliferative disorders .....	141
	Malignant lymphoproliferative disorders/NHL.....	142
	Treatment of lymphoproliferative disorders .....	143
	Other hematological manifestations .....	145
	Dermatologic and other manifestations .....	147
8.	Management of HCV/HIV Coinfection.....	149
	<i>Christoph Boesecke, Stefan Mauss and Jürgen Kurt Rockstroh</i> .....	149
	Epidemiology of HIV/ HCV coinfection.....	149
	Diagnosing HCV in HIV coinfection .....	150
	The natural history of hepatitis C in HIV+ patients.....	152
	Effect of hepatitis C on HIV infection .....	152

Effect of HAART on hepatitis C .....	153
Treatment .....	153
Antiretrovirals while on HCV therapy.....	158
Liver transplant in HIV/HCV-coinfected patients.....	159
Conclusion.....	161
9. Management of HBV/HCV Coinfection.....	162
<i>Carolynne Schwarze-Zander and Jürgen Kurt Rockstroh</i> .....	162
Epidemiology .....	162
Screening.....	163
Viral interactions .....	163
Treatment .....	166
Conclusion.....	167
10. References.....	168





# 1. Epidemiology, Transmission and Natural History

*Christoph Boesecke and Jan-Christian Wasmuth*

## **Epidemiology**

Hepatitis C is a disease of significant global impact. According to the World Health Organization there are about 150 million people chronically infected with hepatitis C virus (HCV). There are considerable regional differences: in some countries, eg, Egypt, the prevalence is >10% (WHO 2013). In Africa and the Western Pacific prevalence is significantly higher than in North America and Europe (CDC 2012). It is estimated that there are 2-5 million HCV-positive persons in Europe. Certain groups are preferentially affected, like injection drug users. In Europe and the United States chronic hepatitis C is the most common chronic liver disease. The majority of liver transplants performed in these regions are for chronic HCV. It is difficult to determine the number of new HCV infections, as most acute cases are not noticed clinically. Recent numbers from Europe still show an ongoing epidemic of acute HCV especially among IVDU and MSM (Rockstroh 2012).

## Transmission

Parenteral exposure to hepatitis C is the most efficient means of transmission. The majority of patients infected with HCV in Europe and the United States acquired the disease through intravenous drug use or blood transfusion, which has become rare since routine testing of the blood supply for HCV began. The following possible routes of infection have been identified in blood donors (in descending order of transmission risk):

- Injection drug use
- Blood transfusion
- Sex with an intravenous drug user
- Having been in jail more than three days
- Religious scarification
- Having been struck or cut with a bloody object
- Pierced ears or body parts
- Immunoglobulin injection

Very often in patients with newly diagnosed HCV infection no clear risk factor can be identified.

Factors that may increase the risk of HCV infection include greater numbers of sex partners, history of sexually transmitted diseases, and failure to use a condom. Whether underlying HIV infection increases the risk of heterosexual HCV transmission to an uninfected partner is unclear. The seroprevalence of HCV in MSM (men who have sex with men) ranges from about 4 to 8%, which is higher than the HCV prevalence reported for general European populations, increasing globally over the last decade (Boesecke 2011, Rockstroh 2012).

The risk of perinatal transmission of HCV in HCV RNA-positive mothers is estimated to be 5% or less (Ohto 1994). Cesarean section has not been shown to reduce transmission. There is no evidence that breastfeeding is a risk factor.

Hemodialysis risk factors include blood transfusions, the duration of hemodialysis, the prevalence of HCV infection in the

dialysis unit, and the type of dialysis. The risk is higher with in-hospital hemodialysis vs peritoneal dialysis.

Contaminated medical equipment, traditional medicine rites, tattooing, and body piercing are considered rare transmission routes.

There is some risk of HCV transmission for health care workers after unintentional needle-stick injury or exposure to other sharp objects (Sarrazin 2010).

## Acute hepatitis

After HCV inoculation, there is a variable incubation period. HCV RNA in blood (or the liver) can be detected by PCR within several days to eight weeks (Hoofnagle 1997). Aminotransferases become elevated approximately 6-12 weeks after exposure (range 1-26 weeks) and they tend to be more than 10-30 times the upper limit of normal. HCV antibodies can be found about 8 weeks after exposure although it may take several months. However, the majority of newly infected patients will be asymptomatic and have a clinically non-apparent or mild course. Periodic screening for infection may be warranted in certain groups of patients who are at high risk of infection, eg, HIV positive MSM. Symptoms include malaise, nausea, and right upper quadrant pain. In patients who experience such symptoms, the illness typically lasts for 2-12 weeks. Along with clinical resolution of symptoms, aminotransferases will normalize in about 40% of patients. Loss of HCV RNA, which indicates a hepatitis C cure, occurs in fewer than 20% of patients. Fulminant hepatic failure due to acute HCV infection may happen in patients with underlying chronic hepatitis B virus infection (Chu 1999).

## Chronic hepatitis

The risk of chronic HCV infection is high. About 75% of patients with acute hepatitis C do not eliminate HCV RNA and progress to chronic infection. Most of these will have persistently elevated liver enzymes in follow-up. Hepatitis C is considered to be

chronic after six months. Once chronic infection is established, there is a very low rate of spontaneous clearance.

Most patients with chronic infection are asymptomatic or have only mild nonspecific symptoms as long as cirrhosis is not present (Lauer 2001, Merican 1993). The most frequent complaint is fatigue. Less common manifestations are nausea, weakness, myalgia, arthralgia, and weight loss (Merican 1993).

Aminotransferase levels can vary considerably over the natural history of chronic hepatitis C.

### **Natural history**

The risk of developing cirrhosis within 20 years is estimated to be around 10 to 20%, with some studies showing estimates of up to 50% (Poynard 1997, Wiese 2000, Sangiovanni 2006). About 30% of patients will not develop cirrhosis for at least 50 years (Poynard 1997). It is not completely understood why there are such differences in disease progression. An influence of host and viral factors has to be assumed, such as the IL28B polymorphism.

### **Cirrhosis and hepatic decompensation**

Complications of hepatitis C occur almost exclusively in patients who have developed cirrhosis. Non-liver-related mortality is higher in cirrhotic patients as well.

The risk for decompensation is estimated to be close to 5% per year in cirrhotics (Poynard 1997). Once decompensation has developed, the 5-year survival rate is roughly 50% (Planas 2004). Liver transplantation is then the only effective therapy. Hepatocellular carcinoma (HCC) also develops solely in patients with cirrhosis (in contrast to chronic hepatitis B).

### **Disease progression**

Chronic HCV progression may differ depending on several factors. Other factors not yet identified may also be important.

**Age and gender:** More rapid progression is seen in males older than 40-55 (Svrtlih 2007), while a less rapid progression is seen in children (Child 1964).

**Ethnic background:** A slower progression has been noted in African-Americans (Sterling 2004).

**HCV-specific cellular immune response:** Genetic determinants like HLA expression (Hraber 2007) probably guide the inflammatory response.

**Alcohol intake:** Even moderate amounts of alcohol increase HCV replication, enhance the progression of chronic HCV, and accelerate liver injury (Gitto 2009).

**Daily use of marijuana:** may cause a more rapid progression.

**Other host factors:** TGF B1 phenotype or PNPLA-3 (adiponutrin) and fibrosis stage are correlated with fibrosis progression rate (Zimmer 2011). Moderate to severe steatosis correlates with developing hepatic fibrosis.

**Viral coinfections:** HCV progression is more rapid in HIV-infected patients. Acute hepatitis B in a patient with chronic hepatitis C may be more severe. Liver damage is usually worse and progression faster in patients with dual HBV/HCV infections.

**Geography and environmental factors:** Clear, but not understood (Lim 2008).

**Use of steroids:** increases HCV viral load.

**Viral factors:** There seems to be no significant role of different genotypes and quasispecies on fibrosis progression or outcome. However, coinfection with several genotypes may have a worse outcome as compared to mono-infection. Liver biopsy is the best predictor of disease progression (Gebo 2002).

In patients with cirrhosis, the MELD score (Model for End-Stage Liver Disease) and the Child score (Table 1.1) are used to stage disease and to describe the prognosis. An online calculator and further information can be found at the website of the United Network for Organ Sharing (UNOS) (<http://www.unos.org>).

However, the best way to slow down liver fibrosis is successful treatment of HCV (van der Meer 2012). The new directly acting antivirals (DAA), with high efficacy and increasingly improving safety profiles, can greatly contribute to lowering the disease

burden caused by chronic HCV infection if we can identify infection earlier.

For details on extrahepatic manifestations, please see Chapter 7.

**Table 1.1 – Child-Pugh classification of severity of liver disease (Child 1964)**

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin, mg/dL	<2	2-3	>3
Albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time			
Prothrombin time	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3
Encephalopathy	None	Grades 1-2	Grades 3-4

A total score of 5-6 is considered stage A (well-compensated disease); 7-9 is stage B (significant functional compromise); and 10-15 is stage C (decompensated disease). These grades correlate with one- and two-year patient survival: stage A - 100 and 85 percent; stage B - 80 and 60 percent; and stage C - 45 and 35 percent.

## 2. HCV Structure and Viral Replication

*Bernd Kupfer*

### **Taxonomy and genotypes**

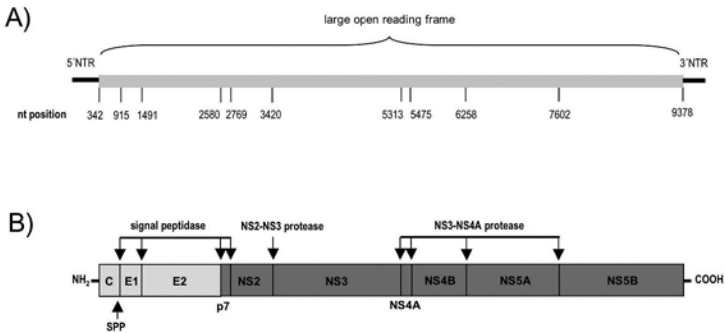
HCV is a small-enveloped virus with one single-stranded positive-sense RNA molecule of approximately 9.6 kb. It belongs to the genus hepacivirus, a member of the *Flaviviridae* family. The high replication rate of the virus together with the error-prone RNA polymerase of HCV is responsible for the large interpatient genetic diversity of HCV strains. Moreover, the extent of viral diversification of HCV strains within a single HCV-positive individual increases significantly over time resulting in the development of quasispecies (Bukh 1995). A very recent study revealed the presence of at least 7 different HCV genotypes and 67 subtypes, respectively (Smith 2014). However, the fast growing number of full-length HCV genome sequences will probably lead to even higher numbers of HCV genotypes.

### **Viral structure**

Structural analyses of HCV virions are very limited because for a long time the virus was difficult to cultivate in cell culture systems, a prerequisite for yielding sufficient virions for electron microscopy. Moreover, serum-derived virus particles are

associated with serum low-density lipoproteins (Thomssen 1992), which makes it difficult to isolate virions from serum/plasma of subjects via centrifugation.

It has been shown that HCV virions isolated from cell culture have a spherical envelope containing tetramers (or dimers of heterodimers) of the HCV E1 and E2 glycoproteins (Heller 2005, Wakita 2005, Yu 2007). Inside the virions a spherical structure has been observed (Wakita 2005) representing the nucleocapsid (core) that harbours the viral genome.



**Figure 2.1 – Genome organization and polyprotein processing**

A) Nucleotide positions correspond to the HCV strain H77 genotype 1a, accession number NC\_004102. nt, nucleotide; NTR, nontranslated region. B) Cleavage sites within the HCV precursor polyprotein for the cellular signal peptidase, the signal peptide peptidase (SPP) and the viral proteases NS2-NS3 and NS3-NS4A, respectively

## Genome organization

The genome of the hepatitis C virus consists of one 9.6 kb single-stranded RNA molecule with positive polarity. Similar to other positive-strand RNA viruses, the genomic RNA of the hepatitis C virus serves as messenger RNA (mRNA) for the translation of viral proteins. The linear molecule contains a single open reading frame (ORF) coding for a precursor polyprotein of approximately 3000 amino acid residues flanked by two regulatory nontranslated regions (NTR) (Figure 2.1).



**Table 2.1 – Size and main function of HCV proteins.** MW, molecular weight in kd (kilodalton)

Protein	MW	Function
Core	21 kd	Capsid-forming protein. Regulatory functions in translation, RNA replication, and particle assembly.
F-protein or ARFP	16-17 kd	Unknown.
Envelope glycoprotein 1 (E1)	35 kd	Transmembrane glycoprotein in the viral envelope. Adsorption, receptor-mediated endocytosis.
Envelope glycoprotein 2 (E2)	70 kd	Transmembrane glycoprotein in the viral envelope. Adsorption, receptor-mediated endocytosis.
p7	7 kd	Forms an ion-channel in the endoplasmic reticulum. Essential formation of infectious virions.
NS2	21 kd	Portion of the NS2-3 protease which catalyses cleavage of the polyprotein precursor between NS2 and NS3 (Figure 2.1).
NS3	70 kd	NS2-NS3 protease, cleavage of the downstream HCV proteins (Figure 2.1). ATPase/helicase activity, binding and unwinding of viral RNA.
NS4A	4 kd	Cofactor of the NS3-NS4A protease.
NS4B	27 kd	Crucial in HCV replication. Induces membranous web at the ER during HCV RNA replication.
NS5A	56 kd	Multi-functional phosphoprotein. Contains the IFN $\alpha$ sensitivity-determining region (ISDR) that plays a significant role in the response to IFN $\alpha$ -based therapy. Involved in HCV RNA replication, virus assembly and virion release.
NS5B	66 kd	Viral RNA-dependent RNA polymerase. NS5B is an error-prone enzyme that incorporates wrong ribonucleotides at a rate of approximately $10^{-3}$ per nucleotide per generation.

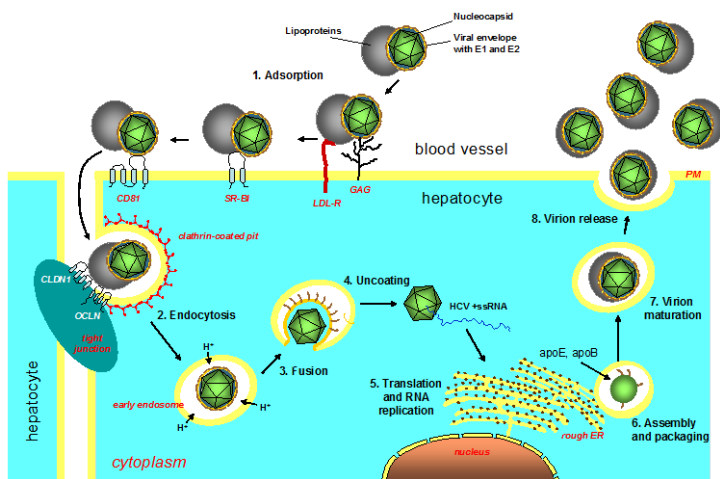
## HCV proteins

Translation of the HCV polyprotein is initiated through involvement of some domains in the NTRs of the genomic HCV RNA. The resulting polyprotein consists of ten proteins that are co-translationally or post-translationally cleaved from the polyprotein. In addition, the F (frameshift) or ARF (alternate reading frame) protein has been explored (Walewski 2001).

During translation ARFP is the product of ribosomal frameshifting within the core protein-encoding region.

## Viral lifecycle

The recent development of small animal models and more efficient *in vitro* HCV replication systems has offered the opportunity to analyze in detail the different steps of viral replication (Figure 2.2).



**Figure 2.2 – Model of the HCV lifecycle.** Designations of cellular components are in *italics*. For a detailed illustration of viral translation and RNA replication, see [Pawlotsky 2007](#). HCV +ssRNA, single stranded genomic HCV RNA with positive polarity; rough ER, rough endoplasmic reticulum; PM, plasma membrane. For other abbreviations see text

### Adsorption and viral entry

A cascade of virus-cell interactions is necessary for the infection of hepatocytes. The precise mechanism of viral entry is complex and still not completely understood. The current model of viral adsorption assumes that HCV is associated with low-density lipoproteins (LDL). The binding step includes binding of the LDL

component to the LDL-receptor (LDL-R) on the cell surface (Agnello 1999) and simultaneous interaction of the viral glycoproteins with cellular glycosaminoglycans (GAG) (Germi 2002). This initiation step is followed by consecutive interactions of HCV with scavenger receptor B type I (SR-BI) (Scarselli 2002) and the tetraspanin CD81 (Pileri 1998). More recent findings indicate subsequent transfer of the virus to the tight junctions, a protein complex located between adjacent hepatocytes. Two components of tight junctions, claudin-1 (CLDN1) and occludin (OCLN) have been shown to interact with HCV (Evans 2007, Ploss 2009). Although the precise mechanism of HCV uptake in hepatocytes is still not clarified, these cellular components may represent the complete set of host cell factors necessary for cell-free HCV entry. Interaction of HCV with CLDN1 and OCLN seems to induce the internalisation of the virion via clathrin-mediated endocytosis (Hsu 2003). Finally, it has been shown that two receptor tyrosine kinases (RTKs) and the Niemann–Pick C1-like 1 (NPC1L1) cholesterol uptake receptor are cellular cofactors for HCV entry into hepatocytes (Lupberger 2011, Sainz 2012). Subsequent HCV E1-E2 glycoprotein mediation fuses the viral envelope with the endosome membrane (Meertens 2006).

Despite having identified several host factors that probably interact with the viral glycoproteins, the precise mechanisms of interaction need to be investigated further.

### **Translation and post-translational processes**

As a result of the fusion of the viral envelope and the endosomal membrane, the genomic HCV RNA is released into the cytoplasm of the cell (uncoating). The viral genomic RNA possesses a nontranslated region (NTR) at each terminus. It contains an internal ribosome entry site (IRES) involved in ribosome binding and subsequent initiation of translation (Tsukiyama-Kohara 1992). The synthesized HCV precursor polyprotein is subsequently processed by at least four distinct peptidases. The cellular signal peptidase (SP) cleaves the N-terminal viral protein's immature core protein, E1, E2, and p7 (Hijikata 1991),

while the cellular signal peptide peptidase (SPP) is responsible for the cleavage of the E1 signal sequence from the C-terminus of the immature core protein, resulting in the mature form of the core (McLauchlan 2002). The E1 and E2 proteins remain within the lumen of the ER where they are subsequently N-glycosylated with E1 having 5 and E2 harbouring 11 putative N-glycosylation sites (Duvet 2002). The remaining HCV proteins are post-translationally cleaved by the viral NS2-NS3 and the NS3-NS4A protease, respectively.

### **HCV RNA replication**

The process of HCV RNA replication is poorly understood. The key enzyme for viral RNA replication is NS5B, an RNA-dependent RNA polymerase (RdRp) of HCV. After the RdRp has bound to its template, the NS3 helicase is assumed to unwind putative secondary structures of the template RNA in order to facilitate the synthesis of minus-strand RNA (Jin 1995, Kim 1995). In turn, the newly synthesized antisense RNA molecule serves as the template for the synthesis of numerous plus-stranded RNA. The resulting sense RNA may be used subsequently as genomic RNA for HCV progeny as well as for polyprotein translation. Another important viral factor for the formation of the replication complex appears to be NS4B, which is able to induce an ER-derived membranous web containing most of the non-structural HCV proteins including NS5B (Egger 2002).

### **Assembly and release**

After the viral proteins, glycoproteins, and the genomic HCV RNA have been synthesized, these components have to be arranged in order to produce infectious virions. Viral assembly is a multi-step procedure involving most viral components along with many cellular factors. Recent findings suggest that viral assembly takes place within the endoplasmic reticulum (Gastaminza 2008) and that lipid droplets are involved in particle formation (Miyahari 2007, Shavinskaya 2007). However, the

precise mechanisms for the formation and release of infectious HCV particles are still unknown.

### **Model systems for research**

**Small animal models.** Recently, substantial progress has been made in establishing two mouse models for HCV infection via genetically humanized mice (Dorner 2011). These models will be useful to investigate the early steps of HCV infection *in vivo*. Moreover, the approach should be suitable for the evaluation of HCV entry inhibitors and vaccine candidates.

A second group of investigators depleted murine hepatocytes and cotransplanted human CD34(+) hematopoietic stem cells and hepatocyte progenitors into transgenic mice leading to efficient engraftment of human leukocytes and hepatocytes, respectively (Washburn 2011). As a consequence, HCV infection induced liver inflammation, hepatitis, and fibrosis. Furthermore, due to the cotransplantation of CD34(+) human hematopoietic stem cells, an HCV-specific T cell immune response was detected.

Both strategies are promising and have already delivered new insights into viral replication and the pathogenesis of HCV but need to be improved in order to achieve higher HCV replication rates as well as to better study the HCV-specific antibody response.

### 3. Diagnostic Tests in Acute and Chronic Hepatitis C

*Christian Lange and Christoph Sarrazin*

Hepatitis C is often diagnosed accidentally and, unfortunately, remains heavily underdiagnosed. HCV diagnostics should be performed thoroughly in all patients presenting with increased aminotransferase levels, with chronic liver disease of unclear etiology and with a history of enhanced risk of HCV transmission.

#### **Serologic assays**

With 2<sup>nd</sup> generation enzyme-linked immunoassays (EIAs), HCV-specific antibodies can be detected approximately 10 weeks after infection (Pawlotsky 2003b). To narrow the diagnostic window from viral transmission to positive serological results, a 3<sup>rd</sup> generation EIA has been introduced that includes an antigen from the NS5 region and/or the substitution of a highly immunogenic NS3 epitope, allowing the detection of anti-HCV antibodies approximately four to six weeks after infection with a sensitivity of more than 99% (Colin 2001). Anti-HCV IgM measurement can narrow the diagnostic window in only a minority of patients and cannot discriminate between acute and chronic hepatitis C.

False-positive results are more frequent in patients with rheuma factors and in populations with a low hepatitis C prevalence, for example in blood and organ donors. False-negative HCV antibody results may occur in patients on hemodialysis or in severely immunosuppressed patients or those with hematological malignancies.

One **quantitative HCV core antigen assay** (Architect HCV Ag, Abbott Diagnostics) has been approved so far. This assay comprises 5 different antibodies, is highly specific (99.8%) and shows somewhat less sensitivity for determination of chronic hepatitis C as HCV RNA measurement (Morota 2009). False-negative results are obtained in patients with impaired immunity (Mederacke 2009, Medici 2011). For careful monitoring of treatment with standard dual combination therapies or directly acting antiviral agents, prospective studies are being performed to determine proper rules and time points for response-guided treatment algorithms.

## Nucleic acid testing for HCV

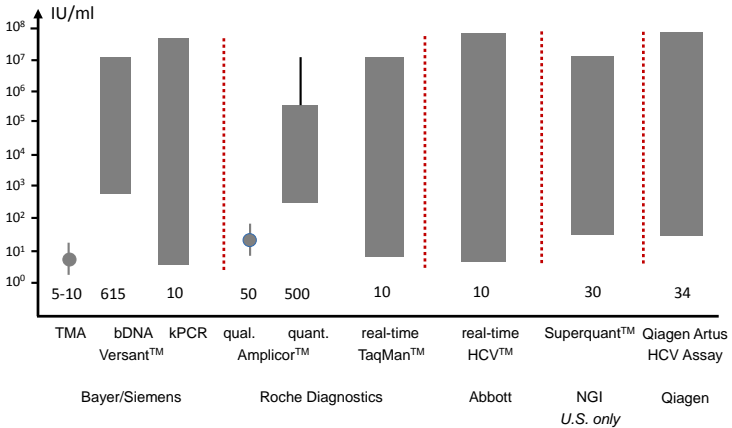
Because of the importance of an exact HCV RNA load determination for therapeutic management, the World Health Organization (WHO) established the HCV RNA international standard based on international units (IU) which is used in all clinically applied HCV RNA tests. Currently, several HCV RNA assays are commercially available.

**Qualitative HCV RNA tests** include the **qualitative RT-PCR**, of which the AmpliCor™ HCV 2.0 (Roche) is an FDA- and CE-approved RT-PCR system for qualitative HCV RNA testing that allows detection of HCV RNA concentrations down to 50 IU/ml of all HCV genotypes (Nolte 2001).

Transcription-mediated amplification- **(TMA)-based qualitative HCV RNA detection** has a very high sensitivity (lower limit of detection 5-10 IU/ml) (Sarrazin 2002, Hendricks 2003). A commercially available TMA assay is the Versant™ HCV RNA Qualitative Assay (Siemens). This system is accredited by

FDA and CE and provides an extremely high sensitivity, superior to RT-PCR-based qualitative HCV RNA detection assays (Sarrazin 2000, Sarrazin 2001, Hofmann 2005).

**HCV RNA quantification** can be achieved either by **target amplification techniques** (competitive and real-time PCR) or by **signal amplification techniques** (branched DNA (bDNA) assay). Several FDA- and CE-approved standardized systems are commercially available. The Cobas AmpliCor™ HCV Monitor is based on a competitive PCR technique whereas the Versant™ HCV RNA Assay is based on a bDNA technique. Both have restricted lower limits of detection (500-615 IU/ml). More recently, the Cobas TaqMan assay and the Abbott RealTime™ HCV test, both based on real-time PCR technology, have been introduced and now replace the qualitative and quantitative methods.



**Figure 3.1 – Detection limits and linear dynamic ranges of commercially available HCV RNA detection assays**

All commercially available HCV RNA assays are calibrated to the WHO standard based on HCV genotype 1. It has been shown that results may vary significantly between assays with different HCV



genotypes despite standardization (Chevaliez 2007, Vehrmeren 2008). The **Cobas TaqMan** assay makes both highly sensitive qualitative (limit of detection approx. 10 IU/ml) and linear quantitative HCV RNA detection (35-107 IU/ml) feasible with high specificity and excellent performance in one system with complete automation. The **Abbott RealTime™** HCV Test provides a lower limit of detection of 12 IU/ml, a specificity of more than 99.5% and a linear amplification range from 12 to 10,000,000 IU/ml independent of the HCV genotype (Michelin 2007, Sabato 2007, Schutten 2007, Vermehren 2008). Qiagen has developed a novel real-time based HCV RNA assay, the **Artus HCV QS-RGQ assay**. The Artus HCV RNA assay has a lower limit of quantification of 30 IU/mL and a linear range of quantification up to  $10^8$  IU/mL. Compared to the Cobas® TaqMan® assay, the artus HCV assay had a slightly lower sensitivity (Paba 2012). For replacement of the qualitative TMA and the quantitative bDNA-based assays, a real-time-based PCR test (Versant® kPCR Molecular System) has been introduced recently. While little is known for the use of this assay in response guided conventional dual and triple therapies in HCV genotype 1 infected patients a limitation of this assay seems to be a substantial underquantification of HCV RNA concentrations in certain HCV subtypes (2a, 3a, 4a) (Kessler 2013).

## HCV genotyping

HCV is heterogeneous with an enormous genomic sequence variability due to its rapid replication cycle producing  $10^{12}$  virions a day and the low fidelity of the HCV RNA polymerase. Six genotypes (1-6), multiple subtypes (a, b, c...) and most recently a seventh HCV genotype have been characterized. Within one subtype, numerous quasispecies exist and may emerge during treatment with specific antivirals. Because the currently recommended treatment durations and ribavirin doses depend on the HCV genotype, HCV genotyping is mandatory in every patient considering antiviral therapy (Bowden 2006). With

the new oral treatment modalities and those yet to come, HCV subtype determination will help to reveal possible barriers to resistance. Both direct sequence analysis and reverse hybridization technology allow HCV genotyping.

The **Versant™ HCV Genotype 2.0 System** is suitable for indentifying genotypes 1-6 and more than 15 different subtypes and is currently the preferred assay for HCV genotyping. By simultaneous analyses of the 5'UTR and core region, a high specificity is achieved especially to differentiate the genotype 1 subtypes (1a versus 1b). The **TruGene direct sequence assay** determines the HCV genotype and subtype by direct analysis of the nucleotide sequence of the 5'UTR region. Incorrect genotyping rarely occurs with this assay. However, the accuracy of subtyping is poor. The current **RealTime™ HCV Genotype II** assay is based on real-time PCR technology, which is less time-consuming than direct sequencing. Preliminary data reveal a 96% concordance at the genotype level and a 93% concordance on the genotype 1 subtype level when compared to direct sequencing of the NS5B and 5'UTR regions.

## **Implications for diagnosis and management**

### **Diagnosing acute hepatitis C**

When acute hepatitis C is suspected, the presence of both anti-HCV antibodies and HCV RNA should be tested. For HCV RNA detection, sensitive qualitative techniques with a detection limit of 50 IU/ml or less are required, for example TMA, qualitative RT-PCR or the newly developed real-time PCR systems. HCV RNA may fluctuate during acute hepatitis C, making a second HCV RNA test necessary several weeks later in all negatively tested patients with a suspicion of acute hepatitis C. When HCV RNA is detected in seronegative patients, acute hepatitis C is very likely. When patients are positive for both anti-HCV antibodies and HCV RNA, it may be difficult to discriminate between acute and acutely exacerbated chronic hepatitis C. Anti-HCV IgM detection

will not suffice because its presence is common in both situations.

### **Diagnosing chronic hepatitis C**

Chronic hepatitis C should be considered in every patient presenting with clinical, morphological or biological signs of chronic liver disease. When chronic hepatitis C is suspected, screening for HCV antibodies by 2<sup>nd</sup> or 3<sup>rd</sup> generation EIAs is adequate because their sensitivity is >99%. When anti-HCV antibodies are detected, the presence of HCV RNA has to be determined in order to discriminate between chronic hepatitis C and resolved HCV infection.

### **Diagnostics in the management of therapy**

Exact HCV subtyping appears to be highly important in direct-acting antiviral agent (DAA) therapy because some HCV subtypes (especially 1a vs 1b) behave differently regarding development of resistance. Low HCV RNA concentration (<600,000–800,000 IU/ml) at baseline is a positive predictor of a sustained virological response (SVR). Genotyping is mandatory for the selection of the optimal treatment regimen and duration of therapy, since many DAA agents are effective for only some HCV genotypes (Lange 2010), and since treatment durations generally can be shorter for patients infected with HCV genotypes 2 or 3 compared to patients infected with genotypes 1 or 4 (Manns 2006). Due to the differences in HCV RNA concentrations of up to a factor of 4 between the different commercially available assays, despite standardization of the results to IU, and due to intra- and interassay variability of up to a factor of 2, it is recommended to always use the same assay in a given patient before, during and after treatment and to repeat HCV RNA measurements at baseline in cases with HCV RNA concentrations between 400,000 and 1,000,000 IU/ml. Furthermore, the new stopping rules for boceprevir and telaprevir triple therapies based on viral cut-offs of 100 and 1000 IU/ml respectively, were assessed by the Cobas® TaqMan® assay, which results, at least for telaprevir, in a higher

proportion of patients with negative HCV RNA and shortened treatment duration compared to the RealTime™ assay (lower limit of quantification 12 IU/mL) (Sarrazin 2013, Vermehren 2013). For many other DAA regimens, stopping rules and response-guided therapies have been developed as well. Since all patients on Sofosbuvir-based combination therapies achieved undetectable HCV RNA concentrations during antiviral therapy, no response guided therapy approaches have been developed and on treatment monitoring of HCV RNA is not necessary for this potent DAA (Jacobson 2013, Lawitz 2013).

## Outlook

It can be anticipated that in the near future many patients will be treated with interferon-free or interferon  $\alpha$ -based combination therapies including two or more DAAs. For the success of such regimens, a thorough determination of novel algorithms to define treatment duration, treatment failure, or the selection of optimal regimens for individual patients will be crucial. Careful monitoring of antiviral resistance development might be decisive, for example for triple therapy containing the NS3-4A inhibitor simeprevir, which is appeared to be less efficient in patients in whom a variant at position Q80K in the NS3-4A protease was detected (see chapter 5 for details). Currently, resistance testing is still a domain of research using “home-brew” assays, but commercially available assays can be expected in the near future.

## 4. Standard Therapy of Chronic Hepatitis C Virus Infection

*Markus Cornberg, Christoph Höner zu Siederdisen, Benjamin Maasoumy, Svenja Hardtke, Katja Deterding, Kerstin Port, Michael P. Manns, Heiner Wedemeyer*

### **Goal of antiviral therapy**

Globally, there are approximately 130-170 million people chronically infected with hepatitis C virus (HCV), in Europe 8-11 million (Cornberg 2011, Shepard 2005). Despite the implementation of blood-donor screening in the early '90s, the global prevalence of anti-HCV antibodies has increased from 2.3% to 2.8% between 1990 and 2005 (Mohd Hanafiah 2013) and there is an anticipated increase of HCV-related cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) over the course of the next decade (Davis 2010, Maasoumy 2012). The goal of antiviral therapy is to cure hepatitis C via a sustained elimination of the virus. A sustained elimination of HCV is achieved if the HCV RNA remains negative six months after the end of treatment (sustained virological response, SVR) (Table 4.1). Follow-up studies document that more than 99% of patients who achieve an SVR remain HCV RNA negative 4-5 years after the end of treatment and no signs of hepatitis have been

documented (Manns 2008, Swain 2010). Importantly, long-term benefits of SVR are the reduction of HCV-related hepatocellular carcinoma and overall mortality (Backus 2011, Veldt 2007, van der Meer 2012). In 2011, the FDA accepted SVR-12 (HCV RNA negativity 12 weeks after end of treatment) as endpoint for future trials because HCV relapse usually occurs within the first 12 weeks after the end of treatment. However, virologic relapses at later time points may appear in rare cases, and have been reported for interferon-based therapy (Swain 2010, Manns 2013a) as well as interferon-free therapy (Lawitz 2012). In addition to liver disease, several other hepatic manifestations such as cryoglobulinemia, non-Hodgkin's lymphoma, membranoproliferative glomerulonephritis or porphyria cutanea tarda have been reported in the natural history of hepatitis C virus infection (HCV). Antiviral treatment may improve symptoms even if an SVR is not achieved. In HIV coinfecting patients SVR leads to a reduction of non liver-related mortality (Berenguer 2012). On the other hand, antiviral therapy may worsen extrahepatic manifestations (Pischke 2008, Zignego 2007, Maasoumy 2013a).

## Basic therapeutic concepts and medication

Before the identification of HCV as the infectious agent for non-A, non-B hepatitis (Choo 1989), interferon  $\alpha$  (IFN) led to a normalisation of transaminases and an improvement of liver histology in some patients (Hoofnagle 1986). After the identification of HCV it became possible to measure success of therapy as the long-lasting disappearance of HCV RNA from serum, the SVR. Since then, SVR rates have increased from 5-20% with IFN monotherapy up to 40-50% with the combination of IFN + ribavirin (RBV) (McHutchison 1998, Poynard 1998). Different HCV genotypes (HCV GT) show different SVR rates. Patients with the most frequent HCV GT1 require a longer treatment duration and still get a lower SVR compared to HCV GT2 and HCV GT3 (Figure 4.1). The development of pegylated

interferon  $\alpha$  (PEG-IFN) improved the pharmacokinetics of IFN, allowing more convenient dosing intervals and resulting in higher SVR, especially for HCV GT1. Two PEG-IFNs are available; PEG-IFN  $\alpha$ -2b (PEG-Intron<sup>®</sup>, Merck) and PEG-IFN  $\alpha$ -2a (PEGASYS<sup>®</sup>, Roche). Although smaller trials from southern Europe have suggested slightly higher SVR rates in patients treated with PEG-IFN  $\alpha$ -2a (Ascione 2010, Rumi 2010), a large US multicentre study did not detect any significant difference between the two PEG-IFNs + RBV regarding SVR (McHutchison 2009b).

The two PEG-IFNs do have different pharmacokinetic profiles due to their different polyethylene glycol moieties. PEG-IFN  $\alpha$ -2b is bound to a single linear 12 kDa polyethylene glycol molecule, whereas PEG-IFN  $\alpha$ -2a is covalently attached to a 40 kDa branched chain polyethylene glycol moiety. The distinct sizes of the PEG-IFN influence the volume of distribution. PEG-IFN  $\alpha$ -2b is dosed according to body weight (1.5  $\mu\text{g}/\text{kg}$  once weekly), while the larger PEG-IFN  $\alpha$ -2a is given in a fixed dose of 180  $\mu\text{g}$  once weekly (reviewed in Cornberg 2002) (Table 4.2). PEG-IFN  $\alpha$ -2b may also be dosed at 1.0  $\mu\text{g}/\text{kg}$  once patients become negative for HCV RNA without major declines in SVR rates (Manns 2011a, McHutchison 2009b). This may be important for patients with leucopenia or thrombopenia. RBV should be administered according to the bodyweight of the patient. A retrospective analysis of the large PEG-IFN  $\alpha$ -2b + RBV pivotal trial revealed that the optimal dose of RBV (Rebetol<sup>®</sup>) is at least 11 mg/kg (Manns 2001). A prospective, multicentre, open-label, investigator-initiated study confirmed that PEG-IFN  $\alpha$ -2b plus weight-based RBV is more effective than flat-dose ribavirin, particularly in HCV GT1 patients (Jacobson 2007). A RBV dose of 15 mg/kg would be ideal, although higher doses are associated with higher rates of anemia (Snoeck 2006).

When combined with PEG-IFN  $\alpha$ -2a, a RBV dose of 1000 mg if  $<75$  kg or 1200 mg if  $\geq 75$  kg is recommended for HCV GT1 patients while a flat dose of 800 mg RBV was initially suggested for patients with HCV GT2 and 3 (Hadziyannis 2004). However, a

weight-based dose of ribavirin (12-15 mg/kg) may be preferred, especially in difficult-to-treat patients and in response-guided therapy (RGT) approaches (Sarrazin 2010, EASL 2014).

The development of direct-acting antiviral agents (DAA) against HCV has revolutionized the treatment of chronic hepatitis C. The main targets for DAA are the NS3/4A protease, NS5B polymerase and the NS5A replication complex. Combinations of different DAAs from different classes will allow very potent treatments. In 2011, the first selective protease inhibitors (PI) were approved for patients with HCV GT1. Boceprevir (Victrelis<sup>®</sup>) and telaprevir (Incivek<sup>®</sup>; Incivo<sup>®</sup>) improve SVR rates by up to 75% in naïve HCV GT1 patients (Jacobson 2011b, Poordad 2011b) and 29-88% in treatment-experienced HCV GT1 (Bacon 2011, Zeuzem 2011) patients. However, both PIs require combination with PEG-IFN + RBV because monotherapy results in rapid emergence of drug resistance. Also, these two PIs cannot be combined as they have the same target and cross-resistance. Either of the two PIs can be combined with PEG-IFN  $\alpha$ -2a or PEG-IFN  $\alpha$ -2b (Sarrazin 2012). TLV has to be administered at least twice daily (Buti 2013) and BOC three times daily and both PIs are associated with severe side effects, especially anemia (Hézode 2013, Maasoumy 2013b, Backus 2014).

In 2014, new DAAs have already been approved or regulatory approval is expected. Simeprevir (Olysio<sup>®</sup>, Sovriad<sup>®</sup>) and faldaprevir will be the first once-daily PIs. Again, both PIs still require combination therapy in 2014 with PEG-IFN + RBV. The SVR rates for treatment-naïve GT1 patients increase to 72-80% (Jensen 2013, Jacobson 2013a), which is not a major improvement over BOC or TLV triple therapy. However, more patients achieve an early treatment response (HCV RNA <25 IU/ml at week 4 and negative at week 8-12) and qualify for shorter treatment duration of 24 weeks. In addition, the new PIs have significantly less side effects. Patients with prior treatment failure respond according to their PEG-IFN/RBV responsiveness, with relapsers having the best response and null responders the poorest (Jacobson 2013a, Zeuzem 2013a). Sofosbuvir (Sovaldi<sup>®</sup>) is the first



available once-daily NS5B polymerase inhibitor (Approved 12/2013 by FDA and 1/2014 by EMA). For genotype 1, PEG-IFN/RBV + SOF for just 12 weeks leads to 89% SVR in treatment-naïve patients (Lawitz 2013a).

The resistance barrier of SOF is much higher compared to the available PIs. Very few individuals have developed a confirmed selection of SOF-resistant variants. Thus, combination with just RBV may be sufficient for some patients. Valid data are available for genotypes 2 and 3 (Lawitz 2013a, Zeuzem 2013b) with SVR rates of 85-100% for treatment-naïve GT2/3 patients. SOF could potentially be combined with a PI or a NS5A inhibitor. Data are available for SOF + SMV (simeprevir) showing >90% SVR with 12 weeks treatment (Jacobson 2013b).

In early January 2014, the European Medicines Agency (EMA) accepted the marketing authorization application for the use of daclatasvir (DCV), an NS5A inhibitor, for the treatment of adults with chronic hepatitis C with compensated liver disease. The application seeks approval of DCV for use in combination with other agents, including sofosbuvir. Importantly, the combination SOF + DCV for 24 weeks showed 98% SVR in 41 GT1 patients with treatment failure to PEG-IFN/RBV/PI triple therapy (Sulkowski 2014). It may well be possible, that daclatasvir (Daklinza®) will be available by autumn 2014. In 2015, the approval of other DAAs is expected that will allow IFN-free combination therapies for all patients.

**Table 4.1 – Relevant definitions for HCV treatment**

Abbreviation	Term	Description
SVR	Sustained Virological Response	HCV RNA-negative 6 months after the end of therapy
SVR-12	Sustained Virological Response	HCV RNA-negative 12 weeks after the end of therapy; FDA-accepted endpoint for future trials
RVR	Rapid Virological Response	HCV RNA-negative after 4 weeks of therapy
EVR	Early Virological Response	HCV RNA-positive at week 4 but negative at week 12

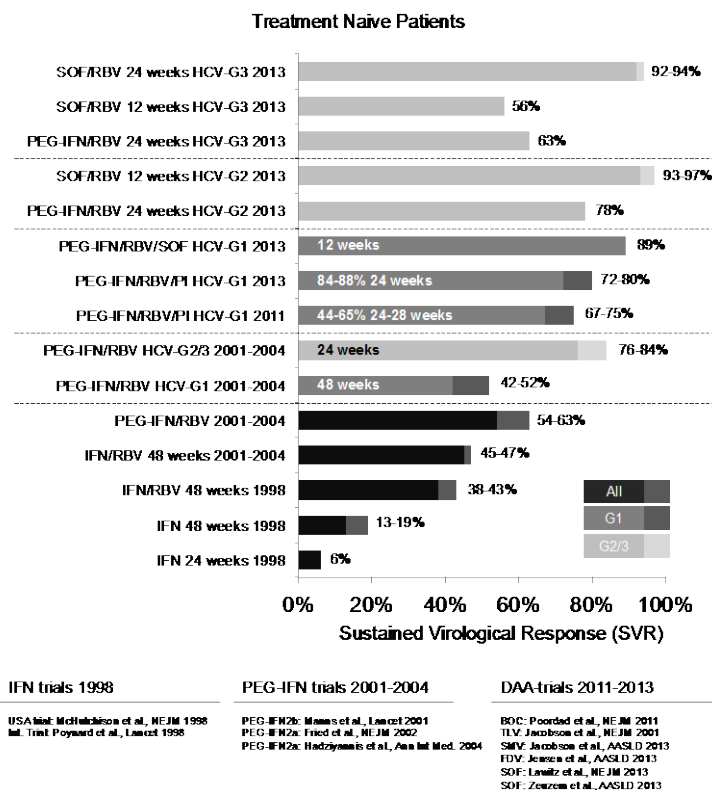
Abbreviation	Term	Description
DVR	Delayed Virological Response	HCV RNA decline $\geq 2 \log_{10}$ decrease from baseline but detectable HCV RNA at week 12, then undetectable at week 24
eRVR (BOC)	Extended Rapid Virological Response (for boceprevir)	HCV RNA-negative (LLD, not LLQ) between week 8 and week 24 of BOC therapy: RGT criterion for BOC
eRVR (TLV)	Extended Rapid Virological Response (for telaprevir)	HCV RNA-negative (LLD, not LLQ) between week 4 and week 12 of TLV therapy: RGT criterion for TLV
<sup>1</sup> ETS (FDV)	Early Treatment Success	HCV RNA $< 25$ IU/ml at week 4 and negative at week 8: RGT criterion for FDV
<sup>2</sup> ETS (SMV)	Early Treatment Success	HCV RNA $< 25$ IU/ml at week 4 and negative at week 12: RGT criterion for SMV
NR (BOC)	Non-response (boceprevir)	HCV RNA $\geq 100$ IU/mL at week 12; or HCV RNA positive at week 24, futility rule for BOC
NR (TLV)	Non-response (telaprevir)	HCV RNA $\geq 1000$ IU/mL at week 4 or week 12; or HCV RNA positive at week 12, futility rule for TLV
<sup>3</sup> NR (SMV)	Non-response (simeprevir)	HCV RNA $\geq 25$ IU/mL at week 4, 12 or 24, futility rule for SMV
NR (FDV)	Non-response (faldaprevir)	not defined in 1/2014
RL	Relapse	HCV RNA negative at EOT and recurrence of HCV RNA during the follow-up
PR	Partial Response	HCV RNA decline $\geq 2 \log_{10}$ at week 12 but positive at week 24 during PEG-IFN + RBV
NULR	Null response	HCV RNA decline $< 2 \log_{10}$ at week 12 during PEG-IFN + RBV
LI	Lead-In	4 weeks PEG-IFN + RBV before adding a PI

LLD, lower limit of detection ( $< 10$ - $15$  IU/mL; here indicated as negative); LLQ, lower limit of quantification; EOT, end of treatment; RGT, response-guided therapy

<sup>1</sup>as defined in the Phase III trials; Recommendation in the final prescribing information may differ.

<sup>2</sup>as defined in the Phase III trials; Recommendation for RGT are different in the final prescribing information of the US (no RGT) and Canada (undetectable result required at week 4)

<sup>3</sup>as defined in the US (FDA) label. In Canada futility rules are met if HCV RNA is detectable at any level at week 12 or 24 or  $\geq 25$  IU/ml at week 4.



**Figure 4.1 – Development of chronic hepatitis C therapy.** The sustained virologic response rates have improved from around 5% with interferon monotherapy in the early 90s to >80% today with triple therapy of PEG-IFN + RBV + PI or SOF or even SOF + RBV (data for treatment-naïve patients). Indicated trials are not head-to-head and it is difficult to compare SVR between different studies because the populations had significant differences in genetic and socioeconomic backgrounds.

**Table 4.2 – Approved drugs for the treatment of chronic hepatitis C and drugs that will be most likely approved in 2014**

Medication	Dosing
<b>Type I interferons</b>	<b>Subcutaneous injection</b>
Pegylated interferon $\alpha$ -2a (Pegasys®)	180 $\mu$ g once weekly
Pegylated interferon $\alpha$ -2b (PEG-Intron®)	1.5 $\mu$ g/kg once weekly
Interferon $\alpha$ -2a (Roferon®)	3 - 4.5 Mill IU three times weekly
Interferon $\alpha$ -2b (Intron A®)	3 Mill IU three times weekly
Consensus Interferon (Infergen®)	9 $\mu$ g three times weekly
<b>Ribavirin</b>	<b>Oral</b>
Ribavirin (Copegus®)	800 - 1200 mg daily (200 mg or 400 mg tablets)
Ribavirin (Rebetol®)	600 - 1400 mg daily (200 mg capsules or solution)
<b>HCV NS3/4A protease inhibitors</b>	<b>Oral</b>
Boceprevir (Victrelis®)	800 mg (4 x 200 mg capsules) every 7-9 hours
Telaprevir (Incivek®, Incivo®)	750 mg (2 x 375 mg tablets) every 7-9 hours* *3 x 375 mg every 12 hours is as effective in treatment-naïve patients ( <a href="#">Buti 2013</a> )
Simeprevir (Olysio® (US), Sovriad® (Japan), Galexos® (Canada))	150 mg (1 x 150 mg capsules) once daily 100 mg in Japan
Faldaprevir	120 mg once daily or 240 mg once daily Loading dose (240 mg or 480 mg) at the first day
<b>HCV NS5B polymerase inhibitors</b>	<b>Oral</b>
Sofosbuvir (Sovaldi®)	1 x 400 mg once daily
<b>HCV NS5A replication complex inhibitor</b>	<b>Oral</b>
Daclatasvir (Daklinza®)	1 x 60 mg once daily

## Predictors of treatment response

Over the last decade, tailoring treatment duration and dosing according to individual parameters associated with response has improved SVR. Predicting SVR before the start of antiviral

treatment helps in making treatment decisions. Important baseline factors associated with SVR to PEG-IFN/RBV are the HCV genotype, the degree of liver fibrosis and steatosis, baseline viral load, presence of insulin resistance, age, gender, body mass index, ethnicity, and HIV coinfection (Berg 2011, [McHutchison 2009b](#)).

Many of these factors may have less relevance for triple therapy, ie, insulin resistance seems not to impact SVR to PEG-IFN/RBV/PI (Berg 2011, Serfaty 2010) whereas low-density lipoprotein (LDL) was associated with SVR (at least for TLV) (Berg 2011). On the other hand, new parameters seem to be more important such as HCV subtypes 1a and 1b. Patients with HCV GT1a have a higher risk of developing resistance during PI-based therapy compared to HCV GT1b because HCV GT1a requires an exchange of only one nucleotide versus two for HCV GT1b at position 155 in order to develop resistance (reviewed in [Sarrazin and Zeuzem 2010b](#)). This will remain important also for future IFN-free therapies. For simeprevir, a GT1a variant with the so-called Q80K mutation is important. In the PROMISE trial of PEG-IFN/RBV relapse patients, only 47% of HCV GT1a Q80K+ infected patients achieved SVR after re-therapy with SMV/PEG-IFN/RBV triple therapy. In contrast, SVR rates increased to 79% in patients with HCV GT1a infection with the Q80K wild type (Forns 2013). Similar results were observed in treatment-naïve patients.

In the QUEST-1 study, in which almost half of the patients were recruited in the US, there was no significant increase in SVR rates compared to placebo if patients with HCV GT1a Q80K+ were treated with SMV (Jacobson 2013c), while cure rates between HCV GT1a Q80K- and GT1b appear to be almost similar. In the US prescribing information, testing for the Q80K mutation is recommended for HCV GT1a patients. It is unclear whether this is cost-effective, in particular in areas of the world where the Q80K mutation is rare. While the Q80K variant was present in 41% of the HCV GT1a patients in the QUEST-1 study, only 23% of the HCV GT1a patients had this specific variant in the QUEST-2 trial that mainly took place in Europe (Zeuzem 2013a). Although

SVR rates were markedly impaired in the PROMISE and the QUEST-2 trial if the Q80K variant was detected at baseline, patients still had significantly higher chances to achieve SVR if SMV was part of the regimen (Forns 2013, Manns 2013b).

During treatment, the kinetics of the HCV RNA decline is a strong predictor of response. HCV RNA measurements at weeks 4, 12 and 24 are important for a response-guided treatment approach for PEG-IFN/RBV but also for the new triple therapy including BOC, TLV, SMV and FDV. Definitions of response and futility rules are summarized in Table 4.1. (Futility means that if at certain time points, the viral load threshold is exceeded or detected in serum, therapy should be stopped). In contrast to the Phase III trials, RGT is not recommended for SMV in the US label (Figure 4.2C), while in the Canadian prescribing information recommended HCV RNA thresholds differ from those applied in the pivotal trials. So far, there is no RGT for triple therapy with sofosbuvir as treatment duration is 12 weeks for all patients (Figure 4.2D).

For the interpretation of on-treatment HCV RNA results, different assay performances have to be considered. It has been shown that the Roche HPS/TaqMan Test v2.0, which was used in most of the clinical trials, has a significantly lower sensitivity compared with, ie, the Roche Cobas Ampliprep/Cobas TaqMan (CAP/CTM) v.2.0 or the Abbott RealTime assay (ART). A retrospective analysis of 164 patients treated with TLV revealed that 67% and 31% had undetectable HCV RNA at week 4 by CAP/CTM and ART, respectively. However, 58% of eligible patients for RGT treatment based on CAP had detectable HCV RNA by ART at week 4, but relapse was not observed in these patients. Thus if the Abbott RealTime assay is used, shortening of treatment may also be discussed if HCV RNA is detected but below the assay level of quantification (Vermehren 2014).

Furthermore, it has to be considered that the reliability of all HCV RNA assays is limited if HCV RNA yields levels close to or below the assay's so-called "limit of detection" (LOD). The LOD is defined as the threshold where HCV RNA can be detected in 95%

of the cases. If levels drop below the LOD HCV RNA may still be found and reported as detected but in less than 95%. Recently it has been shown that residual viremia could be detected after two repeated tests in 32-50% of the week 4 samples that initially tested HCV RNA negative (Maasoumy 2014). In a post-hoc analysis of the BOC and TLV Phase III trials it was shown that SVR chances are best in those achieving HCV RNA undetectability early during treatment even compared to those with only residual viremia at levels below the assay's limit of quantification (Harrington 2012). In difficult-to-treat patients (advanced fibrosis, previous PEG-IFN/RBV treatment failure) SVR chances further increased if a negative HCV RNA result can be confirmed by repeat testings, which may be considered in single patients with a poor treatment tolerability (Maasoumy 2014).

Recently, genome-wide association studies have identified host genetic polymorphisms (ie, rs12979860, rs8099917) located on chromosome 19 located upstream of the region coding for IL28B (or IFN  $\lambda$ 3) associated with spontaneous HCV clearance and SVR to treatment with PEG-IFN/RBV in HCV GT1 patients (Ge 2009, Rauch 2010, Suppiah 2009, Tanaka 2009) but also to a lesser extent for HCV GT2/3 (Sarrazin 2011b, Mangia 2010). Data on IL28B explain the different responses to PEG-IFN/RBV between different ethnic groups, ie, the low SVR in African Americans and the high SVR in Asian patients. However, the negative predictive value is not strong enough to recommend general testing (EASL 2014).

Recently, a new dinucleotide variant ss469415590 (TT or  $\Delta$ G) upstream of IL28B (or IFN  $\lambda$ 3), which is in high linkage disequilibrium with IL28B rs12979860, was discovered (Prokunina-Olsson 2013). IFN  $\lambda$ 4 ss469415590[ $\Delta$ G] is a frameshift variant that creates a novel gene, encoding the IFN  $\lambda$ 4 protein. Compared to the IL28B SNP, the IFN  $\lambda$ 4 DNP is more strongly associated with HCV clearance in individuals of African ancestry, although it provides comparable information in Europeans and Asians (Prokunina-Olsson 2013). Viral kinetics, especially

response at week 4, have a higher predictive value (Sarrazin 2011a, Poordad 2012), and the relevance of IL28B as a predictive marker for the success of triple therapy with PEG-IFN/RBV/PI is less significant (Jacobson 2011a, Pol 2011a, Poordad 2012). However, IL28B testing may be useful to determine the IFN responsiveness and the likelihood of achieving RVR with PEG-IFN/RBV before starting triple therapy with PEG-IFN/RBV plus one DAA, especially in countries with limited health budgets. It may be of relevance to discuss treatment options with the individual patient (see below). Additional predictive markers are being evaluated. For example, low serum levels of interferon  $\gamma$  inducible protein 10 (IP-10) are associated with SVR and may improve the predictive value for discrimination between SVR and non-response (Darling 2011, Fattovich 2011). Predictive markers for the first IFN-free regimen SOF plus RBV patients are, ie, female sex and to a lesser degree with a baseline viremia of  $<6 \log_{10}$  IU/mL, a body weight  $<30 \text{ kg/m}^2$ . However, apart from female sex, the predictive markers are of lesser value in the subgroups of treatment-experienced and cirrhotic patients. Further studies are needed, given the overall lower number of treated patients so far (Lawitz 2013a, Jacobson 2013d). For HCV GT3 patients on-treatment HCV RNA kinetics may predict a later relapse (Osinusi 2013).

## Antiviral resistance

The development of direct antiviral agents leads to the emerging problem of drug resistance due to so-called resistance-associated amino acid variants (RAVs) of the virus. Patients who received monotherapy with BOC or TLV developed resistance within a few days (Sarrazin 2007). Due to their overlapping resistance profiles, one PI cannot substitute the other in the case of viral breakthrough. Also, a combination of the two PIs will not work. As mentioned above, combination with PEG-IFN/RBV or other DAA classes is mandatory for the usage of these PIs. Importantly, if patients have a decreased PEG-IFN/RBV response, the risk of



developing significant RAVs is higher. Measures for the prevention of drug resistance are adherence to the dose of the medications (most importantly to the PI) and compliance with the futility rules (see below). If RAVs emerge, it is not completely known for how long they persist and if this has any significant consequences for future therapies. Some studies suggest that the majority of PI resistant variants revert to wild type within 1-2 years after the end of therapy (Sarrazin 2007, Sherman 2011b). At this stage there is no rationale to routinely analyse HCV sequences either before therapy or during treatment because it has no practical consequence. One exception is the testing for the Q80K variant in GT1a patients, especially in North America, as discussed earlier. The combination of different DAA classes may overcome the problem of resistance and allow IFN-free combinations. SOF has a very high resistance barrier and even SOF plus the weak antiviral RBV lead to high SVR rates (Lawitz 2013a, Jacobson 2013d, Osinusi 2013, Sulkowski 2013a). Theoretically, SOF could be combined with a PI or an NS5A inhibitor if these drugs are available. However, is not recommended to combine SOF with BOC or TLV due to lack of data and potential drug interactions via the Pgp transporter. So far, the combination of SOF and SMV has been evaluated in the COSMOS trial, which showed >90% SVR for 12 weeks SOF plus SMV, even without RBV (Jacobson 2013b). This combination may be considered in patients with an urgent need for treatment and IFN intolerance. SOF plus DCV has been studied in 221 patients with GT1-3, among those 41 GT1 patients with treatment failure to PEG-IFN/RBV/PI triple therapy. The SVR was achieved in all 41 patients with previous PI failure (Sulkowski 2014) (Table 4.7).

## Treatment of HCV genotype 1

### Treatment of naïve patients

In 2014, untreated patients with HCV genotype 1 (HCV GT1) have various treatment options, which can be different around the world as not all new treatment options will be available in all countries at the same time. For detailed information regarding dual treatment with PEG-IFN/RBV we would like to refer to the Hepatology Textbook 2013 (available at [www.FlyingPublisher.com/9003.php](http://www.FlyingPublisher.com/9003.php)). Here we describe the different treatment strategies including the DAAs available in 2014 (boceprevir, telaprevir, simeprevir, faldaprevir, sofosbuvir and daclatasvir) (Table 4.2). However, dual therapy in easy-to-treat patients may still be an option also in this setting as later discussed.

Triple therapy with PEG-IFN + RBV + PI increases the overall SVR by around 30% (Table 4.3, Table 4.4). Many patients qualify for response-guided therapy (RGT) based on viral kinetics. For BOC and TLV, 44-65% of patients achieve eRVR and treatment duration can be reduced to 24-28 weeks (Figures 4.2A, 4.2B), some 4-6 times more than with PEG-IFN/RBV. SMV and FDV triple therapy increase the rate of patients that qualify for shorter treatment of 24 weeks, up to 84-91% according to the RGT criteria that were applied in the respective Phase III trials (Table 4.4). However, according to the US label of SMV all treatment-naïve patients are supposed to receive only 24 weeks of treatment (Figure 4.2C). If HCV RNA is detected at levels are  $\geq 25$  IU/ml after 4 weeks of treatment discontinuation of all drugs is recommended. Also the recommended treatment regimens differ from those in the pivotal trials. Here, detectable HCV RNA levels  $< 25$  IU/ml are not sufficient to recommend shortening of treatment. Instead an undetectable result was required at weeks 4 and 12.

**Table 4.3 – Phase III studies with BOC or TLV treatment regimens in treatment-naïve patients with HCV genotype 1.** Studies are not head-to-head and it is difficult to compare SVR between different studies because the populations had significant differences in genetic and socioeconomic backgrounds.

Study	Dosing	eRVR, SVR
SPRINT-2 (Poordad 2011b)  n=938 non- black (NB) n=159 black  *28 weeks if eRVR BOC	a) 1.5 µg/kg PEG-IFN $\alpha$ -2b, 600-1400 mg RBV 48 weeks 44 weeks placebo (wk 4-48)	a) eRVR: 40/363 (11%) / NB: 12% SVR: 137/363 (38%) / NB: 40%
	b) 1.5 µg/kg PEG-IFN $\alpha$ -2b, 600-1400 mg RBV <u>28*-48 weeks</u> <u>24 weeks 800 mg TID BOC</u> (wk 4-28)	b) eRVR: 156/368 (42%) / NB: 45% SVR: 233/368 (63%) / NB: 67%
	c) 1.5 µg/kg PEG-IFN $\alpha$ -2b, 600-1400 mg RBV 48 weeks 44 weeks 800 mg TID BOC (wk 4-48)	c) eRVR: 155/366 (42%) / NB: 44% SVR: 242/366 (66%) / NB: 68%
ADVANCE (Jacobson 2011b)  n=1088  *24 weeks if eRVR TLV	a) 180 µg PEG-IFN $\alpha$ -2a, 1000-1200 mg RBV 24*-48 weeks, <u>12 weeks</u> 750 mg TID TLV (wk 0-12) (T12PR)	a) eRVR: 210/363 (58%) SVR: 271/363 (75%)**
	b) 180 µg PEG-IFN $\alpha$ -2a, 1000-1200 mg RBV 24*-48 weeks, <u>8 weeks</u> 750 mg TID TLV, 4 weeks placebo (wk 0-12)	b) eRVR: 207/363 (57%) SVR: 250/364 (69%)
	c) 180 µg PEG-IFN $\alpha$ -2a, 1000-1200 mg RBV 48 weeks, 12 weeks placebo (wk 0-12)	c) SVR: 158/361 (44%)
ILLUMINATE (Sherman 2011a)  n=540 n=352 (65%) eRVR  n=322 randomised	a) eRVR: 180 µg PEG-IFN $\alpha$ -2a, 1000-1200 mg RBV <u>24 weeks</u> , 12 weeks 750 mg TID TLV (wk 0-12)	a) SVR: 149/162 (92%)
	b) eRVR: 180 µg PEG-IFN $\alpha$ -2a, 1000-1200 mg RBV <u>48 weeks</u> , 12 weeks 750 mg TID TLV (wk 0-12)	b) SVR: 140/160 (88%)
	c) no eRVR: 180 µg PEG-IFN $\alpha$ -2a, 1000-1200 mg RBV 48 weeks, 12 weeks 750 mg TID TLV (wk 0-12)	c) SVR: 76/118 (64%)

\*\*numbers from the published data are different from the numbers accepted by FDA, ie, 79% SVR for telaprevir 12 weeks, PEG-IFN/RBV

**Table 4.4 – Phase III studies with SMV or FDV treatment regimens in treatment-naïve patients with HCV genotype 1.** Studies are not head-to-head and it is difficult to compare SVR between different studies because the populations had significant differences in genetic and socioeconomic backgrounds.

Study	Dosing	eRVR, SVR
QUEST 1&2 (Jacobson 2013a) n=785 *24 weeks if ETS SMV	a) 180 µg PEG-IFN α-2a, 1000-1200 mg RBV 48 weeks 12 weeks placebo b) 180 µg PEG-IFN α-2a/2b, 1000-1200 mg RBV 24*-48 weeks 12 weeks 150 mg QD SMV (wk 0-12)	SVR: 50% SVR: 80% ETS: 88%, SVR 90%
STARTVerso 1&2 (Jensen 2013) n=1309 *24 weeks if ETS FDV *STARTVerso 2	a) 180 µg PEG-IFN α-2a, 1000-1200 mg RBV 48 weeks, 12 weeks placebo b) 180 µg PEG-IFN α-2a, 1000-1200 mg RBV 24*-48 weeks, 12-24* weeks 120 mg QD FDV c) 180 µg PEG-IFN α-2a, 1000-1200 mg RBV 24*-48 weeks, 12 weeks 240 mg QD FDV	SVR: 131/264 (50%) ETS: 436/521 (84%), SVR 83% SVR: 382/521 (73%) ETS: 441/524 (84%), SVR 83%
		SVR: 378/524 (72%)

\*\*numbers from the published data are different from the numbers accepted by FDA, i.e., 79% SVR for telaprevir 12 weeks, PEG-IFN/RBV

At the time of writing, it is unclear what the recommendations will look like in Europe. The same may be true of the final recommendations for FDV regimens. Triple therapy with SOF plus PEG-IFN/RBV is just a 12-week treatment with SVR rates of 89% for GT1 (Table 4.5). The cost for SOF will be much higher than for other therapies. In countries with limited health care budgets and where approval of new DAAs is not foreseeable within the next year, dual therapy with PEG-IFN/RBV may still be an option for patients with favourable predictors for SVR (low baseline HCV RNA, IL28B-CC, no advanced fibrosis). In those patients, a lead-in of 4 weeks with PEG-IFN/RBV can identify patients with RVR who will achieve a high SVR rate without adding a PI. Patients with low viral load at baseline who achieve an RVR have demonstrated 78-100% SVR with 24 weeks of PEG-IFN/RBV dual therapy alone (Berg 2009, Ferenci 2008, Jensen 2006, Sarrazin 2011a, Zeuzem 2006) (Table 4.6). One prospective trial confirmed that 24 weeks of dual therapy is not inferior

compared to 28 weeks PEG-IFN/RBV/BOC in patients with low viral load and RVR (Pearlman 2014). Not adding a DAA will reduce costs and adverse events. The number of patients who qualify for dual therapy varies depending on the distribution of IL28B (IFN  $\lambda$ 3) polymorphisms.

**Table 4.5 – Phase II and III study with SOF treatment regimens in treatment-naïve patients with HCV genotype 1.** Studies are not head-to-head and it is difficult to compare SVR between different studies because the populations had significant differences in genetic and socioeconomic backgrounds.

Study	Dosing	SVR
NEUTRINO (Lawitz 2013a) N=292	180 $\mu$ g PEG-IFN $\alpha$ -2a, 1000-1200 mg RBV + 400 mg SOF QD 12 weeks	89% Cirrhosis: 80%
(Osinusi 2013) N=60	a) 1000-1200 mg RBV + 400 mg SOF QD 24 weeks b) 1000-1200 mg RBV + 400 mg SOF QD 24 weeks c) 600mg RBV + 400 mg SOF QD 24 weeks	F0-F2: 90% F0-F4: 68%; including compensated cirrhosis F0-F4: 48%; including compensated cirrhosis
PHOTON (Sulkowski 2013a) N=182 (HIV-coinfected)	a) 1000-1200 mg RBV + 400 mg SOF QD 24 weeks N=114, GT1 b) 1000-1200 mg RBV + 400 mg SOF QD 12 weeks N=68, GT2/3 c) 1000-1200 mg RBV + 400 mg SOF QD 24 weeks N=41, GT2/3	76% G2: 88% G3: 67% n.a.
COSMOS (Jacobson 2013b ) N=167 (n=121 with data)	a) 400 mg SOF QD + 150 mg SMV12-24 weeks N=80 b) 400 mg SOF QD + 150 mg SMV 12 weeks N=41 (SVR4 data)	Naive (F0-F2): 79-96% All fibrosis stages: Naive: 100% NR: 93-100%

SMV: simeprevir, SOF: sofosbuvir, RBV: ribavirin, SVR: sustained virological response, NR: null response

On the other hand, a lead-in therapy may identify patients with a poor response to IFN with a high chance of developing resistance. Other negative predictors (HCV GT1a, cirrhosis) together with the lead-in concept may increase the negative predictive value of achieving an SVR with PEG-IFN/RBV and a PI. In that case a wait-and-see strategy may be considered if other options (ie, SOF combination) are not yet available.

**Table 4.6 – High SVR in naïve patients with HCV genotype 1 and low baseline viral load treated with 24 weeks of PEG-IFN/RBV**

Study	Treatment	Subgroups (fast responder)	Wks	SVR
(Zeuzem 2006) n=235	1.5 µg/kg PEG-IFN α-2b 800-1400 mg ribavirin	<600,000 IU/ml TW0	24	50%
		<600,000 IU/ml TW0 & <29 IU/ml TW4 (RVR)	24	89%
(Berg 2009) n=433	1.5 µg/kg PEG-IFN α-2b 800-1400 mg ribavirin	<5.3 IU/ml TW4 (RVR)	18-24	80%
		<800,000 IU/ml TW0 & <5.3 IU/ml TW4 (RVR)	18-24	100%
(Sarrazin 2011a) n=398	1.5 µg/kg PEG-IFN α-2b 800-1400 mg ribavirin	<800,000 IU/ml TW0 & <5-10 IU/ml TW4 (RVR)	24	88%
				1.
(Jensen 2006) n=216	180 µg PEG-IFN α-2a or 800 mg or 1000-1200 mg ribavirin	<50 IU/ml TW4 (RVR)	24	89%
		>50 IU/ml TW4 (RVR)	24	19%
(Ferenci 2008) n=120	180 µg PEG-IFN α-2a or 1000-1200 mg ribavirin	<50 IU/ml TW4 (RVR)	24	74% ITT 79% PP
(Pearlman 2014) n=171	1.5 µg/kg PEG-IFN α-2b 1000-1200 mg ribavirin	Patients with <25 IU/ml TW4 (RVR) were randomized 1:1	24	89% Relapse 6%
		1.5 µg/kg PEG-IFN α-2b, 1000-1200 mg RBV 800 mg TID BOC (wk 4-28)	28	90% Relapse 3%

\* SVR, sustained viral response; RVR, rapid virologic response

The 4-week lead-in strategy also proved useful in assessing compliance, tolerability and safety before initiating the PI. The lead-in concept was developed in the BOC studies with the hypothesis of reducing resistance and improving SVR (Kwo 2010). However, the lead-in seems to have no significant effect on the SVR or on the development of antiviral resistance (Kwo 2010, Zeuzem 2011). For newer treatment options, this strategy will be less important. It is recommended to discuss the lead-in option and the consequences with the patient before initiation of treatment.

Another option for many patients without an urgent treatment indication in 2014 is to use a wait-and-see strategy as new IFN-free regimes for GT1 are foreseeable for 2015 (see Chapter 5).

Again, this may be different in many countries around the world. In contrast, for some patients with urgent treatment indication and IFN intolerance, even RBV-free combinations of SOF and SMV or SOF and DCV may be considered in 2014. Some companies may provide DAAs in compassionate use or early access programmes. For example, the European Medicines Agency advises on compassionate use of DCV in combination with SOF in patients in urgent need of therapy to prevent progression of liver disease (Anonymous 2014, <http://goo.gl/XMqr01>).

### **Approved DAA treatment regimens (1/2014)**

#### **Treatment regimens with boceprevir**

Boceprevir (BOC) is a linear peptidomimetic ketoamide serine protease inhibitor that binds reversibly to the HCV non-structural 3 (NS3) active site. BOC results in a significant decline of HCV RNA but given as monotherapy leads to rapid emergence of viral resistance (Sarrazin and Zeuzem 2010b). Thus, combination with PEG-IFN/RBV is necessary (Mederacke 2009). 800 mg BOC is given as 200 mg capsules every 7-9 hours together with food in combination with the optimal dose of PEG-IFN/RBV (Table 4.2). In all Phase III trials BOC was added after the 4-week lead-in period as described above. In SPRINT-2 (serine protease inhibitor therapy 2), the Phase III study with 1097 treatment-naïve HCV GT1 patients, safety and efficacy of two regimens of BOC added to PEG-IFN  $\alpha$ -2b/RBV after a 4-week lead-in with PEG-IFN/RBV were compared to PEG-IFN/RBV/placebo (Table 4.3) for 44 weeks. The two groups receiving BOC were treated with an RGT concept or a fixed duration of BOC. Patients in the RGT group received 24 weeks triple combination after the lead-in period. Treatment with PEG-IFN/RBV was continued through week 48 only if the criteria for eRVR were not met (HCV RNA levels undetectable from week 8 through week 24). Patients in the fixed therapy duration group received PEG-IFN/RBV/BOC for 44 weeks following the 4-week lead-in phase. Based on published data for response rates being lower for African-American

patients, black and non-black patients were analysed as two different pre-defined cohorts in the SPRINT-2 study. Overall, adding BOC to PEG-IFN/RBV significantly improved SVR in previously untreated patients with HCV genotype 1 leading to approval in 2011. Non-black patients achieved 27-28% higher SVR, black patients increased SVR by 19-30%.

The responsiveness to PEG-IFN/RBV is very important for the success of treatment with BOC. This is highlighted by the fact that the HCV RNA decline at week 4 is highly predictive of SVR. Patients with more than 1  $\log_{10}$  HCV RNA decrease after the 4-week lead-in phase demonstrates an SVR of about 80% if treated with BOC, while only 28-38% responded if HCV RNA declined less than 1  $\log_{10}$ . Thus, the lead-in phase can be valuable in predicting responsiveness to PEG-IFN/RBV for further individualization of therapy as discussed above. Importantly, the overall SVR rates between the RGT group and the fixed 48-week therapy group were comparable (Table 4.4). Patients achieving eRVR were eligible for a 28 week total therapy duration and almost all patients (96%) went on to achieve SVR (Poordad 2011b). Of note, HCV RNA-negative means below the limit of detection (LLD) and not below limit of quantification (LLQ). This is important because SVR is diminished in patients with LLQ at weeks 8-24 who were treated for a shorter duration (Harrington 2012). However, this may depend on the HCV RNA assay as discussed above.

FDA and EMA have approved RGT for treatment-naïve patients except for patients with liver cirrhosis (Figure 4.2A) but the accepted treatment duration for BOC RGT is different than the definition within the Phase III study (32 vs 24 weeks BOC for patients without eRVR) (Figure 4.2A). In addition, futility rules on prescription information differ from those applied in the Phase III trials, ie, there was no week 12 stopping criteria in the SPRINT-2 study, while patients were supposed to discontinue treatment if they had detectable HCV RNA at week 12 in the RESPOND-2 trial. None of the 65 patients with HCV RNA level >100 IU/ml at week 12 achieved SVR in the SPRINT-2 study (Jacobson 2012). However, 21 patients achieved SVR despite

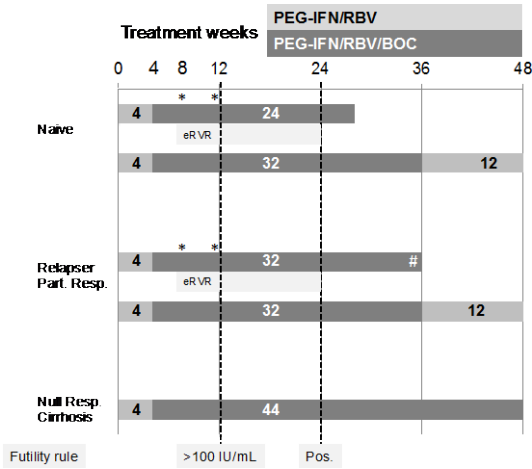


detectable HCV RNA but <100 IU/ml at week 12. Based on a retrospective analysis in a small number of patients, this supports the futility rule of >100 IU/ml at week 12. There is no week 8 stopping rule in the prescribing information for BOC, while comparable stopping criteria have been established for TLV (4 weeks of triple therapy). However, Phase III data provide some support for a stopping rule at week 8. A futility rule of <3 log<sub>10</sub> decline at week 8 would have missed SVR in only 2/53 patients (Jacobson 2012). The question is whether achieving SVR in two more patients, while exposing 51 patients unnecessarily to four more weeks of triple therapy with the associated costs and AEs is reasonable. Treatment discontinuation could be discussed in these patients on an individual basis.

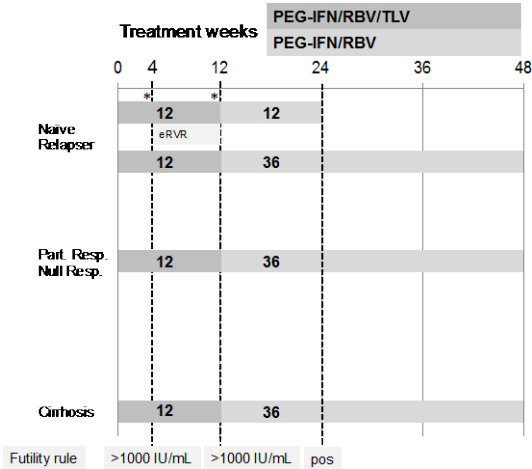
BOC was initially combined with PEG-IFN  $\alpha$ -2b. Recently, a study in therapy-experienced patients including relapsers and partial responders showed similar results with PEG-IFN  $\alpha$ -2a/RBV (Flamm 2013). Thus, both PEG-IFNs can be combined with BOC. This concept seems to be valid for all other DAA.

### **Treatment regimens with telaprevir**

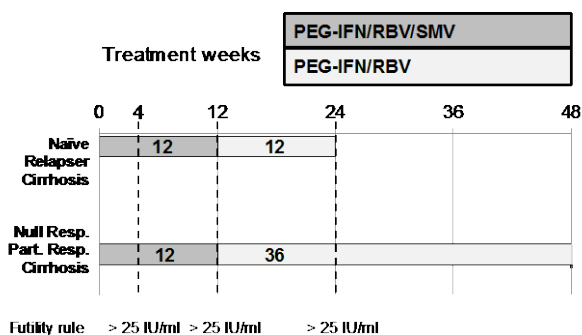
Telaprevir (TLV) is also an orally administered reversible, selective, peptidomimetic NS3/4A serine protease inhibitor, which leads to a significant decline of HCV RNA although viral resistance emerges rapidly if given as monotherapy (Sarrazin 2007). Thus, 750 mg TLV given as 375 mg tablets every 7-9 hours together with food (ideally >20 g fat) is combined with optimal PEG-IFN/RBV. One prospective trial has demonstrated similar response rates with 750 mg three times a day or with 1125 mg twice daily in treatment-naïve patients (Buti 2013). TLV was administered for a maximum of 12 weeks in the Phase III trials; longer treatment duration is associated with increasing adverse events (McHutchison 2010). Two large Phase III studies (ADVANCE and ILLUMINATE) with a total of 1628 treatment-naïve HCV GT1 patients showed that PEG-IFN/RBV/TLV significantly improved SVR compared to PEG-IFN/RBV and RGT is possible (Jacobson 2011b, Sherman 2011a).



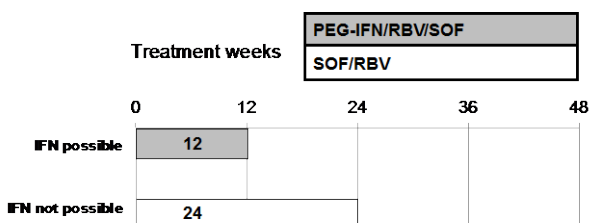
**Figure 4.2A – Treatment with BOC/PEG-IFN/RBV: Approved treatment algorithm for HCV GT1 patients.** \*, RGT if eRVR (HCV RNA LLD week 8-24); #, EMA did not approve RGT for BOC regimens in previously-treated patients.



**Figure 4.2B – Treatment with TLV/PEG-IFN/RBV: Approved treatment algorithm for HCV GT1 patients.** \*RGT if eRVR (HCV RNA LLD week 4-12).



**Figure 4.2C – Treatment with SMV/PEG-IFN/RBV: Treatment algorithm for HCV GT1 patients according to FDA approval**



**Figure 4.2D – Treatment with SOF/PEG-IFN/RBV: Treatment algorithm for HCV GT1 patients according to FDA and EMA approval.** If patients have contraindications for PEG-IFN, treatment with SOF/RBV can be given for 24 weeks. Although not evaluated, SOF combination therapy has been also approved for patients with previous treatment failure.

TLV was approved for the treatment of HCV GT1 in 2011. In the ADVANCE trial, 3 treatment groups were assessed for efficacy and safety using RGT in treatment-naïve patients (Jacobson 2011b). 12 weeks of TLV versus 8 weeks of TLV in combination with 24-48 weeks PEG-IFN/RBV were compared to 48 weeks PEG-IFN/RBV alone. Patients who achieved eRVR qualified for 24 weeks of therapy (Table 4.3). SVR was significantly higher among those receiving TLV compared to the placebo group; 12 weeks TLV resulted in the highest SVR (Table 4.3). In all treatment

groups, more than 80% of patients who achieved eRVR attained SVR (89%, 83%, and 97%, respectively) (Jacobson 2011b).

To validate RGT, telaprevir 750 mg every 8 hours for 12 weeks was evaluated in an open-label study (ILLUMINATE trial) to prospectively assess 24 vs 48 weeks of treatment for HCV GT1 patients who achieved eRVR. If HCV RNA levels were undetectable at weeks 4 and 12, patients were randomly assigned to continue with PEG-IFN/RBV for an additional 24 or 48 weeks. If eRVR was not attained, patients received PEG-IFN/RBV for up to 48 weeks. Of the 540 subjects, 389 (72%) achieved HCV RNA levels LLD at week 4 and 352 (65%) achieved eRVR. Patients who achieved eRVR and were randomized to the 24-week cohort experienced 92% SVR, versus 88% who were treated for 48 weeks (Table 4.3) (Sherman 2011a). Importantly, patients with liver cirrhosis showed higher relapse rates with shorter treatment, therefore RGT for TLV has only been approved for naïve HCV GT1 patients without liver cirrhosis. Also, retrospective analysis of the data showed that early HCV RNA measurement at week 4 is predictive of non-response to TLV. Patients with HCV RNA values >1000 IU/mL after 4 weeks PEG-IFN/RBV/TLV did not achieve SVR. Therefore, therapy must be stopped (Figure 4.2B).

In contrast, some easy-to-treat patients may only require 12 weeks of treatment. A retrospective analysis of the PROVE2 study revealed that all 12 naïve patients with IL28B CC genotype without cirrhosis achieved SVR after 12 weeks of PEG-IFN/RBV/TLV (Bronowicki 2012). However, the prospective CONCISE trial that evaluated 12 weeks PEG-IFN/RBV/TLV in 239 IL28B CC patients showed that those patients with RVR who were treated for 12 weeks showed 87% SVR while those patients who continued PEG-IFN/RBV for an additional 12 weeks achieved 97% (Nelson 2013).

### **Treatment regimens with simeprevir**

Simeprevir (SMV) is an orally administered reversible, selective, macrocyclic NS3/4A serine protease inhibitor, which leads to a significant decline of HCV RNA although viral resistance emerges

rapidly if given as monotherapy (Reesink 2010). Standard therapy is SMV 150 mg given once daily together with food, and requires combination with PEG-IFN/RBV. SMV is given for the first 12 weeks of therapy. Regimens with a longer 24 weeks treatment phase were investigated in the Phase II study PILLAR but revealed no significant benefit in terms of SVR rates (Fried 2013). Two large Phase III trials QUEST-1 and QUEST-2 were performed to prove the efficacy and safety of SMV in treatment-naïve HCV GT1 infected patients. A total number of 785 patients were randomized to receive either SMV (n=521) or placebo (n=264), both in combination with PEG-IFN/RBV. Patients that received SMV achieved SVR in 80% of the cases compared to only 50% in placebo group (Table 4.4).

At the end of 2013, SMV was approved in Japan, Canada and the US. All large Phase IIb and III study (Jacobson 2013a, Fried 2013) patients were treated for only 24 weeks if they showed a rapid decline in HCV RNA levels (ETS, Table 4.1). The applied RGT criteria were HCV RNA <25 IU/ml even if still detectable at week 4 and undetectable HCV RNA at week 12. 85% and 91% of the patients in QUEST-1 and QUEST-2 achieved this, respectively. Patients with an HCV RNA level  $\geq$ 25 IU/ml at week 4 achieved SVR in only 25%. Thus, the US prescribing information recommends treatment discontinuation in these cases. If the HCV RNA was <25 IU/ml but still detectable SVR rates were slightly lower compared with those with an undetectable result at week 4 (68% vs. 90%) (Jacobson 2013a). In contrast with TLV and BOC regimes, the recommended treatment duration for patients with compensated cirrhosis does not differ from those with lower stages of liver fibrosis (Figure 4.2C).

SMV increases SVR rates irrespective of the type of PEG-IFN (2a or 2b) that is used. This was shown in the QUEST-2 study, in which 245 patients were randomized to receive either PEG-IFN 2a or PEG-IFN 2b. There was a numerically higher SVR rate in the PEG-IFN 2a group. However, there was no difference between the PEG-IFN 2b group and a third group of patients that received PEG-IFN 2a without randomization (Manns 2013b). Furthermore,

the aim was not nor was the study appropriately powered to directly compare the two types of PEG-IFN. The aim was simply to show that SVR rates are improved independent of the type of PEG-IFN. While it remains unclear whether there is a benefit for any of the two types of PEG-IFN, it was shown that both can safely be used in combination with SMV.

### **Treatment regimens with sofosbuvir**

Sofosbuvir (SOF) is an oral NS5B polymerase inhibitor (Sofia 2010). SOF has a pangenotypic activity and a very high barrier to resistance (Lam 2012), although SOF should only be taken in combination with other antiviral(s), and monotherapy should be avoided. It is taken once daily at a dosage of 400 mg (Table 4.2). The NEUTRINO trial evaluated the use of PEG-IFN/RBV and SOF in 327 treatment-naïve patients with HCV GT1, GT4, GT5 and GT6 infection. 292 of these patients had HCV GT1. Therapy was given for 12 weeks. The total SVR for all GT1 patients was 89%. Cirrhotic patients achieved SVR in 80% (Table 4.5). However, there was no control group, so direct comparison with PEG-IFN/RBV or other therapies is not possible (Lawitz 2013a).

SOF was also evaluated as an interferon-free regimen in combination with RBV in HCV-monoinfected patients (Osinusi 2013) and HIV-coinfected patients in the PHOTON-1 trial (Sulkowski 2013a) (Table 4.5). A patient population with predictors of a negative treatment outcome was selected (Osinusi). Most of the patients were male African Americans, had HCV GT1a infection and the IL28B CT/TT genotype. In the first part of the study 10 patients with mild to moderate fibrosis (F0-F2) were treated with weight-based RBV and 400 mg SOF for 24 weeks. 90% achieved SVR. In the second part of the study 50 patients were equally randomized to either weight-based RBV and 400 mg SOF or 600 mg RBV and 400 mg SOF for 24 weeks. In the low dose RBV group, 48% achieved SVR, whereas in the weight-based RBV group the SVR rate was 68% (Table 4.5).

More data on SOF and RBV in HCV GT1 infection and HIV/HCV coinfecting patients in the PHOTON-1 trial was presented. 114

treatment-naïve patients were selected for treatment with SOF and RBV for 24 weeks. Several ART regimens for HIV treatment were allowed. CD4 T cell count needed to be  $>200$  cells/mm<sup>3</sup> and HIV RNA  $<50$  cop/ml. Although cirrhotic patients were allowed, only 4% of patients had cirrhosis. 76% achieved SVR (Sulkowski 2013a). Similar to the Osinusi trial, the majority of patients were male. Other predictors of a negative treatment outcome, ie, GT1a infection and African American background, were less common.

So far, SOF in combination with RBV with or without PEG-IFN has not been tested in patients with HCV GT1 infection and previous relapse or null response. Because of missing control arms in the existing studies, a direct comparison with other treatment regimens is not possible. As the label of SOF allows combination with antiviral therapies, the potential combination with other approved drugs such as SMV or DCV may be considered. However, so far there are only data from Phase II trials for these combinations (Table 4.5, Table 4.7). Still, the SVR rates are  $>90\%$  for 12-24 weeks of IFN and RBV-free treatment with SOF + SMV or DCV (Jacobson 2013b, Sulkowski 2014)

### **Not yet approved DAA treatment regimens (1/2014)**

#### **Treatment regimens with faldaprevir**

Faldaprevir (FDV) is an inhibitor of the HCV NS3/4A protease, binding to this enzyme active site non-covalently and reversibly, impacting viral replication in HCV-infected host cells. The half-life of FDV is approximately 20-30 hours allowing for a once daily administration. FDV was studied in Phase III clinical trials in a broad population of naïve patients infected by HCV GT1 (Jensen 2013) and previously experienced to interferon-based treatments (relapsers, partial and null responders) (Jacobson 2013e) as well as in HIV-coinfected patients (STARTVerso 4) (Rockstroh 2013). Overall, 1314 naïve GT1 patients were recruited into two double-blinded placebo-controlled trials. STARTVerso 1 was conducted in Europe and Japan and STARVerso 2 in North America, South

Korea and Taiwan. A combined analysis of the two studies was presented at AASLD 2013 (Jensen 2013). In group 1, patients received 48 weeks of PEG-IFN/RBV. Group 2 received 24 weeks PEG-IFN/RBV in combination with 120 mg FDV for 12 or 24 weeks (STARTVerso 1: FDV for 12 weeks; STARTVerso 2: FDV for 24 weeks) in the case of an early treatment response (ETS = HCV RNA <25 after week 4 and negative at week 8). Patients without ETS were treated for 48 weeks with PEG-IFN/RBV and 24 weeks with 120 mg FDV. Patients in group 3 received 24 weeks PEG-IFN/RBV plus 12 weeks 240 mg FDV if ETS was achieved and if not, an additional 24 weeks (total 48 weeks) PEG-IFN/RBV (Table 4.4). Overall, FDV triple therapy resulted in 72-73% SVR, which was 22-23% higher vs. dual PEG-IFN/RBV. 84% of patients treated with FDV achieved ETS and could be treated for the shorter period of 24 weeks with 83% SVR. Response rates in Asia (PEG-IFN/RBV 62% vs. PEG-IFN/RBV/FDV 88%) were higher compared to Europe (PEG-IFN/RBV 49% vs. PEG-IFN/RBV/FDV 77-78%) or North America (PEG-IFN/RBV 45% vs. PEG-IFN/RBV/FDV 60-63%). At baseline, the Q80K variant that was associated with poorer response to SMV was present in 34% of GT1a patients. However, importantly, SVR rates were not associated with Q80K in patients treated with FDV. Patients with GT1a showed slightly higher rates of breakthrough (10-11% vs. 4%) and relapse (10-16% vs. 6-8%) compared with GT1b patients. The exact treatment algorithm for FDV is currently (1/2014) not known. The efficacy and safety results indicate that the possible treatment regimen is similar to the one used for TLV and SMV, an initial 12 week period of 120 mg FDV combined with PEG-IFN/RBV, followed by a 12 week period of PEG-IFN/RBV in the case of ETS in naive as well as relapse patients. Similar to SMV, patients with cirrhosis and ETS did not benefit from longer treatment. It is not clear if FDA and EMA will approve RGT (48 weeks for non-ETS patients). Futility rules are also not clear at this point. They may be similar to SMV triple therapy.



### **Treatment regimens with daclatasvir**

Daclatasvir (DCV) is an inhibitor of the HCV NS5A replication complex (Gao 2010). DCV is given one daily at a dose of 60 mg. DCV has been tested in combination regimens with PEG-IFN/RBV as well as with other DAAs including asunaprevir (Lok 2012, Suzuki 2013) and sofosbuvir (Sulkowski 2014). Details of the DCV studies are given in Chapter 5. Due to the recent marketing authorization application for the use of DCV for the treatment of adults with chronic hepatitis C with compensated liver disease and possible early access programs with DCV, we will focus on some aspects of DCV in the section of patients with treatment failure below. Of interest are the IFN-free data with DCV plus SOF (Table 4.7) that may be considered for patients with an urgent treatment indication.

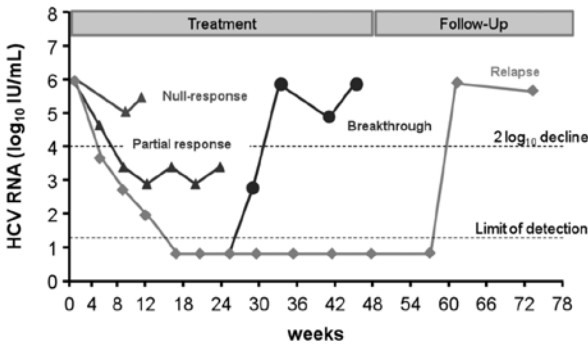
### **Treatment of patients with prior antiviral treatment failure**

As more patients are treated, the size of the population of patients who have failed to achieve SVR with PEG-IFN/RBV and PEG-IFN/RBV/PI also has expanded. Many non-responder patients have advanced liver disease and successful treatment may extend life expectancy (Backus 2011, Veldt 2007, van der Meer 2012). Retreatment of patients with previous treatment failure is one of the most important current topics in the treatment of chronic hepatitis C.

#### **Definition of treatment failure**

Definition of response to or failure on antiviral therapy is very important when considering retreating patients with chronic hepatitis C because the success of PI-based regimens depends on the IFN responsiveness. So far there is lack of data with SOF triple therapy in prior nonresponders. Patients may have been treated with different treatment regimens and compliance on those therapies may have varied greatly. Most importantly, HCV RNA kinetics and the response profile during the previous therapy have to be taken into account before starting a new treatment. It is crucial to screen the patient's records and check

treatment duration, drug dosing and HCV RNA of the previous therapy. Non-response is the failure of a patient to clear HCV RNA at any point during treatment. Definitions used for trials assessing novel therapy approaches have generally defined non-response as the failure to achieve  $\geq 2 \log_{10}$  reduction of HCV RNA after 12 weeks. Classifications of non-response include null response, partial response, relapse, and breakthrough (see Table 4.1, Figure 4.3).



**Figure 4.3 – Different scenarios of antiviral treatment failure in chronic hepatitis C**

### **Retreatment of HCV GT1 patients with relapse after PEG-IFN/RBV**

Retreatment with PEG-IFN/RBV of relapse patients after IFN/RBV or PEG-IFN/RBV resulted in an SVR of 24-34% (Bacon 2011, Poynard 2009, Zeuzem 2011). Triple therapy with PEG-IFN/RBV/PI increases SVR dramatically to 69-89% (Bacon 2011, Zeuzem 2011, Zeuzem 2013a) (Table 4.7). Relapse patients are the ideal patients for retreatment with a PI-based triple therapy regimen. Patients have already proven to respond to PEG-IFN and RBV. Thus, the backbone to prevent PI resistance is effective and a lead-in strategy may not be as important as in other situations. RGT is possible with TLV and BOC based regimes

(Figures 4.2A, 4.2B) if cirrhosis is excluded (Ghany 2011, [Sarrazin 2012](#)). However, BOC RGT has only been approved by the FDA and not by the EMA because SVR was slightly lower in the RESPOND-2 RGT group (Table 4.7). The EMA label for SMV and FDV is currently uncertain. The FDA recommends that relapsers and naïve patients should be treated with the same 24-week regimen if SMV/PEG-IFN/RBV triple therapy is considered (Figure 4.2C). Importantly, this also includes relapse patients with liver cirrhosis. So far there are no data for PEG-IFN/RBV/SOF in relapsers but FDA and EMA have approved treatment. The use of DCV has not yet been discussed, so the EMA label is not clear.

### **Retreatment of HCV GT1 patients with previous partial response**

Patients who are partial responders (PR) to standard PEG-IFN/RBV combination therapy have demonstrated SVRs ranging between 7% and 15% with a standard PEG-IFN/RBV retreatment ([Bacon 2011](#), [Zeuzem 2011](#)). Retreatment with PI based triple therapy increases SVR to 40%-86% ([Bacon 2011](#), [Zeuzem 2011](#), [Zeuzem 2013a](#)) (Table 4.7). FDA, but not EMA, has approved RGT for BOC (Figures 4.2A, 4.2B). Treatment duration for PEG-IFN/RBV/TLV or SMV is 48 weeks for all PR patients (Figure 4.2B, 4.2C). The 4-7-fold increase justifies retreatment. However, SVR decreases significantly in patients with cirrhosis (ie, 34% with TLV) and other negative response factors (Pol 2011b). So far there are no data for PEG-IFN/RBV/SOF in partial responders, but FDA and EMA have approved treatment. The use of DCV has not yet been discussed, so the EMA label is not known.

### **Retreatment of HCV GT1 patients with previous null response**

Patients who are null responders (NULR) to standard PEG-IFN/RBV combination therapy have demonstrated SVR ranging between 5% and 16% with an optimised PEG-IFN/RBV retreatment (Jensen 2009, Poynard 2009, [Zeuzem 2011](#)). Retreatment with PEG-IFN/RBV/PI increased SVR more than 6-

fold in the REALIZE trial (Zeuzem 2011). However, overall SVR with triple therapy is limited to 29-59% (Zeuzem 2011, Vierling 2013) (Table 4.7). If further negative predictive factors are present (GT1a, cirrhosis), SVR rates are low. This may justify the lead-in concept to decide if treatment with a PI is beneficial. Patients who do not achieve a 1  $\log_{10}$  decline of HCV RNA after 4 weeks demonstrate only 15% SVR with PEG-IFN/RBV/TLV (Zeuzem 2011). Response rates have been slightly more promising with SMV regimens in the Phase II study ASPIRE (Zeuzem 2013a). Here, cirrhotic NULR achieved SVR in 31-46% of the cases. However, the number of patients was small and unfortunately previous NULR were excluded from Phase III trials. Futility rules are the same for treatment-experienced patients as for treatment-naïve patients (Figures 4.2A, 4.2B, 4.2C). So far there are no data for SOF triple therapy in NULR patients, but FDA and EMA have approved treatment based on data in naïve difficult-to-treat IL28B TT patients. As more potent IFN-free combination therapies are expected by 2015, patients without an urgent treatment indication may consider waiting for new treatment options.

### **Retreatment of HCV GT1 patients with failure to previous PI based triple therapy**

Data for retreatment of patients with HCV GT1 infection and failure to previous therapy with PEG-IFN/RBV + TLV or BOC have been presented in cohorts (Sulkowski 2014). 41 patients with nonresponse, relapse or breakthrough to the aforementioned therapies were randomized into two cohorts. Cohort 1 (n=21) received 60 mg of DCV and 400 mg of SOF daily for 24 weeks. Cohort 2 (n=20) received 60 mg of DCV, 400 mg of SOF and 1000-1200 mg of RBV daily for 24 weeks. All patients were non-cirrhotic. Cohort 1 achieved 100% SVR and cohort 2 achieved 95% SVR. However, 1 patient in cohort 2 missed his follow up visit at week 12 but tested HCV RNA negative 12 weeks later, thus all patients were cured (Table 4.7). No grade 3 or higher adverse events occurred in the DCV/SOF cohort and 1 SAE was documented in the DCV/SOF/RBV cohort. DCV is submitted for

approval in combination with SOF in Europe and may be available by Q3 2014 in some countries, providing patients with failure to previous PI-based therapy and other patients with an urgent treatment indication a possible solution.

**Table 4.7 – Phase III studies with PI treatment regimens in treatment-experienced patients infected with HCV genotype 1.** Studies are not head-to-head and SVR between studies are difficult to compare because they had significant differences in genetic and socioeconomic backgrounds.

Study	Dosing	SVR12, SVR24
RESPOND-2 (Bacon 2011) n=403  *36 weeks if eRVR BOC	a) 1.5 µg/kg PEG-IFN $\alpha$ -2b, 600-1400 mg RBV 48 weeks 44 weeks placebo (wk 4-48)	REL: 29% All: 21% PR: 7%
	b) 1.5 µg/kg PEG-IFN $\alpha$ -2b, 600-1400 mg RBV <u>36*-48 weeks</u> <u>32 weeks 800 mg TID BOC (wk 4-36)</u>	REL: 69% All: 59% PR: 40%
	c) 1.5 µg/kg PEG-IFN $\alpha$ -2b, 600-1400 mg RBV 48 weeks 44 weeks 800 mg TID BOC (wk 4-48)	REL: 75% All: 66% PR: 52%
(Flamm 2013) n=201	a) 180 µg PEG-IFN $\alpha$ -2a, 1000-1200 mg RBV 48 weeks 44 weeks placebo (wk 4-48)	REL, PR: 21%
	b) 180 µg PEG-IFN $\alpha$ -2a, 1000-1200 mg RBV 48 weeks 44 weeks 800 mg TID BOC (wk 4-48)	REL, PR: 64%
PROVIDE (Vierling 2013) n=164	1.5 µg/kg PEG-IFN $\alpha$ -2b, 600-1400 mg RBV 48 weeks 44 weeks 800 mg TID BOC (wk 4-48)	38% (20/52) NULR 67% (57/85) PR 93% (27/28) REL
REALIZE (Zeuzem 2011) n=663	a) 180 µg PEG-IFN $\alpha$ -2a, 1000-1200 mg RBV 48 weeks, 12 weeks placebo (wk 0-12)	REL: 24% PR: 15% NULR: 5%
	b) 180 µg PEG-IFN $\alpha$ -2a, 1000-1200 mg RBV 48 weeks, <u>4 weeks placebo (wk 0-4), 12 weeks 750 mg TID TLV (wk 4-16)</u> → Lead-in cohort	REL: 88% PR: 54% NULR: 33%
	c) 180 µg PEG-IFN $\alpha$ -2a, 1000-1200 mg RBV 48 weeks, 12 weeks 750 mg TID TLV (wk 0-12), <u>4 weeks placebo (wk 12-16)</u>	REL: 83% PR: 59% NULR: 29%

Study	Dosing	SVR12, SVR24
ASPIRE (Zeuzem 2013) n=462	a) 180 µg PEG-IFN $\alpha$ -2a, 1000-1200 mg RBV 48 weeks, 12/24/48 weeks placebo	REL: 37% PR: 9% NULR: 19%
	b) 180 µg PEG-IFN $\alpha$ -2a, 1000-1200 mg RBV 48 weeks, 12/24/48 weeks 100/150 mg QD SMV	REL: 77-89% PR: 48-86% NULR: 38-59%
PROMISE (Forns 2013) n=393	a) 180 µg PEG-IFN $\alpha$ -2a, 1000-1200 mg RBV 48 weeks, 12 weeks placebo	REL: 37%
	b) 180 µg PEG-IFN $\alpha$ -2a, 1000-1200 mg RBV 24-48 weeks, 12 weeks 150 mg QD SMV	REL: 79%
STARTVerso 3 (Jacobson 2013e) n=677	a) 180 µg PEG-IFN $\alpha$ -2a, 1000-1200 mg RBV 48 weeks, 12 weeks placebo	REL: 14% PR: 3% NULR: n.a.
	b) 180 µg PEG-IFN $\alpha$ -2a, 1000-1200 mg RBV 48 weeks, 12 weeks 240 mg QD FDV	REL: 70% (RGT possible) PR: 58% NULR: 33%
	c) 180 µg PEG-IFN $\alpha$ -2a, 1000-1200 mg RBV 48 weeks, 24 weeks 240 mg QD FDV	REL: 70% (RGT possible) PR: 47% NULR: 33%
(Sulkowski 2014) n=41 failure to previous PI based therapy (TLV, BOC)	a) DCV 60 mg + SOF 400 mg qd 24 weeks b) DCV 60 mg + SOF 400 mg qd and 1000-1200 mg RBV 24 weeks	100% (SVR12) 100%* (1 patient LTFU achieved SVR24)

## PEG-IFN maintenance therapy

There has been much interest in the past concerning the use of low-dose PEG-IFN maintenance therapy in patients with a null response since data has suggested that IFN may halt progression of liver disease (Nishiguchi 1995). There are two major published trials that have analyzed if maintenance treatment with IFN alters the natural course of chronic hepatitis C (EPIC<sup>3</sup> trial, HALT-C trial). However, both studies revealed no benefit (Bruix 2011, Di Bisceglie 2008). In conclusion, long-term treatment with low-dose PEG-IFN cannot be recommended (Sarrazin 2010a). This information may be still relevant for some areas of the world.

## Treatment of HCV genotypes 2 and 3

### Naïve patients

Therapy of GT2/3 will see a major change in 2014 with the approval of sofosbuvir (SOF). As previously mentioned, SOF is a new NS5B polymerase inhibitor with pangenotypic efficacy and extensive data were acquired in the treatment of GT2- and GT3-infected patients in 2013 prior to approval as the first IFN-free regimen for hepatitis C. The FISSION trial evaluated the direct comparison of SOF/RBV for 12 weeks and PEG-IFN/RBV for 24 weeks in treatment-naïve patients (Lawitz 2013a). Of note, in the PEG-IFN/RBV arm, RBV was given as a flat dosage of 800 mg and not weight-based. Both regimens showed an overall SVR of 67% but the subgroup analysis demonstrated a superior result for SOF/RBV in GT2. In GT2 the overall SVR rate was 97%, whereas for the PEG-IFN/RBV arm the SVR was 78% (Table 4.8). The POSITRON trial evaluated the use of SOF/RBV in patients who were intolerant to PEG-IFN, due to contraindication or patient's decision (Jacobson 2013d). This trial showed an SVR of more than 90% in both cirrhotic and non-cirrhotic patients for patients with GT2.

GT3 patients had an inferior response to 12 weeks of SOF/RBV with an SVR of 56% in the FISSION trial and 61% in the POSITRON trial (Lawitz 2013a, Jacobson 2013d). In GT3 cirrhotic patients SVR rates even decreased to 21%. Therefore a treatment extension to 24 weeks was looked at in the VALENCE trial (Zeuzem 2013b). The VALENCE trial was initially designed for a shorter treatment period, but given the data from POSITRON and FISSION, an amendment for treatment prolongation in GT3 to 24 weeks was proposed. An SVR of up to 94% was reached in treatment-naïve patients (Zeuzem 2013b) (Table 4.8).

Given the availability of SOF, previous considerations of the addition of TLV or BOC in GT2/3 are outdated. Indeed, in their latest recommendations, the AASLD and IPSA advocate the sole use of SOF/RBV and advice against the use of PEG-IFN/RBV. However, treatment with PEG-IFN/RBV dual therapy may be still

considered depending on the health care system, especially for easy-to-treat patients (Figure 4.4). Treatment with IFN-free SOF for 12-24 weeks in GT2/3 can be 10-20 times more expensive vs. PEG-IFN-based treatment.

**Table 4.8 – SVR rates of sofosbuvir in HCV GT2/3 infection\***

Study	Treatment	SVR GT2	SVR GT3
Lawitz 2013a (FISSION) n=253	RBV (1-1.2g) + SOF 12W	97%	56%
	PEG-IFN/RBV (0.8 g) 24W	78%	53%
Jacobson 2013d (POSITRON) n=207; IFN intolerant pts	RBV (1-1.2g) + SOF 12W	no cirrhosis: 92%; cirrhosis: 94%	no cirrhosis: 68%; cirrhosis: 21%
Jacobson 2013d (FUSION) n=201	RBV (1-1.2g) + SOF 12W	no cirrhosis: 96.2% cirrhosis: 60%	no cirrhosis: 36.8% cirrhosis: 19.2%
NullR or Rel.	RBV (1-1.2g) + SOF 16W	no cirrhosis: 100% cirrhosis: 77.8%	no cirrhosis: 62.5% cirrhosis: 60.9%
Zeuzem 2013b (VALENCE) n=334	RBV (1-1.2g) + SOF 12W	naive: 97%	naive: 94%
	RBV (1-1.2g) + SOF 24W	naive, cirrhosis: 100% exp.: 91% exp., cirrhosis: 88%	naive, cirrhosis: 92% exp.: 81% exp., cirrhosis: 60%
Lawitz 2013b (LONESTAR-2) n=47	PEG-IFN/RBV + SOF 12W	exp.: 100% exp., cirrhosis: 93%	exp.: 83% exp., cirrhosis: 83%

NullR: Null Response, Rel: Relapse, PEG-IFN: pegylated-interferon alpha, RBV: ribavirin, SOF: sofosbuvir, W: weeks, exp.: treatment-experienced patients

For PEG-IFN/RBV a fixed duration of treatment (24 weeks) has been suggested, although the optimal results are likely to be achieved when the duration of therapy is adjusted based on viral kinetics. Many studies have investigated the reduction of treatment duration for HCV GT2/3 to 16, 14, or even 12 weeks. Overall, reducing the treatment duration to less than 24 weeks increases the number of relapses (Andriulli 2008, Dalgard 2008, Mangia 2005, Manns 2011a, Shiffman 2007b). However, some HCV GT2/3 patients may indeed be treatable for 12-16 weeks if certain prerequisites are fulfilled, especially the rapid virologic response (RVR) by week 4 of therapy (Slavenburg 2009). Only patients with RVR have high SVR rates after 16 weeks (Manns



2011a, von Wagner 2005), 14 weeks (Dalgard 2008), or even 12 weeks of therapy (Mangia 2005) (Table 4.9).

In addition to the RVR, the specific HCV genotype and the baseline viral load are associated with response. Similar to the IFN-free treatment with SOF, patients with GT2 respond better to PEG-IFN/RBV than those infected with GT3 (Zeuzem 2004b).

Furthermore, the shorter treatment schedules reveal that HCV GT3 patients with low baseline viremia (<400-800,000 IU/ml) had a much better chance of responding than those with high viral load (>400-800,000 IU/ml) (Shiffman 2007b, von Wagner 2005). Patients with GT3 plus low viral load who achieve RVR can be treated for less than 24 weeks. However, reducing treatment duration is not recommended in patients with advanced liver fibrosis or cirrhosis, insulin resistance, diabetes mellitus or BMI >30 kg/m<sup>2</sup> (Aghemo 2006, Sarrazin 2010a, Sarrazin 2011). Patients treated with a response-guided approach should be started on high-dose ribavirin, which appears to increase the rate of RVR in patients with HCV GT2/3 undergoing short treatment (Mangia 2010b).

In contrast, GT2/3 patients who do not achieve RVR (especially HCV GT3 with high viral load) may be treated for longer than 24 weeks (ie, 36-48 weeks) if SOF is not available. However, most data are retrospective (Willems 2007). The prospective N-Core study investigated 24 weeks versus 48 weeks of PEG-IFN  $\alpha$ -2a/RBV. This study was prematurely terminated because of slow enrolment and could only show a significant difference in those patients who completed the study (73% vs. 54% SVR), but not in the intent-to-treat analysis (Cheinquer 2012). A prospective study from Italy showed a numerically significant benefit of 36 weeks versus 24 weeks (75% vs. 62%) (Mangia 2010a). Depending on the assay used to determine RVR, around 25-30% of GT2/3 patients belong to this difficult-to-treat population not achieving RVR (Table 4.9). Patients without RVR are the patients that may benefit most from SOF treatment. Tailoring treatments individually for patients with HCV GT2/3 will reduce costs and side effects and further optimise the response rates.

**Table 4.9 – Response-guided therapy with PEG-IFN and RBV for patients with HCV genotypes 2 and 3**

Study	Treatment	Subgroups	Therapy weeks	SVR*
(von Wagner 2005) n=153	180 µg PEG-IFN $\alpha$ -2a 800-1200 mg ribavirin	>600 IU/ml TW4	24	36%
		<600 IU/ml TW4	24	80%, 84% if HCV RNA<800,000 IU/ml
		<600 IU/ml TW4	16	82%, 93% if HCV RNA<800,000 IU/ml
(Shiffman 2007b) n=1469	180 µg PEG-IFN $\alpha$ -2a 800 mg ribavirin	All patients	24	70%
		All patients	16	62%
		<50IU/ml TW4 (RVR)	24	85%
		<50IU/ml TW4 (RVR)	16	79%
		<400,000IU/ml TW0 (LVL)	24	81%
		<400,000IU/ml TW0 (LVL)	16	82%
(Mangia 2005) n=283	1.0 µg PEG-IFN $\alpha$ -2b 1000-1200 mg ribavirin	Standard group	24	76%
		Standard group	24	91% if TW4 HCV RNA <50 IU/ml
		>50 IU/ml TW4 (no RVR)	24	64%
		<50 IU/ml TW4 (RVR)	12	85%
		<50 IU/ml TW4 (RVR)	24	91% ITT, 93% with F24 HCV RNA test
(Dalgard 2008) n=428	1.5 µg PEG-IFN $\alpha$ -2b 800-1400 mg ribavirin	<50 IU/ml TW4 (RVR)	24	91% ITT, 93% with F24 HCV RNA test
		<50 IU/ml TW4 (RVR)	14	81% ITT, 86% with F24 HCV RNA test
		>50 IU/ml TW4 (no-RVR)	24	55% ITT, 59% with F24 HCV RNA test
		<50 IU/ml TW4 (RVR)	24	91% ITT, 93% with F24 HCV RNA test
(Manns 2011a) n=682	1.0 µg PEG-IFN $\alpha$ -2b 1.5 µg PEG-IFN $\alpha$ -2b 800-1400 mg ribavirin	All patients	24 (1.5)	67% ITT, 82% as-treated
		All patients	24 (1.0)	64% ITT, 80% as-treated
		All patients	16 (1.5)	57% ITT, 68% as-treated

\* SVR, sustained viral response; RVR, rapid virologic response; LVL, low baseline viral load.

**Table 4.10 – SVR of patients with HCV genotypes 2 or 3 not achieving RVR**

Study	Frequency of patients without RVR	SVR without RVR (24 wks therapy)
(von Wagner 2005) 180 µg PEG-IFN α-2a 800-1200 mg ribavirin	7% (HCV RNA >600 IU/ml TW4)	24 weeks 36% SVR
(Shiffman 2007b) 180 µg PEG-IFN α-2a 800 mg ribavirin	36% (HCV RNA >50 IU/ml TW4) (24 wk group)	24 weeks 45% SVR
(Mangia 2005) 1.0 µg/kg PEG-IFN α-2b 1000-1200 mg ribavirin	36%-38% (HCV RNA >50 IU/ml TW4)	24 weeks 48%-64% SVR
(Dalgard 2004) 1.5 µg/kg PEG-IFN α-2b 800-1400 mg ribavirin	22% (HCV RNA >50 IU/ml TW4/TW8)	24 weeks 56% SVR
(Dalgard 2008) 1.5 µg/kg PEG-IFN α-2b 800-1400 mg ribavirin	29% (HCV RNA >50 IU/ml TW4)	24 weeks 55% SVR
(Cheinquer 2012) 180 µg PEG-IFN α-2a 1000-1200 mg ribavirin	n=188 patients with non-RVR were randomized for 24 versus 48 weeks	24 weeks 52% ITT SVR 24 weeks 54% SC SVR 48 weeks 61% ITT SVR 48 weeks 73% SC SVR

ITT: intention to treat, SC: study completers

### **Treatment of HCV GT2/3 patients with prior antiviral treatment failure**

The use of SOF was specifically studied in patients with non-response or relapse to a previous therapy with PEG-IFN/RBV in the FUSION trial (Jacobson 2013d). Treatment-experienced patients with GT2 infection showed a favourable response to 12 weeks of SOF/RBV with an SVR of 86%. However, a significant drop in response could be shown for treatment-experienced cirrhotic patients with a mere SVR of 60%. Treatment prolongation to 16 weeks was able to remedy this issue and raise SVR rates to 94% and 77.8% in non-cirrhotic and cirrhotic

patients, respectively (Table 4.8). However, the FDA label recommends 12 weeks SOF/RBV for GT2 patients.

Results for 12 weeks of treatment with SOF/RBV in patients with GT3 infection and relapse or non-response to previous treatment showed an SVR of 30% in non-cirrhotic patients and only 19.2% in cirrhotic patients. Treatment prolongation to 24 weeks was evaluated in the VALENCE trial (Zeuzem 2013b), and the SVR raised to 60% for treatment-experienced, cirrhotic patients and to 87% for treatment experienced, non-cirrhotic patients. In treatment-experienced patients with cirrhosis and GT3 infection the addition of PEG-IFN to the SOF/RBV regimen for 12 weeks should be considered. This regimen was evaluated in the LONESTAR-2 trial and showed an SVR of 83% in treatment-experienced patients, irrespective of the degree of fibrosis, including patients with compensated cirrhosis (55% of patients had cirrhosis) (Lawitz 2013b) (Figure 4.4). A total of 24 patients with GT3 were included and 22 patients completed treatment. One patient discontinued the treatment due to adverse events and 1 patient was lost to follow-up.

Although a direct head-to-head comparison of an IFN-free treatment with SOF/RBV and PEG-IFN/RBV/SOF regimen was not done, data indicates that the addition of PEG-IFN can still lead to a shorter treatment duration with better response rates in the difficult-to-treat patients with HCV GT3, cirrhosis and failure of previous treatment. However, SOF will not be available in all countries and retreatment with PEG-IFN/RBV for 24 weeks is a viable option in patients with relapse after a short course of PEG-IFN/RBV (Mangia 2009). In patients with unfavourable predictors, longer treatment duration for 48 weeks is advisable (EASL 2014). Non-responders can be retreated with an additional course of PEG-IFN/RBV. It is important to optimise dose and duration of treatment.

Future DAAs will be pan-genotypic and therefore also effective for HCV GT3 (see Chapter 5). Also DCV will be effective in GT3 patients and may be considered in difficult-to-treat patients when available after regulatory approval. Nevertheless, non-

responder patients with mild fibrosis may wait for new treatment options that become available in 2015, but it is important to understand that fibrosis progression is faster in patients with HCV GT3 (Bochud 2009).

Naïve G2/3, (LVL), no cirrhosis	PEG-IFN/RBV	16-24 weeks if RVR
G2	SOF/RBV	12 weeks*
G3	SOF/RBV	24 weeks
Difficult G3**	SOF/RBV/PEG-IFN	12 weeks

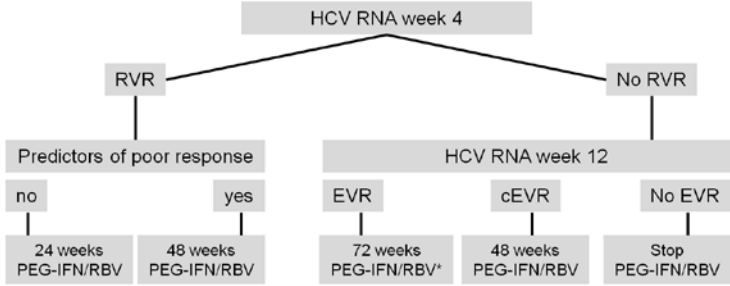
**Figure 4.4 – Suggestions for the treatment of HCV genotypes 2 and 3 for 2014 in countries where SOF is available.** Interferon free regimens should be preferred due to the much better adverse event profile. Due to economical reasons, we suggest to consider PEG-IFN/RBV in easy to treat patients with G2 or 3, i.e. with LVL = low viral load at baseline <800,000 IU/ml. Sensitive HCV RNA assays (limit of detection 12-15 IU/ml or 50 IU/ml) at weeks 4 is important to define rapid virological response (RVR). Patients should not have cirrhosis. \*16 weeks for G2 with cirrhosis may result in higher SVR. \*\* Treatment experienced G3 patients with cirrhosis may benefit from 12 weeks triple therapy with PEG-IFN/RBV/SOF.

## Treatment of HCV genotypes 4, 5, and 6

All new DAAs have barely been tested in patients with HCV GT4, 5, or 6. There are some data for SMV showing adequate antiviral efficacy for GT4-6 (Lenz 2013) which may be considered. Also DCV has shown considerable results in GT4 patients (Wang 2012). Triple therapy of SOF + PEG-IFN/RBV for 12 weeks has resulted in 96-100% SVR in GT4-6 patients (Lawitz 2013a). However, the number of patients was low (n=35) although the data was sufficient for the approval of SOF for all genotypes (EMA label 1/2014).

GT4-6 are the major genotypes in Africa and Asia (see below) and in many of these countries PEG-IFN/RBV will remain the

SOC in 2014. In general, treatment duration of 48 weeks PEG-IFN/RBV is recommended based on the results of large, randomized Phase III trials (Fried 2002, Hadziyannis 2004, Manns 2001). However, these trials included few patients with HCV GT4, 5, and 6 and large, prospective randomized studies with RGT are rare. Importantly, GT4, 5, and 6 are very common in areas where chronic hepatitis C is highly prevalent. For example, HCV GT4 is most prevalent in the Middle East and Egypt where it accounts for >80% of all HCV cases (approximately 34 million people) (Khattab 2011). HCV GT5 is most prevalent in South Africa, and genotype 6 in Southeast Asia (Nguyen 2005). Available study results, although limited, suggest that patients with HCV GT4, 5 and 6 may show different clinical courses and treatment outcomes. Ethnicity-related factors (ie, IL28B, regional aspects) may contribute to these findings.



**Figure 4.5 – Suggestion for treatment of HCV genotypes 4, 5, and 6 2014 if SOF + PEG-IFN/RBV is not possible.** This algorithm was initially proposed for HCV GT4 (adapted from Khattab 2011). Sensitive HCV RNA assays (limit of detection 12-15 IU/ml or 50 IU/ml) at weeks 4 and 12 may determine treatment duration. Reducing treatment duration is not recommended in patients with predictors of poor response (liver cirrhosis, insulin resistance, diabetes mellitus or hepatic steatosis, high baseline viral load >800,000 IU/mL).

**Table 4.11 - Efficacy of antiviral treatment with PEG-IFN plus ribavirin in patients with chronic hepatitis C infected with genotypes 4, 5, and 6. Selected trials**

Study	Treatment	HCV genotype /Duration	SVR
(Diago 2004) n=49	180 µg PEG-IFN $\alpha$ -2a 800/1000/1200 mg ribavirin	G4 24 weeks	0% (if low RBV)
		24 weeks	67% (if high RBV)
		48 weeks	63% (if low RBV)
		48 weeks	79% (if high RBV)
(Hasan 2004) n=66	1.5 µg/kg PEG-IFN $\alpha$ -2b 1000/1200 mg ribavirin	G4 48 weeks	68%
		48 weeks	55% (if HVL)
		48 weeks	86% (if LVL)
(Kamal 2005) n=287	1.5 µg/kg PEG-IFN $\alpha$ -2b 1000/1200 mg ribavirin	G4 24 weeks	29%
		36 weeks	66%
		48 weeks	69%
(Kamal 2007) n=358	1.5 µg/kg PEG-IFN $\alpha$ -2b 10.6 mg/kg ribavirin RGT	G4 24 weeks RGT	86% (if RVR)
		36 weeks RGT	76% (if EVR)
		48 weeks RGT	56% (if DVR)
		48 weeks	58%
(Ferenci 2008) n=66	180 µg PEG-IFN $\alpha$ -2a 1000/1200 mg ribavirin RGT	G4 24 weeks RGT	87% (if RVR)
(Bonny 2006) n=59	PEG-IFN $\alpha$ -2a or b 800-1200 mg ribavirin	G5 48 weeks	58%
(Lam 2010) n=60	PEG-IFN $\alpha$ -2a 800-1200 mg ribavirin	G6 24 weeks	70%
		48 weeks	79%
(Nguyen 2008) n=35	PEG-IFN $\alpha$ -2a or b 800-1200 mg ribavirin	G6 24 weeks	39%
		48 weeks	75%
(Thu Thuy 2012) n=105	PEG-IFN $\alpha$ -2a 15 mg/kg/day ribavirin	G6 24 weeks	60% ITT, 72% PP
		48 weeks	71% ITT, 79% PP

RBV, ribavirin; LVL, low baseline viral load; HVL, high baseline viral load; RGT, response-guided therapy

Overall, data from smaller studies suggest that GT4, 5 and 6 appear easier-to-treat compared to HCV GT1 but the optimal treatment duration is not clear (Antaki 2010, Nguyen 2005) (Table 4.11). Although some studies show SVR on the same order as for HCV GT2/3 patients, a fixed duration of 24 weeks of treatment as for GT2/3 is not advisable, even for patients with HCV GT6, which appears to show the best SVR (Lam 2010, Nguyen 2008). RGT based on early viral kinetics should be possible. Patients who achieve RVR are candidates for a short treatment regimen of 24 weeks if they do not have predictors of poor response (Figure 4.5). Based on data for GT1 (Berg 2006, Sanchez-Tapias 2006), patients without RVR and/or partial response may be considered for 72 weeks. This has been proposed for HCV GT4 by an international expert panel (Khatab 2011), but the evidence is limited. The proposed algorithm is shown in Figure 4.5. We suggest treating GT5 and 6 also according to this algorithm. Patients with treatment failure may be considered for retreatment, especially if the previous therapy was suboptimal. It is important to optimize dose and duration of treatment during retreatment.

In countries where SOF is available, triple therapy of PEG-IFN/RBV/SOF for 12 weeks is the optimal treatment for GT4-6 (1/2014).

## Optimisation of HCV treatment

### Adherence to therapy

Adherence to therapy is one of the most important factors associated with the success of antiviral treatment (McHutchison 2002). The definition of adherence used here is the “80/80 rule”, that is, patients who receive more than 80% of the medication and are treated for more than 80% of the planned duration of treatment are considered adherent. One of the first studies investigating the effect of adherence in PEG-IFN/RBV treatment demonstrated that patients who fulfilled the 80/80 rule had a 63% SVR compared to 52% of those with less than 80% adherence



(McHutchison 2002). Another study showed that a cumulative ribavirin dose of more than 60% is important to achieve an SVR (Reddy 2007). For the triple therapy, adherence to the PI becomes even more important. Reduction of the PI or irregular intake bears the risk of rapid emergence of drug resistance. Dose reduction of the PI is associated with significantly diminished SVR (Gordon 2011) and is therefore not an option for managing side effects. Thus, the new once-daily DAAs are a step forward in the treatment of HCV infection. An optimal management of PEG-IFN/RBV side effects is essential in order to optimize treatment response. In the case of anemia, dose reduction of ribavirin is possible and not associated with impaired SVR (Roberts 2011). Another important and new issue is drug interactions that can diminish the effectiveness of the PI or induce toxicity of concomitant medications, which may lead to discontinuation of all drugs. Knowledge about drug interactions is therefore important for the optimal management of patients receiving DAA.

### **Management of side effects and complications**

Severe side effects may reduce adherence to therapy and may result in dose modifications that result in a less-than-optimal response. IFN, RBV and some of the PI induce side effects that have to be managed, with involvement of the patient (see Chapter 6). The IFN-related side effects can be divided into IFN-induced bone marrow suppression, flu-like symptoms, neuropsychiatric disorders, and autoimmune syndromes. The main problem of RBV is hemolytic anemia. BOC and TLV are associated with additional side effects such as rash or dysgeusia and additionally an increase of anemia (Jacobson 2011b, Manns 2011b, Vertex 2011, Zeuzem 2011). SMV and FDV are much better tolerated and importantly not associated with higher rates of anemia. SMV and FDV show an increase in unconjugated bilirubin not related to liver toxicity. FDV requires sun protection; otherwise photosensitivity/phototoxicity can occur

more frequently compared to other PIs. The adverse events in the SOF trials are more or less the PEG-IFN/RBV or RBV side effects. Headache may be more frequent (see Chapter 6).

Overall, side effects result in premature withdrawals from therapy and additional patients require dose modifications during treatment. In trials with dual therapy, the frequency of treatment discontinuations and dose modifications were lower in recent studies, suggesting an improved understanding and management of adverse events. Similar developments can be expected for treatment with PI. For example, the reported cases of rash decreased from 60% in Phase II (McHutchison 2009a) to 36% in Phase III (Jacobson 2011b). After photosensitivity was reported in 10-14% in the Phase II trials with FDV, sun protection was provided in the Phase III trials that reduced photosensitivity to 0.6% with 120 mg FDV plus PEG-IFN/RBV, which was similar to PEG-IFN/RBV/placebo with 1%.

However, the frequency of adverse events that occurred in registrational trials with carefully selected patients may differ from general clinical practice, where patients with, eg, history of psychiatric disorders or advanced liver disease are being treated. For example, factors significantly associated with developing anemia on TLV were older age and advanced fibrosis (Roberts 2011). The first real-life cohorts revealed higher serious adverse events in patients with advanced liver cirrhosis (Hézode 2013, Maasoumy 2013b). Thus, the management of side effects is one of the most important factors for the success of treatment and deserves its own chapter (Chapter 6).

## **Drug interactions**

With the introduction of DAAs to the treatment of chronic HCV infection a completely new challenge has to be faced: drug-drug interactions (DDI). First generation PIs undergo extensive hepatic metabolism, especially via the cytochrome P450 CYP3A pathway, which metabolizes more than 50% of clinically used drugs and is often involved in adverse drug interactions

(Maasoumy 2013c, Burger 2012). Thus, both PIs are targets as well as perpetrators of drug interactions. DDIs are not infrequent. Up to 49% of hepatitis C patients are at risk for a DDI if treated with TLV or BOC due to their regular outpatient medication (Maasoumy 2013c).

Next wave PIs SMV and FDV as well as the NS5A inhibitor DCV are also metabolized by CYP3A (Kiser 2013). Concomitant drugs that induce CYP3A may result in decreased plasma concentrations of the respective PI or DCV, which can reduce the therapeutic effect. In contrast, the NS5B polymerase inhibitor SOF seems to be unaffected by the CYP3A pathway. PIs are also inhibitors of CYP3A, which may increase plasma concentrations of concomitant drugs that are metabolized via the same route, leading to prolonged therapeutic effects and/or toxicity. The impact on CYP3A differs between the individual DAA. SMV is only a mild (majorly affecting the intestinal CYP3A), FDV and BOC moderate and TLV a strong inhibitor of CYP3A (Kiser 2013). Co-administration of TLV with the immunosuppressant drug tacrolimus may lead to a 70-fold increase of the plasma levels of tacrolimus, while levels are not influenced at all if co-administered with SMV.

DDIs are not limited to the CYP3A pathway. Interactions may also occur with the p-glycoprotein (Pgp) transport or the organic anion transporting polypeptide 1B1 (OATP1B1). TLV, BOC, and DCV are substrates and inhibitors of P-gp. Co-administration of one of these DAAs with drugs that are substrates for Pgp transport may result in increased plasma concentrations of such drugs, which could increase adverse reactions. SOF and FDV are both substrates of Pgp, which may cause DDI with strong Pgp inhibitors like rifampicin. BOC, DCV, SMV and FDV all inhibit OATP1B1 (Kiser 2013), therefore substrates of OATPs (such as bosentan) should also be used with caution.

Overall, the risk for DDIs seems to be lower with the second-wave DAAs. In particular, SOF seems to interact with only a relatively small number of drugs. Still, the risk of DDI is present and must not be neglected. For optimal therapeutic

management, it is essential to specifically ask patients about concomitant medications and investigate if those drugs may interact with the DAA(s). In some cases a closer monitoring or slight dose modifications may be sufficient while some drugs should be strictly avoided especially if alternatives are available that do not cause interactions. Furthermore, the patient has to be informed that self-medication may also be a problem since interactions are not limited to approved drugs. Even herbals and foods have to be considered, as St. John's Wort is a potent inducer of CYP3A and P-gp. Naringin, a flavinoid of grapefruit is an inhibitor of CYP3A. A list of drug interactions is given in the official prospectus. However, these lists may sometimes not be fully comprehensive. Supportive online tools or apps for mobile devices are available. One example is the very comprehensive drug interaction resource provided by the University of Liverpool (<http://www.hep-druginteractions.org>). The website provides clinically useful and evidence-based information which is updated when new drug interactions are analyzed and published. Drug interactions are usually considered significant if the area under the plasma concentration time curve (AUC) is altered by more than 30%. The table *Overview of drug interactions of HCV PIs with frequently used co-medication* (see [http://hepatologytextbook.com/Table12\\_11.pdf](http://hepatologytextbook.com/Table12_11.pdf)) gives an overview about potential interactions of frequently used drugs with the first generation PIs (TLV and BOC) and implications for management and alternative drugs.

## **Treatment of hepatitis C in special populations**

### **Patients with acute hepatitis C**

The goal of acute hepatitis C treatment is the prevention of persistent HCV infection. The natural rate of HCV evolution to a chronic state is 50-90%. As a vaccine is not yet available, early treatment of acute HCV infection with IFN is the only option to prevent persistent HCV infection; however, the diagnosis of acute primary HCV infection may be difficult and its distinction

from exacerbation of an underlying unrecognized chronic HCV infection may be difficult (Sarrazin 2010a). The immediate treatment of patients with symptomatic acute hepatitis C with recombinant IFN or PEG-IFN monotherapy for 24 weeks can prevent the development of chronic hepatitis C in approximately 90% of cases (Broers 2005, Jaeckel 2001, Santantonio 2005, Vogel 1996, Wiegand 2006). However, good patient adherence to therapy is necessary to achieve these response rates (Wiegand 2006). Co-administration with ribavirin does not seem to be necessary. This may be different in patients with HIV coinfection (Grebely 2011a). DAAs have not been tested in patients with acute HCV infection. Symptomatic patients also have a good chance of clearing HCV spontaneously (Gerlach 2003, Hofer 2003), occurring usually in the first 12 weeks after the onset of symptoms.

As for patients with treatment-induced SVR, spontaneous clearance of HCV is also associated with IL28B polymorphisms and IP-10 (Beinhardt 2012, Grebely 2010, Thomas 2009, Tillmann 2010), which may be useful for decision-making. The treatment of only those patients who remain HCV RNA-positive 12 weeks after the onset of symptoms results in an overall SVR (self-limited and treatment-induced) in >90% of patients with adherence. However, in those cases PEG-IFN/RBV is required for 24 weeks (Gerlach 2003, Deterding 2013). Thus, the decision to wait for 12 weeks after diagnosis or to treat immediately may be made individually. Importantly, the compliance of the patient should be assessed. Host genetics (IL28B), other markers (IP-10), or HCV RNA kinetics during the first weeks may help to decide when to treat. For example, asymptomatic patients with IL28B rs12979860-CT or TT may be treated immediately since these patients have a higher risk for evolution to a chronic state. However, early treatment of acute HCV infection to prevent chronic disease does have its limitations. A main problem is that primary HCV infection is usually asymptomatic and most patients are not identified in this early stage of disease. Another reason is that a number of patients have medical

contraindications for treatment with IFN or may not be ready for therapy because they are still active intravenous drug users (IDU).

There are two concerns in treating active IDUs with IFN. In case of successful therapy there is a risk of reinfection with HCV (Grebely 2012). The second concern is the side effect profile of IFN, especially the neuropsychiatric problems that may result in a worsening of addictive behaviour (Wiegand 2006). In addition, it has been shown that the acceptance of and adherence to antiviral therapy by these patients can be low due to the side effects of IFN (Broers 2005). While a recent meta-analysis did see a difference in drug-using populations vs. those not using drugs in hepatitis C treatment trials that broke out the difference (68.5% vs 81.5% SVR), the same authors went on to note that this difference may be bridged by enrolment in drug treatment or multidisciplinary treatment programs and/or requirements of abstinence from actively using drugs in order to facilitate optimal treatment outcomes (Hellard 2009).

Soon we will see the first results of DAA regimens that allow IFN-free therapies in acute HCV infection. However, the role of DAAs in acute HCV infection has to be defined. The risk of HCV reinfection in high-risk populations needs to be addressed. The minimal required treatment duration and the time for starting antiviral therapy are unclear.

### **Patients with normal aminotransferase levels**

Approximately 30% of patients with chronic hepatitis C maintain persistently normal alanine aminotransferase (ALT) levels despite having detectable HCV RNA in serum. These patients have generally mild liver disease and show a slow progression to cirrhosis. However, up to one third of patients with normal ALT can present with significant liver fibrosis necessitating an effective treatment (Bacon 2002, Zeuzem 2004a). In current guidelines, ALT elevation is not a prerequisite to start antiviral therapy and the assessment of liver disease severity should be made regardless of ALT (EASL 2014).

### **Patients with compensated liver cirrhosis**

Successful therapy of patients with advanced fibrosis and liver cirrhosis is associated with decreased incidence of HCC, decompensation and liver-related mortality (Morgan 2010, Veldt 2007, van der Meer 2012). In addition, in patients awaiting liver transplantation, successful therapy prevents graft reinfection (Everson 2005, Fornis 2003). Thus, patients should be considered for therapy if no contraindications are present. However, SVR is diminished in patients with cirrhosis, for triple therapy with PEG-IFN/RBV plus DAA as well (Pol 2011b, Lawitz 2013a) and also for IFN free combinations in GT1 but also GT2/3 (Lawitz 2013a, Jacobson 2013d, Osinusi 2013, Sulkowski 2013a).

Treatment of patients with liver cirrhosis requires close patient monitoring. With PEG-IFN/RBV-based regimens, hematological adverse events are more frequent than in non-cirrhotic patients (EASL 2013, Hézode 2012). In the first real-life cohorts, a platelet count <100,000-110,000/ $\mu$ l was associated with serious adverse events and hospitalization (Hézode 2013, Maasoumy 2013b). The rate of severe anemia requiring blood transfusions is significantly higher in patients with advanced liver cirrhosis. Some patients even experienced severe complications with fatal outcomes mainly due to septicemia as a consequence of infections. In general, PEG-IFN-based treatment should be limited to patients with early compensated cirrhosis. In patients with advanced cirrhosis (ie, low platelets as surrogate for portal hypertension), therapy may be only considered in individual cases in experienced centres. If ascites is present, antibiotic prophylaxis should be given.

IFN-free DAA combinations are the best option for patients with advanced liver cirrhosis. In 2014, different compassionate use programmes will allow treatment of patients with advanced liver cirrhosis with DAA combination therapy. So far, we have very little data to predict exact SVR rates in patients with advanced liver cirrhosis.

If patients with cirrhosis achieve SVR, it is important to perform HCC surveillance because cirrhosis remains and HCC development is reduced but not abolished (EASL 2014).

### **Patients after liver transplantation**

HCV reinfection occurs in almost all patients after liver transplantation. While the course of hepatitis C in liver transplant recipients was believed to be rather benign in the late '80s and early '90s (Boker 1997), HCV has led to a more rapid progression post-transplant in recent years (Berenguer 2005, Neumann 2004) with cirrhosis within the first 5-10 years in 20-30% of patients. HCV definitely takes a more rapid course post-transplant than in immunocompetent individuals and treatment needs are obvious.

Antiviral therapy of HCV may be started before transplant to prevent reinfection of the graft. If this approach is successful, reinfection can be prevented in two-thirds of patients who received IFN-based therapies (Forns 2003). However, treatment with IFN/RBV and even more so with triple therapy including TLV or BOC is poorly tolerated in individuals with decompensated cirrhosis with a high risk for infections and is feasible in only a minority of patients (Everson 2005, Forns 2003, Maasoumy 2013b). Treatment with IFN-free therapies will hopefully change this. At AASLD 2013, data from patients with HCC awaiting liver transplantation treated with SOF and RBV until transplantation was presented. In 23 of 37 patients reinfection was prevented (Curry 2013). However, all patients had a MELD score <22. Data in decompensated cirrhosis so far (1/2014) are lacking.

Patients with HCV reinfection after liver transplantation have an urgent treatment indication due to the fast progression to cirrhosis. Treatment with IFN-based therapies of HCV reinfection after liver transplantation will now be replaced by IFN-free regimens. IFN-based therapies, especially triple therapies including TLV or BOC are associated with severe adverse events and the problem of drug interactions with



immunosuppressive drugs. For example, TLV increases levels of tacrolimus by approximately 70-fold (Garg 2011). In some studies with triple therapies, the frequency of severe anemia was more than 50% and mortality has also been reported (Coilly 2013). The use of PEG-IFN/RBV-based triple therapies must be carefully evaluated after liver transplantation in relation to drug-drug interactions and tolerance. Preliminary data of an IFN-free combination of SOF+RBV for 24 weeks were presented at AASLD 2013 (Charlton 2013). 40 patients with established HCV reinfection after transplantation were included. 88% of them were treatment-experienced and 40% of them had cirrhosis at the time of treatment. 80% had GT1 infection. At week 4 after end of treatment (SVR4), 77% were HCV RNA negative. Although SVR4 is too early to predict a long-term response, SOF/RBV is a potential all-oral therapy after transplantation. The treatment discontinuation rate was 5% and no interaction between the treatment regimen and the immunosuppressive medication was observed. As SOF should be available at centers that perform liver transplantation, we suggest using SOF-based IFN-free regimens in those patients. Compassionate use programmes may allow combinations with other DAAs.

### **Hemodialysis patients**

Treatment needs for dialysis patients with hepatitis C are obvious, especially if patients are considered for kidney transplantation. The outcome of HCV post-kidney transplantation is worse than for HCV-negative patients after renal transplantation. However, IFN-based therapies are contraindicated post-transplantation since they may induce rejection. Thus, if possible, HCV should be eliminated before transplantation. There have been several smaller reports on the treatment of HCV with IFN monotherapy in patients with end-stage renal disease (Fabrizi 2002). Surprisingly, the results for IFN monotherapy on dialysis were better than in patients not undergoing dialysis, with SVR results of 21-64%. Data on combination with ribavirin are limited since ribavirin is

contraindicated in this setting. However, ribavirin can be given at lower doses in dialysis patients, usually at 200–400 mg daily (Bruchfeld 2001). It has to be considered that there may be significant differences between the two pegylated-interferons in the setting of dialysis since PEG-IFN  $\alpha$ -2a is eliminated mainly by the liver while PEG-IFN  $\alpha$ -2b is cleared via the kidney (reviewed in Cornberg 2002). Thus, only PEG-IFN  $\alpha$ -2a should be used in this setting. The efficacy of BOC and TLV has not been tested in many HCV patients with end stage renal disease or in patients undergoing hemodialysis. Theoretically, BOC and TLV can be administered in patients with compensated renal insufficiency and dose adjustment is not necessary because both drugs are metabolized through the liver and mainly eliminated via the feces with minimal urinary excretion (Ghany 2011, Wiegand 2013). Data for SOF are limited in this patient population (1/2014). In accordance with the FDA and EMA label, SOF is not recommended in patients with GFR <30 ml/min.

### **Drug abuse and patients on stable maintenance substitution**

Treatment of patients with active drug use is an individual approach and should only be performed in an experienced multidisciplinary setting including hepatologists, psychiatrists and addiction specialists. Drug interactions with DAAs need to be considered.

### **Patients with coinfections**

Due to the similar routes of transmission, patients with chronic hepatitis C are frequently coinfecting with hepatitis B virus, hepatitis D virus or human immunodeficiency virus. These important patient groups are discussed in the full Hepatology book in Chapters 10, 17 and 18.

### **Patients with hemophilia**

Due to contaminated clotting factor concentrates, many patients with hemophilia are infected with HCV and/or HIV. Studies investigating PEG-IFN/RBV in hemophilia patients are limited and often include small numbers of patients. Review of available

data suggest that treatment success of HCV-infected hemophiliacs is similar to that achieved in the general HCV-infected population (Franchini 2008).

### **Patients with extrahepatic manifestations**

More than 50% of HCV-infected patients suffer from extrahepatic manifestations ranging from fatigue to severe symptoms of mixed cryoglobulinemia (Cacoub 1999). The primary goal of treatment is HCV eradication, which is associated with improvement of clinical symptoms, especially in patients with mixed cryoglobulinemia (Cresta 1999, Pischke 2008, Zignego 2007, Maasoumy 2013a). Insulin resistance can be improved in HCV GT1 patients with SVR (Thompson 2012). In patients with severe symptoms of mixed cryoglobulinemia, treatment with rituximab may be considered (Cacoub 2008). Recent studies have also tested the combination of PEG-IFN/RBV and rituximab. The clinical response may be achieved faster and SVR is not diminished in patients who receive rituximab (Dammacco 2010, Saadoun 2010). Exacerbation of certain extrahepatic manifestations may occur with IFN-based therapy or IFN may be contraindicated (Zignego 2007). Studies using HCV PIs were done in patients with HCV and mixed cryoglobulinemia vasculitis. After 3 months, triple therapy was highly effective in terms of virological response as well as clinical response, but adverse events were frequent (>80% anemia, >50% infections) (Saadoun 2012). Similar to patients after transplantation, a PI regimen should be administered cautiously considering the high rates of side effects. In 2014, SOF combination therapies may be an option for this group of patients but so far data are lacking.

## 5. Hepatitis C: New Drugs

*Christian Lange, Christoph Sarrazin*

### **Introduction**

Over the past few years, surprisingly efficient drugs have been introduced in the treatment of chronic hepatitis C infection. Recently published clinical trials, reporting 90% cure rates (Sulkowski 2014, Kowdley 2014; see page 120), suggest that we might soon be able to cure a very substantial number of patients, both treatment-naïve and those treated previously without success. These results will likely lead to a paradigm shift in the management of hepatitis C, but caution is always prudent when revolutionary changes are announced in medicine. However, 25 years after the discovery of the hepatitis C virus (Choo 1989) and after nearly as many years of limited treatment options with lengthy, adverse-laden and often unsuccessful drug regimens, the so-called directly acting antiviral agents (DAAs) have the potential to change the lives of millions of HCV patients and thousands of HCV specialists.

**Table 5.1 – Selected directly acting antiviral agents (DAAs) and host targeting agents (HTAs) in the pipeline**

Drug name	Company	Target/Active site	Phase
<b>NS3/4A protease inhibitors</b>			
Telaprevir (VX-950)	Vertex	Active site / linear	IV
Boceprevir (SCH503034)	Merck	Active site / linear	IV
Simeprevir (TMC435)	Janssen / Medivir	Active site / macrocyclic	IV
Danoprevir (R7227)	Roche / InterMune	Active site / macrocyclic	III
Vaniprevir (MK-7009)	Merck	Active site / macrocyclic	III
MK-5172	Merck	Active site / macrocyclic	III
Faldaprevir (BI201335)	Boehringer Ingelheim	Active site / linear	IV
Asunaprevir (BMS-650032)	Bristol-Myers Squibb	Active site	III
GS-9256	Gilead	Active site	II
GS-9451	Gilead	Active site	II
ABT-450	Abbott	Active site	III
IDX320	Idenix	Active site	II
ACH-1625	Achillion	Active site / macrocyclic?	II
<b>Nucleoside analog NS5B polymerase inhibitors (NI)</b>			
Mericitabine (R7128)	Roche / Pharmasset	Active site	III
Sofosbuvir (GS-7977)	Gilead	Active site	III
VX-135 (ALS-2200)	Vertex / Alios	Active site	II
IDX 20963	Idenix	Active site	I
ACH-3422	Achillion	Active site	I
<b>Non-nucleoside NS5B polymerase inhibitors (NNI)</b>			
Deleobuvir (BI207127)	Boehringer Ingelheim	NNI site 1 / thumb 1	HALTED
BMS-791325	Bristol-Myers Squibb	NNI site 1 / thumb 1	II
TMC647055	Janssen	NNI site 1 / thumb 1	I
VX-222	Vertex	NNI site 2 / thumb 2	II
GS-9669	Gilead	NNI site 3 / palm 1	II
ABT-333	Abbott	NNI site 3 / palm 1	III
Tegobuvir (GS-9190)	Gilead	NNI site 4 / palm 2	II
Setrobuvir (ANA598)	Anadys / Roche	NNI site 4? / palm 1	II
<b>NS5A inhibitors</b>			
Daclatasvir (BMS-790052)	Bristol-Myers Squibb	NS5A domain 1 inhibitor	III
BMS-824393	Bristol-Myers Squibb	NS5A protein	I
PPI-461	Presidio	NS5A protein	II
PPI-668	Presidio	NS5A protein	II
Ledipasvir (GS-5885)	Gilead	NS5A protein	III
GS-5816	Gilead	NS5A protein	II
ABT-267	Abbott	NS5A protein	III
ACH-2928	Achillion	NS5A protein	I
MK-8742	Merck	NS5A protein	II
<b>Host targeting agents</b>			
SCY-635	Scynexis	Cyclophilin inhibitor	II
Alisporivir (Debio-025)	Novartis	Cyclophilin inhibitor	II
Miravirsen	Santaris	miRNA122 antisense RNA	II

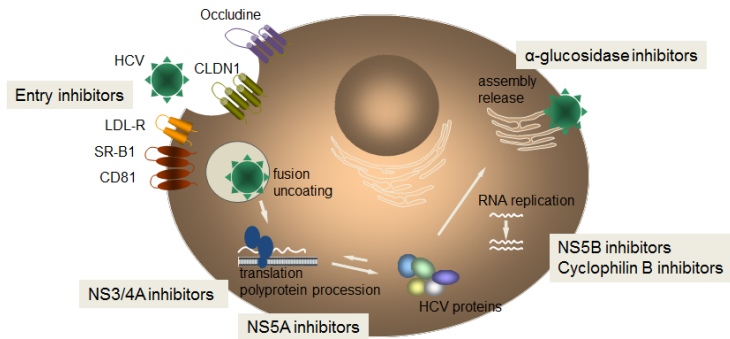
**Table 5.1a – Selected directly acting antiviral agents (DAAs) and host targeting agents whose development has been stopped or temporarily halted**

Drug name	Company	Target / Active site
<b>NS3/4A protease inhibitors</b>		
Ciluprevir (BILN 2061)	Boehringer Ingelheim	Active site / macrocyclic
Narlaprevir (SCH900518)	Schering-Plough	Active site / linear
PHX1766	Pheromix	Active site
<b>Nucleoside analog NS5B polymerase inhibitors (NI)</b>		
Valopicitabine (NM283)	Idenix/ Novartis	Active site
R1626	Roche	Active site
GS-938	Gilead	Active site
IDX184	Idenix	Active site
<b>Non-nucleoside NS5B polymerase inhibitors (NNI)</b>		
BILB 1941	Boehringer Ingelheim	NNI site 1 / thumb 1
MK-3281	Merck	NNI site 1 / thumb 1
VX-759	Vertex	NNI site 2 / thumb 2
VX-916	Vertex	NNI site 2 / thumb 2
Filibuvir (PF-00868554)	Pfizer	NNI site 2 / thumb 2
ABT-072	Abbott	NNI site 3 / palm 1
HCV-796	ViroPharma / Wyeth	NNI site 4 / palm 2
IDX375	Idenix	NNI site 4 / palm 2
<b>Host targeting agents</b>		
NIM811	Novartis	Cyclophilin inhibitor

In the past, combination therapy with pegylated-interferon (PEG-IFN)  $\alpha$  plus weight-based ribavirin led to sustained virologic response (SVR, defined by undetectable HCV RNA 24 weeks after treatment completion) in approximately 50% of all HCV genotype 1-infected patients, compared to 70-90% of those infected with HCV genotypes 2 and 3 (Zeuzem 2009). The limited treatment success especially in HCV genotype 1 patients, the need for long treatments (up to 72 weeks), the numerous side effects of PEG-IFN  $\alpha$  plus ribavirin therapy, and the exploding knowledge of the HCV life cycle and of structural features of the HCV proteins has spurred development of many promising DAAs (Bartenschlager 2004, Lange 2012, Moradpour 2013, Moradpour 2007).

In principle, each of the four HCV structural and six non-structural proteins, HCV-specific RNA structures such as the IRES, as well as host factors on which HCV depends, are suitable targets for DAA agents. In the following section, DAA compounds

currently in clinical development are presented (Table 5.1, Figure 5.1). Recently, the NS3/4A protease inhibitors telaprevir, boceprevir, and simeprevir as well as the nucleoside analog sofosbuvir were approved in combination with PEG-IFN  $\alpha$  plus ribavirin (triple therapy). However, especially for patients with previous failure to PEG-IFN  $\alpha$  / RBV therapy, the efficacy of the triple regimens is limited and a large proportion of patients continue to be intolerant to the side effects associated with IFN  $\alpha$ . As a first step into an interferon-free treatment world for HCV genotype 2-infected patients the recently approved combination of the nucleoside analog sofosbuvir plus ribavirin seems to be highly effective. Therefore, the approval of novel interferon-free DAA combination regimens with coverage also of other HCV genotypes is eagerly awaited.

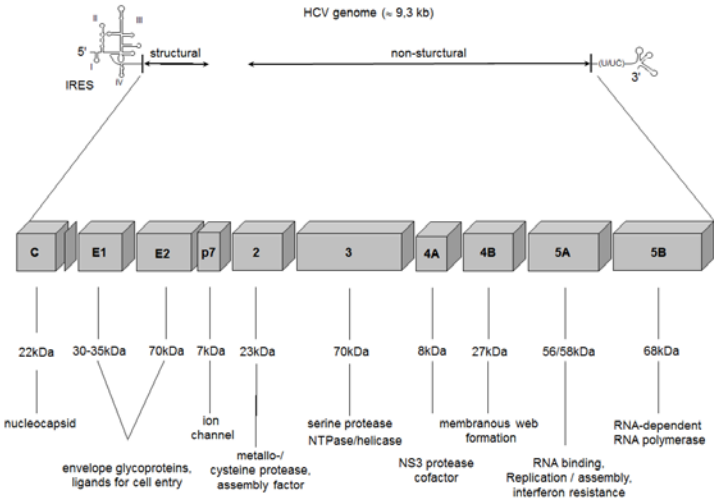


**Figure 5.1 – HCV life cycle and targets for directly acting antiviral (DAA) agents**

## HCV life cycle and treatment targets

HCV is a positive-sense single-stranded RNA virus of approximately 9600 nucleotides. The HCV genome contains a single large open reading frame encoding for a polyprotein of about 3100 amino acids. From this initially translated polyprotein, the structural HCV protein core (C) and envelope

glycoproteins 1 and 2 (E1, E2), p7, and the six non-structural HCV proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B, are processed by both viral and host proteases. The core protein forms the viral nucleocapsid carrying E1 and E2, the receptors for viral attachment and host cell entry. The non-structural proteins are multifunctional proteins essential for the HCV life cycle (Bartenschlager 2004, Moradpour 2007). P7 is a small hydrophobic protein that oligomerizes into a circular hexamer, most likely serving as an ion channel through the viral lipid membrane. The large translated section of the HCV genome is flanked by the strongly conserved HCV 3' and 5' untranslated regions (UTR). The 5' UTR is comprised of four highly structured domains forming the internal ribosome entry site (IRES), which plays an important role in HCV replication (Figure 5.2).



**Figure 5.2 – Genomic organisation of HCV**

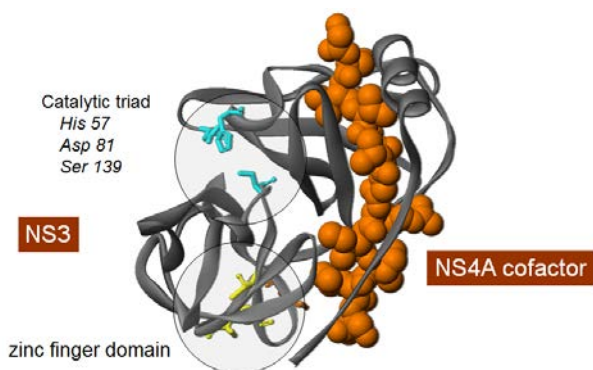


## NS3/4A protease inhibitors

### Molecular biology

After receptor-mediated endocytosis, the fusion of HCV with cellular membranes and uncoating of the viral nucleocapsid, the single-stranded positive-sense RNA genome of the virus is released into the cytoplasm to serve as messenger RNA for the HCV polyprotein precursor. HCV mRNA translation is under the control of the internal ribosome entry site (IRES) (Bartenschlager 2004, Moradpour 2007). IRES mediates the HCV polyprotein translation by forming a stable complex with the 40S ribosomal subunit, eukaryotic initiation factors and viral proteins.

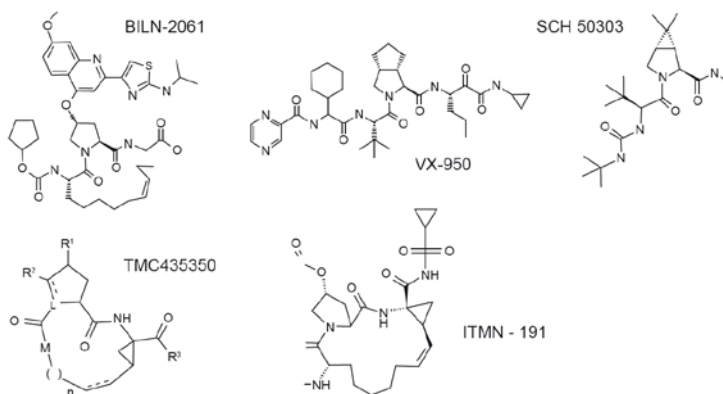
From the initially translated HCV polyprotein, the three structural and seven non-structural HCV proteins are processed by both host and viral proteases (Bartenschlager 2004, Moradpour 2007). NS2 is a metalloproteinase that cleaves itself from the NS2/NS3 protein, leading to its own loss of function and to the release of the NS3 protein (Lorenz 2006), which activates the serine protease, located in a small groove, and the helicase/NTPase (Kim 1998, Kim 1996). NS3 forms a tight, non-covalent complex with its cofactor and enhancer NS4A, which is essential for proper protein folding (Figure 5.3). The NS3/4A protease cleaves the junctions between NS3/NS4A, NS4A/NS4B, NS4B/NS5A and NS5A/NS5B. Besides its essential role in protein processing, NS3 is integrated into the HCV RNA replication complex, supporting the unwinding of viral RNA by its helicase activity. Moreover, NS3 may play an important role in HCV persistence via blocking TRIF-mediated toll-like receptor signaling and Cardif-mediated RIG-I signaling, subsequently resulting in impaired induction of type I interferons (Meylan 2005). Thus, pharmacologic NS3 inhibition might support viral clearance by restoring the innate immune response.



**Figure 5.3 – Molecular structure of the HCV NS3/4A protease**

The location of the active site of the NS3/4A protease, the shallow groove mentioned previously, makes the design of compound inhibitors relatively difficult. Nevertheless, many NS3/4A protease inhibitors have been developed and they can be divided into two classes, the macrocyclic inhibitors and the linear tetrapeptide-based  $\alpha$ -ketoamide derivatives (examples are shown in Figure 5.4). In general, NS3/4A protease inhibitors have been shown to strongly inhibit HCV replication during monotherapy but can also cause the selection of resistant mutants followed by viral breakthrough. The additional administration of pegylated interferon plus ribavirin, however, was shown to reduce the frequency of development of resistance. The logical aim for combination therapies with different antiviral drugs is to be efficacious while preventing the development of resistance.

Telaprevir and boceprevir (both  $\alpha$ -ketoamide derivatives) were approved for the treatment of chronic hepatitis C virus genotype 1 infection by FDA, EMA and several other agencies in 2011. A detailed description of these agents is provided in Chapter 4.



**Figure 5.4 - Molecular structure of selected NS3/4A inhibitors**

### Other NS3 protease inhibitors

Other NS3 protease inhibitors are currently in various stages of development - danoprevir (R7227), faldaprevir (BI201335), simeprevir (TMC435), asunaprevir (BMS-650032), ACH-1625, IDX320, ABT-450, MK-5172, GS-9256, GS-9451 - and should significantly increase treatment options for chronic hepatitis C in the near future. In general, comparable antiviral activities to telaprevir and boceprevir in HCV genotype 1-infected patients were observed during mono- and triple- therapy studies (Brainard 2010, Dvory-Sobol 2012, Ferenci 2013, Lawitz 2012, Manns 2013, Manns 2011, Manns 2011, Reesink 2010, Summa 2012, Zeuzem 2013).

Potential advantages of these second and third generation protease inhibitors may be improved tolerability, broader genotypic activity (eg, MK-5172, danoprevir, simeprevir), different resistance profiles (eg, MK-5172), and/or improved pharmacokinetics for once-daily dosing (eg, simeprevir, faldaprevir). Different resistance profiles between linear tetrapeptide and macrocyclic inhibitors binding to the active site of the NS3 protease have been shown. R155 is the main resistance codon and different mutations at this amino acid site

within the NS3 protease confer cross-resistance to nearly all protease inhibitors currently in advanced clinical development (Sarrazin 2010). An exception is MK-5172, which exhibits potent antiviral activity against variants carrying mutations at position R155 (Romano 2012). MK-5172 also shows potent antiviral activity against HCV genotypes 1 and 3 isolates, although the required doses to suppress HCV genotype 3 may be limited by toxicity issues (Brainard 2010).

The currently most advanced second wave NS3/4A protease inhibitors are faldaprevir and simeprevir. Simeprevir was approved by FDA in 2013 for the treatment of HCV genotype 1 infection; the approval of simeprevir in Europe and of faldaprevir is expected for 2014 (see Chapter 4 for details). In recently completed approval studies (QUEST 1 and QUEST 2 for treatment-naïve patients; PROMISE and ASPIRE for relapsers and non-responders), simeprevir (150 mg) was administered for 12 weeks once daily plus PEG-IFN  $\alpha$ -2a or PEG-IFN  $\alpha$ -2b and ribavirin, followed by 12 or 36 weeks of PEG-IFN  $\alpha$ -2a and ribavirin alone. Overall, this regimen led to SVR rates of approximately 80% in treatment-naïve HCV genotype 1 patients / relapsers and 50% in previous partial- and null-responders. SVR rates were lower in patients with advanced liver fibrosis as well as in patients carrying a variant at position 80 (Q80R/K) of the HCV NS3 protein at the start of antiviral therapy (see below). Approximately 90% of treatment naïve and relapse patients were eligible for shortening treatment duration to 24 weeks (Forns 2013, Jacobson 2013, Zeuzem 2013).

Several Phase III studies assessed faldaprevir-based triple therapy in treatment-naïve HCV genotype 1 patients (STARTverso<sup>TM</sup>1 and 2), in treatment-experienced HCV genotype 1 patients (STARTverso<sup>TM</sup>3), and in patients with HIV coinfection (STARTverso<sup>TM</sup>4). In these studies, faldaprevir was administered for 12-24 weeks together with PEG-IFN  $\alpha$  and ribavirin for 24-48 weeks. Generally, most patients were eligible for a total treatment duration of 24 weeks. Overall SVR rates for faldaprevir-based triple therapy were 70-80% in treatment-naïve

HCV genotype 1 patients / HIV-coinfected patients and 30-70% in treatment-experienced patients (Jacobson 2013, Jensen 2103, Rockstroh 2013).

### **Resistance to NS3/4A inhibitors**

Because of the high replication rate of HCV and the poor fidelity of its RNA-dependent RNA polymerase, numerous variants (quasispecies) are continuously produced during HCV replication. Among them, variants carrying mutations altering the conformation of the binding sites of DAA compounds can develop. During treatment with specific antivirals, these pre-existing drug-resistant variants have a fitness advantage and can be selected to become the dominant viral quasispecies. Many of these resistant mutants exhibit an attenuated replication with the consequence that, after termination of exposure to specific antivirals, the wild type may displace the resistant variants (Sarrazin 2007, Sarrazin 2010). HCV quasispecies resistant to NS3/4A protease inhibitors or non-nucleoside polymerase inhibitors can be detected at low levels in some patients (approximately 1%) who have never been treated with these specific antivirals before (Gaudieri 2009). The clinical relevance of these pre-existing mutants is not completely understood, although there is evidence that they may reduce the chance of achieving an SVR with DAA-based triple therapies if the patient's individual sensitivity to pegylated-interferon  $\alpha$  plus ribavirin is low.

More recently, the Q80R/K variant has been described as conferring low-level resistance to simeprevir (TMC435), a macrocyclic protease inhibitor. Interestingly, the Q80K variant can be detected in up to 50% of HCV genotype 1a-infected patients (approximately 20% in Europe and 50% in the US), while in <1% in 1b isolates, and a slower viral decline and lower SVR rates on simeprevir-based triple therapy were observed (Jacobson 2013, Lenz 2011, Zeuzem 2013). Table 5.2 summarizes the resistance profile of selected NS3/4A inhibitors.

**Table 5.2 – Resistance mutations to selected HCV NS3 protease inhibitors**

	36	54	55	80	155	156A	156B	168	170
Telaprevir* (linear)	■	■			■	■	■		
Boceprevir* (linear)	■	■	■		■	■			■
SCH900518* (linear)	■	■			■	■	■		■
Faldaprevir (BI201335*) (linear)					■			■	
BILN 2061** (macrocylic)					■		■	■	
Danoprevir* (macrocylic)					■			■	
MK-7009* (macrocylic)					■		■	■	
Simeprevir (TMC435*) (macrocylic)				■	■		■	■	
Asunaprevir (BMS-650032*) (macrocylic)				■	■			■	
GS-9451* (macrocylic)					■			■	
ABT-450* (macrocylic)					■			■	
IDX320** (macrocylic)								■	
ACH-1625** (macrocylic)								■	
MK-5172*** (macrocylic)								■	

36: V36A/M; 54: T54S/A; 55: V55A; 80: Q80R/K; 155: R155K/T/Q; 156A: A156S; 156B: A156T/V; 168: D168A/V/T/H; 170: V170A/T

\* mutations associated with resistance in patients

\*\* mutations associated with resistance *in vitro*

\*\*\* no viral breakthrough on 7 days monotherapy

# Q80 variants have been observed in approximately 10% of treatment-naïve patients and was associated with slower viral decline during simeprevir (TMC435) triple therapy

Although the resistance profiles differ significantly, R155 is an overlapping position for resistance development and different mutations at this position confer resistance to nearly all protease inhibitors (although not MK-5172) currently in advanced clinical development (Sarrazin 2010). Importantly, many resistance mutations can be detected *in vivo* only by clonal sequencing. For example, mutations at four positions conferring telaprevir resistance have been characterized so far (V36A/M/L, T54A, R155K/M/S/T and A156S/T), but only the A156 was identified initially *in vitro* in the replicon system (Lin 2005).

These mutations, alone or as double mutations, conferred low (V36A/M, T54A, R155K/T, A156S) to high (A156T/V, V36M + R155K, V36M + 156T) levels of resistance to telaprevir (Sarrazin 2007). It is thought that the resulting amino acid changes of these mutations alter the configuration of the catalytic pocket of the protease, which impedes binding of the protease inhibitor (Welsch 2008).

As shown for other NS3/4A protease inhibitors (eg, danoprevir), the genetic barrier to telaprevir resistance differs significantly between HCV subtypes. In all clinical studies of telaprevir alone or in combination with PEG-IFN  $\alpha$  plus RBV, viral resistance and breakthrough occurs much more frequently in patients infected with HCV genotype 1a compared to genotype 1b. This difference was shown to result from nucleotide differences at position 155 in HCV subtype 1a (aga, encodes R) versus 1b (cga, also encodes R). The mutation most frequently associated with resistance to telaprevir is R155K. Changing R to K at position 155 requires 1 nucleotide change in HCV subtype 1a, and 2 nucleotide changes in subtype 1b isolates (McCown 2009). In addition, HCV genotype 1a isolates generally display a higher fitness compared to HCV genotype 1b isolates, which explains a higher risk of resistance development at other positions within NS3/4A and other genomic regions of HCV genotype 1a (Romano 2012).

It will be important to better define whether treatment failure due to the development of variants resistant to DAA agents has a

negative impact on re-treatment with the same or other DAA treatment regimens. Follow-up studies of telaprevir and boceprevir Phase III studies have revealed a rapid decline of resistant variants to below the limit of detection (>20% of quasispecies) using population sequencing techniques (Barnard 2011, Sherman 2011). However, telaprevir- and boceprevir-resistant variants were detectable by a clonal sequencing approach several years after treatment in single patients who had been treated with telaprevir or boceprevir within smaller Phase Ib studies (Susser 2011). Furthermore, re-treatment with simeprevir-based triple therapy in 5 patients who had developed simeprevir resistance previously during monotherapy resulted in SVR in only 3 out of 5 patients, indicating a possible effect of low-level persistence of resistant variants (Lenz 2012).

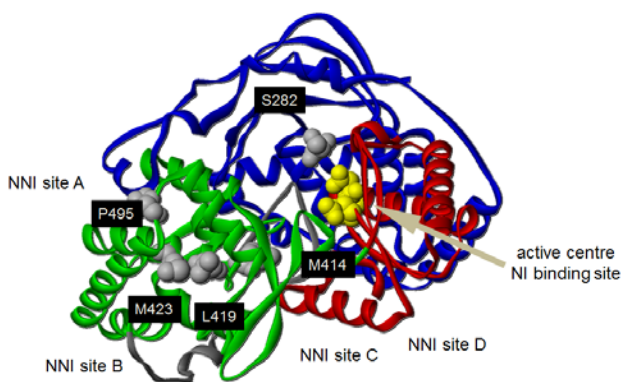
## **NS5B polymerase inhibitors**

### **Molecular biology**

HCV replication is initiated by the formation of the replication complex, a highly structured association of viral proteins and RNA, of cellular proteins and cofactors, and of rearranged intracellular lipid membranes derived from the endoplasmic reticulum (Moradpour 2007). The key enzyme in HCV RNA replication is NS5B, an RNA-dependent RNA polymerase that catalyzes the synthesis of a complementary negative-strand RNA by using the positive-strand RNA genome as a template (Lesburg 1999) (Figure 5.5). From this newly synthesized negative-strand RNA, numerous RNA strands of positive polarity are produced by NS5B activity that serve as templates for further replication and polyprotein translation. Because of poor fidelity leading to a high rate of errors in its RNA sequencing, numerous different isolates are generated during HCV replication in any given patient, termed HCV quasispecies. Due to the lack of proofreading of the NS5B polymerase together with the high replication rate of HCV, every possible mutation is generated every day.



NS5B RNA polymerase inhibitors can be divided into two distinct categories. Nucleoside analog inhibitors (NIs) like mericitabine, sofosbuvir, or ALS-220 mimic the natural substrates of the polymerase and are incorporated into the growing RNA chain, thus causing direct chain termination by blocking the active site of NS5B (Koch 2006). Because the active centre of NS5B is a highly conserved region of the HCV genome, NIs are potentially effective against different genotypes. Single amino acid substitutions in every position of the active centre may result in loss of function or in extremely impaired replicative fitness. Thus, there is a relatively high barrier to the development of resistance to NIs.

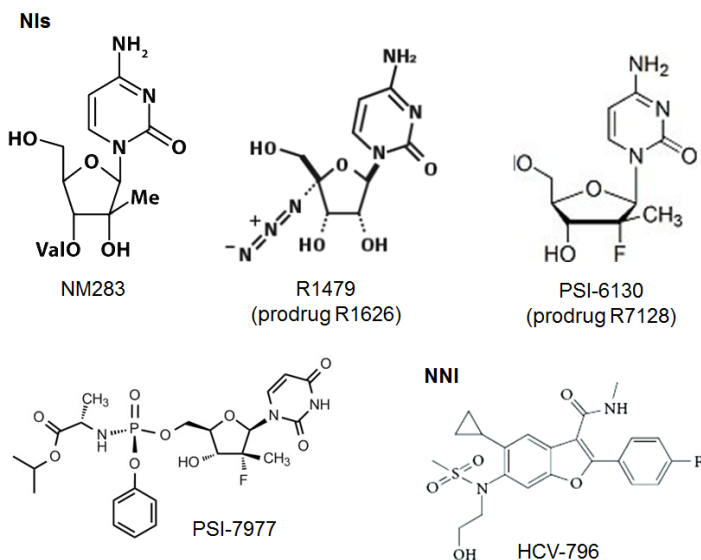


**Figure 5.5 – Structure of the HCV NS5B RNA polymerase and binding sites**

In contrast to NIs, the heterogeneous class of non-nucleoside inhibitors (NNIs) achieves NS5B inhibition by binding to different allosteric enzyme sites, which results in conformational protein change before the elongation complex is formed (Beaulieu 2007). For allosteric NS5B inhibition high chemical affinity is required. NS5B is structurally organized in a characteristic “right hand motif”, containing finger, palm and

thumb domains, and offers at least four NNI binding sites, a benzimidazole-(thumb 1)-, thiophene-(thumb 2)-, benzothiadiazine-(palm 1)- and benzofuran-(palm 2)-binding site (Lesburg 1999) (Figure 5.5). Because of their distinct binding sites, different NNI (polymerase) inhibitors can theoretically be used in combination or in sequence to manage the development of resistance.

But because NNIs bind relatively distantly from the active center of NS5B (Figure 5.6), their application may rapidly lead to the development of resistant mutants *in vitro* and *in vivo*. Moreover, mutations at the NNI binding sites do not necessarily lead to impaired function of the enzyme. Figure 5.6 shows the structure of selected nucleoside and non-nucleoside inhibitors as well as the active center.



**Figure 5.6 – Molecular structure of selected NS5B polymerase inhibitors**

## Nucleoside analogs

Mericitabine (RG7128) is safe and well tolerated, moderately effective against all HCV genotypes, and thus far viral resistance against mericitabine has been observed very rarely in clinical studies. Mericitabine-based triple therapies in HCV genotype 1-, 2-, 3-infected patients revealed superior SVR rates compared to PEG-IFN  $\alpha$  alone (Pockros 2011). In an all-oral regimen, administration of mericitabine in combination with the protease inhibitor R7227 (danoprevir) for 14 days, a synergistic antiviral activity of both drugs was observed (Gane 2010). No viral breakthrough with selection of resistant variants has been reported.

Very promising clinical data have been published recently for sofosbuvir, a nucleoside analog NS5B inhibitor strongly effective against all HCV genotypes. Striking Phase II results were obtained for triple therapy including sofosbuvir, which resulted in 90% and 90-100% SVR after only 12 weeks of treatment in treatment-naïve HCV genotype 1 patients and HCV genotype 2 and 3 patients, respectively (Kowdley 2013, Lawitz 2013). These high SVR rates were confirmed by a 90% SVR rate in a Phase III trial in treatment-naïve patients with genotypes 1, 4, 5 and 6 (Lawitz 2013). However, in the Phase III Lonestar-2 trial only 83% of treatment-experienced HCV genotype 3 patients with or without liver cirrhosis (but 93-100% of treatment-experienced HCV genotype 2 patients) achieved SVR after 12 weeks of sofosbuvir-based triple therapy (Lawitz 2013). In all studies, no sofosbuvir-associated side effects have been reported, and no virologic breakthrough was observed during triple therapy. Furthermore, some very promising sofosbuvir-based interferon-free regimens are in development (see below). Thus far, sofosbuvir resistance has only been observed in single patients after sofosbuvir monotherapy (mutation S282T) (Svarovskaia 2012).

Overall, nucleoside analogs like sofosbuvir demonstrate high antiviral activities that, together with their high genetic barrier

to resistance, suggest that they are optimal candidates for all-oral combination therapies (see below).

### **Non-nucleoside analogs**

At least 4 different allosteric binding sites have been identified for inhibition of the NS5B polymerase by non-nucleoside inhibitors. Currently, numerous non-nucleoside inhibitors are in Phase I and II clinical evaluation (eg, thumb 1 inhibitors BI207127, BMS-791325; thumb 2 inhibitors filibuvir and VX-222; palm I inhibitor ANA598 and ABT-333; palm II inhibitors tegobuvir and IDX-375) (Ali 2008, Cooper 2007, Erhardt 2009, Kneteman 2009, Larrey 2012). In general, these non-nucleoside analogs display a low to medium antiviral activity and a low genetic barrier to resistance, evidenced by frequent viral breakthrough during monotherapy studies and selection of resistance mutations at variable sites of the enzyme. In line with these experiences in Phase I studies, a Phase II triple therapy study with filibuvir in combination with pegylated interferon plus RBV showed high relapse and relative low SVR rates (Jacobson 2010). In contrast to nucleoside-analogs, non-nucleoside analogs in general do not display antiviral activity against different HCV genotypes (Sarrazin 2010). Due to their low antiviral efficacy and low genetic barrier to resistance, non-nucleoside analogs will probably only be developed as a component of multiple drug all-oral regimens (see below).

### **NS5A inhibitors**

The HCV NS5A protein seems to play a manifold role in HCV replication, assembly and release (Moradpour 2007). It was shown that NS5A is involved in the early formation of the replication complex by interacting with intracellular lipid membranes, and it initiates viral assembly at the surface of lipid droplets together with the HCV core (Shi 2002). NS5A may also serve as a channel that helps to protect and direct viral RNA within the membranes of the replication complex (Tellinghuisen 2005). Moreover, it was demonstrated that NS5A is able to

interact with NS5B, which results in an enhanced activity of the HCV RNA polymerase. Besides its regulatory impact on HCV replication, NS5A has been shown to modulate host cell signaling pathways, which has been associated with interferon resistance (Wohnsland 2007). Furthermore, mutations within the NS5A protein have been clinically associated with resistance / sensitivity to IFN-based antiviral therapy (Wohnsland 2007).

Daclatasvir (BMS-790052) was the first NS5A inhibitor to be clinically evaluated. Even low doses of daclatasvir display high antiviral efficacy against all HCV genotypes *in vitro*. Monotherapy with daclatasvir led to a sharp initial decline of HCV RNA concentrations, though its genetic barrier to resistance is relatively low (Gao 2010). In HCV genotype 1 and 4 patients, daclatasvir-based triple therapies for 24 or 28 weeks led to extended RVR (eRVR) rates of up to 83% of patients, compared to 9% in the control group (Pol 2012). SVR rates in this study ranged from 59-100%, according to daclatasvir dosage and HCV genotype / subtype (Hezode 2012).

During monotherapy, rapid selection of variants resistant to daclatasvir occurred (Nettles 2011). The most common resistance mutations in HCV genotype 1a patients were observed at residues M28, Q30, L31, and Y93 of NS5A. In HCV genotype 1b patients, resistance mutations were observed less frequently, predominantly at positions L31 and Y93. These resistance mutations increased the EC<sub>50</sub> to daclatasvir moderately to strongly (Fridell 2011). Interestingly and different to NS3 protease inhibitor resistance mutations, variants conferring resistance to NS5A inhibitors are not associated with impaired replication fitness and thus during follow-up after the end of treatment do not disappear. Indeed, in a first follow-up study for approximately 1 year, persistence of the majority of NS5A resistance mutations was seen (McPhee 2013). However, no cross-resistance between daclatasvir and other DAA agents has been reported.

Other NS5A inhibitors (eg, BMS-824393, PPI-461, ledipasvir (GS-5885), ABT-267) are in clinical development. Like daclatasvir,

these NS5A inhibitors are characterised by broad genotypic coverage, high antiviral activity, but also by a low genetic barrier to resistance development and overlapping resistance profiles (cross-resistance). Collectively, daclatasvir and other NS5A inhibitors are highly promising agents for both triple therapy and – most importantly – for all-DAA combination therapy approaches.

## **Compounds targeting viral attachment and entry**

The tetraspanin protein CD81, claudin-1, occludine, scavenger receptor class B type 1 (SR-B1), the low-density lipoprotein (LDL) receptor, glycosaminoglycans and the dendritic cell- /lymph node-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN/L-SIGN) have been identified as putative ligands for E1 and E2 during viral attachment and entry (Moradpour 2007).

HCV entry inhibition might enrich future hepatitis C treatment opportunities, in particular in the prevention of HCV liver graft reinfection. HCV entry inhibition can be theoretically achieved by the use of specific antibodies or small molecule compounds either blocking E1 and E2 or their cellular receptors. So far, only results from clinical trials using polyclonal (eg, civacir) (Davis 2005) or monoclonal (eg, HCV-AB 68) (Schiano 2006) HCV-specific antibodies are available. The clinical benefit of these antibodies has been poor, however. The development of small molecule entry inhibitors is in a preclinical stage and is complicated by difficulties in the crystallographic characterization of the HCV envelope proteins.

## **Host factors as targets for treatment**

### **Cyclophilin B inhibitors**

HCV depends on various host factors throughout its life cycle. Cyclophilin B is expressed in many human tissues and provides a cis-trans isomerase activity, which supports the folding and

function of many proteins. Cyclophilin B enhances HCV replication by incompletely understood mechanisms, like the modulation of NS5B activity. Alisporivir (Debio-025) is an orally bioavailable cyclophilin B inhibitor exerting an antiviral impact on both HCV and HIV replication. In clinical trials in HIV/HCV-coinfected patients, treatment with 1200 mg alisporivir twice daily for two weeks led to a mean maximal  $\log_{10}$  reduction of HCV RNA of 3.6 and of HIV DNA of 1.0 (Flisiak 2008). Alisporivir was well-tolerated and no viral breakthrough occurred during the 14 days of treatment.

Combination therapy of alisporivir 200 mg, 600 mg or 1000 mg and PEG-IFN  $\alpha$ -2a was evaluated in a double-blind placebo-controlled Phase II trial in treatment-naïve patients monoinfected with HCV genotypes 1, 2, 3 or 4. Treatment was administered for 29 days. Mean  $\log_{10}$  reductions in HCV RNA at day 29 were 4.75 (1000 mg), 4.61 (600 mg) and 1.8 (200 mg) in the combination therapy groups compared to 2.49 (PEG-IFN  $\alpha$ -2a alone) and 2.2 (1000 mg alisporivir alone) in the monotherapy groups. No differences in antiviral activity were observed between individuals infected with the different genotypes. Alisporivir was safe and well tolerated but led to a reversible bilirubin increase in some of the patients treated with 1000 mg alisporivir daily (Flisiak 2009). A high genetic barrier to resistance of alisporivir and a broad HCV genotypic activity highlight the potential of drugs targeting host proteins.

In a Phase II clinical trial in treatment-naïve HCV genotype 1 patients, combination therapy with alisporivir, PEG-IFN  $\alpha$ -2a plus ribavirin for 24-48 weeks resulted in SVR rates of 69-76% compared to 55% in the control group (Flisiak 2011). Furthermore, interesting first studies with interferon-free treatment regimens including alisporivir and ribavirin have been conducted. Despite these promising data, the development of alisporivir was put on hold due to rare cases of severe pancreatitis during combination therapy with alisporivir and

PEG-IFN  $\alpha$ -2a and only very recently further development of alisporivir was re-initiated.

### **Nitazoxanide**

Nitazoxanide with its active metabolite tizoxanide is a thiazolide antiprotozoal approved for the treatment of *Giardia lamblia* and *Cryptosporidium parvum* infections. *In vitro* studies have revealed an essential inhibitory impact on HCV and HBV replication by still unknown mechanisms.

Results of two Phase II studies evaluating 500 mg nitazoxanide twice daily for 12 weeks followed by nitazoxanide, PEG-IFN  $\alpha$ -2a  $\pm$  RBV for 36 weeks yielded conflicting results with SVR rates of 79% in treatment-naïve genotype 4 patients, but of only 44% in HCV genotype 1 patients (Rossignol 2009). However, additional studies revealed a less impressive gain in SVR rates with the addition of nitazoxanide to PEG-IFN  $\alpha$ -2a plus RBV.

### **Silibinin**

Silymarin, an extract of milk thistle (*Silybum marianum*) with antioxidant activity, has been empirically used to treat chronic hepatitis C and other liver diseases. Silibinin is one of the six major flavonolignans in silymarin. Surprisingly, recent reports demonstrated that silibinin inhibits HCV at various steps of its life cycle (Ahmed-Belkacem 2010, Wagoner 2010). In addition, intravenous silibinin in non-responders to prior IFN-based antiviral therapy led to a decline in HCV RNA between 0.55 to 3.02  $\log_{10}$  IU/ml after 7 days and a further decrease after an additional 7 days in combination with PEG-IFN  $\alpha$ -2a/RBV in the range of 1.63 and 4.85  $\log_{10}$  IU/ml (Ferenci 2008). On a case report basis, it was shown that treatment with silibinin can prevent recurrent hepatitis C after liver transplantation in selected cases (Neumann 2010).

### **Miravirsen**

MicroRNA-122 (miRNA-122) is a liver-specific microRNA that has been shown to be a critical host factor for HCV (Landford 2010).



MiRNA-122 binds to the 5' NTR region of the HCV genome, which appears to be vital in the HCV replication process. Miravirsen is a modified antisense oligonucleotide that targets miRNA-122 and thereby prevents binding of miRNA-122 to the HCV genome. In a Phase IIa proof-of-principle study, weekly subcutaneous injections of miravirsen led to a reduction of HCV RNA serum concentration of up to 2.7 log<sub>10</sub> IU/mL, indicating that an antisense oligonucleotide-based approach of miRNA-122 inhibition could be a promising modality for antiviral therapy (Janssen 2013). No relevant side effects were seen in this study.

### **Newer combination therapies**

The approval of the HCV protease inhibitors telaprevir and boceprevir in 2011 constitutes a milestone in the treatment of chronic HCV genotype 1 infection. Nevertheless, telaprevir- or boceprevir-based triple therapy has certain limitations. In particular, treatment success still depends on the interferon sensitivity of individual patients because a slow decline of HCV viral load during triple therapy is associated with a high risk of antiviral resistance development. Consequently, viral breakthrough of drug resistant variants was observed in a significant number of patients with previous partial or null response to treatment with PEG-IFN  $\alpha$  plus ribavirin, in patients with limited HCV viral load decline during lead-in treatment with PEG-IFN  $\alpha$  plus ribavirin only, or in difficult-to-cure populations like blacks (who have a lower percentile of successful SNPs at the IL28B gene) or patients with advanced liver fibrosis. In addition, triple therapy is not an option for patients with contraindications to PEG-IFN  $\alpha$  or ribavirin, such as patients with decompensated liver cirrhosis or liver transplant failure.

To overcome these limitations, triple therapy regimens including more potent DAAs, or quadruple therapies based on the combination of two different DAAs plus PEG-IFN  $\alpha$  / ribavirin may be applicable. Several triple therapy regimens including

newer NS3/4A, NS5A, or NI NS5B inhibitors have been shown to be possibly superior over telaprevir or boceprevir-based triple therapy (Feld 2012, Gane 2013, Jacobson 2013, Lenz 2012, Rockstroh 2013, Zeuzem 2013). As described above, this applies in particular for combination therapies with the NI sofosbuvir plus PEG-IFN  $\alpha$  / ribavirin, which results in high SVR rates in HCV genotype 1-6 patients after short treatment periods.

Furthermore, a high potential of the quadruple therapy approach has already been demonstrated in Phase I and II clinical trials, with outstanding SVR rates even in previous null responders to PEG-IFN  $\alpha$  plus ribavirin alone. However, these clinical trials were performed in highly selected patients, and neither triple nor quadruple therapy approaches are an option for patients with contraindications to PEG-IFN  $\alpha$  or ribavirin, such as patients with decompensated liver cirrhosis or liver transplant failure.

For that reason, numerous trials have been initiated to investigate the potential of interferon-free combination therapies with different DAA agents (+/- ribavirin) alone (Table 5.3). As is well established in the treatment of HIV infection, combining agents with different antiviral resistance profiles should result in a substantially decreased risk of viral breakthrough of resistant variants. Nucleoside analog NS5B inhibitors plus drugs targeting host factors such as the cyclophilin inhibitor alisporivir display a high genetic barrier to resistance development and may therefore be key agents for effective DAA combinations (Sarrazin 2010).

**Table 5.3 – Selected trials evaluating DAA combination therapies**

<b>DAAs</b>	<b>Additional agents</b>	<b>Phase</b>
<b>Nucleoside NS5B inhibitor</b>		
Sofosbuvir	+ / - ribavirin, + / - PEG-IFN $\alpha$ plus RBV	III
<b>Nucleoside NS5B inhibitor + NS3/4A protease inhibitor</b>		
Mericitabine + danoprevir/ritonavir	+ / - ribavirin, + / - PEG-IFN $\alpha$ plus RBV	III
Sofosbuvir + simeprevir	+ / - ribavirin	II
<b>Nucleoside NS5B inhibitor + NS5A inhibitor</b>		
Sofosbuvir + daclatasvir	+ / - ribavirin	II
Sofosbuvir + ledipasvir	+ / - ribavirin	III
<b>Non-nucleoside NS5B inhibitor + NS3/4A protease inhibitor</b>		
Faldaprevir + deleobuvir	+ ribavirin, + / - PEG-IFN $\alpha$ plus RBV	Halted
Tegobuvir + GS-9256	+ / - ribavirin, + / - PEG-IFN $\alpha$ plus RBV	II
ABT-333 + ABT-450/r	+ ribavirin + / - PEG-IFN $\alpha$	III
ABT-072 + ABT-450/r	+ ribavirin	Stopped
VX-222 + telaprevir	+ / - ribavirin, + / - PEG-IFN $\alpha$ plus RBV	III
<b>NS3/4A protease inhibitor + NS5A inhibitor</b>		
Asunaprevir + daclatasvir	+ / - ribavirin, + / - PEG-IFN $\alpha$ plus RBV	III
MK-5171 + MK-8742	+ / - ribavirin	II
<b>Multiple DAA agent combinations</b>		
NS5A inhibitor (GS-5885) + NS3/4A inhibitor (GS-9451) + NNI (tegobuvir)	+ ribavirin	II
NS5A inhibitor (ABT-267) + NS3/4A inhibitor (ABT-450/r) + NNI (ABT-333)	+/- ribavirin	III
NS5A inhibitor (PPI-668) + NS3/4A inhibitor (faldaprevir) + NNI (deleobuvir)	+/- ribavirin	II
NS5A inhibitor (daclatasvir) + NS3/4A inhibitor (asunaprevir) + NNI (BMS-791325)	-	III
<b>Host targeting agents</b>		
Alisporivir	+ / - ribavirin, + / - PEG-IFN $\alpha$ plus RBV	Halted
Miravirsen	+ PEG-IFN- $\alpha$ and ribavirin	II

In contrast, NS3/4A and NS5A inhibitors display a low genetic barrier to resistance development, but in view of their high antiviral efficacy they appear to be promising combination partners for nucleoside analogs or cyclophilin inhibitors. Despite their low antiviral efficacy and low genetic barrier to resistance development, some NNI NS5B inhibitors have been shown to be valuable partners in all-oral regimens.

In the following section, current data on combination therapies of different DAAs, with or without PEG-IFN  $\alpha$  and / or RBV will be summarized.

### **PEG-IFN $\alpha$ -based quadruple therapy**

Preliminary SVR data of a small but highly informative trial serves as proof-of-concept for the potential of a quadruple therapy approach for patients with previous null response to PEG-IFN  $\alpha$  plus RBV (Lok 2012). In one Phase II study, 11 HCV genotype 1 patients with prior null response were treated with a combination of the NS5A inhibitor daclatasvir and the protease inhibitor asunaprevir together with PEG-IFN  $\alpha$  plus ribavirin for 24 weeks. Quadruple therapy resulted in 100% SVR 12 weeks after treatment completion in both HCV genotype 1a- and 1b-infected patients. Even though the number of patients included in this trial was very limited, the high SVR rate seems impressive compared to SVR rates of ~30% that were achieved with telaprevir-based triple therapy in prior null responders (Zeuzem 2011). The efficacy of this quadruple regimen in both HCV genotype 1a and 1b patients with prior null response has since been confirmed in a larger trial (Lok 2012).

A Phase II clinical trial assessed quadruple therapy with the non-nucleoside NS5B inhibitor tegobuvir in combination with the NS3/4A protease inhibitor GS-9256 + PEG-IFN  $\alpha$  plus RBV for 28 days in treatment-naïve HCV genotype 1 patients (Zeuzem 2011). The primary endpoint of this study was rapid virologic response (RVR), which was achieved in 100% of patients. After 28 days of quadruple therapy, treatment with PEG-IFN  $\alpha$  and

ribavirin was continued, which led to complete early virologic response (cEVR) in 94% of patients.

Another Phase II clinical trial investigated a response-guided approach during quadruple therapy containing the non-nucleoside NS5B inhibitor VX-222 (100 mg or 400 mg) in combination with the NS3/4A inhibitor telaprevir + PEG-IFN  $\alpha$  plus RBV in treatment-naïve HCV genotype 1 patients (Nelson 2011). Quadruple treatment was administered for 12 weeks. All treatment was stopped after 12 weeks in patients who were HCV RNA-negative at treatment weeks 2 and 8. Patients in whom HCV RNA was detectable at treatment week 2 or 8 received an additional 12 weeks of PEG-IFN  $\alpha$  plus ribavirin alone. Up to 50% of patients met the criteria for the 12-week treatment. Of those, 82-93% achieved an SVR 12 weeks after treatment. In patients who were treated with an additional 12 weeks of PEG-IFN  $\alpha$  plus RBV, the end-of-treatment response was 100%.

Recently, a head-to-head comparison of triple-therapy, quadruple therapy, and interferon-free therapy based on the NI mericitabine was reported (Matterhorn trial) (Feld 2012). In this study, HCV genotype 1a and 1b patients with prior partial- or null-response were randomized to treatment with either mericitabine plus PEG-IFN  $\alpha$  / RBV (triple therapy), mericitabine in combination with the NS3/4A protease inhibitor danoprevir/ritonavir plus PEG-IFN  $\alpha$  / RBV (quadruple therapy), or mericitabine in combination with danoprevir/ritonavir and ribavirin (interferon-free). According to an incomplete preliminary analysis, SVR rates were 95%, 100%, and 44-72% in the triple-, quadruple, and interferon-free treatment arm, respectively. HCV genotype 1a patients in particular experienced high rates of viral breakthrough on the interferon-free therapy. Importantly, viral breakthrough was associated with resistance to danoprevir but not to mericitabine. Collectively, the quadruple therapy approach appears to be highly promising in patients with limited sensitivity to IFN  $\alpha$ , even in patients with HCV subtype 1a and prior null response to PEG-IFN  $\alpha$  / RBV. However, the current development of potent triple therapy and

IFN-free therapy regimens will probably make the quadruple approach unnecessary for the vast majority of patients.

## **All-oral therapy with or without ribavirin**

### **Nucleoside analog NS5B inhibitors with or without ribavirin**

The NI sofosbuvir displays a high antiviral efficacy and a high barrier to resistance development. In small Phase II clinical trials, sofosbuvir plus ribavirin administered for 12 weeks led to impressive SVR rates of 84–100% in treatment-naïve HCV genotype 1, 2 and 3 patients, but to a significantly lower SVR rate (11% (1/9)) in treatment-experienced HCV genotype 1 patients (Gane 2013). The large Phase III Fission trial compared 12 weeks of sofosbuvir plus ribavirin with 24 weeks of PEG-IFN  $\alpha$  and ribavirin in treatment-naïve HCV genotypes 2 and 3 patients. Both treatment arms resulted in overall SVR rates of 67%. However, in patients infected with HCV genotype 3, SVR rates were significantly lower (34 and 61% in patients with or without liver cirrhosis, respectively) than in HCV genotype 2 patients (91% and 98% in patients with or without liver cirrhosis, respectively) (Lawitz 2013). The Phase III Positron study yielded comparable SVR rates in IFN-intolerant, -ineligible or -unwilling HCV genotype 2 and 3 patients after treatment with sofosbuvir and ribavirin for 12 weeks (Jacobson 2013). Additional studies (Fusion and Valence) assessed longer treatment durations (16–24 weeks) of sofosbuvir plus ribavirin in treatment-naïve and treatment-experienced HCV genotype 2 and 3 patients. Generally, 12 weeks of sofosbuvir and ribavirin was sufficient to achieve SVR in the vast majority of HCV genotype 2 patients, at least in the absence of liver cirrhosis. However, in HCV genotype 3 patients with or without liver cirrhosis, SVR rates after 12 weeks were only 19 and 37%, respectively, but 61–87% and 63–60% after 16–24 weeks of therapy (Jacobson 2013, Zeuzem 2013). Overall, therapy with sofosbuvir plus ribavirin for 12 weeks seems a potent and promising regimen for HCV genotype 2 patients, but for other HCV genotypes, especially in patients

with liver cirrhosis, alternative strategies such as longer treatment durations, or the addition of another DAA or of PEG-IFN  $\alpha$  appear to be necessary.

Importantly, sofosbuvir plus ribavirin appears to be a potent option to prevent recurrent hepatitis C after liver transplantation as well - in one study, treatment with sofosbuvir plus ribavirin before liver transplantation led to HCV eradication in 64% of patients who were HCV RNA negative at the time of transplantation (Curry 2013).

### **Combinations of nucleoside analog NS5B inhibitors and NS3/4A protease inhibitors with or without ribavirin**

A first interferon-free clinical trial (INFORM-1 study) evaluated the combination of the NI mericitabine with the NS3/4A inhibitor danoprevir. In this proof of concept study, patients received both compounds for up to 14 days (Gane 2010). HCV RNA declined up to 5.2 log<sub>10</sub> IU/ml, viral breakthrough occurred in a single patient, and HCV RNA was undetectable at the end of dosing in up to 63% of patients. However, the fundamental question of whether an SVR can be achieved with combination therapies of different DAA compounds without PEG-IFN  $\alpha$  plus RBV will have to be answered by subsequent trials.

In the meantime, the INFORM-SVR study provided SVR data for the combination of mericitabine and danoprevir/r (ritonavir-boosted) with or without ribavirin for 12-24 weeks (Gane 2012). SVR rates in HCV genotype 1a and 1b patients were 26% and 71% in treatment arms including ribavirin (n=83), respectively, but significantly lower in all the RBV-free treatment groups (n=86). Importantly, resistance-associated variants in patients with viral breakthrough were predominantly identified within NS3/4A while a resistance mutation in NS5B was discovered only in one single patient (S282T). Recently, the large Matterhorn trial has shown in a head-to-head comparison that, in prior partial and null responders, IFN-free therapy containing mericitabine, danoprevir and ribavirin generally resulted in lower SVR rates

than danoprevir-based triple therapy or quadruple therapy, especially in patients with HCV genotype 1a (Feld 2012).

The NI sofosbuvir has a higher antiviral activity than mericitabine. The Cosmos trial evaluated the IFN-free combination of sofosbuvir plus the NS3-4A protease inhibitor simeprevir with or without ribavirin for 12-24 weeks in treatment-naïve and treatment-experienced HCV genotype 1 patients (Jacobson 2013). Overall, this regimen led to SVR rates of approximately 90%, independent of previous treatment history, presence of liver cirrhosis, IL28B genotype or presence of the Q80K variant in the HCV NS3 protein at baseline. Furthermore, the addition of ribavirin did not appear to improve SVR rates in this study, and a treatment duration of 12 weeks did not result in lower SVR rates compared to 24 weeks of therapy. As both compounds, sofosbuvir and simeprevir, are approved and available in the US and are expected to be available in Europe by mid-2014, combination therapy theoretically is possible and highly effective although formally not approved.

### **Combinations of nucleoside analog NS5B inhibitors plus NS5A inhibitors with or without ribavirin**

Impressive results have been shown for the combination of the NS5A inhibitor daclatasvir with the NI sofosbuvir, with or without ribavirin for 24 weeks (Sulkowski 2012). In approximately 90 treatment-naïve HCV genotype 1 patients, SVR rates were 100% and 86-88% in HCV genotype 2 and 3 patients, respectively. In this study, the addition of RBV did not improve virologic response rates but resulted in anemia in a significant proportion of patients. Furthermore, an unfavorable IL28B genotype apparently did not decrease the chance of cure in this study. Importantly, this regimen given for 24 weeks resulted in a 100% SVR rate in 41 HCV genotype 1 patients who had failed protease inhibitor-based triple therapy (Sulkowski 2013).

In addition, sofosbuvir was evaluated in combination with another NS5A inhibitor (ledipasvir, GS-5885) with or without ribavirin (Lonestar study) as well as in combination with the NNI



GS-9669 plus ribavirin. In both treatment-naïve and treatment-experienced HCV genotype 1 patients, treatment with these combinations resulted in SVR rates >90%. Importantly, treatment duration of 8-12 weeks with sofosbuvir plus ledipasvir appeared to be sufficient to cure most HCV genotype 1 patients, even in the presence of advanced liver fibrosis or in patients with previous failure of protease inhibitor based triple therapies (Gane 2013, Lawitz 2013). These high SVR rates recently have been confirmed in large Phase III studies (ION studies, Gilead press release December 2013) In the very first study of three strong DAAs (sofosbuvir, ledipasvir plus the non-nucleoside NS5B GS-9669 or the NS3 protease inhibitor GS-9451), even with only 6 weeks of treatment, high SVR rates (>90%) seems to be achievable in non-cirrhotic genotype 1-infected patients (NIH Synergy study) (Kohli 2013).

### **Combinations of NS3/4A protease inhibitors and non-nucleoside analog NS5B inhibitors with or without ribavirin**

The SOUND-C1 trial assessed the combination of the NS3/4A inhibitor faldaprevir (BI201335), the NNI deleobuvir (BI207127) (400 or 600 mg q8h) and ribavirin for 4 weeks (Zeuzem 2011). Virologic response rates in patients treated with 600 mg q8h of deleobuvir were 82%, 100% and 100% at treatment days 15, 22, and 29, respectively (SVR rates for this regimen were not provided). Overall virologic response rates were lower in subtype 1a vs. subtype 1b patients. Importantly, the large SOUND-C2 trial provided SVR rates for faldaprevir in combination with deleobuvir with or without RBV, administered for 16-40 weeks in approximately 360 treatment-naïve HCV genotype 1 patients (Zeuzem 2013). Overall, SVR12 rates ranged from 56% to 68% in treatment arms including ribavirin, compared to 39% in a single RBV-free treatment arm. In all treatment arms, SVR rates were consistently higher in HCV genotype 1b than in 1a patients, or in patients with the “good response” IL28B genotype. Importantly, SOUND-C2 included a significant number of patients with liver cirrhosis. In these patients, SVR rates were promising, though

lower than in patients without advanced liver disease (Soriano 2012). In SOUND-C2, the predominantly observed resistance-associated variants in patients with virologic failure were at position R155 in NS3 and at position P495 in NS5B, including double mutations in numerous patients, especially those with on-treatment failure (Cote-Martin 2012). SOUND-C3 is a Phase III study evaluating faldaprevir plus deleobuvir and ribavirin for 16 weeks in treatment-naïve HCV genotype 1 patients. SVR was achieved in 95% of HCV genotype 1b patients, but only in 17% of HCV genotype 1a patients (Dufour 2013). To improve SVR rates in HCV genotype 1a patients, a regimen containing faldaprevir, deleobuvir and the NS5A inhibitor PPI-668 is under development (see below).

The combination of tegobuvir (GS-9190), another NNI, together with GS-9256, a NS3/4A inhibitor, +/- ribavirin was assessed in a trial of treatment-naïve HCV genotype 1 patients (Zeuzem 2011). Again, tegobuvir + GS-9256 + ribavirin led to higher RVR rates compared to tegobuvir + GS-9256 alone (38% versus 7%, respectively), further proving the benefit of ribavirin in distinct interferon-free DAA combination therapies.

A comparable approach can be seen in the ZENITH trial, assessing the antiviral activity of the NS3/4A inhibitor telaprevir and the NNI VX-222 alone, in combination with RBV, or in combination with PEG-IFN  $\alpha$  plus ribavirin (quadruple therapy) in treatment-naïve HCV genotype 1 patients. Again, quadruple therapy led to high SVR rates. However, in the all-oral treatment arms, high rates of viral breakthrough were observed (Jacobson 2012, Nelson 2011).

The above described data for all-oral combinations with NS3/4A inhibitors plus NNIs are contrasted by strongly encouraging results of the recent Co-Pilot study. In Co-Pilot, 12 weeks of combination therapy with the NS3/4A inhibitor ABT-450/r (ritonavir-boosted), the NNI ABT-333, plus RBV resulted in 93% and 47% SVR in treatment-naïve HCV genotype 1 patients and in previous null-responders to PEG-IFN  $\alpha$  plus RBV alone, respectively (Poordad 2013). Furthermore, in the single arm Pilot

study evaluating ABT-450 in combination with the NNI ABT-072 plus ribavirin, SVR was achieved in 91% (10/11) of treatment-naïve HCV genotype 1 patients, all of whom had the “good-response” IL28B genotype (Lawitz 2012, Poordad 2013). Importantly, a single patient in Pilot who achieved SVR 24 weeks after treatment completion experienced a late viral relapse between weeks 24 and 36 post-treatment. Sequencing analyses in this patient identified a resistant mutant in NS5B, possibly indicating that interferon-free treatment regimens may require longer follow-up times than conventional PEG-IFN  $\alpha$  and ribavirin therapy. Sequencing analyses in patients who experienced viral breakthrough during treatment or early relapse after therapy (in Pilot or Co-Pilot) identified resistance variants in both NS3 and NS5B. Interestingly, in NS3 substitutions were predominantly observed at position D168, whereas R155K was identified only in a single patient.

### **Combinations of NS3/4A inhibitors and NS5A inhibitors**

The first clinical trial to report SVR data for an interferon-free regimen investigated the combination of the NS5A inhibitor daclatasvir with the NS3/4A protease inhibitor asunaprevir for 24 weeks in 10 HCV genotype 1 patients with prior null response to PEG-IFN  $\alpha$  plus RBV (Lok 2012). 36% of patients achieved SVR. Importantly, viral breakthrough was observed only in patients infected with HCV genotype 1a, and in all of them resistance mutations against both agents were identified. Nevertheless, this trial constituted a proof-of-principle that SVR can be achieved by all-oral regimens, especially in patients infected with HCV subtype 1b. This has been confirmed in a larger follow-up study (Lok 2012), as well as by a 100% SVR rate in a small study evaluating the same agents (daclatasvir plus asunaprevir) in Japanese HCV genotype 1b infected previous null responder patients (Chayama 2012), and in a subsequent Japanese study in HCV genotype 1b patients with prior null response (n=21) or ineligibility to IFN (n=22), in whom SVR rates of 91% and 64% were seen, respectively (Suzuki 2012). For HCV genotype 1a

patients, promising data were presented for a more potent all-oral regimen including daclatasvir, asunaprevir plus the NNI BMS-791325 (see below).

The C-Worthy study evaluated the potent NS3-4A inhibitor MK-5171 in combination with the NS5A inhibitor MK-8742 with or without ribavirin for 12 weeks in treatment-naïve HCV genotype 1 patients. SVR rates in this study ranged from 89-100%. In HCV genotype 1b patients the addition of ribavirin did not improve SVR rates (Lawitz 2013).

### **Combinations of multiple DAAs with or without ribavirin**

A first study evaluating a multiple DAA regimen, namely the combination of the NS5A inhibitor GS-5885, the NS3/4A inhibitor GS-9451, the NNI tegobuvir plus RBV was recently presented (Sulkowski 2012). In this so-called QUAD study, treatment-naïve HCV genotype 1 patients were treated for 12-24 weeks with this all-oral quadruple regimen. Patients were switched to a PEG-IFN  $\alpha$ -based rescue therapy if HCV RNA did not fall below the limit of detection until treatment week 2. Approximately 70% of all patients were eligible for all-oral therapy in this study, and of those, at least 77% and 89% of HCV genotype 1a and 1b patients achieved SVR, respectively.

Another study evaluating an all-oral quadruple therapy included the NS3/4A protease inhibitor ABT-450/r, the NS5A inhibitor ABT-267, the NNI ABT-333, plus ribavirin. Strikingly, this regimen administered for 12 weeks led to SVR in 99% and 93% of treatment-naïve and prior null responders with HCV genotype 1 infection, respectively (Kowdley 2012). The AVIATOR study evaluated an all-oral quadruple therapy including the NS3-4A inhibitor ABT-450/r, the NS5A inhibitor ABT-267 and/or the NNI ABT-333, plus ribavirin for 8-24 weeks. In both treatment-naïve patients and prior null-responders with HCV genotype 1 infection, combination of three DAAs plus ribavirin led to comparable SVR rates after 12 or 24 weeks of treatment (higher than 90%), whereas slightly higher relapse rates were observed after 8 weeks of therapy (Kowdley 2013). Overall, the 12 week

duration of this regimen appeared to be sufficient and showed a high tolerability. Most recently, the high efficacy of this multiple DAA combination regimen in non-cirrhotic genotype 1 infected patients has been confirmed in a large Phase III study (Sapphire; Abbvie press release November 2013). Results of the subsequent Pearl-I study suggest that dual therapy with the NS3-4A inhibitor ABT-450/r and the NS5A inhibitor ABT-267 might be sufficient to cure HCV genotype 1b (but probably not 1a) patients, as even 90% of previous null-responders without liver cirrhosis achieved SVR12 (Lawitz 2013).

Encouraging results were also achieved with the all-oral combination of the NS3-4A inhibitor asunaprevir plus the NS5A inhibitor daclatasvir and the NNI BMS-791325 for 12 weeks. This regimen cured 92-98% of treatment-naïve HCV genotype 1a and 1b patients, including a small number of patients with liver cirrhosis (Everson 2013). Finally, the NS3-4A inhibitor faldaprevir, the NNI deleobuvir and the NS5A inhibitor PPI-668 are assessed in combination with or without ribavirin in a recently finished trial in HCV genotype 1a patients. The SVR rates of this regimen were less than desired and Boehringer has stopped the development of deleobuvir (BI press release, 17.01.2014).

### **Cyclophilin inhibitor-based therapies**

The VITAL-1 Phase IIb clinical study evaluated the cyclophilin inhibitor alisporivir with or without RBV for 24 weeks in treatment-naïve HCV genotype 2 and 3, complemented by the addition of PEG-IFN  $\alpha$  if RVR was not achieved (Pawlotsky 2012). SVR rates in the per protocol analysis were approximately 90% in patients treated with alisporivir plus RBV, and 70% in patients treated with alisporivir alone, but only 29-42% of all patients were eligible for treatment with all-oral therapy. Alisporivir resistance was rarely observed in patients with virologic failure.

## Novel interferons

Over the years, attempts have been made to lessen the side effects and treatment discomfort of PEG-IFN  $\alpha$ . However, interferons with longer half-life and sustained plasma concentrations (eg, albinterferon, a fusion protein of IFN  $\alpha$ -2b with human albumin) have so far shown no overall benefit with respect to SVR rates (Zeuzem 2010). Still promising is the development of PEG-IFN lambda 1 (though the importance of IFN to treat HCV infection is generally declining). Like other type 3 interferons, IFN lambda 1, also called interleukin-29 (IL-29), binds to a different receptor than IFN  $\alpha$ , but downstream the signaling pathways of IFN lambda and IFN  $\alpha$  are largely comparable. The IFN lambda receptor is predominantly expressed in hepatocytes. Thus, interferon-related side effects may be less frequent during PEG-IFN lambda treatment. A Phase I clinical trial evaluating pegylated interferon lambda with or without ribavirin was completed (Muir 2010). Interferon lambda was well-tolerated and the majority of patients achieved a greater than 2  $\log_{10}$  decline of HCV RNA by 4 weeks. According to an interim analysis of a subsequent Phase II clinical trial, PEG-IFN lambda (240 ug, 180 ug, or 120 ug once weekly) was compared to PEG-IFN  $\alpha$ -2a. PEG-IFN lambda at doses of 240 or 180 ug resulted in approximately 10% higher RVR and approximately 20% higher cEVR rates, a lower frequency of flu-like symptoms, but with more frequent aminotransferase and bilirubin elevations than PEG-IFN  $\alpha$ -2a (Zeuzem 2011). There is now a full Phase III development plan for IFN lambda with DAAs.

## Conclusions

Telaprevir-, boceprevir- or simeprevir-based triple therapy of treatment-naïve and treatment-experienced HCV genotype 1 patients results in substantially increased SVR rates compared to PEG-INF  $\alpha$  plus ribavirin alone. The approval of these agents represents a major breakthrough in the treatment of chronic

hepatitis C. However, successful use of these drugs requires a precise classification of response patterns to previous treatment, careful on-treatment monitoring of HCV viral load and emergence of antiviral resistance as well as of additional side effects and numerous possible drug-drug interactions. Triple therapies including some next-generation NS3/4A protease inhibitors, NS5A inhibitors, and especially the NI NS5B inhibitor sofosbuvir may have even more favorable properties than the currently approved DAAs in terms of HCV genotype coverage and safety profiles, less pronounced drug-drug interactions and shorter treatment durations. However, the triple therapy approach has several limitations. First of all, concomitant IFN  $\alpha$  plus ribavirin are necessary to avoid the development of antiviral resistance. Consequently, the efficacy of triple therapy was lower in prior null responders to PEG-IFN  $\alpha$  and ribavirin, and triple therapy cannot be administered to patients with contraindications to PEG-IFN  $\alpha$  or ribavirin. Recent data indicate that DAA combinations in quadruple treatment regimens will likely be a very potent option for difficult-to-cure patient populations such as HCV genotype 1a patients with prior null response. Yet, impressive data have clearly shown that numerous patients will likely have the chance to be cured by these new all-oral IFN-free treatment regimens. In such interferon-free combination regimens, the inclusion of drugs with a high genetic barrier to resistance such as nucleoside NS5B inhibitors as well as of drugs with a high antiviral efficacy such as NS3/4A or NS5A inhibitors appears to be important. Intensive research will be necessary to determine which treatment regimen is optimal in terms of safety and efficacy in individual patients.

## 6. Adverse Events and Drug Interactions

*Martin Schaefer and Stefan Mauss*

Good adherence is a key factor in the successful treatment of chronic hepatitis C infection. In 2014, interferon-free therapy will become available by prescription in some parts in the world as dual therapy with sofosbuvir and ribavirin is approved in Europe and the US. The recently studied interferon-free regimens have a substantially improved tolerability compared to interferon-based therapies. However, in 2014, for most patients interferon-based therapies will remain the standard of care. Almost all patients on treatment with interferon plus ribavirin-based therapy will experience adverse events that can significantly influence their adherence. Therefore, proactive clinical management is crucial in order to avoid suboptimal therapy and/or unnecessary treatment discontinuations. In this chapter we will first discuss adverse events associated with dual therapy with interferon plus ribavirin and then address the adverse events associated with triple therapy with a third direct antiviral (boceprevir, telaprevir, simeprevir, faldaprevir or sofosbuvir).



## Interferon-based therapies

### Systemic symptoms

**Flu-like symptoms**, fever, arthralgia and myalgia will usually diminish spontaneously during the first weeks of treatment.

**Gastrointestinal disorders.** Nausea and loss of appetite, dry mouth.

**Weight loss** in interferon-based studies is around 6-10% at 48 weeks (Seyam 2005) due to loss of appetite and reduction in calorie intake.

**Asthenia and fatigue** are frequent complaints that usually increase slowly in intensity over the first couple weeks of therapy. Asthenia is also reported by patients without marked anemia. In these patients hypothyroidism needs to be excluded. Treatment in patients without an underlying complication such as anemia, depression or hypothyroidism is difficult. For chronic fatigue, currently available data does not point to specific treatment recommendations.

**Cough** is frequently reported and is most probably due to edema of the mucosa of the respiratory system. Advanced, not well-controlled asthma bronchiale may be a contraindication for hepatitis C therapy. Dyspnea is another frequent complaint.

**Hypothyroidism and hyperthyroidism** are seen, possibly due to an interferon-induced thyroiditis or the induction of thyroid antibodies. Premature termination of interferon-based therapy is usually not necessary.

### Psychiatric adverse events

The most common IFN  $\alpha$ -induced psychiatric adverse events are outlined in Tables 6.1 and 6.2. Most hepatology trials are only monitored for “major depression” without using depression scales, leading to an underreporting of mild to moderate depressive episodes.

**Table 6.1 – Incidence of the most reported IFN  $\alpha$ -induced psychiatric side effects**

	Incidence
Fatigue	40-80%
Sleep disturbances	20-45%
Irritability	20-45%
Cognitive disturbances with impairment of concentration and memory	20-30%
Depressive episodes	20-70%
- Mild	40-70%
- Moderate	20-40%
- Severe	5-20%
Delirium, psychosis	1-3%
Suicidal thoughts	3-10%
Suicidal attempts	0-0.02%

**Table 6.2 – Frequency of psychiatric adverse events with IFN  $\alpha$  + RBV**

Incidence	
>50%	Sleep disorders, chronic fatigue, irritability or cognitive disturbances (Schaefer 2007a, Schaefer 2002, Dieperink 2000, Renault 1987)
30-45%	Anxiety, esp. during first two months
30-60%	Mild depression – reduced self-esteem, anhedonia, loss of interest, rumination, diminished libido, spontaneous crying
20-30%	Moderate to severe depressive episodes (Bonnaccorso 2002, Dieperink 2000, Renault 1987, Schaefer 2002, Malaguarnera 2002)
5-6%	Suicidal ideation
Individual Cases	Suicide attempts (Janssen 1994)
Sporadic	Mania

Treatment adherence should be assessed by monitoring serum levels before patients are switched to a different antidepressant.

Although history of major depression or suicide attempts is considered a contraindication for interferon-based therapy, treatment of patients with pre-existing psychiatric disorders can be initiated in close collaboration with an experienced

psychiatrist in a well-controlled setting (Schaefer 2004, Schaefer 2007b).

Treatment with antidepressants can be started at a relatively low dose, increasing depending on the effect and tolerability.

Current data supports the view that all patients with pre-existing depressive symptoms should receive a prophylactic treatment with antidepressants (Musselman 2001, Capuron 2002, Krauss 2005, Raison 2007). In the largest trial to date, the overall incidence of depression, major depression and severe depression was significantly lower in patients who received a preemptive antidepressant therapy (Schaefer 2012). A second trial also showed less depressive symptoms in patients with escitalopram pre-treatment (de Kneegt 2011).

As sleeping disorders can be a symptom of depression, it is also important to identify and assess existing depressive symptoms when considering the use of sleeping aids.

### **Hematologic and immunologic effects**

In general the incidence of serious infections is low (<5%) in patients on interferon-based therapy. In general G-CSF can be used to correct neutropenia, but it has not been studied for this purpose and its use is off-label.

For mild to moderate thrombocytopenia in advanced liver fibrosis, eltrombopag may be used cautiously (Afdhal 2011).

### **Skin disorders**

Skin disorders such as lichen ruber planus, necrotising vasculitis or porphyria cutanea tarda are associated with hepatitis C infection. Local skin reactions to the injection of pegylated interferon are common. Repeated injections at the same site may cause ulcers and should be avoided. Hair loss is frequent, usually appearing after the first months of therapy and continuing for some weeks after the cessation of therapy but is usually fully reversible, although the structure of the hair may be different after therapy. Alopecia is very rare. Many other side effects are outlined in Tables 6.3 and 6.4.

**Table 6.3 – What to expect and what to do (I)**

Symptom	When/why/ Duration (D)	Treatments	Caution
Flu-like symptoms	Immediately post-IFN injection / D: 3 days	<2 g paracetamol, NSAIDs	Low platelets, liver toxicity
Loss of appetite		Pre-RBV: metoclopramide, domperidone	
Dry mouth	With RBV / D: May continue post-therapy		
Weight loss	During treatment / D: On treatment	Reversible on discontinuation	6-10% loss over 48 wks
Anemia, asthenia, fatigue	First few weeks of treatment / D: Increases over time	Erythropoietin, reduce RBV dosage, red blood cell transfusion, antidepressants, tryptophan, odanestron	

**Table 6.4 – What to expect and what to do (II)**

Symptom	When/why/ Duration (D)	Treatments	Caution
Hypothyroidism	Can occur at any time	L-thyroxin replacement therapy	
Cough	Edema of resp. mucosa / D: On treatment	Local therapy of fluticasone or budesonide	
Hypothyroidism	IFN / 3-10% reversible on discontinuation	Substitution of thyroid hormone	
Hyperthyroidism	1-3%	B-blockers, carbimazole	
Psychiatric effects	On IFN, pre-existing <sup>1</sup> or not <sup>6</sup>	SSRIs (citalopram <sup>2</sup> , paroxetine) Mirtazapine <sup>3</sup> Nortriptyline <sup>4</sup> Tricyclics (doxepine)	Tricyclics are 2 <sup>nd</sup> choice – interactions and delirium, heart, liver complications
Agitation/aggression		Antipsychotics (risperidone, olanzapine)	Monitor with psychiatrist
Severe sleep disturbances, irritability,		Benzodiazapines <sup>5</sup> , zolpidem, trimipramine	<sup>5</sup> Can induce addiction

Symptom	When/why/ Duration (D)	Treatments	Caution
depression			
Hemolytic anemia	RBV	RBV dose reduction RBC transfusion Erythropoetin <sup>7</sup>	
Thrombocytopenia	In advanced liver fibrosis	IFN dose reduction Eltrombopag <sup>8</sup>	
Dry skin, itching, eczema, exacerbation of psoriasis	HCV, IFN, RBV	Urea ointments, steroids	Involve dermatologist May continue post-treatment
Hypersensitivity	PEG-IFN		Anecdotal

1. Schaefer 2005. 2. Krauss 2008. 3. Krauss 2001. 4. Valentine 1995. 5. Schaefer & Mauss 2008. 6. Schaefer 2007b; Schaefer 2003; Pariante 2002. 7. Afdahl 2004; Pockros 2004; Shiffman 2007. 8. McHutchinson 2007.

## Direct acting antiviral agents (DAAs)

### Telaprevir and boceprevir

Boceprevir has to be taken three times a day with food. Telaprevir has to be taken with a fat-containing meal two or three times a day. Pill burden is high with 12 pills for boceprevir and 6 for telaprevir. Dosing and taking the medication not fasting are crucial for efficacy. Boceprevir or telaprevir doses should never be reduced in case of toxicities, but rather discontinued or kept at the standard dose. Reducing the dose of these HCV protease inhibitors will result in treatment failure due to lower drug exposure.

Frequent adverse events seen with **telaprevir** are itching and rash, with the first occurring in the majority of patients (Jacobson 2011, McHutchinson 2010). Itching can be orally treated with antihistamines, eg, cetirizine, but efficacy seems limited. Rash is usually mild to moderate while serious skin reactions seem to be rare. Discontinuation is rarely necessary. Use of corticosteroid-based ointments, eg, prednicarbate 0.4% together with rehydrating and/or urea-containing creams are

the treatments of choice for rash. For a serious case of psoriasis a consultation with an experienced dermatologist is advisable.

Anal symptoms ranging from discomfort to pain and bleeding are also common. Depending on the severity, local therapy with a zinc paste or corticosteroid ointments are used. Anal fissures can be treated with nitroglycerine ointment or diltiazem hydrochloride 2% ointment.

A more frequent and more pronounced anemia than what is seen with interferon plus ribavirin may require early dose adjustment of ribavirin or red blood cell transfusion. Early dose reduction of ribavirin does not seem to reduce efficacy (pooled analysis of the ADVANCE and ILLUMINATE study, Janssen data on file). The use of erythropoietin for mitigation of anemia is not approved, but can be tried where reimbursement is possible.

Nausea and diarrhea are frequently seen in patients on telaprevir and may require symptomatic therapy (Hézode 2009, McHutchison 2009, McHutchison 2010, Marcellin 2010).

**Table 6.5 – Adverse event profile associated with telaprevir (Jacobson 2011) and boceprevir (Poordad 2011) in therapy-naive patients in clinical studies**

Telaprevir (ADVANCE study)	TLP + PEG-IFN $\alpha$ -2a + RBV	PEG-IFN $\alpha$ -2a + RBV + RBV
Serious adverse event	11%	9%
Discontinuation due to adverse event	7%	4%
Anemia (<10g/dl)	45%	16%
Rash	37%	24%
Itching	50%	36%
Anal discomfort/pruritis	17%	4%
Boceprevir (SPRINT-2 study)	BOC + PEG-IFN $\alpha$ -2b + RBV	PEG-IFN $\alpha$ -2b + RBV + RBV
Serious adverse event	11%	9%
Discontinuation due to adverse event	12%	16%
Anemia (<10 g/dl)	49%	29%
Dysgeusia	37%	18%

**Table 6.6 – Common side effects (>5% of patients) recorded in the PEG-IFN/RBV/PI Phase II & III trials.**

The incidence of side effects between different studies is difficult to compare because there were significant differences in genetic and socioeconomic backgrounds, as well as methodological differences in assessing side effects. Patients were selected on the basis of well-defined inclusion and exclusion criteria. Important differences between PEG-IFN/RBV and PEG-IFN/RBV/PI are highlighted in bold

Side effects	Incidence with PEG-IFN/RBV	Incidence with PEG-IFN/RBV/BOC	Incidence with PEG-IFN/RBV/TLV
Fatigue	50%†, 57%*	57%*	56%†
Insomnia	31%‡,*	32%*	32%‡
Headache	39%‡, 43%*	44%*	41%-43%‡
Pyrexia	24%‡, 31%*	31%*	26%-30%‡
Nausea	31%‡, 40%*	<b>45%*</b>	<b>40-43%‡</b>
Diarrhea	17%†, 18%*	23%*	<b>26%†</b>
Alopecia	25%*	26%*	n.a.
Depression	20%*	20%*	No difference‡
Anemia	17%†, 29% §,*	<b>49%§*</b>	<b>36%†</b>
Neutropenia	18%*,**	23%*	23%**
Dysgeusia	3%†, 15%*	<b>37%*</b>	10%†
Rash	17%*, 34%†	16%*	<b>56%†</b>
Pruritus	23%*, 28%†	21%*	<b>47%†</b>
Anorectal discomfort	1%*, 3%†	1%*	<b>11%†</b>
Anal pruritus	1%†	n.a.	<b>6%†</b>
Hemorrhoids	3%*,†	4%*	<b>12%†</b>

\* Manns 2011b, † Vertex 2011, ‡ Jacobson 2011b, § EPO was allowed,

\*\* Zeuzem 2011

With boceprevir, anemia is the most important adverse event requiring dose adjustment of ribavirin or red blood cell transfusion in a considerable number of patients (Bacon 2011, Poordad 2011). Again, early ribavirin dose reduction in patients with a considerable decline in hemoglobin is possible without

reducing efficacy. The use of erythropoietin does not seem to result in higher antiviral efficacy compared to ribavirin dose reduction (Sulkowski 2012).

Dysgeusia is another frequent complaint that resolves upon discontinuation (Bacon 2011, Poordad 2011).

In one study including patients with compensated liver cirrhosis treated with telaprevir or boceprevir an unexpected proportion of serious adverse events (up to 50% of the patients) was observed including sepsis, hepatic decompensation and death (Hézode 2012). Preliminary data from other cohort studies presented at recent conferences suggest better safety outcomes in cirrhotic patients possibly due to a more cautious use of triple therapy.

### **Simeprevir and faldaprevir**

The approval of simeprevir and faldaprevir for combination with interferon and ribavirin is expected in 2014. Both drugs are second generation HCV protease inhibitors administered as one pill with once daily dosing and no specific food requirements. This is a marked simplification. In addition, interactions with the cytochrome P450 system are lesser, resulting in a smaller number of relevant drug-drug interactions (for details see [www.hep-druginteractions.org](http://www.hep-druginteractions.org)). These drugs do not have an additive effect on the bone marrow. In particular, there was no increase in anemia compared to dual therapy with interferon and ribavirin (Fried 2013, Sulkowski 2013, Sulkowski 2013, Zeuzem 2013). However, skin toxicity remains an issue. Faldaprevir has shown considerable phototoxicity as a very common feature which can be successfully managed *via* patient education (no sunbathing, long-sleeved shirts, long trousers, hat, no tanning) (Sulkowski 2013, Sulkowski 2013). Other adverse events which are at least partially attributable to faldaprevir and are increased compared to dual therapy are rash (20%), jaundice (12%) and nausea (40%). The rash management is the same as for telaprevir. The jaundice is clinically innocuous and an increase of bilirubin, an element of liver toxicity. In trials simeprevir also



showed photosensitivity (3-4%). Other adverse events which were more frequently seen in combination with simeprevir are rash (25%), itching (20%) and jaundice due to inhibition of the UDP-glucuronyltransferase (Fried 2013, Zeuzem 2013). Management of these adverse events is as outlined above for telaprevir or faldaprevir.

### **Sofosbuvir**

The main problem in assessing the adverse event profile of sofosbuvir is the almost complete lack of controlled trials. As PEG-IFN + ribavirin and ribavirin as monotherapy do cause adverse events and laboratory abnormalities, a comparator group is essential to show an increase due to the addition of sofosbuvir. At present mostly historic controls are used to draw conclusions. Having said this, sofosbuvir has not shown a specific adverse event pattern if added to PEG-IFN and ribavirin (Lawitz 2013). However, most of these trials were carried out in rather healthy patients with no substantial co-morbidities or polypharmacy. Studies with sofosbuvir and ribavirin have no ribavirin monotherapy arm as comparator and meaningful historic controls are not available, making it difficult to draw conclusions on eventual adverse events specific for sofosbuvir (Jacobson 2013). In any case, adverse events while on treatment with sofosbuvir and ribavirin are rather infrequent and usually not serious in nature (Jacobson 2013, Younossi 2013).

Sofosbuvir has no interaction with the cytochrome P450 system and is excreted mainly via the kidney as active metabolite. Potential interactions may involve the P-glycoprotein as sofosbuvir is a substrate of this enzyme.

### **Conclusion**

In summary, the toxicity of interferon-based therapy in combination with ribavirin is considerable and requires the medical team to be fully knowledgeable for an interactive management with the patient.

The first generation of HCV protease (and polymerase) inhibitors is combined with interferon and ribavirin as triple therapy, at the cost of increased toxicity. In this setting, early assessment and robust management of adverse events may help improve the quality of life of patients, prevent premature treatment discontinuations and improve the efficacy of the new hepatitis C therapy.

Second generation protease inhibitors improve the adverse event profile, are easier to take and have less drug-drug interactions. At present the first approved polymerase inhibitor, sofosbuvir, seems to have an advantageous adverse event profile when added to interferon-based therapy and has very limited drug-drug interactions. Dual therapy with sofosbuvir and ribavirin has a clearly better tolerability compared to interferon-based triple therapy, but is limited in efficacy in some populations.

## 7. Extrahepatic Manifestations

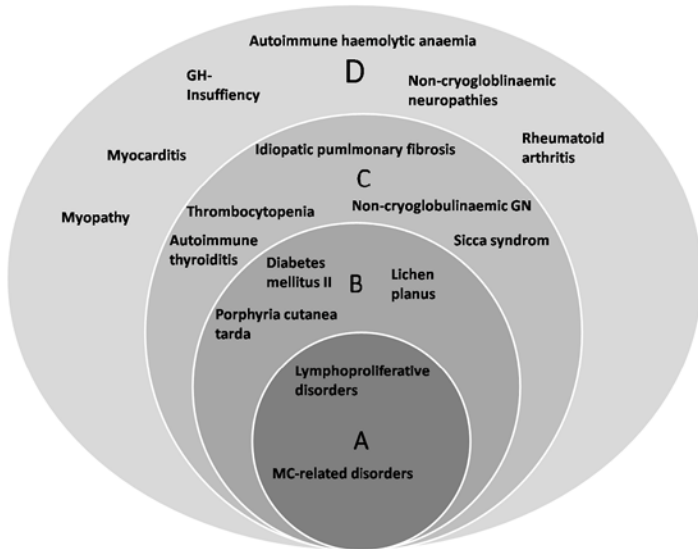
*Albrecht Böhlig, Karl-Philipp Puchner and Thomas Berg*

Patients with chronic hepatitis C virus (HCV) infection are at risk of a great number of extrahepatic manifestations (EHMs) (Table 7.1) – up to 40-76% of patients infected with HCV develop at least one EHM during the course of the disease (Cacoub 2000, Cacoub 1999). EHMs are often the first and only clinical sign of chronic hepatitis C infection. Evidence of HCV infection should always be sought out in cases of non-specific chronic fatigue and/or rheumatic, hematological, endocrine or dermatological disorders. The pathogenesis of EHM is not fully understood, although most studies suggest that the presence of mixed cryoglobulinemia (MC), particular lymphotropism of the virus, molecular mimicry and non-cryoglobulinemic autoimmune phenomena constitute the major pathogenic factors (Ferri 2007). The pathogenesis and epidemiology of many EHMs require further investigation (Figure 7.1). Our aim is to give an insight into the epidemiology, pathogenesis, clinical relevance and therapeutic management of HCV-associated EHM (Zignego 2007a).

**Table 7.1 – HCV-related extrahepatic manifestations**

Organ / System	Manifestation
Endocrine disorders	Autoimmune thyroidopathies (in particular, Hashimoto thyroiditis)
	Insulin resistance/diabetes mellitus*
	GH insufficiency
	Vitamin D deficiency
Rheumatic disorders	Mixed cryoglobulinemia*
	Cryoglobulinemic vasculitis*
	Peripheral neuropathy*
	Membranoproliferative glomerulonephritis (GN)*
	Membranous GN*
	Rheumatoid arthralgias/oligopolyarthrititis
	Rheumatoid factor positivity*
Hematologic disorders	Sicca syndrome
	Lymphoproliferative disorders/Non-Hodgkin Lymphomas*
	Immune thrombocytopenic purpura (ITP)
	Monoclonal gammopathies*
Dermatologic disorders	Autoimmune hemolytic anemia
	Palpable purpura
	Porphyria cutanea tarda (PCT)
	Lichen planus
Central nervous system disorders	Pruritus
	Chronic fatigue*, subclinical cognitive impairment, psychomotoric deceleration, symptoms of depression*
	Neurocognitive disorders
Miscellaneous	Myopathy
	Cardiomyopathy/Myocarditis
	Idiopathic pulmonal fibrosis

\* Associations with strong epidemiological prevalence and/or clear pathogenetic mechanisms



**Figure 7.1 – Schematic representation of EHM categories** (modified after Zignego 2007a). A) Associations with strong epidemiological evidence and clear pathogenetic mechanisms; B) Associations with high prevalence, but unclear pathogenetic mechanisms; C) Associations for which high prevalence in HCV could be due to HCV infection and/or confounding factors; D) Anecdotal observations

## Lymphoproliferative disorders

**Cryoglobulinemia** refers to the presence of abnormal immunoglobulins in the serum. Cryoglobulins (CGs) are classified into three types. Type II CGs, consisting of monoclonal and/or polyclonal immunoglobulins, are prevalent in patients with chronic HCV infection, while type I CGs, consisting exclusively of monoclonal components, are mostly found in patients with lymphoproliferative disorders. Type II or type III mixed cryoglobulinemia (MC) are found in 19% - 50% of patients but leads to clinical manifestations in only 30% of them (Lunel 1994, Wong 1996). Patients with symptomatic mixed cryoglobulinemia exhibit higher cryoglobulin concentrations (Weiner 1998) and

lower concentrations of complement factors C3 and C4. Factors that seem to favour the development of MC are female sex, age, alcohol intake (>50g/d), advanced liver fibrosis and steatosis (Lunel 1994, Wong 1996, Saadoun 2006). The diagnosis of MC syndrome is based on serologic, pathologic and clinical criteria (Table 7.2).

**Table 7.2 – Diagnostic criteria of cryoglobulinemic syndrome**

Serologic	Histologic	Clinical
C4 reduction	Leukocytoclastic vasculitis	Purpura
Positive rheumatoid factor (RF)	Infiltrates of monoclonal B cells	Fatigue
CGs type II or III		Arthralgia
HCV antibodies		Membranoproliferative GN Peripheral neuropathy

In the presence of mixed CG, low C4 counts, leucocytoclastic vasculitis and purpura, a definite symptomatic MC can be diagnosed. Rheumatoid factor (RF) determination constitutes a reliable surrogate parameter for detection of CG.

**Clinical features of mixed cryoglobulinemia.** HCV-related MC proceeds mostly asymptotically and has no significant influence on the course of chronic liver inflammation. On the other hand, symptomatic mixed cryoglobulinemia is associated with higher mortality (Ferri 2004). Clinical manifestations of symptomatic mixed cryoglobulinemia are systemic vasculitis, renal impairment, peripheral neuropathy and cirrhosis.

## **Malignant lymphoproliferative disorders/NHL**

The most prevalent HCV-associated lymphoproliferative disorders according to the REAL/WHO classification are: follicular lymphoma, B cell chronic lymphocytic leukemia/small lymphocyte lymphoma, diffuse large B cell lymphoma and marginal zone lymphoma, including the mucosa-associated lymphoid tissue lymphoma. Marginal zone lymphoma appears to be the most frequently encountered low grade B cell lymphoma

in HCV patients. 8%-10% of mixed cryoglobulinemia type II evolves into B cell NHL after long-lasting infection. However, a remarkably high prevalence of B cell NHL was also found in HCV patients without mixed cryoglobulinemia (Silvestri 1997). Genetic predisposition and other factors seem to have a major impact on the development of LPDs in HCV-positive patients (Matsuo 2004).

**Etiology and pathogenesis of LPDs.** In the development of LPDs direct and indirect pathogenic HCV-associated factors are seen. Sustained B cell activation and proliferation in chronic HCV infection is an indirect pathogenic mechanism. Direct pathogenic mechanisms are based on lymphotropic properties of HCV, hence on the invasion of HCV into the B cells. A direct involvement of HCV in the immortalisation of B cells can be envisioned (Zignego 2000, Machida 2004).

## Treatment of lymphoproliferative disorders

Because of the close correlation between the level of viral suppression and improvement of HCV-associated extrahepatic symptoms, the most effective antiviral strategy should be considered when dealing with HCV-related extrahepatic diseases. The protease inhibitors boceprevir and telaprevir have been shown to improve significantly sustained virologic response rate in HCV type 1-infected patients when given in combination with PEG-IFN plus ribavirin as compared to PEG-IFN and ribavirin alone, and can be therefore regarded as the treatment of choice in HCV type 1-infected patients with extrahepatic manifestations.

While asymptomatic **mixed cryoglobulinemia** *per se* does not constitute an indication for treatment, symptomatic mixed cryoglobulinemia should always be treated. Because asymptomatic cryoglobulinemia may evolve into symptomatic in the course of disease, vigilant monitoring is required and introduction of antiviral therapy in terms of prophylaxis should be considered. A therapeutic approach should primarily

concentrate on the eradication of the virus. Clinical improvement of MC is reported in 50 to 70% of patients receiving antiviral therapy with IFN  $\alpha$  and RBV and mostly correlates with a drastic reduction of HCV RNA concentrations (Calleja 1999). IFN  $\alpha$  may lead to clinical amelioration even in virological nonresponders. Alternative therapeutic strategies such as cytostatic immunosuppressive therapy and/or plasmapheresis should be considered (Craxi 2008) (Figure 7.2). Recent data show rituximab as an effective and safe treatment option for MC even in advanced liver disease. Moreover, B cell depletion has been shown to improve cirrhotic syndrome by mechanisms that remain to be further studied (Petrarca 2010).

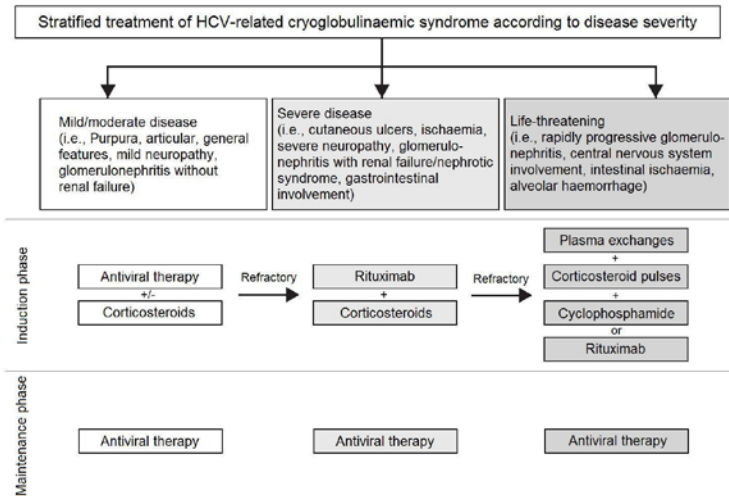
In cases of severe **systemic vasculitis**, initial therapy with rituximab, a monoclonal chimeric antibody against CD20 B cell specific antigen, is suggested. A combined application of rituximab with PEG-IFN  $\alpha$  plus ribavirin in cases of severe mixed cryoglobulinemia-related vasculitis resistant to antiviral therapy seems to be the optimal therapeutic strategy (Saadoun 2008). In severe rituximab-refractory mixed cryoglobulinemia-related vasculitis or acute manifestations, cycles of plasma exchange plus corticosteroids and eventually cyclophosphamide are indicated.

Low-dose interleukin 2 can lead to clinical improvement of vasculitis and has immunologic effects such as recovery of regulatory T cells (Saadoun 2011).

As eradication of *Helicobacter pylori* may lead to complete remission of MALT lymphoma, antiviral therapy can lead to regression of **low-grade NHL** in patients with HCV-related malignant lymphoproliferative disorders. PEG-IFN  $\alpha$  plus ribavirin (+/- protease inhibitors) should be regarded as first line therapy (Giannelli 2003).

Treatment of HCV infected patients with **high-grade NHL** should be based on cytostatic chemotherapy. Current data suggest that antiviral treatment may serve as maintenance therapy for maintaining remission of NHL post-chemotherapy (Gianelli 2003).





**Figure 7.2 – Therapy algorithm for symptomatic HCV-related mixed cryoglobulinemia** (modified according to Ramos-Casals 2012). In patients with severe manifestations, treatment should focus on immunosuppression with rituximab ( $\pm$  plasmapheresis).

## Other hematological manifestations

**Thrombocytopenic conditions** are often observed in patients with chronic hepatitis C and result mainly from advanced liver fibrosis and manifest cirrhosis (Wang 2004). Along with classical therapeutic approaches such as corticosteroids, intravenous immunoglobulins and splenectomy, antiviral therapy constitutes another option. Caution is recommended with PEG-IFN  $\alpha$  plus ribavirin as significant aggravation of HCV-related immune thrombocytopenic purpura may occur (Fattovich 1996). On the other hand, long-term use of steroids and immunosuppressive drugs is limited by an increased risk of fibrosis progression and a substantial elevation of virus. Eltrombopag may be an option, as the FDA recently approved a new indication for eltrombopag for patients with thrombocytopenia with chronic hepatitis C to allow the initiation and maintenance of interferon-based

therapy (FDA website, accessed 22 January 2013). In case of refractory disease or aggravation during the course of antiviral therapy, rituximab should be considered (Weitz 2005).

**Autoimmune hemolytic anemia** (AHA) has been frequently observed in HCV patients treated with IFN  $\alpha$  with and without ribavirin and consequently recognized as a possible side effect of antiviral treatment (Nomura 2004) although there is conflicting evidence for regarding AHA as a possible EHM of chronic HCV infection.

**Glomerulonephritis** (GN) constitutes a rare extrahepatic complication of chronic HCV. Predominant manifestations are cryoglobulinemic or non-cryoglobulinemic membranous proliferative GN and mesangioproliferative GN. GN prevalence in HCV patients is estimated at 1.4% and is comparably high due to its prevalence among blood donors (Paydas 1996).

Patients with HCV-related GN should be primarily treated with antivirals. PEG-IFN and ribavirin dosage must be cautiously adjusted to glomerular filtration rate (GFR), in order to prevent mainly ribavirin accumulation and a resulting hemolytic anemia (Fabrizi 2008).

Fulminant manifestations with impending acute renal failure make administration of corticosteroids, immunosuppressive drugs such as cyclophosphamide and eventually plasmapheresis necessary (Garini 2007, Margin 1994). In cases of simultaneous bone marrow B cell infiltration and/or resistance to conventional therapy, application of rituximab is indicated (Roccatello 2004). ACE inhibitors or AT1 receptor antagonists are supplemental (Kamar 2006). About 13% of HCV-infected patients have **hypothyroidism** and up to 25% have thyroid antibodies (Antonelli 2004). There is evidence that IFN  $\alpha$  may induce thyroid disease or unmask preexisting silent thyroidopathies (Graves disease, Hashimoto thyroiditis) (Prummel 2003). Some studies suggest that thyroid autoimmune disorders were significantly present in patients with chronic hepatitis C during but not before IFN  $\alpha$  therapy (Vezali 2009). Monitoring of the thyroid function should be performed during treatment.

## Dermatologic and other manifestations

**Table 7.3 – Overview**

Manifestation	Feature	Note
Porphyria cutanea tarda	Correlated with HCV	Geographic distinctions
Lichen planus	Associated with HCV	Geographic distinctions/HLA-DR6
Idiopathic pulmonary fibrosis	Potential EHM	
Chronic alveolitis	Correlated with IFN treatment	
Ischemic and hemorrhagic strokes	Younger HCV patients	
Transverse myopathies/symmetrical paraparesis/sensory deficiency	HCV	
Chronic fatigue/subclinical cognitive impairment/psychomotor deceleration	35-68% of HCV patients	
Depression	2-30% of HCV patients	<a href="#">Perry 2008</a> , <a href="#">Forton 2003</a>
Altered neurotransmission	HCV	<a href="#">Weissenborn 2006</a>
Tryptophan deficiency – depressive disorders	HCV/lack of serotonin	
Chronic myocarditis/dilatative/hypertrophic cardiomyopathy	Genetic/immunologic factors	<a href="#">Matsumori 2000</a>

A meta-analysis of retrospective and prospective studies confirms a high risk for the development of **diabetes mellitus type II** in patients with chronic HCV infection ([White 2008](#)). Insulin resistance represents an independent risk factor for progression of liver fibrosis in patients with chronic HCV infection ([Moucari 2008](#)).

Numerous **central nervous system** manifestations have been described associated with HCV infection. Manifestations range from cryoglobulinemic and non-cryoglobulinemic vasculitis of cerebral blood vessels ([Cacoub 1998](#)) via chronic fatigue to depression with evidence that antiviral therapy can lead to elevation of tryptophan blood levels contributing to amelioration of depressive symptoms in HCV patients ([Zignego 2007c](#)). Cognitive dysfunction seems to rely on direct viral

neurotoxic effects and induction of cerebral and/or systemic inflammation (Senzolo 2011).

## 8. Management of HCV/HIV Coinfection

*Christoph Boesecke, Stefan Mauss and Jürgen Kurt Rockstroh*

### **Epidemiology of HIV/ HCV coinfection**

Of the 35 million HIV-infected persons worldwide in 2012 it is estimated that at least 5 million of them had hepatitis C virus infection. Whereas both viruses are transmitted with high efficacy via blood-to-blood contact, HCV is less easily transmitted sexually. Thus, the prevalence of hepatitis C coinfection within different countries, regions and populations is closely related to the prevalence of blood-borne transmission (mainly intravenous drug use) of HIV (Table 8.1).

HCV may well be sexually transmitted and should therefore also be taken into account at regular STD screenings (Gotz 2005, Danta 2007, Vogel 2009a, Vogel 2010, Rockstroh 2012). HCV is detected in 4-8% of infants born to HCV-infected mothers (Bevilacqua 2009). However, in HIV/HCV-coinfected mothers receiving HAART and undergoing cesarean section the risk of HCV transmission is reduced to less than 1%. The average estimated risk of transmission for hepatitis C in HIV is depicted in Table 8.2.

**Table 8.1 – Geographic differences in coinfection rates**

	HIV/HCV coinfection rates
Europe, Australia	25%
Belarus, Ukraine	70%
Belgium, Austria, Germany	10-15%
Australia, UK	10-15%
US general population	18-25%
US prison population	65-70%
Chinese blood donors	85%
Thailand	10%
Sub-Saharan Africa	Relatively low

**Table 8.2 – Average estimated risk of transmission for HIV, HCV and HCV/HIV simultaneously**

Mode of transmission	HIV	HCV	HCV/HIV coinfection
Perinatal	7-50%	1-7%	1-20%
Sexual contact*	1-3%	<1%	<4%
Needlestick injury	0.3%	<1%	Unknown

\*With sexual contact the risk refers to cumulative exposure

## Diagnosing HCV in HIV coinfection

The presence of HCV can be confirmed serologically by the detection of antibodies with ELISA testing. Loss of HCV antibodies does not necessarily indicate viral clearance (Cribier 1995). One negative HCV antibody ELISA does not necessarily exclude HCV infection in HIV-positive patients, especially in severe immune deficiency. A rise of liver transaminases has been proven to be more sensitive in the detection of acute HCV infection in HIV-positive patients than repeated testing for HCV antibodies (Thomson 2009).

The levels of HCV viremia increase eight times faster in HIV-positive individuals than in patients with hepatitis C who are not infected with HIV. The highest concentrations for HCV viremia have been reported in patients who subsequently develop liver

failure. Regular monitoring of HCV RNA levels is warranted in HIV/HCV-coinfected patients (Rockstroh 2007).

**Table 8.3 – Diagnostic procedures for hepatitis C in HIV coinfection (adapted from Rockstroh 2008)**

**Diagnosis of hepatitis C**

HCV Ab (positive 1-5 months after infection, may rarely be lost with immunosuppression)

HCV RNA level\* (while not prognostic for progression, it is for response to treatment)

---

**Status of liver damage**

Grading of fibrosis (e.g., Fibroscan®, liver biopsy, serum fibromarkers\*\*)

Hepatic synthetic function (e.g., coagulation, protein, albumin, CHE)

Ultrasound and AFP every 6 months in cirrhotic patients (gastroscopy upon diagnosis of cirrhosis and every 1-2 years thereafter)

---

**Before HCV treatment**

HCV genotype and serum HCV RNA

Auto-antibodies (ANA, SMA, ANCA and LKM1\*\*\*)

TSH, thyroid autoantibodies if applicable

---

**Monitoring of HCV treatment**

Differential blood count and liver enzymes every 2-4 weeks

HCV RNA at week 4 (to evaluate rapid virological response), week 12, 24, 48, (72 if applicable) and 24 weeks after stopping HCV therapy

CD4 count every 12 weeks

TSH every 12 weeks

\*Low viral load defined as less than 400,000 IU/L when using PEG-IFN+RBV; there is no standard formula for converting the amount of HCV RNA in copies/ml to IU. The conversion factor ranges between one and five HCV RNA copies per IU.

\*\*Serum fibromarkers include APRI, FIB-4, hyaluronic acid, Fibrometer, Fibrotest, Forns, Hepascore and other indices; recently Fibrometer, Fibrotest and Hepascore have shown more accuracy in predicting liver fibrosis than simple biochemical tests such as APRI, FIB-4 or Forns.

\*\*\*Patients with positive anti-LKM or anti-ANA with homogeneous pattern should be evaluated for concurrent autoimmune hepatitis, especially in the presence of ALT elevation while on treatment.

## The natural history of hepatitis C in HIV+ patients

Various studies have demonstrated that underlying HIV infection weakens the immune response to hepatitis C. Interestingly, data in HIV-positive individuals suggest that despite underlying HIV infection spontaneous resolution of HCV may occur in up to 20-30% of newly infected patients (Vogel 2010, Thomson 2011). Single nucleotide polymorphisms (SNP) near the IL28B gene encoding for interferon lambda may explain the differences in spontaneous clearance rates between ethnicities (Clausen 2011, Thomas 2009). Numerous large cohort studies have demonstrated that once chronic hepatitis C is established the presence of HIV leads to a faster progression of liver fibrosis due to the lack of critical CD4+ T cell responses against HCV (Danta 2008).

In addition, within 10-15 years of HCV infection, 15-25% of HIV-coinfected patients develop cirrhosis compared with 2-6% of HIV-negative patients (Soto 1997). Mortality due to advanced liver disease starts ten years earlier in coinfecting hemophiliacs than in HIV-negative hemophiliacs with hepatitis C (Darby 1997). The incidence of hepatocellular carcinoma is also higher in HIV-coinfected patients (Giordano 2004).

## Effect of hepatitis C on HIV infection

Updated information from an analysis of the large EuroSIDA cohort, after taking into account ongoing chronic and resolved hepatitis C infection, confirms that no difference in CD4 cell count recovery is observed in patients with chronic hepatitis C infection and detectable HCV RNA in comparison to HIV-monoinfected patients (Rockstroh 2005). In addition, data from the same cohort revealed that CD4+ T cell recovery in HIV-positive patients with maximal suppression of HIV replication is not influenced by HCV serostatus, HCV genotype or level of HCV (Peters 2009).



## Effect of HAART on hepatitis C

There is increasing evidence that HAART-induced immune reconstitution might reverse the accelerated course for hepatitis C in patients with severe HIV-associated immune deficiency (Verma 2006, Vogel 2009b). Several cohort analyses show that HIV/HCV-coinfected individuals on HAART had significantly lower liver-related mortality than patients receiving either suboptimal or no antiretroviral therapy (Qurishi 2003).

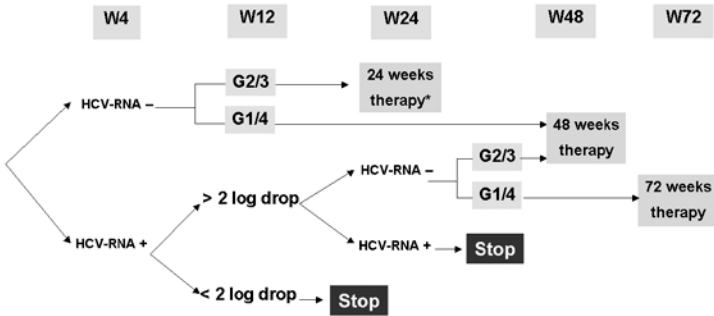
The EACS antiretroviral treatment guidelines recommend earlier initiation of antiretroviral therapy in HIV+ patients with HCV coinfection (CD4+ cell count between 350-500/ $\mu$ l in asymptomatic patients). Various studies have shown that the presence of HCV is independently associated with an increased risk of rises in serum aminotransferases, highlighting the need for close monitoring.

## Treatment

Once viral clearance is achieved with hepatitis C combination therapy, the prognosis of liver disease dramatically improves, and once HCV infection is eradicated, further liver complications are very unlikely. The goal of hepatitis C treatment is to achieve persistently negative HCV RNA levels. Treatment of hepatitis C will change dramatically with the licensing of further directly acting antivirals (DAA) in the very near future (see chapter 5 for further details). Subsequently, treatment guidelines and algorithms will need to be updated. However, as treatment with the new DAAs will be expensive access to these drugs will be limited in most healthcare systems. Thus the current guidelines mostly dealing with dual therapy with interferon and ribavirin remain important for a substantial proportion of the global HCV HIV coinfecting patient population.

The combination of pegylated interferon and ribavirin will still be regarded as standard therapy in patients with HCV GT 1, 2, 3 and 4 infections where no licensed DAAs are currently available. In the current guidelines, daily administration of ribavirin 1000

mg (<75 kg body weight) and 1200 mg (>75 kg body weight) BID is recommended. The standard dosage for PEG-IFN  $\alpha$ -2a is 180  $\mu$ g SC once weekly and for PEG-IFN  $\alpha$ -2b 1.5  $\mu$ g/kg body weight SC once weekly. Duration of therapy is individualized taking into account factors for HCV treatment response such as genotype, baseline viral load and virologic response (see Figure 8.1).



**Figure 8.1 – Proposed optimal duration of hepatitis C virus (HCV) therapy in HIV/HCV-coinfected patients treated with pegylated interferon and ribavirin (for genotype 1 infection only when HCV PIs are not available) (W:week; G:genotype) (modified from Rockstroh 2009)**

\*In patients with low baseline viral load (<400,000 IU/l) and minimal liver fibrosis

Noninvasive markers such as blood tests or transient elastography constitute a new means of assessing liver disease in HIV and hepatitis-coinfected individuals (Rockstroh 2009b, Resino 2011). When liver biopsy or non-invasive tests for assessing hepatic fibrosis (e.g., elastometry by Fibrosan®) demonstrate lower grades of liver fibrosis (F0-F1) regardless of HCV genotype, treatment may be deferred. Assessment of fibrosis should be repeated frequently to monitor progression in these cases. Therapy is particularly recommended in patients with a high likelihood of achieving an SVR, ie, patients infected with genotype 2 or 3 and those infected with genotype 1 with an

IL28B CC genotype or GT 1 patients with a previous relapse under dual therapy which now can be retreated with triple therapy (EACS 2012). If chronic hepatitis C is detected early in the course of HIV infection (before the initiation of HAART), treatment for chronic HCV may be started in the absence of antiretroviral therapy. However, if a coinfecting patient has pronounced immune deficiency (CD4 count <200 cells/ml), the CD4 count should be improved via HAART before beginning HCV treatment. Patients with a CD4 relative percentage of >25% are more likely to achieve SVR than those with lower CD4 percentages (Opravitl 2008). At present most experts recommended to initiate antiretroviral therapy to stabilise the immune system before starting interferon based therapy for chronic hepatitis C.

Based on four baseline variables (serum HCV RNA, HCV genotype, liver fibrosis staging using elastometry, and IL28B genotyping), the Prometheus Index has been developed and can be used as a risk calculator for predicting the likelihood of SVR using PEG-IFN/ribavirin therapy in HIV/HCV-coinfecting patients. It is freely available on the web (<http://goo.gl/oPBj9>), like the Framingham Score for predicting cardiovascular risk (EACS 2011).

With the first pilot studies in HIV/HCV-coinfecting individuals with HCV genotype 1 demonstrating significantly higher SVR12 rates with triple therapy compared to dual therapy, HCV protease inhibitor-based therapy with either boceprevir or telaprevir is the standard of care in HCV genotype 1 infection in HIV-infected individuals, where available. Telaprevir is added to PEG-IFN/RBV treatment for 12 weeks at 1125mg every 12 hours. In case of successful treatment response at week 4 (HCV RNA <1000 IU/mL), telaprevir should be continued until week 12. If HCV RNA at week 12 is still <1000 IU/mL, dual therapy with PEG-IFN/RBV should be continued until week 24. If HCV RNA is undetectable at week 24, dual therapy with PEG-IFN/RBV should be continued for another 24 weeks resulting in a total treatment duration of 48 weeks.

Boceprevir can be added to PEG-IFN/RBV after a lead in of 4 weeks of PEG-IFN/RBV dual therapy. In case of an HCV RNA >100 copies/mL at week 12 or a detectable HCV RNA at week 24, all HCV therapy needs to be discontinued and interpreted as lack of response and as high risk for boceprevir resistance selection. Overall treatment duration of a boceprevir-based therapy is 48 weeks. The use of the new HCV PIs is associated with additional toxicities, in particular higher rates of anemia for both drugs, rash and anal itching for telaprevir and dysgeusia for boceprevir. Anemia management is therefore very important and requires more frequent monitoring of hemoglobin levels during the first weeks of HCV treatment. Early ribavirin reduction and EPO use have both been demonstrated to be effective in anemia management while not lowering overall SVR rates. Data from monoinfected subjects with cirrhosis suggest even higher anemia rates and blood cell counts need to be determined in such patients at least every 2 weeks after starting HCV therapy. In addition, careful surveillance should be addressed regarding severe infectious complications including deaths due to sepsis and liver decompensation, observed in 3-8% of monoinfected cirrhotic patients on triple therapy in an observational study where a mortality rate greater than 1% was recorded.

So far, similar severe complications have not been reported in the early results from the ANRS coinfection trials looking at either telaprevir or boceprevir containing triple therapy in coinfecting patients with virologic failure on pegIFN and RBV (Cotte 2013, Poizot-Martin 2013).

In addition, due to the inhibition of the cytochrom P450 3A isoenzyme and the fact that telaprevir and boceprevir are substrates of the same enzyme complex drug drug interactions are the consequence and treatment should only be performed by experienced physicians.

For coinfecting patients in countries with access to the new DAAs HCV treatment will change dramatically. Three DAAs are expected to be licensed in 2014. The first one in the first half of 2014 will be the once-daily nucleotide analogue HCV

polymerase inhibitor sofosbuvir. In the PHOTON trial assessing the combination of sofosbuvir and ribavirin without interferon in treatment-naïve GT1 and treatment-naïve and experienced GT2/3 coinfecting patients over 12 and 24 weeks SVR12 rates of 76%, 88% and 67%, respectively were observed (Sulkowski 2013). In treatment-naïve patients, this will clearly allow successful treatment of GT1 infection over 24 weeks and of GT2 infection over 12 weeks, for GT3 infection 12 weeks of therapy appears to be too short. In treatment-experienced GT2 and all GT3 patients 24 weeks of therapy will be needed, and for GT1 a third DAA or interferon might be required. Sofosbuvir also contains antiviral activity against GT4 (and 5/6) but data in the setting of coinfection are not available yet.

In the second half of 2014 approval of the two second generation, once-daily HCV protease inhibitors simeprevir and faldaprevir is expected. In the STARTVerso trial assessing faldaprevir plus pegIFN and RBV in HIV HCV GT1 infection over 24 or 48 weeks in treatment-naïve and relapsers patients including cirrhotics an overall SVR4 rate of 74% could be observed (Rockstroh 2013). Interestingly, there was not statistically significant difference in patients with and without cirrhosis. In the C212 study assessing simeprevir plus pegIFN and RBV in HIV HCV GT1 infection over 24 or 48 weeks in treatment-naïve, relapsers, partial and null responder patients including cirrhotics an overall SVR12 rate of 74% could be observed (Dieterich 2013). SVR12 rates for treatment-naïve patients, relapsers, partial and null responders were 79, 87, 70 and 57%, respectively. Simeprevir also contains antiviral activity against GT4 (and 5/6) but data in the setting of coinfection are not available yet.

These soon available, simplified DAA based HCV therapy regimens are characterized by a smaller pill burden, better tolerability, mostly shorter treatment duration and an at least equal efficacy compared to the current triple therapy regimens. It can be assumed that once approved sofosbuvir and

depending on the local situation simeprevir and faldaprevir will be widely used also in the coinfecting patient population.

Further co-infection studies include studies with a combination of PegIFN-lambda (a potentially better tolerated IFN) with ribavirin and the NS5a inhibitor daclatasvir also for G1, 2, 3 and 4 infections and ABT-450/r, a ritonavir-boosted protease inhibitor together with NS5a inhibitor ABT-267, non-nucleoside polymerase inhibitor ABT-333 combined with ribavirin for G1 patients.

### **Antiretrovirals while on HCV therapy**

Didanosine use has been independently associated with increased adverse event rates including lactic acidosis and hepatic decompensation in patients who have liver cirrhosis prior to commencement of PEG-IFN/RBV therapy (Mauss 2006). The use of AZT and d4T are also discouraged whenever possible, as increased toxicity can be expected.

Patients on atazanavir may develop jaundice due to an increase in total serum bilirubin levels following initiation of ribavirin (Rodriguez-Novoa 2008). The role of abacavir is uncertain at this point but cohort data suggest lower success rates (Bani-Sadr 2007). Due to drug-drug interactions, telaprevir can currently only be safely combined with boosted atazanavir, raltegravir, rilpivirine, etravirine or efavirenz (with efavirenz, telaprevir doses need to be increased to 1125 mg every 8 hours). Using tenofovir or abacavir in combination with emtricitabine or lamivudine as backbone seems safe. Due to drug-drug interactions, boceprevir can only be currently safely combined with raltegravir or etravirine in combination with tenofovir or abacavir and emtricitabine or lamivudine. The EMA has also suggested considering boceprevir in combination with boosted atazanavir on a case-by-case basis in patients with no previous HIV treatment failure and no drug resistance who have suppressed HIV RNA when starting HCV therapy.

To date, there are no known significant drug-drug interactions between sofosbuvir and cART agents. Under efavirenz-based

cART Faldaprevir dosage must be 240mg qd and 120mg qd when darunavir- or atazanavir-based cART. It is not possible to co-administer simeprevir with HIV protease inhibitors except boosted darunavir.

Table 8.4 summarizes possible interventions for HCV/HIV-coinfected non-responders and relapsers to previous interferon-based therapies.

### **Liver transplant in HIV/HCV-coinfected patients**

The presence of esophageal varices using upper gastrointestinal endoscopy should be monitored in patients with liver cirrhosis every 1-2 years; in addition, an ultrasound of the liver and a serum  $\alpha$ -fetoprotein determination should be performed at least every 6 months in patients with F3/F4 fibrosis according to the European Consensus Guidelines (Alberti 2005).

For patients to be eligible for liver transplantation, they need to have either undetectable HIV viremia (<40 copies/ml) or at least treatment options to control HIV infection successfully after liver transplantation. Contraindications for transplantation are opportunistic diseases, ongoing alcohol or drug overuse, HCC metastasis in other organs, a second malignant disease, cardiopulmonary disease, or older age with an elevated risk of mortality related to the operation.

Combination therapy with pegylated interferon plus ribavirin seems to be the best management option 1-3 months after liver transplantation and after reinfection with hepatitis C virus is detected. Data on the use of DAAs for the treatment of recurrent HCV after oLTX are still sparse. So far, triple therapy appears to be feasible under intensive monitoring of drug levels. A new and safer option is the use of sofosbuvir with ribavirin or a second DAA such as daclatasvir.

**Table 8.4 – Classification of and interventions for HCV/HIV-coinfected patients who are non-responders/relapsers to prior IFN-based therapies with no access to new DAAs**

Category	Subgroup	Recommended Intervention
Suboptimal treatment	1. Suboptimal schedule – Interferon monotherapy – Low doses of ribavirin – Short length of therapy 2. Limiting toxicities & poor adherence	Re-treatment using combination therapy of PEG-IFN plus weight-based ribavirin  Optimal support (SSRI, paracetamol/NSAID*, adherence support, use of hematopoietic growth factors**)
Optimal treatment with virologic failure	1. Relapse (HCV RNA negative at the end of treatment)  2. Non-response (no HCV RNA negativization during treatment)	For genotype 1 patients, wait and monitor if low levels of fibrosis (F0/1) and no or little progression, otherwise retreat with triple therapy. For genotypes 2, 3 and 4 for patients with mild fibrosis, wait and monitor. If rapid progression or >moderate fibrosis, retreatment using combination therapy with PEG-IFN plus weight-based ribavirin dosing (consider longer treatment duration) For G1 patients with F3/4 fibrosis or those with other stages of fibrosis and rapid progression, consider triple therapy treatment with telaprevir or boceprevir. In patients without a 2 log decrease of HCV RNA or with no data on HCV RNA decrease in the previous treatment cycle, triple therapy is recommended if there is an HCV RNA decrease of 1 log after a 4-week lead in with PEG-IFN/RBV.

\*NSAID, non-steroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitors. \*\*Data on the use of hematopoietic growth factors in HIV/HCV coinfection is limited to an improvement in quality of life but not antiviral efficacy; treatment with growth factors is generally off-label in Europe.



In the context of post-transplant immunosuppression, it is important to point out that there are crucial pharmacokinetic drug-drug interactions between the key immunosuppressive drugs tacrolimus or cyclosporin A and the ARVs used for HIV therapy. Determinations of the plasma levels of the antiretroviral drugs are necessary. The doses of cyclosporin A or tacrolimus usually need to be reduced when the patient is treated concomitantly with a protease inhibitor, especially if boosted with ritonavir (Vogel 2004). In contrast, NNRTIs can lower the concentrations of immunosuppressive drugs.

## Conclusion

HIV has been shown to accelerate the progression of hepatitis C, resulting in higher liver disease-related mortality and morbidity in HIV/HCV-coinfected patients compared to HCV- or HIV-monoinfected individuals. Dual therapy comprising PEG-IFN plus ribavirin is still the current gold standard in countries with no access to the new DAAs allowing sustained virologic response rates of almost 50% in HIV/HCV-coinfected individuals under optimized management conditions (weight-based ribavirin and individualized treatment duration). For HCV GT1 infection triple therapy containing PEG-IFN, ribavirin and either telaprevir or boceprevir where available still is the outgoing standard of care allowing sustained virologic response rates of almost 70% in HIV/HCV-coinfected individuals. But with the licensing of three new DAAs in 2014 HCV treatment algorithms will change dramatically including treatment of patients with previously failed response to dual therapy and patients with cirrhosis. Drug-drug interactions between cART, ribavirin and especially the new HCV protease inhibitors require careful selection of both HIV and HCV drugs as well as subsequent close monitoring.

## 9. Management of HBV/HCV Coinfection

*Carolynne Schwarze-Zander and Jürgen Kurt Rockstroh*

### **Epidemiology**

Due to shared routes of transmission, coinfection with HBV and HCV is not uncommon among individuals in HBV endemic areas who also have a high risk of parenteral infections, such as injection drug users (Pallas 1999), patients on hemodialysis (Reddy 2005), patients undergoing organ transplantation (Aroldi 2005) and HIV-positive individuals (Zhou 2007). Due to a lack of large-scale population-based studies the exact number of HBV/HCV-coinfected patients is unknown. Dual infection with HBV and HCV in the same host ranges from 9% to 30% depending on the geographic region (Zarski 1998, Liaw 1995, Tyson 2013). These numbers may underestimate the true number of people with HBV/HCV coinfection as there is a well-known entity of occult HBV infection (ie, patients with negative hepatitis B surface antigen [HBsAg] but detectable serum HBV DNA) in patients with chronic hepatitis C (Cacciola 1999).

## Screening

Persons with a first episode of acute hepatitis should be screened for all viral causes including HBV and HCV (see Chapter 3). Some patients may be inoculated with both viruses simultaneously and will present with acute hepatitis due to both viruses.

Superinfection of both viruses, one on top of the other, has been reported (Liaw 2000, Liaw 2002, Liaw 2004). Episodes of acute hepatitis in patients with known chronic HBV or HCV infection should prompt screening for superinfection. In addition, in patients with chronic hepatitis C, ruling out occult HBV infection beyond HBsAg testing, ie. by polymerase chain reaction (PCR), should be done when clinically indicated.

## Viral interactions

Coinfected patients may show a large spectrum of virologic profiles (Raimondo 2006). HCV infection can suppress HBV replication and it has been shown that HBV/HCV-coinfected patients have lower HBV DNA levels, decreased activity of HBV DNA polymerase, and decreased expression of HBsAg and hepatitis B core antigen in the liver (Chu 1998). Patients with chronic HBV infection who become superinfected with HCV can undergo seroconversion of HBsAg (Liaw 1991). HBV can inhibit HCV replication as well (Sato 1994). HBV DNA replication has been shown to correlate with decreased HCV RNA levels in coinfecting patients (Zarski 1998).

Simultaneous suppression of both viruses by the other does occur (Jardi 2001). Thus, HBV or HCV can play the dominant role, HBV and HCV can inhibit each other simultaneously and they can alternate their dominance (Liaw 1995). Both viruses have the ability to induce seroconversion of the other. The chronology of infection may have a role in determining the dominant virus. The overall effect appears to be HCV suppression of HBV (Liaw 2001). Interestingly, recent *in vitro* studies found no evidence of direct interference between the two viruses, making interindividual differences in innate and/or adaptive host

immune responses responsible for viral interference observed in coinfecting patients (Bellecave 2009, Eyre 2009).

**Acute simultaneous coinfection with HBV and HCV** is rarely seen, but the interaction of HBV and HCV appears to be similar to chronic infection. In acute infection with HBV and HCV, patients show delayed HBsAg appearance and a shorter hepatitis B surface antigenemia compared to those with acute HBV alone (Mimms 1993). Biphasic alanine aminotransferase (ALT) elevation is found in some patients, although rates of viral clearance were similar to those in HBV- or HCV-monoinfected patients (Alberti 1995).

**HCV superinfection** is frequent in HBV endemic areas, such as in Asia, South America and sub-Saharan Africa (Liaw 2002, Liaw 2004), and can result in the suppression of HBV replication and termination of HBsAg carriage. Long-term follow-up analyses have described a higher rate of liver cirrhosis and hepatocellular carcinoma. Fulminant hepatic failure was significantly higher among patients with underlying HBV infection than those without (23% vs. 3%) (Chu 1999, Chu 1994).

**HBV superinfection** is less common in HCV-infected patients and very limited data is available. Superinfection of HBV may lead to suppression of HCV (Liaw 2000, Wietzke 1999). HBV superinfection may be associated with acute deterioration of liver function among patients with chronic HCV infection, and the risk of fulminant hepatitis may be increased (Sagnelli 2002).

**Occult HBV infection**, defined as detectable HBV DNA in liver or serum and undetectable HBsAg (Ozaslan 2009, Torbenson 2002), has been identified in up to 50% of patients with chronic HCV. A relation to HCV treatment outcomes has been described (Zignego 1997, Fukuda 2001, Sagnelli 2001). HCV infection with occult HBV infection has been associated with higher ALT levels, greater histological activity index and liver disease more often progressing to liver cirrhosis (Fukuda 1999, Cacciola 1999, Sagnelli 2001).

Patients with **chronic hepatitis** and concurrent detectable serum HBV DNA and HCV RNA are at highest risk of progression

to cirrhosis and liver decompensation and therefore should be considered for treatment (Table 9.1). Active HCV infection (HCV RNA+) in the setting of inactive HBsAg (HBsAg+/HBV DNA-) behaves similarly to HCV mono-infection. Another possibility is active HBV infection in patients with inactive or prior HCV infection (HBV-DNA +/HCV-RNA-/anti-HCV+). This immune profile is less common, and may indicate HBV suppression of HCV. Close follow-up of levels of viremia is needed for correct diagnosis and decision on the most successful treatment strategy.

**Table 9.1 – Immune profiles in HBV/HCV-coinfected patients with chronic hepatitis**

	HBV and HCV active	Occult HBV in chronic active HCV	HCV active in HBs Ag carrier
HBsAg	+	-	+
HBV DNA	+	+	-
Anti-HCV	+	+	+
HCV RNA	+	+	+

Higher rates of **cirrhosis** and more **decompensated liver disease** are found in HBV/HCV-coinfected patients compared to HBV-mono-infected patients (Fong 1991) and HCV-mono-infected patients (Mohamed Ael 1997). The incidence of **hepatocellular carcinoma** (HCC) was three times as likely in HCV/HBV-coinfected patients than in HBV- and twice as likely in HCV-mono-infection. The cumulative risk of developing HCC after 10 years was 45% in HBV/HCV-coinfected patients compared with 16% in HBV and 28% in HCV mono-infected patients (Chiaromonte 1999). HBV/HCV-coinfected patients should undergo a screening routine for HCC with liver ultrasound and  $\alpha$ -fetoprotein levels in serum at least every 6 months.

## Treatment

Generally, treatment guidelines for monoinfected patients should be applied to coinfecting patients. In patients with HBV/HCV coinfection, treatment should be initiated when inclusion criteria for standard treatment guidelines of HBV and HCV monoinfection are met (see Chapters 4 and 5). As with HBV and HCV monoinfection, treatment of coinfecting patients should be started in patients with active chronic hepatitis or cirrhosis before liver decompensation. Due to the variety of virological profiles in HBV/HCV coinfection it is important to assess the dominant virus prior to initiating therapy.

In coinfecting patients with dominance of HCV infection, combination therapy with PEG-IFN and ribavirin has been shown to be efficient (Liu 2012). HCV RNA response was similar to results seen in HCV monoinfection with up to 88% in HCV genotype 2/3 and 72% in HCV genotype 1 achieving sustained virological response (Liu 2009, Kim 2011). The durability of HCV SVR was shown to be maintained in 97% of patients by a recent five-year follow-up study (Yu 2013). In addition, risk reduction of HCC and improved survival was achieved by treatment of HBV/HCV coinfecting patients after therapy with pegylated IFN and ribavirin (Liu 2013). HBV replication may become undetectable, thus close monitoring of both viruses is recommended during and after combination therapy.

The introduction of new direct acting antivirals has opened new pathways in the treatment of HCV, which need to be evaluated in HBV/HCV-coinfecting patients. However, currently no data exists for telaprevir and boceprevir, which have recently been approved for the treatment of HCV genotype 1 infection.

In patients with dominance of HBV disease, IFN +/- HBV polymerase inhibitors is an option currently being investigated. A recent study looked at tolerability and efficacy of several anti-HBV nucleos(t)ide analogs (lamivudine plus adefovir, entecavir, telbivudine, tenofovir disoproxil fumarate) (Coppola 2013). Clearance of HBV DNA was found in 96% of patients after 18

months, while HCV reactivation was low (12.5%). However, deterioration of liver cirrhosis was seen in as many as 33% of the participants. Patients who were HCV RNA positive at baseline deteriorated more frequently.

In HBV/HCV cirrhotic patients with detectable HCV RNA treatment with nucleos(t)ide analogs alone has a high risk of clinical failure. However, further studies are needed to estimate the treatment value of these drugs in the different clinical scenarios.

## **Conclusion**

No treatment standard has been established for HBV/HCV-coinfected patients. Treatment decisions must be made based upon identification of the dominant virus. Recent studies indicate that in patients with dominant HCV replication PEG-IFN plus ribavirin should be the treatment of choice. Treatment with the new DAA agents is now being studied, and their eventual availability will open new pathways in treatment, which can be replicated in HBV/HCV coinfection. Patients with dominant HBV disease should be treated with nucleoside or nucleotide analogues alone or in combination with pegylated interferon and ribavirin. Caution must be exercised in treating coinfecting patients, as flares of the untreated virus may occur.

## 10. References

- Afdhal N, Dusheiko G, Giannini EG, et al. Final results of enable 1, a phase 3, multicenter study of eltrombopag as an adjunct for antiviral treatment of hepatitis c virus-related chronic liver disease associated with thrombocytopenia. *Hepatology* 2011;54:1427A-28A.
- Afdhal N, O'Brien C, Godofsky E. Valopicitabine alone or with PEG-interferon/ribavirin retreatment in patients with HCV-1 infection and prior non-reponse to PEGIFN/RBV: One-year results. *J Hepatol* 2007;46:55.
- Afdhal NH, Dieterich DT, Pockros PJ, et al. Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. *Gastroenterol* 2004;126:1302-11. (Abstract)
- Afdhal NH, Dusheiko G, Giannini EG, et al. Final Results of ENABLE 1, a Phase 3, Multicenter Study of Eltrombopag as an Adjunct for Antiviral Treatment of Hepatitis C Virus-Related Chronic Liver Disease Associated With Thrombocytopenia. *Hepatology* 2011; 54:1427-8.
- Afdhal NH, McHutchison JG, Zeuzem S, et al. Hepatitis C pharmacogenetics: state of the art in 2010. *Hepatology* 2011; 53:336-45. (Abstract)
- Agnello V, Abel G, Elfahal M, et al. Hepatitis C virus and other Flaviviridae viruses enter cells via low-density lipoprotein receptor. *Proc Natl Acad Sci USA* 1999;96:12766-71. (Abstract)
- Ahmed-Belkacem A, Ahnou N, Barbotte L, et al. Silibinin and related compounds are direct inhibitors of hepatitis C virus RNA-dependent RNA polymerase. *Gastroenterol* 2010;138:1112-22. (Abstract)
- Akuta N, Suzuki F, Hirakawa M, et al. Amino acid substitution in hepatitis C virus core region and genetic variation near the interleukin 28B gene predict viral response to telaprevir with peginterferon and ribavirin. *Hepatology* 2010;52:421-429. (Abstract)
- Alberti A, Clumeck N, Collins S, et al. ECC Jury. Short statement of the first European Consensus Conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. *J Hepatol* 2005;42:615-24. (Abstract)
- Alberti A, Pontisso P, Chemello L, et al. The interaction between hepatitis B virus and hepatitis C virus in acute and chronic liver disease. *J Hepatol* 1995;22(1 Suppl):38-41. (Abstract)
- Ali S, Leveque V, Le Pogam S, et al. Selected replicon variants with low-level in vitro resistance to the hepatitis C virus NS5B polymerase inhibitor PSI-6130 lack cross-resistance with R1479. *Antimicrob Agents Chemother* 2008;52:4356-69. (Abstract)
- Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med* 1999;341:556-62. (Abstract)
- Amorosa VK, Slim J, Mounzer K, et al. The influence of abacavir and other antiretroviral agents on virological response to HCV therapy among antiretroviral-treated HIV-infected patients. *Antivir Ther.* 2010;15:91-9. (Abstract)
- Anonymous. Boceprevir. *Drugs R D* 2010;10:203-10. (Abstract)
- Anonymous. European Medicines Agency - News and Events - European Medicines Agency advises on compassionate use of daclatasvir. Available at: <http://goo.gl/XMqr01> [Accessed January 13, 2014].
- Anonymous. Hepatitis C: RKI-Ratgeber Infektionskrankheiten. *Epidemiologisches Bulletin* 2004;17:141-5.
- Antaki N, Craxi A, Kamal S et al. The neglected hepatitis C virus genotypes 4, 5 and 6: an international consensus report. *Liver Int* 2010;30:342-55. (Abstract)



- Antonelli A, Ferri C, Pampana A, et al. Thyroid disorders in chronic hepatitis C. *Am J Med* 2004;117:10-13. (Abstract)
- Aroldi A, Lampertico P, Montagnino G, et al. Natural history of hepatitis B and C in renal allograft recipients. *Transplantation* 2005;79:1132-6. (Abstract)
- Ascione A, De Luca M, Tartaglione MT et al. Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection. *Gastroenterology* 2010;138:116-22. (Abstract)
- Backus LI, Belperio PS, Shahoumian TA, et al. Comparative effectiveness of the hepatitis C virus protease inhibitors boceprevir and telaprevir in a large U.S. cohort. *Aliment Pharmacol Ther* 2014;39:93-103. (Abstract)
- Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clin Gastroenterol Hepatol* 2011;9:509-516.e1. (Abstract)
- Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011;364:1207-17. (Abstract)
- Bacon BR, Gordon SC, Lawitz E, et al. HCV respond-2 final results: high sustained virologic response among genotype 1 previous non-responders and relapsers to peginterferon/ribavirin when re-treated with boceprevir plus peginteron (peginteron alfa-2b) / ribavirin. *Hepatology* 2010a;52:S430.
- Bacon BR, Shiffman ML, Lim JK, et al. Phase 2 randomized, double-blind, placebo-controlled study of nitazoxanide plus peginterferon and ribavirin in HCV genotype 1 naive patients: week 12 sustained virologic response rate. *J Hepatol* 2010b;52:S463.
- Bani-Sadr F, Denoel L, Morand P, et al and the Agence Nationale pour la Recherche contre le SIDA et les Hépatites Virales HC02-Ribavir Study Team. Early virologic failure in HIV-coinfected hepatitis C patients treated with the peginterferon-ribavirin combination: does abacavir play a role? *J Acquir Immune Defic Syndr* 2007;45:123-5. (Abstract)
- Barnard RJ, Zeuzem S, Vierling J, Sulkowski M, Manns M, Long J. Analysis of resistance-associated amino acid variants in non-SVR patients enrolled in a retrospective long-term follow-up analysis of boceprevir phase 3 clinical trials. *Hepatology* 2011;54:164.
- Bartenschlager R, Frese M, Pietschmann T. Novel insights into hepatitis C virus replication and persistence. *Adv Virus Res* 2004;63:71-180. (Abstract)
- Beaulieu PL. Non-nucleoside inhibitors of the HCV NS5B polymerase: progress in the discovery and development of novel agents for the treatment of HCV infections. *Curr Opin Investig Drugs* 2007;8:614-34. (Abstract)
- Beinhardt S, Aberle JH, Strasser M et al. Serum Level of IP-10 Increases Predictive Value of IL28B Polymorphisms for Spontaneous Clearance of Acute HCV Infection. *Gastroenterology* 2012;142:78-85.e2. (Abstract)
- Bellecave P, Gouttenoire J, Gajer M et al. Hepatitis B and C virus coinfection: a novel model system reveals the absence of direct viral interference. *Hepatology* 2009;50:46-55. (Abstract)
- Benhamou Y, Moussalli J, Ratziu V, et al. Activity of telaprevir monotherapy or in combination with peginterferon-alfa-2a and ribavirin in treatment-naive genotype 4 hepatitis-C patients: final results of study C210. *Hepatology* 2010;52:S719.
- Berenguer J, Rodríguez E, Miralles P, et al. Sustained virological response to interferon plus ribavirin reduces non-liver-related mortality in patients coinfecting with HIV and Hepatitis C virus. *Clin. Infect. Dis.* 2012;55:728-36. (Abstract)
- Berg T, Andreone P, Pol S, et al. Predictors of virologic response with telaprevir-based combination treatment in HCV genotype 1-infected patients with prior peginterferon/ribavirin treatment failure: post-hoc analysis of the phase III realize study. *Hepatology* 2011;54:375A-376A.

- Berg T, Kronenberger B, Hinrichsen H, Gerlach T, Buggisch P, Herrmann E, et al. Triple therapy with amantadine in treatment-naive patients with chronic hepatitis C: a placebo-controlled trial. *Hepatology* 2003;37:1359-67. (Abstract)
- Berg T, von Wagner M, Nasser S, et al. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterol* 2006;130:1086-97. (Abstract)
- Berg T, Weich V, Teuber G, et al. Individualized treatment strategy according to early viral kinetics in hepatitis C virus type 1-infected patients. *Hepatology* 2009;50:369-77. (Abstract)
- Bevilacqua E, Fabris A, Floreano P, et al and the EPHN collaborators. Genetic factors in mother-to-child transmission of HCV infection. *Virology* 2009;Jul 20;390:64-70. (Abstract)
- Boesecke C, Vogel M. HIV and hepatitis C co-infection: acute HCV therapy. *Curr Opin HIV AIDS*. 2011;6:459-64. (Abstract)
- Bonaccorso S, Marino V, Puzella A, et al. Increased depressive ratings in patients with hepatitis C receiving interferon-alpha-based immunotherapy are related to interferon-alpha-induced changes in the serotonergic system. *J Clin Psychopharmacol* 2002;22:86-90. (Abstract)
- Bowden DS, Berzsényi MD. Chronic hepatitis C virus infection: genotyping and its clinical role. *Future Microbiol* 2006;1:103-12. (Abstract)
- Brainard DM, Petry A, Van Dyck K, et al. Safety and antiviral activity of MK-5172, a novel HCV NS3/4A protease inhibitor with potent activity against known resistance mutants, in genotype 1 and 3 HCV-infected patients. *Hepatology* 2010;52:S706.
- Broers B, Helbling B, Francois A, Schmid P, Chuard C, Hadengue A, Negro F. Barriers to interferon-alpha therapy are higher in intravenous drug users than in other patients with acute hepatitis C. *J Hepatol* 2005;42:323-28. (Abstract)
- Bronowicki, JP, Davis, M, Flamm, S et al. Sustained Virologic Response (SVR) in Prior PegInterferon/ribavirin (PR) Treatment Failures After Retreatment with Boceprevir (BOC) + PR: The PROVIDE Study Interim Results. *J Hepatol* 56:S6.
- Bronowicki, JP, Hezode, C, Bengtsson, L et al. 100% SVR in IL28B CC patients treated with 12 weeks of telaprevir, peginterferon and ribavirin in the PROVE2 trial. *J Hepatol* 2012;56:S430-S431.
- Bruchfeld A, Lindahl K, Schvarcz R, Stahle L. Dosage of ribavirin in patients with hepatitis C should be based on renal function: a population pharmacokinetic analysis. *Ther Drug Monit* 2001;24:701-08. (Abstract)
- Bruix J, Poynard T, Colombo M, et al. Maintenance therapy with peginterferon alfa-2b does not prevent hepatocellular carcinoma in cirrhotic patients with chronic hepatitis C. *Gastroenterology* 2011;140:1990-9. (Abstract)
- Bruno S, Vierling JM, Esteban R, et al. Boceprevir in addition to standard of care enhanced svr in hepatitis c virus (HCV) genotype-1 with advanced fibrosis/cirrhosis: subgroup analysis of sprint-2 and respond-2 studies. *J Hepatol* 2011;54:S4-S4.
- Bukh J, Miller RH, Purcell RH. Biology and genetic heterogeneity of hepatitis C virus. *Clin Exp Rheumatol* 1995; Suppl 13:S3-7. (Abstract)
- Burger, D, Back, D, Buggisch, P et al. Clinical management of drug-drug interactions in HCV therapy: Challenges and solutions. *J Hepatol* 2012
- Buti M, Agarwal K, Horsmans Y, et al. Telaprevir Twice Daily Is Noninferior to Telaprevir Every 8 Hours for Patients With Chronic Hepatitis C. *Gastroenterology* 2013. (Abstract)
- Buti M, Lurie Y, Zakharova NG, et al. Extended Treatment Duration in Chronic Hepatitis C Genotype 1-Infected Slow Responders: Final Results of the Success Study. *J Hepatol* 2009;50:S58-S58.

- Buti, M, Agarwal, K, Horsmans, Y et al. Non-inferiority of twice-daily telaprevir versus administration every 8 hours in treatment-naïve, genotype 1 HCV infected patients. *Hepatology* 2012;56:Abstract: LB-8.
- Cacciola I, Pollicino T, Squadrito G, et al. Occult hepatitis B virus infection in patients with chronic hepatitis C liver disease. *N Engl J Med* 1999;341:22-6. (Abstract)
- Cacoub P, Poynard T, Ghillani P, et al and the MULTIVIRC group. Extrahepatic manifestations of chronic hepatitis C. *Arthritis Rheum* 1999;42:2204-12. (Abstract)
- Cacoub P, Renou C, Rosenthal E, et al. Extrahepatic manifestations associated with hepatitis C virus infection. A prospective multicenter study of 321 patients. *Groupe d' Etude et de Recherche en Medicine Interne et Maladies Infectieuses sur le Virus de l'Hepatite C. Medicine* 2000;79:47-56. (Abstract)
- Calleja JL, Albillos A, Moreno-Otero R, et al. Sustained response to interferon-alpha or to interferon-alpha plus ribavirin in hepatitis C virus-associated symptomatic mixed cryoglobulinaemia. *Aliment Pharmacol Ther* 1999;13:1179-86. (Abstract)
- Capuron L, Ravaud A, Neveu PJ, Miller AH, Maes M, Dantzer R. Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. *Mol Psychiatry* 2002;7:468-73. (Abstract)
- CDC Travelers' Health, Yellow Book, Chapter 3, Infectious Diseases, Hepatitis C, Map 3-05. Prevalence of chronic hepatitis C infection, <http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/hepatitis-c.htm>
- Charlton M, Gane E, Manns M, et al. Sofosbuvir and Ribavirin for the Treatment of Established Recurrent Hepatitis C Infection After Liver Transplantation: Preliminary Results of a Prospective, Multicenter Study. *Annu. Meet. Am. Assoc. Study Liver Dis. (AASLD 2013)*. Washington, DC, Novemb. 1-5, 2013.
- Chayama K, Takahashi S, Toyota J, et al. Dual therapy with the nonstructural protein 5A inhibitor, daclatasvir, and the nonstructural protein 3 protease inhibitor, asunaprevir, in hepatitis C virus genotype 1b-infected null responders. *Hepatology* 2012;55:742-8.
- Chayama K, Takahashi S, Toyota J, et al. Dual therapy with the NS5A inhibitor BMS-790052 and the NS3 protease inhibitor BMS-650032 in HCV genotype 1b-infected null responders. *Hepatology* 2011, in press. (Abstract)
- Cheinquer, H, Shiffman, M, Zeuzem, S et al. The outcome of 24 vs 48 weeks of peginterferon alfa-2a (40KD) plus ribavirin on sustained virologic response rates in patients infected with genotype 2 or 3 hepatitis C virus who do not achieve a rapid viral response: the N-CORE study. *Hepatology* 56:Abstract: A156.
- Chevaliez S, Bouvier-Alias M, Brillet R, Pawlowsky JM. Overestimation and underestimation of hepatitis C virus RNA levels in a widely used real-time polymerase chain reaction-based method. *Hepatology* 2007;46:22-31. (Abstract)
- Chiaromonte M, Stroffolini T, Vian A, et al. Rate of incidence of hepatocellular carcinoma in patients with compensated viral cirrhosis. *Cancer* 1999;85:2132-7. (Abstract)
- Chiaromonte M, Stroffolini T, Vian A, et al. Rate of incidence of hepatocellular carcinoma in patients with compensated viral cirrhosis. *Cancer* 1999;85:2132-7. (Abstract)
- Child CGI, Turcotte JG. Surgery and Portal Hypertension. In: *Child CGI, ed. The Liver and portal hypertension*. Philadelphia: WB Saunders; 1964:50-64.
- Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* 1989;244:359-62. (Abstract)
- Chu CJ, Lee SD. Hepatitis B virus/hepatitis C virus coinfection: epidemiology, clinical features, viral interactions and treatment. *J Gastroenterol Hepatol* 2008;23:512-20. (Abstract)

- Chu CM, Sheen IS, Liaw YF. The role of hepatitis C virus in fulminant viral hepatitis in an area with endemic hepatitis A and B. *Gastroenterology* 1994;107:189-95. (Abstract)
- Chu CM, Yeh CT, Liaw YF. Fulminant hepatic failure in acute hepatitis C: increased risk in chronic carriers of hepatitis B virus. *Gut* 1999;45:613-7. (Abstract)
- Chu CM, Yeh CT, Liaw YF. Low-level viremia and intracellular expression of hepatitis B surface antigen (HBsAg) in HBsAg carriers with concurrent hepatitis C virus infection. *J Clin Microbiol* 1998;36:2084-6. (Abstract)
- Chuang WL, Dai CY, Chang WY, et al. Viral interaction and responses in chronic hepatitis C and B coinfecting patients with interferon-alpha plus ribavirin combination therapy. *Antivir Ther* 2005;10:125-33. (Abstract)
- Coilly A, Roche B, Dumortier J, et al. Safety and efficacy of protease inhibitors to treat hepatitis C after liver transplantation: A multicenter experience. *J Hepatol* 2014;60:78-86.
- Coilly, A, Roche, B, Samuel, D. Current management and perspectives for HCV recurrence after liver transplantation. *Liver Int* 2013;33 Suppl 1:56-62.
- Colin C, Lanoir D, Touzet S, et al. Sensitivity and specificity of third-generation hepatitis C virus antibody detection assays: an analysis of the literature. *J Viral Hepat* 2001;8:87-95. (Abstract)
- Cooper C, Lawitz E, Ghali P, et al. Antiviral activity of the non-nucleoside polymerase inhibitor, VCH-759, in chronic hepatitis C patients: Results from a randomized, double-blind, placebo-controlled, ascending multiple dose study. *Hepatol* 2007;46:S864.
- Coppola N, Stanzione M, Messina V, et al. Tolerability and efficacy of anti-HBV nucleos(t)ide analogues in HBV-DNA-positive cirrhotic patients with HBV/HCV dual infection. *J Viral Hep* 2012;19:890-6.
- Cornberg M, Hadem J, Herrmann E, et al. Treatment with daily consensus interferon (CIFN) plus ribavirin in non-responder patients with chronic hepatitis C: a randomized open-label pilot study. *J Hepatol* 2006;44:291-301. (Abstract)
- Cornberg M, Razavi HA, Alberti A, et al. A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. *Liver Int* 2011;31 Suppl 2:30-60. (Abstract)
- Cornberg M, Wedemeyer H, Manns MP. Treatment of chronic hepatitis C with PEGylated interferon and ribavirin. *Curr Gastroenterol Rep* 2002;4:23-30. (Abstract)
- Costelloe SJ, Wassef N, Schulz J, et al. Thyroid dysfunction in a UK hepatitis C population treated with interferon-alpha and ribavirin combination therapy. *Clin Endocrinol (Oxf)* 2010;73:249-56. (Abstract)
- Cote-Martin A, Berger K, Cartier M, et al. HCV NS3 and NS5B variants that emerged in patients with virologic breakthrough and relapse from the phase II SOUND-C2 trial investigating interferon-free BI 201335 and BI 207127 therapy. *Hepatology* 2012;56:576.
- Cotte L. High end-of-treatment (EOT) response rate with telaprevir-pegIFN-RBV in treatment-experienced HIV co-infected patients with HCV genotype 1: ANRS HC26 telaprevir study. AASLD 2013. Washington, DC, November 1-5, 2013. Abstract 1108.
- Craxì A, Laffi G, Zignego AL. Hepatitis C virus (HCV) infection: a systemic disease. *Mol Aspects Med* 2008;29:85-95. (Abstract)
- Cribier B, Rey D, Schmitt C, et al. High hepatitis C viremia and impaired antibody response in patients coinfecting with HIV. *AIDS* 1995;9:1131-36. (Abstract)
- Crockett SD and Keeffe EB. Natural history and treatment of hepatitis B virus and hepatitis C virus coinfection. *Ann Clin Microbiol Antimicrob* 2005;4:13. (Abstract)
- Crockett SD, Keeffe EB. Natural history and treatment of hepatitis B virus and hepatitis C virus coinfection. *Ann Clin Microbiol Antimicrob* 2005;4:13. (Abstract)

- Curry MP, Forns X, Chung R, et al. Pretransplant Sofosbuvir and Ribavirin to Prevent Recurrence of HCV Infection After Liver Transplantation. *Hepatology* 2013;58:314.
- Dalgard O, Bjoro K, Hellum KB, et al. Treatment with pegylated interferon and ribavirin in HCV infection with genotype 2 or 3 for 14 weeks: a pilot study. *Hepatology* 2004;40:1260-65. (Abstract)
- Dalgard O, Bjoro K, Ring-Larsen H, et al. Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. *Hepatology* 2008;47:35-42. (Abstract)
- Dammacco F, Tucci FA, Lauletta G, et al. Pegylated interferon-alpha, ribavirin, and rituximab combined therapy of hepatitis C virus-related mixed cryoglobulinemia: a long-term study. *Blood* 2010;116:343-53. (Abstract)
- Danta M, Brown D, Bhagani S, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. *AIDS* 2007;21:983-91. (Abstract)
- Danta M, Semmo N, Fabris P, et al. Impact of HIV on host-virus interactions during early hepatitis C virus infection. *J Infect Dis* 2008;197:1558-66. (Abstract)
- Darby SC, Ewart DW, Giangrande PL, et al. Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood products contaminated with hepatitis C. *Lancet* 1997;350:1425-31. (Abstract)
- Darling JM, Aerssens J, Fanning G, et al. Quantitation of pretreatment serum interferon-gamma-inducible protein-10 improves the predictive value of an IL28B gene polymorphism for hepatitis C treatment response. *Hepatology* 2011;53:14-22. (Abstract)
- Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology* 2010;138:513-21, 521.e1-6. (Abstract)
- Davis GL, Balart LA, Schiff ER, et al. Treatment of chronic hepatitis C with recombinant interferon alfa. A multicenter randomized, controlled trial. Hepatitis Interventional Therapy Group. *N Engl J Med* 1989;321:1501-6. (Abstract)
- Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. *Hepatology* 2003;38:645-52. (Abstract)
- de Knegt RJ, Bezemer G, Van Gool AR et al. Randomised clinical trial: escitalopram for the prevention of psychiatric adverse events during treatment with peginterferon-alfa-2a and ribavirin for chronic hepatitis C. *Aliment Pharmacol Ther.* 2011;34:1306-17.
- de Ledinghen V, Trimoulet P, Mannant PR, et al. Outbreak of hepatitis C virus infection during sclerotherapy of varicose veins: long-term follow-up of 196 patients (4535 patient-years). *J Hepatol* 2007;46:19-25. (Abstract)
- Deterding K, Gruener N, Wiegand J, et al. Early Versus Delayed Treatment of Acute Hepatitis C: The German Hep-Net Acute Hcv-Iii Study - a Randomized Controlled Trial. *J Hepatol* 2009;50:S380-S380.
- Deterding K, Grüner N, Buggisch P, et al. Delayed versus immediate treatment for patients with acute hepatitis C: a randomised controlled non-inferiority trial. *Lancet Infect. Dis.* 2013;13:497-506. (Abstract)
- Di Bisceglie AM, Martin P, Kassianides C, et al. Recombinant interferon alfa therapy for chronic hepatitis C. A randomized, double-blind, placebo-controlled trial. *N Engl J Med* 1989;321:1506-10. (Abstract)
- Di Bisceglie AM, Shiffman ML, Everson GT, et al. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. *N Engl J Med* 2008;359:2429-41. (Abstract)
- Dieperink E, Willenbring M, Ho SB. Neuropsychiatric symptoms associated with hepatitis C and interferon alpha: A review. *Am J Psychiatry* 2000;157:867-76. (Abstract)

- Dieterich D, Rockstroh JK, Orkin C, et al. Simeprevir (TMC435) plus peginterferon/ribavirin in patients co-infected with HCV genotype-1 and HIV-1: primary analysis of the C212 study. 14th European AIDS Conference (EACS 2013). Brussels. October 16-19, 2013. Abstract PS9/5.
- Dieterich DT, Asselah T, Guyader D, et al. SILEN-C3: treatment for 12 or 24 weeks with BI 201335 combined with peginterferon alfa-2a and ribavirin in treatment-naïve patients with chronic genotype-1 HCV infection. *Hepatology* 2011;54:378.
- Dieterich DT, Asselah T, Guyader DDufour JF, Buti M, Soriano V, et al. SILEN-C3: Interferon-free treatment for 12 or 24 weeks with BI 201335 combined with peginterferon alfa-2afaldaprevir, deleobuvir, and ribavirin in treatment-naïve patients with chronic genotype-1 SOUND-C3: 95% SVR12 in HCV infection genotype 1-b. *Hepatology* 2011;54:3782013;58:744.
- Dore GJ, Matthews GV, Rockstroh J. Future of hepatitis C therapy: development of direct-acting antivirals. *Curr Opin HIV AIDS*. 2011;6:508-13. (Abstract)
- Dorner M, Horwitz JA, Robbins JB, et al. A genetically humanized mouse model for hepatitis C virus infection. *Nature* 2011;474:208-11. (Abstract)
- Dumortier J, Scoazec JY, Chevallier P, Boillot O. Treatment of recurrent hepatitis C after liver transplantation: a pilot study of peginterferon alfa-2b and ribavirin combination. *J Hepatol* 2004;40:669-74. (Abstract)
- Duvet S, Op de Beeck A, Cocquerel L, et al. Glycosylation of the hepatitis C virus envelope protein E1 occurs posttranslationally in a mannosylphosphoryldolichol-deficient CHO mutant cell line. *Glycobiology* 2002;12:95-101. (Abstract)
- Dvory-Sobol H, Wong KA, Ku KS, et al. Characterization of resistance to the protease inhibitor GS-9451 in hepatitis C virus-infected patients. *Antimicrobial agents and chemotherapy* 2012;56:5289-95.
- EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol* 2011;55:245-64. (PDF: <http://goo.gl/xun82>)
- Egger D, Wölk , Gosert R, et al. Expression of hepatitis C virus proteins induce distinct membrane alterations including candidate viral replication complex. *J Virol* 2002;76:5974-84. (Abstract)
- Erhardt A, Deterding K, Benhamou Y, et al. Safety, pharmacokinetics and antiviral effect of BLB 1941, a novel hepatitis C virus RNA polymerase inhibitor, after 5 days oral treatment. *Antivir Ther* 2009;14:23-32. (Abstract)
- European AIDS Clinical Society. EACS Guidelines. Version 6.0, October 2011. (PDF: <http://goo.gl/HmfG5>)
- European AIDS Clinical Society. EACS Guidelines. Version 6.1, November 2012. <http://www.europeanaidscinicalsociety.org/images/stories/EACS-Pdf/EacsGuidelines-v6.1-2edition.pdf>
- European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatitis C virus infection. *J Hepatol* 2014;60:392-420 (Free full text)
- Evans MJ, von Hahn T, Tscherne DM, et al. Claudin-1 is a hepatitis C virus co-receptor required for a late step in entry. *Nature* 2007;446:801-05. (Abstract)
- Everson GT. Treatment of chronic hepatitis C in patients with decompensated cirrhosis. *Rev Gastroenterol Disord* 2004;4:S31-38. (Abstract)
- Everson GT, Sims KD, Rodriguez-Torres M, et al. An interferon-free, ribavirin-free 12-week regimen of daclatasvir (DCV), asunaprevir (ASV), BMS-791325 yielded SVR4 of 94% in treatment naïve patients with genotype (GT) 1 chronic hepatitis C virus (HCV) infection. *Hepatology* 2012;56:LB-3.
- Everson G, Sims KD, Thuluvath PJ, et al. Phase 2b Study of the Interferon-Free and Ribavirin-Free Combination of Daclatasvir, Asunaprevir, and BMS-791325 for 12 Weeks in Treatment-Naive Patients With Chronic HCV Genotype 1 Infection. *Hepatology* 2013;58:LB-1.

- Eyre NS, Phillips RJ, Bowden S, et al. Hepatitis B virus and hepatitis C virus interaction in Huh-7 cells. *J Hepatol* 2009;51:446-57. (Abstract)
- Fabrizi F, Lunghi G, Messa P, Martin P. Therapy of hepatitis C virus-associated glomerulonephritis: current approaches. *J Nephrol* 2008;21:813-825. (Abstract)
- Fattovich G, Covolo L, Bibert S, et al. IL28B polymorphisms, IP-10 and viral load predict virological response to therapy in chronic hepatitis C. *Aliment Pharmacol Ther* 2011;33:1162-72. (Abstract)
- Fattovich G, Giustina G, Favarato S, Ruol A. A survey of adverse events in 11,241 patients with chronic viral hepatitis treated with alfa interferon. *J Hepatol* 1996;24:38-47. (Abstract)
- Feld JJ, Jacobson I, Jensen DM, et al. Up to 100% SVR4 rates with ritonavir-boosted danoprevir (DNVr), mericitabine (MCB) and ribavirin (R) +/- peginterferon alfa-2a (P) in HCV genotype 1-infected partial and null responders: results from the Matterhorn study. *Hepatology* 2012;56:231.
- Fellay J, Thompson AJ, Ge D, et al. ITPA gene variants protect against anaemia in patients treated for chronic hepatitis C. *Nature* 2010;464:405-8. (Abstract)
- Ferenci P, Asselah T, Foster G, et al. Faldaprevir plus pegylated interferon alfa-2a and ribavirin in chronic HCV genotype 1 treatment naive patients: final results from STARTVerso1, a randomized, double-blind, placebo-controlled phase III trial. *J Hepatol* 2013;58:569-70.
- Ferenci P, Laferl H, Scherzer TM, et al. Peginterferon alfa-2a and ribavirin for 24 weeks in hepatitis C type 1 and 4 patients with rapid virological response. *Gastroenterol* 2008;135:451-58. (Abstract)
- Ferenci P, Scherzer TM, Kerschner H, et al. Silibinin is a potent antiviral agent in patients with chronic hepatitis C not responding to pegylated interferon/ribavirin therapy. *Gastroenterol* 2008;135:1561-7. (Abstract)
- Ferri C, Antonelli A, Mascia MT, et al. B cells and mixed cryoglobulinemia. *Autoimmun Rev* 2007;7:114-20. (Abstract)
- Ferri C, Sebastiani M, Guiggiolo D, et al. Mixed cryoglobulinaemia: demographic, clinical, and serologic features and survival in 231 patients. *Semin Arthritis Rheum* 2004;33:355-74. (Abstract)
- Flamm S, Lawitz E, Jacobson I, et al. High sustained virologic response (SVR) among genotype 1 previous non-responders and relapsers to peginterferon/ribavirin when re-treated with boceprevir (BOC) plus peginterferon alfa-2a/ribavirin. *J Hepatol* 2011;54:S541-S542.
- Flamm SL, Lawitz E, Jacobson I, et al. Boceprevir with peginterferon alfa-2a-ribavirin is effective for previously treated chronic hepatitis C genotype 1 infection. *Clin Gastroenterol Hepatol*. 2013;11:81-87.e4; quiz e5. (Abstract)
- Flisiak R, Feinman SV, Jablkowski M, et al. The cyclophilin inhibitor Debio 025 combined with PEG IFN alpha 2a significantly reduces viral load in treatment-naive hepatitis C patients. *Hepatol* 2009;49:1460-8. (Abstract)
- Flisiak R, Horban A, Gally P, et al. The cyclophilin inhibitor Debio-025 shows potent anti-hepatitis C effect in patients coinfecting with hepatitis C and human immunodeficiency virus. *Hepatol* 2008;47:817-26. (Abstract)
- Flisiak R, Pawlowsky JM, Crabbe R, Callistru PI, Kryczka W, Häussinger D. Once daily alisporivir (Debio025) plus pegIFNalpha2a/ribavirin results in superior sustained virologic response (SVR) in chronic hepatitis C genotype 1 treatment naive patients. *J Hepatol* 2011;54:24.
- Fong TL, Di Bisceglie AM, Waggoner JG, et al. The significance of antibody to hepatitis C virus in patients with chronic hepatitis B. *Hepatology* 1991;14:64-7. (Abstract)
- Forestier N, Reesink HW, Weegink CJ, et al. Antiviral activity of telaprevir (VX-950) and peginterferon alfa-2a in patients with hepatitis C. *Hepatol* 2007;46:640-8. (Abstract)

- Forns X, Garcia-Retortillo M, Serrano T, et al. Antiviral therapy of patients with decompensated cirrhosis to prevent recurrence of hepatitis C after liver transplantation. *J Hepatol* 2003;39:389-96. (Abstract)
- Forns X, Lawitz E, Zeuzem S, et al. Simeprevir (TMC435) with peg-interferon  $\alpha$ -2a/ribavirin for treatment of chronic HCV genotype 1 infection in patients who relapsed after previous interferon-based therapy: efficacy and safety in patient sub-populations in the PROMISE phase III trial. *Hepatology* 2013;58:Abstract 1092.
- Forton DM, Taylor-Robinson SD, Thomas HC. Cerebral dysfunction in chronic hepatitis C infection. *J Viral Hepat* 2003;10:81-6. (Abstract)
- Foster GR, Hezode C, Bronowicki JP, et al. Activity of telaprevir alone or in combination with peginterferon- $\alpha$ -2a and ribavirin in treatment-naïve genotype 2 and 3 hepatitis-C patients: final results of study C209. *J Hepatol* 2010;52:S27.
- 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;141:881-9.e1. (Abstract)
- Fridell RA, Wang C, Sun JH, et al. Genotypic and phenotypic analysis of variants resistant to hepatitis C virus nonstructural protein 5A replication complex inhibitor BMS-790052 in Humans: In Vitro and In Vivo Correlations. *Hepatology* 2011, in press. (Abstract)
- Fried MW, Buti M, Dore GJ, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naïve genotype 1 hepatitis C: The randomized PILLAR study. *Hepatology* 2013;58:1918-29. (Abstract)
- Fried MW, Poordad F, Zeuzem S, et al. Safety and tolerability of simeprevir (TMC435) in combination with peginterferon  $\alpha$ -2a and ribavirin for treatment of HCV genotype 1 infection in treatment-naïve and -experienced patients (Phase IIb PILLAR and ASPIRE Trials). *Hepatology* 2012;56:563.
- Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon  $\alpha$ -2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;347:975-82. (Abstract)
- Fukuda R, Ishimura N, Hamamoto S, et al. Co-infection by serologically-silent hepatitis B virus may contribute to poor interferon response in patients with chronic hepatitis C by down-regulation of type-I interferon receptor gene expression in the liver. *J Med Virol* 2001;63:220-7. (Abstract)
- Fukuda R, Ishimura N, Niigaki M, et al. Serologically silent hepatitis B virus coinfection in patients with hepatitis C virus-associated chronic liver disease: clinical and virological significance. *J Med Virol* 1999;58:201-7. (Abstract)
- Gane E, Pockros P, Zeuzem S, et al. Interferon-free treatment with a combination of mericitabine and danoprevir with or without ribavirin in treatment-naïve HCV genotype 1-infected patients. *J Hepatol* 2012;56:555-6.
- Gane E, Stedman C, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C virus. *The New England journal of medicine* 2013;368:33-44.
- Gane E, Stedman C, Hyland RH, Sorensen RD, Symonds WT, Hindes R. Once daily sofosbuvir (GS-7977) plus ribavirin in patients with HCV genotypes 1, 2, and 3: The ELECTRON trial. *Hepatology* 2012;56:306.
- Gane E, Stedman CA, Hyland RH, et al. Electron: once daily PSI-7977 plus RBV in HCV Gt1/2/3. *J Hepatol* 2012;56:438-9.
- Gane EJ, Roberts SK, Stedman CA, et al. Oral combination therapy with a nucleoside polymerase inhibitor (RG7128) and danoprevir for chronic hepatitis C genotype 1 infection (INFORM-1): a randomised, double-blind, placebo-controlled, dose-escalation trial. *Lancet* 2010;376:1467-75. (Abstract)
- Gane EJ, Roberts SK, Stedman CA, et al. Oral combination therapy with a nucleoside polymerase inhibitor (RG7128) and danoprevir for chronic hepatitis C genotype 1



- infection (INFORM-1): a randomised, double-blind, placebo-controlled, dose-escalation trial. *Lancet* 2010;376:1467-75.
- Gane EJ, Stedman CA, Hyland RH, et al. Once daily PSI-7977 plus RBV: pegylated interferon-alpha not required for complete rapid viral response in treatment-naive patients with HCV Gt2 or Gt3. *Hepatology* 2011;54:18.
- Gane EJ, Stedman CA, Hyland RH, et al. Efficacy of Nucleotide Polymerase Inhibitor Sofosbuvir plus the NS5A Inhibitor Ledipasvir or the NS5B Non-nucleoside Inhibitor GS-9669 Against HCV Genotype 1 Infection. *Gastroenterology* 2013, in press.
- Gao M, Nettles RE, Belema M, et al. Chemical genetics strategy identifies an HCV NS5A inhibitor with a potent clinical effect. *Nature* 2010;465:96-100. (Abstract)
- Garg V, van Heeswijk R, Lee JE, Alves K, Nadkarni P, Luo X. Effect of telaprevir on the pharmacokinetics of cyclosporine and tacrolimus. *Hepatology* 2011;54:20-7. (Abstract)
- Garini G, Allegri L, Lannuzzella F, Vaglio A, Buzio C. HCV-related cryoglobulinemic glomerulonephritis: implications of antiviral and immunosuppressive therapies. *Acta Biomed* 2007;78:51-59. (Abstract)
- Gastaminza P, Cheng G, Wieland S, et al. Cellular determinants of hepatitis C virus assembly, maturation, degradation, and secretion. *J Virol* 2008;82:2120-29. (Abstract)
- Gaudieri S, Rauch A, Pfafferott K, et al. Hepatitis C virus drug resistance and immune-driven adaptations: relevance to new antiviral therapy. *Hepatology* 2009;49:1069-82. (Abstract)
- Gebo KA, Herlong HF, Torbenson MS, et al. Role of liver biopsy in management of chronic hepatitis C: a systematic review. *Hepatology* 2002;36(5 Suppl 1):S161-72. (Abstract)
- Gerlach JT, Diepolder HM, Zachoval R, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. *Gastroenterol* 2003;125:80-88. (Abstract)
- Germi R, Crance JM, Garin D, et al. Cellular glycosaminoglycans and low density lipoprotein receptor are involved in hepatitis C virus adsorption. *J Med Virol* 2002;68:206-15. (Abstract)
- Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. 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;54:1433-44. (Free full-text)
- Giannelli F, Moscarella S, Giannini C, Caini P, Monti M, et al. Effect of antiviral treatment in patients with chronic HCV infection and t(14;18) translocation. *Blood* 2003;102:1196-201. (Abstract)
- Giordano TP, Kramer JR, Soucek J, Richardson P, El-Serag HB. Cirrhosis and hepatocellular carcinoma in (Abstract)
- Gitto S, Micco L, Conti F, Andreone P, Bernardi M. Alcohol and viral hepatitis: A mini-review. *Dig Liver Dis* 2009;41:67-70. (Abstract)
- Gordon FD, Brown RS, Kwo P, et al. Peginterferon alpha-2b and ribavirin for hepatitis C recurrence post-orthotopic liver transplantation (OLT): Final results from the Protect study. *J Hepatol* 2010;52:S10-S11.
- Gordon SC, Lawitz EJ, Bacon BR, et al. Adherence to assigned dosing regimen and sustained virologic response among hepatitis c genotype 1 treatment-naive and peg/ribavirin treatment-failures treated with boceprevir plus peginterferon alpha-2b/ribavirin. *J Hepatol* 2011;54:S173-S174.
- Gotz HM, van Doormun G, Niesters HG, et al. A cluster with acute hepatitis C virus infection among men who have sex with men - results from contact tracing and public health implications. *AIDS* 2005;19:969-74. (Abstract)
- Grebely J, Matthews GV, Dore GJ. Treatment of acute HCV infection. *Nat Rev Gastroenterol Hepatol* 2011a;8:265-74. (Abstract)
- Grebely J, Petoumenos K, Hellard M, et al. Potential role for interleukin-28B genotype in treatment decision-making in recent hepatitis C virus infection. *Hepatology* 2010;52:1216-24. (Abstract)

- Grebely J, Petoumenos K, Hellard M, et al; ATAC Study Group. Potential role for interleukin-28B genotype in treatment decision-making in recent hepatitis C virus infection. *Hepatology*. 2010;52:1216-24. (Abstract)
- Grebely J, Pham ST, Matthews GV, et al. Hepatitis C virus reinfection and superinfection among treated and untreated participants with recent infection. *Hepatology* 2011b. [Epub ahead of print] (Abstract)
- Hadziyannis SJ, Sette Jr H, Morgan TR, et al. Peginterferon alpha 2a and ribavirin combination therapy in chronic hepatitis C; a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004;140:346-55. (Abstract)
- Hanafiah, KM, Groeger, J, Flaxman, AD et al. Global epidemiology of hepatitis C virus infection: New estimates of age-specific antibody to hepatitis C virus seroprevalence. *Hepatology* 2012;doi: 10.1002/hep.26141. [Epub ahead of print].
- Harrington PR, Zeng W, Naeger LK. Clinical relevance of detectable but not quantifiable hepatitis C virus RNA during boceprevir or telaprevir treatment. *Hepatology* 2012;55:1048-57. (Abstract)
- Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. *Clin. Infect. Dis.* 2009;49:561-73. (Abstract)
- Heller TS, Saito J, Auerbach T, et al. An in vitro model of hepatitis C virion production. *Proc Nat Acad Sci USA* 2005;102:2579-83. (Abstract)
- Hendricks DA, Friesenhahn M, Tanimoto L, et al. Multicenter evaluation of the VERSANT HCV RNA qualitative assay for detection of hepatitis C virus RNA. *J Clin Microbiol* 2003;41:651-6. (Abstract)
- Hezode C, Dorival C; Zoulim F, et al. Safety and efficacy of telaprevir or boceprevir in combination with peginterferon alfa/ribavirin, in 497 cirrhotic non responders. Week 16 analysis of the French early access program (ANRS CO20-CUPIC) in real-life setting. *Hepatology* 2012; 56 (suppl): 217A.
- Hézode C, Fontaine H, Dorival C, et al. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. *J Hepatol* 2013;59:434-41. (Abstract)
- Hezode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med* 2009;360:1839-50. (Abstract)
- Hezode C, Hirschfield GM, Ghesquiere W, et al. BMS-790052, a NS5A replication complex inhibitor, combined with peginterferon alfa-2a and ribavirin in treatment-naïve HCV-genotype 1 or 4 patients: phase 2b A1444010 study interim week 12 results. *Hepatology* 2011;54:115.
- Hezode C, Hirschfield GM, Ghesquiere W, et al. Daclatasvir, an NS5A Replication Complex Inhibitor, Combined With Peginterferon Alfa-2a and Ribavirin in Treatment-Naïve HCV-Genotype 1 or 4 Patients: Phase 2b COMMAND-1 SVR12 Results. *Hepatology* 2012;56:553.
- Hezode, C, Dorival, C, Zoulim, F et al. Safety and efficacy of telaprevir or boceprevir in combination with peginterferon alfa/ribavirin, in 455 cirrhotic non responders. Week 16 analysis of the French early access program (ANRS CO20-CUPIC) in real-life setting. *Hepatology* 2012;56:Abstract: A51.
- Hijikata M, Kato N, Ootsuyama Y, et al. Gene mapping of the putative structural region of the hepatitis C virus genome by in vitro processing analysis. *Proc Natl Acad Sci USA* 1991;88:5547-51. (Abstract)
- Hinrichsen H, Benhamou Y, Wedemeyer H, et al. Short-term antiviral efficacy of BILN 2061, a hepatitis C virus serine protease inhibitor, in hepatitis C genotype 1 patients. *Gastroenterol* 2004;127:1347-55. (Abstract)
- HIV-infected veterans with and without the hepatitis C virus: a cohort study, 1992-2001. *Arch Intern Med* 2004;164:2349-54. (Abstract)

- Hofmann WP, Dries V, Herrmann E, et al. Comparison of transcription mediated amplification (TMA) and reverse transcription polymerase chain reaction (RT-PCR) for detection of hepatitis C virus RNA in liver tissue. *J Clin Virol* 2005;32:289-93. (Abstract)
- Hoofnagle JH. Hepatitis C: the clinical spectrum of disease. *Hepatology* 1997;26:15S-20S. (Abstract)
- Hraber P, Kuiken C, Yusim K. Evidence for human leukocyte antigen heterozygote advantage against hepatitis C virus infection. *Hepatology* 2007;46:1713-21. (Abstract)
- Hsu M, Zhang J, Flint M, et al. Hepatitis C virus glycoproteins mediate pH-dependent cell entry of pseudotyped retroviral particles. *Proc Natl Acad Sci USA* 2003;100:7271-76. (Abstract)
- Hung CH, Lee CM, Lu SN, et al. Combination therapy with interferon-alpha and ribavirin in patients with dual hepatitis B and C virus infection. *J Gastroenterol Hepatol* 2005;20:727-32. (Abstract)
- INCIVO (telaprevir) EU SmPC 2011. PDF, 147 pages. Accessed on February 25, 2012.
- Jacobson I (a), Dore G, Foster G, et al. Simeprevir (TMC435) with peginterferon/ribavirin for treatment of chronic HCV genotype 1 infection in treatment-naïve patients: efficacy in difficult-to-treat patient sub-populations in the QUEST 1 and 2 phase III trials. *Hepatology* 2013;58:Abstract 1122.
- Jacobson J (b), Ghalib R, Rodriguez-Torres M, et al. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naïve and prior null responder patients: the COSMOS study. 64th Annu. Meet. Am. Assoc. Study Liver Dis. (AASLD 2013). Washington, DC, Novemb. 1-5, 2013.:Abstract LB-3.
- Jacobson I (c), Dore G, Foster G, et al. Simeprevir (TMC435) with peginterferon/ribavirin for chronic HCV genotype 1 infection in treatment-naïve patients: results from QUEST-1, a phase III trial. *Int. Liver Congr. Amsterdam*, poster 1425 2013.
- Jacobson IM (d), Gordon SC, Kowdley K V, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013;368:1867-77. (Abstract)
- Jacobson (e) et al. I. STARTVerso3: A randomized, double-blind, placebo- controlled Phase III trial of faldaprevir in combination with pegylated interferon alfa-2a and ribavirin in treatment-experienced patients with chronic hepatitis C genotype-1 infection. *Hepatology* 2013;58:742A, Abstract 1100.
- Jacobson I, Sulkowski MS, Gane E, et al. VX-222, telaprevir and ribavirin in treatment-naïve genotype 1 chronic hepatitis C: results of the ZENITH study interferon-free regimen. *Hepatology* 2012;56:308.
- Jacobson IM, Catlett I, Marcellin P, et al. Telaprevir substantially improved SVR rates across all IL28B genotypes in the ADVANCE trial. *J Hepatol* 2011a;54:S542-S543.
- Jacobson IM, Gonzalez SA, Ahmed F, et al. A randomized trial of pegylated interferon alpha-2b plus ribavirin in the retreatment of chronic hepatitis C. *Am J Gastroenterol* 2005;100:2453-62. (Abstract)
- Jacobson IM, Marcellin P, Zeuzem S, et al. Refinement of stopping rules during treatment of hepatitis C genotype 1 infection with boceprevir and peginterferon/ribavirin. *Hepatology* 2012;56:567-75. (Abstract)
- Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011;364:2405-16. (Abstract)
- Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir in combination with peginterferon and ribavirin in genotype 1 HCV treatment-naïve patients: final results of phase 3 advance study. *Hepatology* 2010;52:S427.
- Jaekel E, Cornberg M, Wedemeyer H, et al. Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med* 2001;345:1452-57. (Abstract)

- Janssen HL, Brouwer JT, van der Mast RC, Schalm SW. Suicide associated with alfa-interferon therapy for chronic viral hepatitis. *J Hepatol* 1994;21:241-43. (Abstract)
- Janssen HL, Reesink HW, Zeuzem S, et al. A randomized, double-blind, placebo controlled safety and anti-viral proof of concept study of miravirsin, an oligonucleotide targeting mir-122, in treatment naive patients with genotype 1 chronic HCV infection. *Hepatology* 2010;54:1071. Lawitz EJ, et al. Treatment of HCV Infection by Targeting MicroRNA. *The New England journal of medicine* 2013;368:1685-94.
- Jardi R, Rodriguez F, Buti M, et al. Role of hepatitis B, C, and D viruses in dual and triple infection: influence of viral genotypes and hepatitis B precore and basal core promoter mutations on viral replicative interference. *Hepatology* 2001;34:404-10. (Abstract)
- Jensen DM, Morgan TR, Marcellin P, et al. Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy. *Hepatology* 2006;43:954-60. (Abstract)
- Jensen DM, Wedemeyer H, Herring RW, et al. High rates of early viral response, promising safety profile and lack of resistance-related breakthrough in HCV Gt 1/4 patients treatment with RG7128 plus pegIFN alfa-2A (40kD)/RBV: planned week 12 interim analysis from the propel study. *Hepatology* 2010;52:S360.
- Jensen DM, Asselah T, Dieterich DT, et al. A pooled analysis of two randomized, double-blind placebo-controlled Phase III trials (STARTVerso1&2) of faldaprevir plus pegylated interferon alfa-2a and rib- avirin in treatment-naïve patients with chronic hepatitis C genotype-1 infection. *Hepatology* 2013;58:734A-735A, Abstract 1088.
- Jin F, Prestage GP, Matthews GV, Zablotska I, Rawstorne P, Kippax SC, Kaldor J, Grulich AE. Prevalence, incidence and risk factors for hepatitis C in homosexual men: Data from two cohorts of HIV negative and HIV positive men in Sydney, Australia. *Sex Transm Infect.* 2010; 86:25-8.
- Jin L, Peterson DL. Expression, isolation, and characterization of the hepatitis C virus ATPase/RNA helicase. *Arch Biochem Biophys* 1995;323:47-53. (Abstract)
- Kamal SM, El Tawil AA, Nakano T, et al. Peginterferon alpha 2b and ribavirin therapy in chronic hepatitis C genotype 4; impact of treatment duration and viral. *Gut.* 2005;54:858-66. (Abstract)
- Kamar N, Rostaing L, Alric L. Treatment of hepatitis C-virus-related glomerulonephritis. *Kidney Int* 2006;69:436-39. (Abstract)
- Kessler HH, Hübner M, Konrad PM, Stelzl E, Stübler MM, et al. Genotype impact on HCV RNA levels determined with the VERSANTHCV RNA 1.0 assay (kPCR). *J Clin Virol.* 2013;58:522-7.
- Khattab MA, Ferenci P, Hadziyannis SJ, et al. Management of hepatitis C virus genotype 4: recommendations of an international expert panel. *J Hepatol* 2011;54:1250-62. (Abstract)
- Kim DW, Gwack Y, Han JH, et al. C-terminal domain of the hepatitis C virus NS3 protein contains an RNA helicase activity. *Biochem Biophys Res Commun* 1995;215:160-66. (Abstract)
- Kim JL, Morgenstern KA, Griffith JP, et al. Hepatitis C virus NS3 RNA helicase domain with a bound oligonucleotide: the crystal structure provides insights into the mode of unwinding. *Structure* 1998;6:89-100. (Abstract)
- Kim JL, Morgenstern KA, Lin C, et al. Crystal structure of the hepatitis C virus NS3 protease domain complexed with a synthetic NS4A cofactor peptide. *Cell* 1996;87:343-55. (Abstract)
- Kiser JJ, Burton JR, Everson GT. Drug-drug interactions during antiviral therapy for chronic hepatitis C. *Nat. Rev. Gastroenterol. Hepatol.* 2013;10:596-606. (Abstract)

- Kneteman NM, Howe AY, Gao T, et al. HCV796: A selective nonstructural protein 5B polymerase inhibitor with potent anti-hepatitis C virus activity in vitro, in mice with chimeric human livers, and in humans infected with hepatitis C virus. *Hepatology* 2009;49:745-52. (Abstract)
- Koch U and Narjes F. Recent progress in the development of inhibitors of the hepatitis C virus RNA-dependent RNA polymerase. *Curr Top Med Chem* 2007;7:1302-29. (Abstract)
- Kohli A, Sims Z, Marti M, et al. Combination Oral, Ribavirin Free, Antiviral Therapy to Optimize Treatment Outcomes for Hepatitis C Treatment Naïve Patients: Interim Results from the NIAID SYNERGY Trial (6 & 12 weeks therapy). *Hepatology* 2013;54:LB-8.
- Kowdley KV, Lawitz E, Crespo I, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naïve patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. *Lancet* 2013;381:2100-7.
- Kowdley KV, Lawitz E, Poordad F, et al. A 12-week interferon-free treatment regimen with ABT-450/r, ABT-267, ABT-333 and ribavirin achieves SVR12 rates (observed data) of 99% in treatment-naïve patients and in 93% in prior null responders with HCV genotype 1 infection. *Hepatology* 2012;56:LB-1.
- Kowdley KV, Lawitz E, Poordad F, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. *N Engl J Med* 2014;370:222-32. (Abstract)
- Kowdley KV, Lawitz E, Poordad F, et al. Safety and efficacy of interferon-free regimens of ABT-450/r, ABT-267, ABT-333 +/- ribavirin in patients with chronic HCV GT1 infection: results from the AVIATOR study. *J Hepatol* 2013;58:2.
- Kraus MR, Schafer A, Al-Taie O, Scheurlen M. Prophylactic SSRI during interferon alpha re-therapy in patients with chronic hepatitis C and a history of interferon-induced depression. *J Viral Hepat* 2005;12:96-100. (Abstract)
- Kraus MR, Schafer A, Faller H, Csef H, Scheurlen M. Paroxetine for the treatment of interferon-alpha-induced depression in chronic hepatitis C. *Aliment Pharmacol Ther* 2002;16:1091-9. (Abstract)
- Kraus MR, Schafer A, Scheurlen M. Paroxetine for the prevention of depression induced by interferon alfa. *N Engl J Med* 2001;345:375-6. (Abstract)
- Kraus MR, Schafer A, Schottker K, et al. Therapy of interferon-induced depression in chronic hepatitis C with citalopram: A randomized, double-blind, placebo-controlled study. *Gut* 2008;57:531-6 (Abstract)
- Kuntzen T, Timm J, Beralci A, et al. Naturally occurring dominant resistance mutations to hepatitis C virus protease and polymerase inhibitors in treatment-naïve patients. *Hepatology* 2008;48:1769-78. (Abstract)
- Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naïve patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. *Lancet* 2010;376:705-16. (Abstract)
- Lalezari J, Holland L, Glutzer E, et al. Rapid and Consistent Virologic Responses in a Phase 2 Trial of a New All-Oral Combination of Faldaprevir, Deleobuvir and PPI-668, with and without Ribavirin, in Patients with HCV Genotype-1a Infection. *Hepatology* 2013;58:LB-20.
- Lam AM, Espiritu C, Bansal S, et al. Genotype and subtype profiling of PSI-7977 as a nucleotide inhibitor of hepatitis C virus. *Antimicrob. Agents Chemother.* 2012;56:3359-68. (Abstract)
- Lam KD, Trinh HN, Do ST, et al. Randomized controlled trial of pegylated interferon-alfa 2a and ribavirin in treatment-naïve chronic hepatitis C genotype 6. *Hepatology* 2010;52:1573-80. (Abstract)

- Lamarre D, Anderson PC, Bailey M, et al. An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus. *Nature* 2003;426:186-9. (Abstract)
- Landford RE, Hildebrandt-Eriksen ES, Petri A, et al. Therapeutic silencing of microRNA-122 in primates with chronic hepatitis C virus infection. *Science* 2010;327:198-201.
- Lange CM, Zeuzem S. Perspectives and challenges of interferon-free therapy for chronic hepatitis C. *J Hepatol* 2012, in press.
- Larrey D, Lohse AW, de Ledinghen V, et al. Rapid and strong antiviral activity of the non-nucleosidic NS5B polymerase inhibitor BI 207127 in combination with peginterferon alfa 2a and ribavirin. *J Hepatol* 2012;57:39-46.
- Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med* 2001;345:41-52. (Abstract)
- Lawitz E (a), Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013;368:1878-87. (Abstract)
- Lawitz E (b), Poordad F, Brainard D, et al. Sofosbuvir in Combination With PegIFN and Ribavirin for 12 Weeks Provides High SVR Rates in HCV-Infected Genotype 2 or 3 Treatment- Experienced Patients with and without Compensated Cirrhosis: Results from the LONESTAR-2 Study. 64rd Annu. Meet. Am. Assoc. Study Liver Dis. Washington, DC Nov 1-5 2013: Abstract LB-4.
- Lawitz E, Hezode C, Varunok P, et al. Interferon- and Ribavirin-free Regimen of ABT-450/r + ABT-267 in HCV Genotype 1b-infected Treatment-naïve Patients and Prior Null Responders. *Hepatology* 2013;58:244.
- Lawitz E, Lalezari JP, Hassanein T, et al. Once-daily PSI-7977 plus peg/RBV in treatment-naïve patients with HCV GT1: robust end of treatment response rates are sustained post-treatment. *Hepatology* 2011;54:113.
- Lawitz E, Lalezari JP, Hassanein T, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naïve patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *Lancet Infect Dis* 2013; 13:401-8. (Abstract)
- Lawitz E, Poordad F, Brainard D, et al. Sofosbuvir in Combination With PegIFN and Ribavirin for 12 Weeks Provides High SVR Rates in HCV-Infected Genotype 2 or 3 Treatment-Experienced Patients with and without Compensated Cirrhosis: Results from the LONESTAR-2 Study *Hepatology* 2011;54:1132013;58:LB-4.
- Lawitz E, Poordad F, Kowdley KV, et al. 12-week interferon-free regimen of ABT-450/R, ABT-072, and ribavirin was well tolerated and achieved sustained virologic response in 91% treatment-naïve HCVIL28B-CC genotype-1-infected subjects. *J Hepatol* 2012;56:7.
- Lawitz E, Poordad FF, Pang PS, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naïve and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. *Lancet* 2013, in press.
- Lawitz E, Rodriguez-Torres M, Muir AJ, et al. Antiviral effects and safety of telaprevir, peginterferon alfa-2a, and ribavirin for 28 days in hepatitis C patients. *J Hepatol* 2008;49:163-69. (Abstract)
- Lawitz E, Vierling JM, Murillo A, et al. High Efficacy and Safety of the All-Oral Combination Regimen, MK-5172 / MK-8742 ± RBV for 12 Weeks in HCV Genotype 1 Infected Patients: The C-WORTHY Study. *Hepatology* 2013;58:244.
- Lawitz EJ, Hill JM, Marbury T, et al. A Phase 1, randomized, placebo-controlled, three-day, ascending-dose study of GS-9451, an NS3/4A protease inhibitor, in genotype 1 hepatitis C patients. *Antiviral therapy* 2012, in press.
- Lawitz, E, Poordad, F, Kowdley, K et al. A 12-week interferon-free regimen of ABT-450r, ABT-072 and ribavirin was well tolerated and achieved sustained virological response in 91% of treatment-naïve HCV IL28B-CC genotype-1 infected patients. *J Hepatol* 2012;56:S7.

- Lenz O, de Bruijne J, Vijgen L, et al. Efficacy of re-treatment with TMC435 as combination therapy in hepatitis C virus-infected patients following TMC435 monotherapy. *Gastroenterology* 2012;143:1176-8 e1-6.
- Lenz O, Fevery B, Vigen L, et al. TMC435 in combination with peginterferon alpha-2a/ribavirin in treatment-naive patients infected with HCV genotype 1: virology analysis of the Pillar study. *Hepatology* 2011;54:985.
- Lenz O, Vijgen L, Berke JM, et al. Virologic response and characterisation of HCV genotype 2-6 in patients receiving TMC435 monotherapy (study TMC435-C202). *J Hepatol* 2013;58:445-51. (Abstract)
- Lesburg CA, Cable MB, Ferrari E, et al. Crystal structure of the RNA-dependent RNA polymerase from hepatitis C virus reveals a fully encircled active site. *Nat Struct Biol* 1999;6:937-43. (Abstract)
- Liaw YF, Chen YC, Sheen IS, et al. Impact of acute hepatitis C virus superinfection in patients with chronic hepatitis B virus infection. *Gastroenterology* 2004;126:1024-9. (Abstract)
- Liaw YF, Lin SM, Sheen IS, et al. Acute hepatitis C virus superinfection followed by spontaneous HBeAg seroconversion and HBsAg elimination. *Infection* 1991;19:250-1. (Abstract)
- Liaw YF, Tsai SL, Chang JJ, et al. Displacement of hepatitis B virus by hepatitis C virus as the cause of continuing chronic hepatitis. *Gastroenterology* 1994;106:1048-53. (Abstract)
- Liaw YF, Yeh CT, Tsai SL. Impact of acute hepatitis B virus superinfection on chronic hepatitis C virus infection. *Am J Gastroenterol* 2000;95:2978-80. (Abstract)
- Liaw YF. Concurrent hepatitis B and C virus infection: Is hepatitis C virus stronger? *J Gastroenterol Hepatol* 2001;16:597-8. (Abstract)
- Liaw YF. Hepatitis C virus superinfection in patients with chronic hepatitis B virus infection. *J Gastroenterol* 2002;37 Suppl 13:65-8. (Abstract)
- Liaw YF. Role of hepatitis C virus in dual and triple hepatitis virus infection. *Hepatology* 1995;22:1101-8. (Abstract)
- Lim YS, Kim WR. The global impact of hepatic fibrosis and end-stage liver disease. *Clin Liver Dis* 2008;12:733-46. (Abstract)
- Lin C, Gates CA, Rao BG, et al. In vitro studies of cross-resistance mutations against two hepatitis C virus serine protease inhibitors, VX-950 and BILN 2061. *J Biol Chem* 2005;280:36784-91. (Abstract)
- Lin K, Perni RB, Kwong AD, Lin C. VX-950, a novel hepatitis C virus (HCV) NS3-4A protease inhibitor, exhibits potent antiviral activities in HCV replicon cells. *Antimicrob Agents Chemother* 2006;50:1813-22. (Abstract)
- Lindenbach BD, Evans MJ, Syder AJ, et al. Complete replication of hepatitis C virus in cell culture. *Science* 2005;309:623-6. (Abstract)
- Lisker-Melman M, Di Bisceglie AM, Usala SJ, Weintraub B, Murray LM, Hoofnagle JH. Development of thyroid disease during therapy of chronic viral hepatitis with interferon alfa. *Gastroenterol* 1992;102:2155-60. (Abstract)
- Liu CJ, Chen PJ, Lai MY et al. Ribavirin and interferon is effective for hepatitis C virus clearance in hepatitis B and C dually infected patients. *Hepatology* 2003;37:568-76. (Abstract)
- Liu CJ, Chu YT, Shau WY, Kuo RN, Chen PJ, Lai MS. Treatment of patients with dual hepatitis C and B by peginterferon ? and ribavirin reduced risk of hepatocellular carcinoma and mortality. *Gut*. 2013 May 15. [Epub ahead of print]
- Liu CJ, Chuang WL, Lee CM, et al. Peginterferon alfa-2a plus ribavirin for the treatment of dual chronic infection with hepatitis B and C viruses. *Gastroenterology* 2009;136(2):496-504. (Abstract)

- Liu JY, Sheng YJ, HU HD, et al. The influence of hepatitis B virus on antiviral treatment with interferon and ribavirin in Asian patients with hepatitis C virus/hepatitis B virus coinfection: a meta-analysis. *Virology* 2012;9:186-93.
- Lohmann V, Korner F, Koch J, et al. Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. *Science* 1999;285:110-3. (Abstract)
- Lok AS, Gardiner DF, Hezode C, et al. Sustained virologic response in chronic HCV genotype (GT) 1-infected null responders with combination of daclatasvir (DC; NS5A inhibitor) and asunaprevir (ASV; NS3 inhibitor) with or without peginterferon alfa-2a/ribavirin (PEG/RBV). *Hepatology* 2012;56:230.
- Lok AS, Gardiner DF, Lawitz E, et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. *N. Engl. J. Med.* 2012;366:216-24. (Abstract)
- Lok AS, Gardiner DF, Lawitz E. Quadruple therapy with BMS-790052, BMS-650032 and Peg-IFN/RBV for 24 weeks results in 100% SVR12 in HCV genotype null responders. *J Hepatol* 2011;54:536.
- Lok, AS, Everhart, JE, Wright, EC et al. Maintenance peginterferon therapy and other factors associated with hepatocellular carcinoma in patients with advanced hepatitis C. *Gastroenterology* 2011;140:840-849.
- Lorenz IC, Marcotrigiano J, Dentzer TG, Rice CM. Structure of the catalytic domain of the hepatitis C virus NS2-3 protease. *Nature* 2006;442:831-5. (Abstract)
- Lunel F, Musset L, Cacoub P, et al. Cryoglobulinemia in chronic liver diseases: role of hepatitis C virus and liver damage. *Gastroenterol* 1994;106:1291-1300. (Abstract)
- Lupberger J, Felmlee DJ, Baumert TF. Cholesterol uptake and hepatitis C virus entry. *J Hepatol* 2012;57:215-7.
- Lupberger J, Zeisel MB, Xiao F, et al. EGFR and EphA2 are host factors for hepatitis C virus entry and possible targets for antiviral therapy. *Nat Med* 2011;17:589-95.
- Maasoumy B (a), Port K, Markova AA, et al. Eligibility and safety of triple therapy for hepatitis C: lessons learned from the first experience in a real world setting. *PLoS One* 2013;8:e55285. (Abstract)
- Maasoumy B (b), Port K, Calle Serrano B, et al. The clinical significance of drug-drug interactions in the era of direct-acting anti-viral agents against chronic hepatitis C. *Aliment. Pharmacol. Ther.* 2013;38:1365-72. (Abstract)
- Maasoumy B, Cobb B, Bremer B, et al. Detection of low HCV viraemia by repeated HCV RNA testing predicts treatment failure to triple therapy with telaprevir. *Aliment Pharmacol Ther* 2014;39:85-92. (Abstract)
- Maasoumy, B, Wedemeyer, H. Natural history of acute and chronic hepatitis C. *Best Pract Res Clin Gastroenterol* 2012;26:401-412.
- Machida K, Cheng KT, Sung VM, et al. Hepatitis C virus induces a mutator phenotype: enhanced mutations of immunoglobulin and protooncogenes. *Proc Natl Acad Sci USA* 2004;101:4262-67. (Abstract)
- Malaguarnera M, Laurino A, Di F, et al. Neuropsychiatric effects and type of IFN-alpha in chronic hepatitis C. *J Interferon Cytokine Res* 2001;21:273-78. (Abstract)
- Malcolm BA, Liu R, Lahser F, et al. SCH 503034, a mechanism-based inhibitor of hepatitis C virus NS3 protease, suppresses polyprotein maturation and enhances the antiviral activity of alpha interferon in replicon cells. *Antimicrob Agents Chemother* 2006;50:1013-20. (Abstract)
- Mangia A, Bandiera F, Montalto G, et al. Individualized treatment with combination of Peg-interferon alpha 2b and ribavirin in patients infected with HCV genotype 3. *J Hepatol* 2010a;53:1000-5. (Abstract)
- Mangia A, Dalgard O, Minerva N, et al. Ribavirin dosage in patients with HCV genotypes 2 and 3 who completed short therapy with peg-interferon alpha-2b and ribavirin. *Aliment Pharmacol Ther* 2010b;31:1346-53. (Abstract)



- Mangia A, Minerva N, Bacca D, et al. Individualized treatment duration for hepatitis C genotype 1 patients: A randomized controlled trial. *Hepatology* 2008;47:43-50. (Abstract)
- Mangia A, Santoro R, Minerva N, et al. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2005;352:2609-17. (Abstract)
- Mangia A, Thompson AJ, Santoro R, et al. An IL28B polymorphism determines treatment response of hepatitis C virus genotype 2 or 3 patients who do not achieve a rapid virologic response. *Gastroenterology* 2010;139:821-7, 827.e1. (Abstract)
- Manns MP (a), Pockros PJ, Norkrans G, et al. Long-term clearance of hepatitis C virus following interferon  $\alpha$ -2b or peginterferon  $\alpha$ -2b, alone or in combination with ribavirin. *J. Viral Hepat.* 2013;20:524-9. (Abstract)
- Manns M (b), Marcellin P, Poordad F, et al. Simeprevir (TMC435) with peginterferon/ribavirin for treatment of chronic HCV genotype -1 infection in treatment-naive patients: results from QUEST-2, a phase III trial. *Int. Liver Congr. Amsterdam, Abstr.* 1413 2013.
- Manns M, McHutchison J, Gordon S, 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;358:958-65. (Abstract)
- Manns M, Reesink H, Berg T, et al. Rapid viral response of once-daily TMC435 plus pegylated interferon/ribavirin in hepatitis C genotype-1 patients: a randomized trial. *Antivir Ther* 2011;16:1021-33. (Abstract)
- Manns M, Zeuzem S, Sood A, et al. Reduced Dose and Duration of Peginterferon Alfa-2b+Weight-Based Ribavirin in European and Asian Genotype 2 and 3 Chronic Hepatitis C Patients (Redd 2/3 Trial). *J Hepatol* 2009;50:S59-S59. (Abstract)
- Manns M, Zeuzem S, Sood A, et al. Reduced Dose and Duration of Peginterferon alfa-2b and Weight-Based Ribavirin in Patients With Genotype 2 and 3 Chronic Hepatitis C. *J Hepatol* 2011a;55:554-63. (Abstract)
- Manns MP, Felizarta F, Schiff E, et al. Overall safety profile of boceprevir plus peginterferon alfa-2b/ribavirin. *J Hepatol* 2011b;54:S183-S183.
- Manns MP, Rambusch EG. Autoimmunity and extrahepatic manifestations in hepatitis C virus infection. *J Hepatol.* 1999;31 Suppl 1:39-42.
- Manns MP, Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. *Gut* 2006;55:1350-59. (Abstract)
- Marcellin P, Craxi A, Brandao-Mello CE, et al. A 72-Week Treatment Duration with Peginterferon Alfa-2a (40kd) (Pegasys<sup>®</sup>) Plus Ribavirin (Copegus<sup>®</sup>) Has a Favorable Risk:Benefit Ratio in Non-Responders to Pegylated Interferon Alfa-2b (12kd) Plus Ribavirin: Findings of the Multinational Repeat Study. *Hepatology* 2008;48:1147A-1147A.
- Marcellin P, Forns X, Goefer T, et al. Telaprevir Is Effective Given Every 8 or 12 Hours With Ribavirin and Peginterferon Alfa-2a or -2b to Patients With Chronic Hepatitis C. *Gastroenterology* 2011;140:459-68 (Abstract)
- Marcellin P, Gish RG, Gitlin N, et al. Safety and efficacy of virmidine versus ribavirin in vizer2: randomized, double-blind study in therapy-naive hepatitis C patients. *J Hepatol* 2010;52:32-8. (Abstract)
- Margin S, Craxi A, Fabiano C, et al. Hepatitis C viraemia in chronic liver disease: relationship to interferon alpha or corticosteroid treatment. *Hepatology* 1994;19:273-79. (Abstract)
- Marrone A, Zampino R, D'Onofrio M, et al. Combined interferon plus lamivudine treatment in young patients with dual HBV (HBeAg positive) and HCV chronic infection. *J Hepatol* 2004;41:1064-5. (Abstract)
- Matsumori A, Yutani C, Ikeda Y, Kawai S, Sasayama S. Hepatitis C virus from the hearts of patients with myocarditis and cardiomyopathy. *Lab Invest* 2000;80:1137-42. (Abstract)

- Matsuo K, Kusano A, Sugumar A, Nakamura S, Tajima K, Mueller NE. Effect of hepatitis C virus infection on the risk of non-Hodgkin's lymphoma: a meta-analysis of epidemiological studies. *Cancer Sci* 2004;95:745-52. (Abstract)
- Matthews GV, Pham ST, Hellard M, et al. Patterns and characteristics of hepatitis C transmission clusters among HIV-positive and HIV-negative individuals in the Australian trial in acute hepatitis C. *Clin Infect Dis*. 2011;52:803-11. (Abstract)
- Mauss S, Berger F, Schober A, et al. Screening for autoantibodies in chronic hepatitis C patients has no effect on treatment initiation or outcome. *J Viral Hepatitis* 2013, in press.
- Mauss S, Valenti W, DePamphilis J, et al. Risk factors for hepatic decompensation in patients with HIV/HCV coinfection and liver cirrhosis during interferon-based therapy. *AIDS* 2004;18:F21-25. (Abstract)
- McCown MF, Rajyaguru S, Kular S, et al. GT-1a or GT-1b subtype-specific resistance profiles for hepatitis C virus inhibitors telaprevir and HCV-796. *Antimicrob Agents Chemother* 2009;53:2129-32. (Abstract)
- McHutchison JG, Dusheiko G, Shiffman ML, et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. *N Engl J Med* 2007;357:2227-36. (Abstract)
- McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med* 2009;360:1827-38. (Abstract)
- McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon Alfa-2b or Alfa-2a with Ribavirin for Treatment of Hepatitis C Infection. *N Engl J Med* 2009;361:580-593.
- McHutchison JG, Manns M, Patel K, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterol* 2002;123:1061-69. (Abstract)
- McHutchison JG, Manns MP, Muir AJ, et al. Telaprevir for previously treated chronic HCV infection. *N Engl J Med* 2010;362:1292-303. (Abstract)
- McLauchlan J, Lemberg MK, Hope G, et al. Intramembrane proteolysis promotes trafficking of hepatitis C virus core protein to lipid droplets. *EMBO J* 2002;21:3980-88. (Abstract)
- McPhee F, Hernandez D, Yu F, et al. Resistance analysis of hepatitis C virus genotype 1 prior treatment null responders receiving daclatasvir and asunaprevir. *Hepatology* 2013;58:902-11.
- Mederacke I, Wedemeyer H, Ciesek S, et al. Performance and clinical utility of a novel fully automated quantitative HCV-core antigen assay. *J Clin Virol* 2009;46:210-5. (Abstract)
- Medici MC, Furlini G, Rodella A, et al. Hepatitis C virus core antigen: analytical performances, correlation with viremia and potential applications of a quantitative, automated immunoassay. *J Clin Virol* 2011;51:264-9. (Abstract)
- Meer AJ van der, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012;308:2584-93. (Abstract)
- Meertens L, Bertaux C, Dragic T. Hepatitis C virus entry requires a critical postinternalization step and delivery to early endosomes via clathrin-coated vesicles. *J Virol* 2006;80:11571-78. (Abstract)
- Merican I, Sherlock S, McIntyre N, Dusheiko GM. Clinical, biochemical and histological features in 102 patients with chronic hepatitis C virus infection. *Q J Med* 1993;86:119-25. (Abstract)
- Meylan E, Curran J, Hofmann K, et al. Cardif is an adaptor protein in the RIG-I antiviral pathway and is targeted by hepatitis C virus. *Nature* 2005;437:1167-72. (Abstract)
- Michelin BD, Muller Z, Stezl E, Marth E et al. Evaluation of the Abbott Real Time HCV assay for quantitative detection of hepatitis C virus RNA. *J Clin Virol* 2007;38:96-100. (Abstract)

- Mimms LT, Mosley JW, Hollinger FB, et al. Effect of concurrent acute infection with hepatitis C virus on acute hepatitis B virus infection. *BMJ* 1993;307:1095-7. (Abstract)
- Miyani Y, Atsuzawa K, Usuda N, et al. The lipid droplet is an important organelle for hepatitis C virus production. *Nat Cell Biol* 2007;9:961-69. (Abstract)
- Mohamed Ael S, al Karawi MA and Mesa GA Dual infection with hepatitis C and B viruses: clinical and histological study in Saudi patients. *Hepatogastroenterology* 1997;44:1404-6. (Abstract)
- Mohamed Ael S, al Karawi MA, Mesa GA. Dual infection with hepatitis C and B viruses: clinical and histological study in Saudi patients. *Hepatogastroenterology* 1997;44:1404-6. (Abstract)
- Mohd Hanafiah K, Groeger J, Flaxman AD, et al. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology* 2013;57:1333-42. (Abstract)
- Moradpour D, Penin F, Rice CM. Replication of hepatitis C virus. *Nat Rev Microbiol* 2007;5:453-63. (Abstract)
- Moradpour D, Penin F. Hepatitis C virus proteins: from structure to function. *Current topics in microbiology and immunology* 2013;369:113-42.
- Morgan TR, Ghany MG, Kim HY, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. *Hepatology* 2010;52:833-44. (Abstract)
- Morota K, Fujinami R, Kinukawa H, et al. A new sensitive and automated chemiluminescent microparticle immunoassay for quantitative determination of hepatitis C virus core antigen. *J Virol Methods* 2009;157:8-14. (Abstract)
- Moucarri R, Asselah T, Cazals-Hatem D, et al. Insulin resistance in chronic hepatitis C: Association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. *Gastroenterol* 2008;134:416-23. (Abstract)
- Muir AJ, Poordad FF, McHutchison JG, et al. Retreatment with telaprevir combination therapy in hepatitis C patients with well-characterized prior treatment response. *Hepatology* 2011;54:1538-46. (Abstract)
- Muir AJ, Shiffman ML, Zaman A, et al. Phase 1b study of pegylated interferon lambda 1 with or without ribavirin in patients with chronic genotype 1 hepatitis C virus infection. *Hepatology* 2010;52:822-32. (Abstract)
- Muir AJ, Shiffman ML, Zaman A, et al. Phase 1b study of pegylated interferon lambda 1 with or without ribavirin in patients with chronic genotype 1 hepatitis C virus infection. *Hepatology* 2010;52:822-32.
- Musselman DL, Lawson DH, Gumnick JF, et al. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med* 2001;344:961-66. (Abstract)
- Nattermann J, Vogel M, Nischalke HD, et al. Genetic Variation in IL28B and Treatment-Induced Clearance of Hepatitis C Virus in HIV-Positive Patients With Acute and Chronic Hepatitis C. *J Infect Dis*. 2011;203:595-601. (Abstract)
- Neff GW, Montalbano M, O'Brien CB, et al. Treatment of established recurrent hepatitis C in liver-transplant recipients with pegylated interferon-alfa-2b and ribavirin therapy. *Transplantation* 2004;78:1303-07.
- Nelson D, Poordad F, Feld J, et al. High SVR rates (SVR4) for 12-week total telaprevir combination therapy in IL28b cc treatment-naives and prior relapsers with G1 chronic hepatitis C: CONCISe interim analysis. *Hepatology* 2013;58:Abstract 881.
- Nelson DR, Gane EJ, Jacobson IM, Di Bisceglie AM, Alves K, Koziel MJ. VX-222/Telaprevir in combination with peginterferon-alfa-2a and ribavirin in treatment-naive genotype 1 HCV patients treated for 12 weeks: Zenith study, SVR 12 interim analyses. *Hepatology* 2011;54:1442.

- Nettles RE, Gao M, Bifano M, et al. Multiple ascending dose study of BMS-790052, an NS5A replication complex inhibitor, in patients infected with hepatitis C virus genotype 1. *Hepatology* 2011, in press.
- Nguyen LH, Ko S, Wong SS, et al. Ethnic differences in viral dominance patterns in patients with hepatitis B virus and hepatitis C virus dual infection. *Hepatology* 2011;53:1839-45.
- Nolte FS, Fried MW, Shiffman ML, et al. Prospective multicenter clinical evaluation of AMPLICOR and COBAS AMPLICOR hepatitis C virus tests. *J Clin Microbiol* 2001;39:4005-12. (Abstract)
- Nomura H, Tanimoto H, Kajiwara E, et al. Factors contributing to ribavirin-induced anemia. *J Gastroenterol Hepatol* 2004;19:1312-7. (Abstract)
- Ohto H, Terazawa S, Sasaki N, et al. Transmission of hepatitis C virus from mothers to infants. The Vertical Transmission of Hepatitis C Virus Collaborative Study Group. *N Engl J Med* 1994;330:744-50. (Abstract)
- Opravit M, Sasadeusz J, Cooper DA, et al. Effect of baseline CD4 cell count on the efficacy and safety of peg-interferon- $\alpha$  2a (40 kd) + ribavirin in patients with HIV-HCV coinfection. *J Acquir Immune Def Syndr* 2008;47:36-49. (Abstract)
- Osinusi A, Meissner EG, Lee Y-J, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. *JAMA* 2013;310:804-11. (Abstract)
- Ozaslan E, Purnak T. Controversies about occult hepatitis B virus infection. *World J Gastroenterol* 2009;15:4986-7. (Abstract)
- Paba B, Fabeni L, Perno CF, Ciotti M. Performance evaluation of the Artus hepatitis C virus QS-RGQ assay. *J Virol Methods* 2012, 179:77-80.
- Pallas JR, Farinas-Alvarez C, Prieto D, et al. Coinfections by HIV, hepatitis B and hepatitis C in imprisoned injecting drug users. *Eur J Epidemiol* 1999;15:699-704. (Abstract)
- Pariante CM, Landau S, Carpiniello B. Interferon alfa-induced adverse effects in patients with a psychiatric diagnosis. *N Engl J Med* 2002;347:148-49. (Abstract)
- Pawlotsky JM, Chevalier S, McHutchinson JG. The hepatitis C virus life cycle as a target for new antiviral therapies. *Gastroenterology* 2007;132:1979-98. (Abstract)
- Pawlotsky JM, Flisiak R, Rasenack J, et al. Once daily alisporivir interferon-free regimens achieve high rates of early HCV clearance in previously untreated patients with HCV genotype 2 or 3. *Hepatology* 2011;54:1074.
- Pawlotsky JM, Sarin SK, Foster G, Peng CY, Rasenack J, Flisiak R. Alisporivir plus ribavirin achieves high rates of sustained HCV clearance (SVR24) as interferon (IFN)-free or IFN-add-on regimen in treatment-naive patients with HCV GT2 or GT3: Final results from VITAL-1 study. *Hepatology* 2012;56:309.
- Pawlotsky JM. Use and interpretation of hepatitis C virus diagnostic assays. *Clin Liver Dis* 2003b;7:127-37. (Abstract)
- Paydas S, Seyrek N, Gonlusen G, Saglikler Y. The frequencies of hepatitis B virus markers and hepatitis C virus antibody in patients with glomerulonephritis. *Nephron* 1996;74:617-19. (Abstract)
- Pearlman BL, Ehleben C, Saifee S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis c genotype 1-infected slow responders. *Hepatol* 2007;46:1688-94. (Abstract)
- Pearlman BL, Ehleben C. Hepatitis C genotype 1 virus with low viral load and rapid virologic response to peginterferon/ribavirin obviates a protease inhibitor. *Hepatology* 2014;59:71-7. (Abstract)
- Pearlman, B, Ehlebenet, C. B Pearlman and C Ehlebenet. Hepatitis C virus (HCV) genotype 1 (G1) infection with low viral load (LVL) and rapid virologic response (RVR) to

- peginterferon and ribavirin (PEG/RBV) can be treated without a protease inhibitor (PI), irrespective of IL-28B status or patient ethnicity. *Hepatology* 56:Abstract: A151.
- Perry W, Hilsabeck RC, Hassanein TI. Cognitive dysfunction in chronic hepatitis C: a review. *Dig Dis Sci* 2008;53:307-21. (Abstract)
- Peters L, Mocroft A, Soriano V, et al and the EuroSIDA Study Group. Hepatitis C virus coinfection does not influence the CD4 cell recovery in HIV-1-infected patients with maximum virologic suppression. *J Acquir Immune Defic Syndr* 2009;50:457-63. (Abstract)
- Petrarca A, Rigacci L, Caini P, et al. Safety and efficacy of rituximab in patients with hepatitis C virus-related mixed cryoglobulinemia and severe liver disease. *Blood* 2010;116:335-42. (Abstract)
- Pileri P, Uematsu Y, Campagnoli S, et al. Binding of hepatitis C virus to CD81. *Science* 1998;282:938-41. (Abstract)
- Planas R, Balleste B, Alvarez MA, et al. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. *J Hepatol* 2004;40:823-30. (Abstract)
- Ploss A, Evans MJ, Gaysinskaya VA, et al. Human occluding is a hepatitis C virus entry factor required for infection of mouse cells. *Nature* 2009;457:882-86. (Abstract)
- Pockros P, Jensen DM, Tsai N. First SVR data with the nucleoside analogue polymerase inhibitor mericitabine (RG7128) combined with peginterferon/ribavirin in treatment-naïve HCV G1/4 patients: interim analysis of the JUMP-C trial. *J Hepatol* 2011;54:538.
- Pockros P, Nelson D, Godofsky E, et al. High relapse rate seen at week 72 for patients treated with R1626 combination therapy. *Hepatol* 2008a;48:1349-50. (Abstract)
- Pockros PJ, Nelson D, Godofsky E, et al. R1626 plus peginterferon Alfa-2a provides potent suppression of hepatitis C virus RNA and significant antiviral synergy in combination with ribavirin. *Hepatol* 2008b;48:385-97. (Abstract)
- Pockros PJ, Shiffman ML, Schiff ER, et al and the PROACTIVE Study Group. Epoetin alfa improves quality of life in anemic HCV-infected patients receiving combination therapy. *Hepatol* 2004;40:1450-8. (Abstract)
- Poizot-Martin I. W48 Response Rate of Boceprevir-PegIFN-RBV in Treatment-Experienced HIV Coinfected Patients with HCV genotype 1: ANRS-HC27 BocepreVIH Study. 64th Annual Meeting of the American Association for the Study of Liver diseases, November 1-5, 2013, Washington, USA; abstract 1105
- Pol S, Aerssens J, Zeuzem S, et al. Similar SVR rates in IL28b cc, ct or tt prior relapser, partial- or null-responder patients treated with telaprevir/peginterferon/ribavirin: retrospective analysis of the realize study. *J Hepatol* 2011a;54:S6-S7.
- Pol S, Ghalib RH, Rustgi VK, et al. Daclatasvir for previously untreated chronic hepatitis C genotype-1 infection: a randomised, parallel-group, double-blind, placebo-controlled, dose-finding, phase 2a trial. *The Lancet infectious diseases* 2012;12:671-7.
- Pol S, Roberts SK, Andreone P, et al. Efficacy and safety of telaprevir-based regimens in cirrhotic patients with hcv genotype 1 and prior peginterferon/ribavirin treatment failure: subanalysis of the realize phase III study. *Hepatology* 2011b;54:374A-375A.
- Poordad F, Bronowicki JP, Gordon SC, et al. IL28b polymorphism predicts virologic response in patients with hepatitis c genotype 1 treated with boceprevir (boc) combination therapy. *J Hepatol* 2011;54:S6-S6.
- Poordad F, Lawitz E, Kowdley KV, et al. Exploratory study of oral combination antiviral therapy for hepatitis C. *N Engl J Med* 2013;368:45-53.
- Poordad F, McCone J, Bacon B, et al. Boceprevir combined with peginterferon alfa-2B/ribavirin for treatment-naïve patients with hepatitis C virus genotype (G) 1: SPRINT-2 final results. *Hepatol* 2010;50:S402.
- Poordad F, McCone JJ, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011;364:1195-206. (Abstract)

- Poordad, F, Bronowicki, JP, Gordon, SC et al. Factors that predict response of patients with hepatitis C virus infection to boceprevir. *Gastroenterology* 2012;143:608-18.e1-5.
- Potthoff A, Berg T, Wedemeyer H, et al. Late hepatitis B virus relapse in patients co-infected with hepatitis B virus and hepatitis C virus after antiviral treatment with pegylated interferon- $\alpha$ 2b and ribavirin. *Scand J Gastroenterol* 2009;44:1487-90. (Abstract)
- Potthoff A, Wedemeyer H, Boecher WO, et al. The HEP-NET B/C co-infection trial: A prospective multicenter study to investigate the efficacy of pegylated interferon- $\alpha$ 2b and ribavirin in patients with HBV/HCV co-infection. *J Hepatol* 2008;49:688-94. (Abstract)
- Poustchi H, Negro F, Hui J, Cua IH, Brandt LR, Kench JG, George J. Insulin resistance and response to therapy in patients infected with chronic hepatitis C virus genotypes 2 and 3. *J Hepatol* 2008;48:28-34. (Abstract)
- Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet* 1997;349:825-32. (Abstract)
- Poynard T, Colombo M, Bruix J, et al. Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. *Gastroenterol* 2009;136:1618-28. (Abstract)
- Prokunina-Olsson L, Muchmore B, Tang W, et al. A variant upstream of IFNL3 (IL28B) creating a new interferon gene IFNL4 is associated with impaired clearance of hepatitis C virus. *Nat. Genet.* 2013;45:164-71. (Abstract)
- Prummel MF, Laurberg P. Interferon-alpha and autoimmune thyroid disease. *Thyroid* 2003;13:547-51. (Abstract)
- Qurishi N, Kreuzberg C, Lüchters G, et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C coinfection. *Lancet* 2003;362:1708-13. (Abstract)
- Raimondo G, Brunetto MR, Pontisso P, et al. Longitudinal evaluation reveals a complex spectrum of virological profiles in hepatitis B virus/hepatitis C virus-coinfected patients. *Hepatology* 2006;43:100-7. (Abstract)
- Raison CL, Woolwine BJ, Demetrashvili MF, et al. Paroxetine for prevention of depressive symptoms induced by interferon-alpha and ribavirin for hepatitis C. *Aliment Pharmacol Ther* 2007;25:1163-74. (Abstract)
- Rallón NI, Soriano V, Naggie S, et al. IL28B gene polymorphisms and viral kinetics in HIV/hepatitis C virus-coinfected patients treated with pegylated interferon and ribavirin. *AIDS.* 2011;25:1025-33. (Abstract)
- Ramos-Casals M, Stone JH, Cid MC, Bosch X. The cryoglobulinaemias. *Lancet* 2012;379:348-60.
- Rauch A, Kutalik Z, Descombes P, et al. Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. *Gastroenterology* 2010;138:1338-45. (Abstract)
- Reddy GA, Dakshinamurthy KV, Neelaprasad P, et al. Prevalence of HBV and HCV dual infection in patients on haemodialysis. *Indian J Med Microbiol* 2005;23:41-3. (Abstract)
- Reddy KR, Shiffman ML, Morgan TR, et al. Impact of ribavirin dose reductions in hepatitis C virus genotype 1 patients completing peginterferon alfa-2a/ribavirin treatment. *Clin Gastroenterol Hepatol* 2007;5:124-29. (Abstract)
- Reesink HW, Fanning GC, Farha KA, et al. Rapid HCV-RNA decline with once daily TMC435: a phase I study in healthy volunteers and hepatitis C patients. *Gastroenterol* 2010;138:913-21. (Abstract)
- Reesink HW, Fanning GC, Farha KA, et al. Rapid HCV-RNA decline with once daily TMC435: a phase I study in healthy volunteers and hepatitis C patients. *Gastroenterology* 2010;138:913-21. (Abstract)

- Reesink HW, Zeuzem S, Weegink CJ, et al. Rapid decline of viral RNA in hepatitis C patients treated with VX-950: a phase Ib, placebo-controlled, randomized study. *Gastroenterol* 2006;131:997-1002. (Abstract)
- Reiser M, Hinrichsen H, Benhamou Y, et al. Antiviral efficacy of NS3-serine protease inhibitor BILN-2061 in patients with chronic genotype 2 and 3 hepatitis C. *Hepatol* 2005;41:832-5. (Abstract)
- Renault PF, Hoofnagle JH, Park Y, et al. Psychiatric complications of long-term interferon alfa therapy. *Arch Intern Med* 1987;147:1577-80. (Abstract)
- Resino S, Asensio C, Bellón JM, et al. Diagnostic accuracy of the APRI, FIB-4, and the Forns index for predicting liver fibrosis in HIV/HCV-coinfected patients: A validation study. *J Infect.* 2011;63:402-5. (Abstract)
- RKI. Hepatitis C: RKI-Ratgeber Infektionskrankheiten. *Epidemiologisches Bulletin* 2004;17:141.
- Roberts SK, Andreone P, Pol S, et al. Impact of anemia and ribavirin dose reduction on svr to a telaprevir-based regimen in patients with hcv genotype 1 and prior peginterferon/ribavirin treatment failure in the phase III realize study. *Hepatology* 2011;54:1007A-1008A.
- Roccatello D, Baldovino S, Rossi D, et al. Long-term effects of anti-CD20 monoclonal antibody treatment of cryoglobulinaemic glomerulonephritis. *Nephrol Dial Transplant* 2004;19:3054-61. (Abstract)
- Rockstroh J, Nelson M, Soriano V, et al. STARTVerso4 phase III trial of faldaprevir plus pegylated interferon a-2a and ribavirin in patients with HIV and HCV genotype 1 co-infection. *Hepatology* 2013;58:741.
- Rockstroh J, Grint D, Boesecke C, et al. Increases in acute hepatitis C (HCV) incidence across Europe: which regions and patient groups are affected? : which regions and patient groups are affected? *J Int AIDS Soc* 2012;15:18116.
- Rockstroh J. Highly active antiretroviral therapy in HIV and hepatitis C coinfecting individuals: friend or foe? *Curr Opin HIV AIDS.* 2007 Nov;2(6):449-53
- Rockstroh JK, Bhagani S, Benhamou Y, et al. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults. *HIV Med* 2008;9:82-8. (Abstract)
- Rockstroh JK, Mocroft A, Soriano V, et al. Influence of Hepatitis C virus infection on HIV-1 disease progression and response to highly active antiretroviral therapy. *J Infect Dis* 2005;192:992-1002. (Abstract)
- Rockstroh JK. Hot topics in HIV and hepatitis coinfection: noninvasive diagnosis of liver disease, liver transplantation, and new drugs for treatment of hepatitis coinfection. *HIV Clin Trials* 2009b;10:110-5. (Abstract)
- Rodriguez-Luna H, Khatib A, Sharma P, et al. Treatment of recurrent hepatitis C infection after liver transplantation with combination of pegylated interferon alpha2b and ribavirin: an open-label series. *Transplantation* 2004;77:190-94. (Abstract)
- Rodriguez-Novoa S, Morello J, Gonzalez M, et al. Increase in serum bilirubin in HIV/hepatitis C virus coinfecting patients on atazanavir therapy following initiation of pegylated interferon and ribavirin. *AIDS* 2008;22:2535-7. (Abstract)
- Rodriguez-Torres M, Slim J, Bhatti L, et al. Standard versus high dose ribavirin in combination with peginterferon alfa-2a (40KD) in genotype 1 (G1) HCV patients coinfecting with HIV: Final results of the PARADIGM study. *AASLD 2009, Abstr* 1561.
- Romano KP, Ali A, Aydin C, et al. The molecular basis of drug resistance against hepatitis C virus NS3/4A protease inhibitors. *PLoS pathogens* 2012;8:e1002832.
- Rossignol JF, Elfert A, El-Gohary Y, Keeffe EB. Improved virologic response in chronic hepatitis C genotype 4 treated with nitazoxanide, peginterferon, and ribavirin. *Gastroenterol* 2009;136:856-62. (Abstract)

- Rumi MG, Aghemo A, Prati GM, et al. Randomized study of peginterferon-alpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis C. *Gastroenterology* 2010;138:108-15. (Abstract)
- Saadoun D, Asselah T, Resche-Rigon M, et al. Cryoglobulinemia is associated with steatosis and fibrosis in chronic hepatitis C. *Hepatology* 2006;43:1337-45. (Abstract)
- Saadoun D, Resche-Rigon M, Sene D, et al. Rituximab plus Peg-interferon-alpha/ribavirin compared with Peg-interferon-alpha/ribavirin in hepatitis C-related mixed cryoglobulinemia. *Blood* 2010;116:326-34. (Abstract)
- Saadoun D, Resche-Rigon M, Sene D, Perard L, Piette JC, Cacoub P. Rituximab combined with Peg-Interferon-Ribavirin in refractory HCV-associated cryoglobulinemia vasculitis. *Ann Rheum Dis* 2008;67:1431-36. (Abstract)
- Saadoun D, Rosenzweig M, Joly F, et al. Regulatory T-cell responses to low-dose interleukin-2 in HCV-induced vasculitis. *N Engl J Med* 2011;365:2067-77. (Abstract)
- Saadoun D, Pol S, Lebray P et al. Peg-IFNalpha/Ribavirin/Protease inhibitor combination is highly effective in HCV-mixed cryoglobulinemia vasculitis. *Hepatology* 2012;56:Abstract: A790.
- Sabato MF, Shiffman ML, Langley MR, et al. Comparison of Performance Characteristics of three Real Time Reverse Transcription-PCR test systems for detection and quantification of hepatitis C virus. *J Clin Microbiol* 2007;45:2529-36. (Abstract)
- Sagnelli E, Coppola N, Messina V, et al. HBV superinfection in hepatitis C virus chronic carriers, viral interaction, and clinical course. *Hepatology* 2002;36:1285-91. (Abstract)
- Sagnelli E, Coppola N, Scolastico C, et al. HCV genotype and "silent" HBV coinfection: two main risk factors for a more severe liver disease. *J Med Virol* 2001;64:350-5. (Abstract)
- Sainz Jr. B, Barretto N, Martin DN, et al. Identification of the Niemann-Pick C1-like cholesterol absorption receptor as a new hepatitis C virus entry factor. *Nat Med* 2012;18:281-5.
- Sanchez-Tapias JM, Diago M, Escartin P, et al. Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. *Gastroenterol* 2006;131:451-60. (Abstract)
- Sangiovanni A, Prati GM, Fasani P, et al. The natural history of compensated cirrhosis due to hepatitis C virus: A 17-year cohort study of 214 patients. *Hepatology* 2006;43:1303-10. (Abstract)
- Santantonio T, Fasano M, Sinisi E, et al. Efficacy of a 24-week course of PEG-interferon alpha-2b monotherapy in patients with acute hepatitis C after failure of spontaneous clearance. *J Hepatol* 2005;42:329-33. (Abstract)
- Sarrazin C, Berg T, Cornberg M, et al. [Expert opinion on boceprevir- and telaprevir-based triple therapies of chronic hepatitis C]. *Z. Gastroenterol.* 2012;50:57-72. (Abstract)
- Sarrazin C, Berg T, Ross RS, et al. [Prophylaxis, diagnosis and therapy of hepatitis C virus (HCV) infection: the German guidelines on the management of HCV infection]. *Z Gastroenterol* 2010a;48:289-351. (Abstract)
- Sarrazin C, Diernynck I, Cloherty G, et al. Appropriate use of Abbott RealTime HCV RNA Assay in the Management of HCV patients treated with telaprevir-based regimen: a retrospective analysis of the OPTIMIZE study. Presented at Hep Dart 2013.
- Sarrazin C, Hendricks DA, Sedarati F, Zeuzem S. Assessment, by transcription-mediated amplification, of virologic response in patients with chronic hepatitis C virus treated with peginterferon alpha-2a. *J Clin Microbiol* 2001;39:2850-5. (Abstract)
- Sarrazin C, Kieffer TL, Bartels D, et al. Dynamic hepatitis C virus genotypic and phenotypic changes in patients treated with the protease inhibitor telaprevir. *Gastroenterol* 2007a;132:1767-77. (Abstract)



- Sarrazin C, Rouzier R, Wagner F, et al. SCH 503034, a novel hepatitis C virus protease inhibitor, plus pegylated interferon alpha-2b for genotype 1 nonresponders. *Gastroenterol* 2007b;132:1270-8. (Abstract)
- Sarrazin C, Schwendy S, Moller B, et al. Improved responses to pegylated interferon alfa-2b and ribavirin by individualizing treatment for 24-72 weeks. *Gastroenterology* 2011a;141:1656-64. (Abstract)
- Sarrazin C, Susser S, Doehring A, et al. Importance of IL28B gene polymorphisms in hepatitis C virus genotype 2 and 3 infected patients. *J Hepatol* 2011b;54:415-21. (Abstract)
- Sarrazin C, Teuber G, Kokka R, et al. Detection of residual hepatitis C virus RNA by transcription-mediated amplification in patients with complete virologic response according to polymerase chain reaction-based assays. *Hepatology* 2000;32:818-23. (Abstract)
- Sarrazin C, Zeuzem S. Resistance to direct antiviral agents in patients with hepatitis C virus infection. *Gastroenterology* 2010b;138:447-62. (Abstract)
- Sarrazin C. Highly sensitive hepatitis C virus RNA detection methods: molecular backgrounds and clinical significance. *J Clin Virol* 2002;25:S23-9. (Abstract)
- Sato S, Fujiyama S, Tanaka M, et al. Coinfection of hepatitis C virus in patients with chronic hepatitis B infection. *J Hepatol* 1994;21:159-66. (Abstract)
- Scarselli E, Ansuini H, Cerino R, et al. The human scavenger receptor class B type I is a novel candidate receptor for the hepatitis C virus. *EMBO J* 2002;21:5017-25. (Abstract)
- Schaefer A, Wittchen HU, Seufert J, Kraus MR. Methodological approaches in the assessment of interferon-alfa-induced depression in patients with chronic hepatitis C - a critical review. *Int J Methods Psychiatr Res* 2007a;16:186-201. (Abstract)
- Schaefer M, Sarkar S, Knop V, et al. Escitalopram for the Prevention of Peginterferon-2a-Associated Depression in Hepatitis C Virus-Infected Patients Without Previous Psychiatric Disease. A Randomized Trial. *Ann Intern Med*, 2012; 157: 94-103.
- Schaefer M, Capuron L, Friebe A, et al. Hepatitis C infection, antiviral treatment and Mental Health: A European Expert Consensus Statement. *J Hepatol*, 2012; 57:1379-90.
- Schaefer M, Engelbrecht MA, Gut O, et al. Interferon alpha [IFNalpha] and psychiatric syndromes: a review. *Prog Neuropsychopharmacol Biol Psychiat* 2002;26:731-46. (Abstract)
- Schaefer M, Heinz A, Backmund M. Treatment of chronic hepatitis C in patients with drug dependence: time to change the rules? *Addiction* 2004;99:1167-75. (Abstract)
- Schaefer M, Hinzpeter A, Mohmand A, et al. Hepatitis C treatment in "difficult-to-treat" psychiatric patients with pegylated interferon-alpha and ribavirin: Response and psychiatric side effects. *Hepatol* 2007b;46:991-98. (Abstract)
- Schaefer M, Mauss S. Clinical management of Interferon-alpha-associated psychiatric side effects during hepatitis C treatment in patients with drug addiction. *Cur Drug Abuse Rev* 2008;1:177-87. (Abstract)
- Schaefer M, Schmidt F, Folwaczny C, et al. Adherence and mental side effects during hepatitis C treatment with interferon alfa and ribavirin in psychiatric risk groups. *Hepatol* 2003;37:443-51. (Abstract)
- Schaefer M, Schwaiger M, Garkisch AS, et al. Prevention of interferon-alpha associated depression in psychiatric risk patients with chronic hepatitis C. *J Hepatol* 2005;42:793-8. (Abstract)
- Schiff E, Poordad E, Jacobson I, et al. Boceprevir (B) combination therapy in null responders (NR): Response dependent on interferon responsiveness. *J Hepatol* 2008;48:S46-S46.
- Schmidt AJ, Rockstroh JK, Vogel M, et al. Trouble with bleeding: risk factors for acute hepatitis C among HIV-positive gay men from Germany--a case-control study. *PLoS One* 2011;6:e17781. (Abstract)

- Schutten M, Fries E, Burghoorn-Maas C, Niesters HG. Evaluation of the analytical performance of the new Abbott RealTime RT-PCRs for the quantitative detection of HCV and HIV-1 RNA. *J Clin Virol* 2007;40:99-104. (Abstract)
- Senturk H, Tahan V, Canbakan B, et al. Chronic hepatitis C responds poorly to combination therapy in chronic hepatitis B carriers. *Neth J Med* 2008;66:191-5. (Abstract)
- Senzolo M, Schiff S, D'Aloiso CM, Crivellin C, Cholongitas E, Burra P, et al. Neuropsychological alterations in hepatitis C infection : The role of inflammation. *World J Gastroenterol* 2011;17:3369-74.
- Serfaty L, Fornis X, Goeser T, et al. No impact of insulin resistance on antiviral efficacy of telaprevir-based regimen in hcv genotype 1 treatment-naive patients: sub-analysis of c208 study. *Hepatology* 2010;52:705A-705A.
- Seyam MS, Freshwater DA, O'Donnell K, Mutimer DJ. Weight loss during pegylated interferon and ribavirin treatment of chronic hepatitis C. *J Viral Hepat* 2005;12:531-5. (Abstract)
- SeyedAlinaghi S, Jam S, Mehrkhani F, et al. Hepatitis-C and hepatitis-B co-infections in patients with human immunodeficiency virus in Tehran, Iran. *Acta Med Iran* 2011; 49:252-7. (Abstract)
- Shavinskaya A, Boulant S, Penin F, et al. The lipid droplet binding domain of hepatitis C virus core protein is a major determinant for efficient virus assembly. *J Biol Chem* 2007;282:37158-69. (Abstract)
- Sherman KE, Flamm SL, Afdhal NH, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med* 2011;365:1014-24. (Abstract)
- Sherman KE, Flamm SL, Afdhal NH, et al. Telaprevir in combination with peginterferon alfa-2a and ribavirin for 24 or 48 weeks in treatment-naive genotype 1 HCV patients who achieved an extended rapid viral response: final results of phase 3 ILLUMINATE study. *Hepatology* 2010;52:S401. (Abstract)
- Sherman KE, Rockstroh JK, Dieterich DT, et al. Telaprevir in Combination with Peginterferon Alfa-2a/Ribavirin in HCV/HIV Coinfected Patients: A 24-Week Treatment Interim Analysis. The 62nd Annual Meeting of the American Association for the Study of Liver Diseases 2011, San Francisco, USA. Abstract LB-8.
- Sherman KE, Sulkowski M, Zoulim F, Alberti A. Follow-up of SVR durability and viral resistance in patients with chronic hepatitis C treated with telaprevir-based regimens: interim analysis of the extend study. *Hepatology* 2011;54:1471.
- Sherman KE, Sulkowski MS, Zoulim F, et al. Follow-up of svr durability and viral resistance in patients with chronic hepatitis c treated with telaprevir-based regimens: interim analysis of the extend study. *Hepatology* 2011;54:485A-486A.
- Shi ST, Polyak SJ, Tu H, et al. Hepatitis C virus NS5A colocalizes with the core protein on lipid droplets and interacts with apolipoproteins. *Virology* 2002;292:198-210. (Abstract)
- Shiffman ML, Di Bisceglie AM, Lindsay KL, et al. Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. *Gastroenterology* 2004;126:1015-23. (Abstract)
- Shiffman ML, Hofmann CM, Luketic VA, Sanyal AJ. Use of granulocyte macrophage colony stimulating factor alone or in combination with interferon-alpha-2b for treatment of chronic hepatitis C. *J Hepatology* 1998;28:382-89. (Abstract)
- Shiffman ML, Salvatore J, Hubbard S, et al. Treatment of chronic hepatitis C virus genotype 1 with peginterferon, ribavirin, and epoetin alpha. *Hepatology* 2007;46:371-9. (Abstract)
- Shiffman ML, Suter F, Bacon BR, et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2007;357:124-34. (Abstract)
- Silva M, Kasserra C, Gupta S, Treitel MA, Hughes E, O'Mara E. Antiviral Activity of Boceprevir Monotherapy in Treatment-Naive Subjects With Chronic Hepatitis C Genotype 2/3. APASL 2011.

- Silvestri F, Barillari G, Fanin R, et al. Hepatitis C virus infection among cryoglobulinemic and non-cryoglobulinemic B-cell non-Hodgkin's lymphomas. *Haematologica* 1997;82:314-7. (Abstract)
- Simmonds P, Bukh J, Combet C, et al. Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes. *Hepatology* 2005;42:962-73. (Abstract)
- Smith DB, Bukh J, Kuiken C, et al. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes : Updated criteria and genotype assignment web resource. *Hepatology* 2014 ;59:318-27.
- Sofia MJ, Bao D, Chang W, et al. Discovery of a  $\beta$ -d-2'-deoxy-2'- $\alpha$ -fluoro-2'- $\beta$ -C-methyluridine nucleotide prodrug (PSI-7977) for the treatment of hepatitis C virus. *J. Med. Chem.* 2010;53:7202-18. (Abstract)
- Soriano A, Gane E, Angus PW, et al. Efficacy and safety of the interferon (IFN)-free combination of BI 201335 + BI 207127 +/- ribavirin (RBV) in treatment-naïve patients with HCV genotype 1 infection and compensated liver cirrhosis: results from the SOUND-C2 study. *Hepatology* 2012;56:234.
- Soto B, Sanchez-Quijano A, Rodrigo L, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J Hepatol* 1997;26:1-5. (Abstract)
- Sterling RK, Stravitz RT, Luketic VA, et al. A comparison of the spectrum of chronic hepatitis C virus between Caucasians and African Americans. *Clin Gastroenterol Hepatol* 2004;2:469-73. (Abstract)
- Sulkowski M (a), Rodriguez-Torres M, Lalezari JP, et al. All-Oral Therapy With Sofosbuvir Plus Ribavirin For the Treatment of HCV Genotype 1, 2, and 3 Infection in Patients Co-infected With HIV (PHOTON-1). *Hepatology* 2013;58:313A, Abstract 212.
- Sulkowski M, Gardiner D, Rodriguez-Torres M, et al. Daclatasvir plus Sofosbuvir for Previously Treated or Untreated Chronic HCV Infection. *N Engl J Med* 2014:211-221. (Abstract)
- Sulkowski M, Pol S, Cooper C, et al. Boceprevir Plus Peginterferon/Ribavirin for the Treatment of HCV/HIV Co-Infected Patients. Infectious Diseases Society of America, 49th Annual Meeting 2011, Boston, USA. Abstract LB-37.
- Sulkowski MS (b), Gardiner DF, Rodriguez-Torres M, et al. Sustained virologic response with daclatasvir plus sofosbuvir  $\pm$  ribavirin (RBV) in chronic HCV genotype (GT) 1-infected patients who previously failed telaprevir (TVR) or boceprevir (BOC). *J Hepatol* 2013;58:S570, Abstract 1417.
- Sulkowski MS, Bourliere M, Bronowicki JP, et al. SILEN-C2: sustained virological response (SVR) and safety of BI 201335 combined with peginterferon alfa 2a and ribavirin (PegIFN/RBV) in chronic HCV genotype-1 patients with nonresponse to PegIFN/RBV *J Hepatol* 2011;54:30.
- Sulkowski MS, Emanoil C, Asselah T, et al. SILEN-C1: sustained virological response (SVR) and safety of BI 201335 combined with peginterferon alfa 2a and ribavirin (PegIFN/RBV) in treatment-naïve patients with chronic genotype-1 HCV infection. *J Hepatol* 2011;54:27.
- Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. High rate of sustained virologic response with the all-oral combination of daclatasvir (NS5A inhibitor) plus sofosbuvir (nucleotide NS5B inhibitor), with or without ribavirin, in treatment-naïve patients chronically infected with HCV genotype 1, 2 or 3. *Hepatology* 2012;56:LB-2.
- Sulkowski MS, Poordad F, Manns MP, et al. Anemia during treatment with peginterferon alfa-2b/ribavirin with or without boceprevir is associated with higher svr rates: analysis of previously untreated and previous-treatment-failure patients. *J Hepatol* 2011;54:S194-S195.

- Sulkowski MS, Rodriguez-Torres M, Lawitz E, et al. Complete SVR4 rates in treatment-naïve HCV genotype 1a and 1b patients who achieved vRVR with an interferon-free all-oral regimen. *Hepatology* 2012;56:298.
- Summa V, Ludmerer SW, McCauley JA, et al. MK-5172, a Selective Inhibitor of Hepatitis C Virus NS3/4a Protease with Broad Activity across Genotypes and Resistant Variants. *Antimicrobial agents and chemotherapy* 2012;56:4161-7.
- Susser S, Vermehren J, Forestier N, et al. Analysis of long-term persistence of resistance mutations within the hepatitis C virus NS3 protease after treatment with telaprevir or boceprevir. *J Clin Virol* 2011. (Abstract)
- Susser S, Vermehren J, Forestier N, et al. Analysis of long-term persistence of resistance mutations within the hepatitis C virus NS3 protease after treatment with telaprevir or boceprevir. *J Clin Virol* 2011;52 :321-7.
- Susser S, Welsch C, Wang Y, et al. Characterization of resistance to the protease inhibitor boceprevir in hepatitis C virus-infected patients. *Hepatology* 2009;50:1709-18. (Abstract)
- Suzuki Y, Ikeda K, Suzuki F, et al. Dual Oral Therapy with Daclatasvir and Asunaprevir for Patients with HCV Genotype 1b Infection and Limited Treatment Options. *J Hepatol* 2012, in press.
- Suzuki Y, Ikeda K, Suzuki F, et al. Dual oral therapy with daclatasvir and asunaprevir for patients with HCV genotype 1b infection and limited treatment options. *J Hepatol* 2013;58:655-62. (Abstract)
- Svarovskaia E, Svory-Sobol H, Gontcharova V, et al. Comprehensive resistance testing in patients who experienced relapse after treatment with sofosbuvir (GS-7977)-containing regimens in phase 2 studies. *Hepatology* 2012;56:551.
- Svrtlich N, Jevtovic D, Simonovic J, et al. Older age at the time of liver biopsy is the important risk factor for advanced fibrosis in patients with chronic hepatitis C. *Hepatology* 2007;45:2324-7. (Abstract)
- Swain MG, Lai M-Y, Shiffman ML, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. *Gastroenterology* 2010;139:1593-601. (Abstract)
- Swain MG, Lai MY, Shiffman ML, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. *Gastroenterology* 2010;139:1593-601. (Abstract)
- Swain MG, Lai MY, Shiffman ML, et al. Durable sustained virological response after treatment with peginterferon alpha-2a (PEGASYS®) alone or in combination with ribavirin (COPEGUS®): 5-year follow-up and the criteria of a cure. *J Hepatol* 2007;46:S3-S3.
- Tandon P, Doucette K, Fassbender K, Vandermeer B, Durec T, Dryden DM. Granulocyte colony-stimulating factor for hepatitis C therapy-associated neutropenia: systematic review and economic evaluation. *J Viral Hepat* 2011;18:e381-93. (Abstract)
- Tellinghuisen TL, Marcotrigiano J, Rice CM. Structure of the zinc-binding domain of an essential component of the hepatitis C virus replicase. *Nature* 2005;435:374-9. (Abstract)
- The European AIDS Treatment Network (NEAT) Acute Hepatitis C Infection Consensus Panel. Acute hepatitis C in HIV-infected individuals: recommendations from the European AIDS Treatment Network (NEAT) consensus conference. *AIDS*. 2011;25:399-409. (Abstract)
- Thompson AJ, Patel K, Chuang WL, et al. Viral clearance is associated with improved insulin resistance in genotype 1 chronic hepatitis C but not genotype 2/3. *Gut* 2012;61:128-34. (Abstract)
- Thomson E, Fleming VM, Main J, et al. Predicting spontaneous clearance of acute hepatitis C virus in a large cohort of HIV-1-infected men. *Gut*. 2011;60:837-45. (Abstract)

- Thomson EC, Nastouli E, Main J, Karayiannis P, Eliahoo J, Muir D, McClure MO. Delayed anti-HCV antibody response in HIV-positive men acutely infected with HCV. *AIDS* 2009;23:89-93. (Abstract)
- Thomssen R, Bonk S, Propfe C, et al. Association of hepatitis C virus in human sera with lipoprotein. *Med Microbiol Immunol* 1992;181:293-300. (Abstract)
- Thu Thuy PT, Bunchorntavakul C, Tan Dat H, et al. A randomized trial of 48 versus 24 weeks of combination pegylated interferon and ribavirin therapy in genotype 6 chronic hepatitis C. *J Hepatol* 2012;56:1012-8. (Abstract)
- Tillmann HL, Thompson AJ, Patel K, et al. A polymorphism near IL28B is associated with spontaneous clearance of acute hepatitis C virus and jaundice. *Gastroenterology* 2010;139:1586-92. (Abstract)
- Todros L, Saracco G, Durazzo M, et al. Efficacy and safety of interferon alfa therapy in chronic hepatitis C with autoantibodies to liver-kidney microsomes. *Hepatol* 1995;22:1374-78. (Abstract)
- Tong X, Chase R, Skelton A, et al. Identification and analysis of fitness of resistance mutations against the HCV protease inhibitor SCH 503034. *Antiviral Res* 2006;70:28-38. (Abstract)
- Torbenson M, Thomas DL. Occult hepatitis B. *Lancet Infect Dis* 2002;2:479-86. (Abstract)
- Tran HA, Jones TL, Ianna EA, Reeves GE. The natural history of interferon-alpha induced thyroiditis in chronic hepatitis c patients: a long term study. *Thyroid Res* 2011;4:2. (Abstract)
- Tsukiyama-Kohara K, Iizuka N, Kohara M, et al. Internal ribosome entry site within hepatitis C virus RNA. *J Virol* 1992;66:1476-83. (Abstract)
- Turner J, Bansil L, Gilson R, Gazzard B, Walsh J, Pillay D, et al. The prevalence of hepatitis C virus (HCV) infection in HIV-positive individuals in the UK - trends in HCV testing and the impact of HCV on HIV treatment outcomes. *J Viral Hepat*. 2010; 17:569-77. (Abstract)
- Tyson GL, Kramer JR, Duan Z, Davila JA, Richardson PA, El-Serag HB. Prevalence and predictors of hepatitis B virus coinfection in a United States cohort of hepatitis C virus-infected patients. *Hepatology* 2013;58:538-45.
- Utili R, Zampino R, Bellopede P, et al. Dual or single hepatitis B and C virus infections in childhood cancer survivors: long-term follow-up and effect of interferon treatment. *Blood* 1999;94:4046-52. (Abstract)
- Valentine AD, Meyers CA. Successful treatment of interferon-alpha-induced mood disorder with nortriptyline. *Psychosomat* 1995;36:418-9. (Abstract)
- Vallisa D, Bernuzzi P, Arcaini L, et al. Role of anti-hepatitis C virus (HCV) treatment in HCV-related, low-grade, B-cell, non-Hodgkin's lymphoma: a multicenter Italian experience. *J Clin Oncol* 2005;23:468-73. (Abstract)
- van der Meer, AJ, Veldt, BJ, Feld, JJ et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012;308:2584-2593.
- Van Heeswijk R, Garg V, Boogaerts G, et al. The pharmacokinetic interaction between telaprevir and raltegravir in healthy volunteers. 51st ICAAC Chicago USA 2011, Abstract A1-1738a.
- Van Thiel DH, Friedlander L, Kania RJ, Molloy PJ, Hassanein T, Faruki H. A preliminary experience with GM-CSF plus interferon in patients with HBV and HCV resistant to interferon therapy. *J Viral Hepat* 1997;4:101-06. (Abstract)
- Vehrmeren J, Kau A, Gärtner B, Göbel R, Zeuzem S, Sarrazin C. Differences between two real-time PCR based assays (Abbott RealTime HCV, COBAS AmpliPrep/COBAS TaqMan) and one signal amplification assay (VERSANT HCV RNA 3.0) for HCV RNA detection and quantification. *J Clin Microbiol* 2008;46:880-91. (Abstract)

- Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Ann Intern Med* 2007;147:677-84. (Abstract)
- Verma S, Wang CH, Govindarajan S, Kanel G, Squires K, Bonacini M. Do type and duration of antiretroviral therapy attenuate liver fibrosis in HIV-hepatitis C virus-coinfected patients? *Clin Infect Dis* 2006;42:262-70. (Abstract)
- Vermehren J, Aghemo A, Falconer K, et al. Clinical significance of residual viremia detected by two real-time PCR assays for response-guided therapy of HCV genotype 1 infection. *J Hepatol* 2014.
- Vertex Pharmaceuticals Incorporated. Prescribing Information Incivek (telaprevir). PDF, 23 pages, accessed February 25, 2012.
- Vertex Pharmaceuticals. "65% of people whose prior treatment for hepatitis C was unsuccessful achieved SVR (viral cure) with telaprevir-based therapy in phase 3 REALIZE study". Press Release 2010 <http://investors.vrtx.com/releasedetail.cfm?releaseID=505239>.
- Vezi E, Elefsiniotis I, Mihas C, Konstantinou E, Saroglou G. Thyroid dysfunction in patients with chronic hepatitis C: Virus-or therapy-related? *J Gastroenterol Hepatol* 2009;24:1024-29. (Abstract)
- Vierling JM, Davis M, Flamm S, et al. Boceprevir for Chronic HCV Genotype 1 Infection in Patients with Prior Treatment Failure to Peginterferon/Ribavirin, including Prior Null Response. *J Hepatol* 2013. (Abstract)
- Vierling JM, Flamm SL, Gordon SC, et al. Efficacy of boceprevir in prior null responders to peginterferon/ribavirin: the provide study. *Hepatology* 2011;54:796A-797A.
- Villa E, Grottola A, Buttafoco P, et al. High doses of alpha-interferon are required in chronic hepatitis due to coinfection with hepatitis B virus and hepatitis C virus: long term results of a prospective randomized trial. *Am J Gastroenterol* 2001;96:2973-7. (Abstract)
- Vogel M, Ahlenstiel G, Hintsche B, et al. The influence of HAART on the efficacy and safety of pegylated interferon and ribavirin therapy for the treatment of chronic HCV infection in HIV-positive individuals. *Eur J Med Res* 2010; 15:102-111. (Abstract)
- Vogel M, Deterding K, Wiegand J, et al. German Hepatitis Group Hep-Net. Initial presentation of acute hepatitis C virus (HCV) infection among HIV-negative and HIV-positive individuals—experience from 2 large German networks on the study of acute HCV infection. *Clin Infect Dis* 2009a;49:317-9.
- Vogel M, Rockstroh JK. Liver disease: the effects of HIV and antiretroviral therapy and the implications for early antiretroviral therapy initiation. *Curr Opin HIV AIDS* 2009b;4:171-5. (Abstract)
- Vogel M, Rockstroh JK. Treatment of acute hepatitis C in HIV infection. *J Antimicrob Chemother.* 2010;65:4-9. (Abstract)
- Vogel M, Voigt E, Michaelis HC et al.: Management of drug-to-drug interactions between cyclosporin A and the protease inhibitor saquinavir/ritonavir in liver transplanted HIV-infected patients. *Liver Transplant* 2004;10:939-44. (Abstract)
- von Wagner M, Huber M, Berg T, et al. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. *Gastroenterol* 2005;129:522-27. (Abstract)
- Wagoner J, Negash A, Kane OJ, et al. Multiple effects of silymarin on the hepatitis C virus lifecycle. *Hepatol* 2010;51:1912-21. (Abstract)
- Wakita T, Pietschmann T, Kato T, et al. Production of infectious hepatitis C virus in tissue culture from a cloned viral genome. *Nat Med* 2005;11:791-6. (Abstract)
- Walewski JL, Keller TR, Stump DD, et al. Evidence for a new hepatitis C virus antigen encoded in an overlapping reading frame. *RNA* 2001;7:710-21. (Abstract)

- Wang C, Jia L, Huang H, et al. In vitro activity of BMS-790052 on hepatitis C virus genotype 4 NS5A. *Antimicrob. Agents Chemother.* 2012;56:1588-90. (Abstract)
- Wang CS, Yao WJ, Wang ST, Chang TT, Chou P. Strong association of Hepatitis C virus (HCV) infection and thrombocytopenia: implications from a survey of a community with hyperendemic HCV infection. *Clin Infect Dis* 2004;39:790-96. (Abstract)
- Washburn ML, Bility MT, Zhang L, et al. A humanized mouse model to study hepatitis C virus infection, immune response, and liver disease. *Gastroenterology* 2011;140:1334-44. (Abstract)
- Weiner SM, Berg T, Berthold C, et al. A clinical and virological study of hepatitis C virus-related cryoglobulinemia in Germany. *J Hepatol* 1998;29:375-84. (Abstract)
- Weissenborn K, Ennen JC, Bokemeyer M, et al. Monoaminergic neurotransmission is altered in hepatitis C virus infected patients with chronic fatigue and cognitive impairment. *Gut* 2006;55:1624-30. (Abstract)
- Weitz IC. Treatment of immune thrombocytopenia associated with interferon therapy of hepatitis C with the anti-CD20 monoclonal antibody, rituximab. *Am J Hematol* 2005;78:138-141. (Abstract)
- Welsch C, Domingues FS, Susser S, et al. Molecular basis of telaprevir resistance due to V36 and T54 mutations in the NS3-4A protease of the hepatitis C virus. *Genome Biol* 2008;9:R16. (Abstract)
- Weltman MD, Brotodihardjo A, Crewe EB, et al. Coinfection with hepatitis B and C or B, C and delta viruses results in severe chronic liver disease and responds poorly to interferon-alpha treatment. *J Viral Hepat* 1995;2:39-45. (Abstract)
- Werner, CR, Egetemeyr, DP, Lauer, UM et al. Telaprevir-based triple therapy in liver transplant patients with hepatitis C virus: A 12-week pilot study providing safety and efficacy data. *Liver Transpl* 2012;18:1464-1470.
- Wesche B, Jaeckel E, Trautwein C, et al. Induction of autoantibodies to the adrenal cortex and pancreatic islet cells by interferon alpha therapy for chronic hepatitis C. *Gut* 2001;48:378-83. (Abstract)
- White DL, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: A systematic review and meta-analysis. *J Hepatol* 2008;49:831-44. (Abstract)
- WHO, Factsheet No 164, July 2013. <http://www.who.int/mediacentre/factsheets/fs164/en>, accessed January 5, 2014.
- WHO, Factsheet No 164, June 2011. <http://goo.gl/5m3sY>, accessed 10.01.2012.
- Wiegand J, Buggisch P, Boecher W, et al. Early monotherapy with pegylated interferon alpha-2b for acute hepatitis C infection: the HEP-NET acute-HCV-II study. *Hepatol* 2006;43:250-56. (Abstract)
- Wiegand J, Maasoumy B, Buggisch P, et al. Telaprevir triple therapy in multimorbid chronic hepatitis C genotype 1 patients under hemodialysis. *Hepatology* 2013;58:1112A, Abstract 1879.
- Wiese M, Berr F, Lafrenz M, Porst H, Oesen U. Low frequency of cirrhosis in a hepatitis C (genotype 1b) single-source outbreak in germany: a 20-year multicenter study. *Hepatology* 2000;32:91-6. (Abstract)
- Wietzke P, Schott P, Braun F, et al. Clearance of HCV RNA in a chronic hepatitis C virus-infected patient during acute hepatitis B virus superinfection. *Liver* 1999;19:348-53. (Abstract)
- Wohnslund A, Hofmann WP, Sarrazin C. Viral determinants of resistance to treatment in patients with hepatitis C. *Clin Microbiol Rev* 2007;20:23-38. (Abstract)
- Wong VS, Egner W, Elsey T, Brown D, Alexander GJ. Incidence, character and clinical relevance of mixed cryoglobulinaemia in patients with chronic hepatitis C virus infection. *Clin Exp Immunol* 1996;104:25-31. (Abstract)
- Wu JC, Chen CL, Hou MC, et al. Multiple viral infection as the most common cause of fulminant and subfulminant viral hepatitis in an area endemic for hepatitis B:

- application and limitations of the polymerase chain reaction. *Hepatology* 1994;19:836-40. (Abstract)
- Yalcin K, Degertekin H, Yildiz F, et al. A severe hepatitis flare in an HBV-HCV coinfecting patient during combination therapy with alpha-interferon and ribavirin. *J Gastroenterol* 2003;38:796-800. (Abstract)
- Yalcin K, Degertekin H, Yildiz F, et al. A severe hepatitis flare in an HBV-HCV coinfecting patient during combination therapy with alpha-interferon and ribavirin. *J Gastroenterol* 2003;38:796-800. (Abstract)
- Younossi ZM, Nader FH, Bai C, et al. A phase II dose finding study of darbepoetin alpha and filgrastim for the management of anaemia and neutropenia in chronic hepatitis C treatment. *J Viral Hepat* 2008;15:370-78. (Abstract)
- Yu JW, Sun LJ, Zhao YH, Kang P, et al. Analysis of the efficacy of treatment with peginterferon  $\alpha$ -2a and ribavirin in patients coinfecting with hepatitis B virus and hepatitis C virus. *Liver Int* 2009;29:1485-93. (Abstract)
- Yu ML, Lee CM, Chen CL, et al. Sustained hepatitis C virus clearance and increased hepatitis B surface antigen seroclearance in patients with dual chronic hepatitis C and B during posttreatment follow-up. *Hepatology*. 2013;57:2135-42.
- Yu X, Qiao M, Atanasov I, et al. Cryo-electron microscopy and three-dimensional reconstructions of hepatitis C virus particles. *Virology* 2007;367:126-34. (Abstract)
- Zarski JP, Bohn B, Bastie A, et al. Characteristics of patients with dual infection by hepatitis B and C viruses. *J Hepatol* 1998;28:27-33. (Abstract)
- Zeuzem S (a), Berg T, Gane E, et al. Simeprevir Increases Rate of Sustained Virologic Response Among Treatment-Experienced Patients With HCV Genotype-1 Infection: A Phase IIb Trial. *Gastroenterology* 2013;S0016-5085(13)01576-X.
- Zeuzem S (b), Dusheiko GM, Salupere R, et al. Sofosbuvir and Ribavirin for 12 or 24 Weeks for Patients With HCV Genotype 2 or 3: the VALENCE Trial. *Hepatology*. 2013;58:Abstract 1085.
- Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011;364:2417-28. (Abstract)
- Zeuzem S, Arora S, Bacon B, Box T, Charlton M. Pegylated interferon-lambda shows superior viral response with improved safety and tolerability versus pegIFN- $\alpha$ -2a in HCV patients (G1/2/3/4): merge phase IIb through week 12. *J Hepatol* 2011;54:538.
- Zeuzem S, Asselah T, Angus P, et al. Efficacy of the Protease Inhibitor BI 201335, Polymerase Inhibitor BI 207127, and Ribavirin in Patients With Chronic HCV Infection. *Gastroenterology* 2011;141:2047-55. (Abstract)
- Zeuzem S, Berg, T, Moeller, B, et al. Expert opinion on the treatment of patients with chronic hepatitis C. *J Viral Hepat* 2009;16:75-90. (Abstract)
- Zeuzem S, Buggisch P, Agarwal K, et al. Dual, triple, and quadruple combination treatment with a protease inhibitor (GS-9256) and a polymerase inhibitor (GS-9190) alone and in combination with ribavirin (RBV) or pegIFN/RBV for up to 28 days in treatment naive, genotype 1 HCV subjects. *Hepatology* 2010a;50:S106.
- Zeuzem S, Buggisch P, Agarwal K, et al. The protease inhibitor GS-9256 and non-nucleoside polymerase inhibitor tegobuvir alone, with RBV or peginterferon plus RBV in hepatitis C. *Hepatology* 2011;55:749-58.
- Zeuzem S, Buggisch P, Agarwal K, et al. The protease inhibitor, GS-9256, and non-nucleoside polymerase inhibitor tegobuvir alone, with ribavirin, or pegylated interferon plus ribavirin in hepatitis C. *Hepatology* 2012;55:749-58. (Abstract)
- Zeuzem S, Buti M, Ferenci P, et al. Efficacy of 24 weeks treatment with peginterferon  $\alpha$ -2b plus ribavirin in patients with chronic hepatitis C infected with genotype 1 and low pretreatment viremia. *J Hepatol* 2006;44:97-103. (Abstract)



- Zeuzem S, Diago M, Gane E, et al. Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. *Gastroenterol* 2004b;127:1724-32. (Abstract)
- Zeuzem S, Hultcrantz R, Bourliere M, et al. Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. *J Hepatol* 2004a;40:993-99. (Abstract)
- Zeuzem S, Soriano A, Asselah T, et al. (IFN)-free combination therapy of the NS3-4A protease inhibitor BI 201335 and the non-nucleoside NS5B inhibitor BI 207127 +/- ribavirin (RBV): Final results of SOUND-C2 and predictors of response. *Hepatology* 2012;56:308.
- Zeuzem S, Soriano V, Asselah T, et al. Faldaprevir and deleobuvir for HCV genotype 1 infection. *N Engl J Med* 2013;369:630-9.
- Zeuzem S, Sulkowski M, Lawitz E, et al. Efficacy and Safety of Albinterferon Alfa-2b in Combination with Ribavirin in Treatment-Naive, Chronic Hepatitis C Genotype 1 (Chc G1) Patients. *J Hepatol* 2009;50:S377-S377.
- Zeuzem S, Sulkowski MS, Lawitz EJ, et al. Albinterferon Alfa-2b was not inferior to pegylated interferon-alpha in a randomized trial of patients with chronic hepatitis C virus genotype 1. *Gastroenterol* 2010b;13:1257-66. (Abstract)
- Zhou J, Dore GJ, Zhang F, et al. Hepatitis B and C virus coinfection in The TREAT Asia HIV Observational Database. *J Gastroenterol Hepatol* 2007;22:1510-8. (Abstract)
- Zignego AL, Ferri C, Pileri SA, Caini P, Bianchi FB. Extrahepatic manifestations of the Hepatitis C Virus infection: a general overview and guidelines for clinical approach. *Dig Liver Dis* 2007a;39:2-17. (Abstract)
- Zignego AL, Fontana R, Puliti S, et al. Relevance of inapparent coinfection by hepatitis B virus in alpha interferon-treated patients with hepatitis C virus chronic hepatitis. *J Med Virol* 1997;51:313-8. (Abstract)
- Zignego AL, Giannelli F, Marrocchi ME, et al. T(14;18) translocation in chronic hepatitis C virus infection. *Hepatol* 2000;31:474-9. (Abstract)
- Zimmer V, Lammert F. Genetics and epigenetics in the fibrogenic evolution of chronic liver diseases. *Best Pract Res Clin Gastroenterol*. 2011 Apr;25:269-80. (Abstract)



# Index

- ABT-072 94, 115
- ABT-267 93, 124
- ABT-333 93, 115, 124
- ABT-450 93, 124
- ACH-1625 93
- ACH-2928 93
- Acute hepatitis
  - hepatitis C treatment 84
- Adherence 80
- Adverse events *See* Side effects
- Albinterferon 126
- Alisporivir 93, 115, 125
- Aminotransferase levels 86
- Amplicor 31
- ANA598 93
- Antidepressants 131
- Anti-HCV IgM 30
- Antiviral resistance 48
- Asunaprevir 93, 99, 115
- Autoimmune haemolytic anemia 146
  
- BI201335 93
- BI207127 93
- BILB 1941 94
- Blood transfusion 18
- BMS-650032 93
- BMS-790052 93, 109
- BMS-791325 93, 125
- BMS-824393 93, 109
- Boceprevir 42, 44, 55, 93, 98, 113
- Branched DNA assay 32
  
- Child-Pugh classification 22
  
- Ciluprevir 94
- Cirrhosis 20
- Cobas Amplicor 32
- Cobas TaqMan 32
- Coinfections 90
- Consensus Interferon 44
- Copegus 44
- Cryoglobulinemia 141
- Cyclophilin B inhibitors 110
  
- DAA 35, 40
- Daclatasvir 65, 93, 115, 125
- Danoprevir 93, 99, 115, 119
- Debio-025 93
- Delayed virological response 42
- Deleobuvir 115, 121
- Dermatologic manifestations 147
- Diabetes mellitus 147
- Diagnosis
  - acute hepatitis C 34
  - chronic hepatitis C 35
- Diagnostic tests 30
- Direct-acting antiviral agent *See* DAA
- Disease progression 20
- Drug abuse 90
- Drug interactions 82, 128
- DVR 42
  
- Early treatment success 42
- Early virological response 41
- Enzyme-linked immunoassays 30
- Epidemiology 17

- eRVR 42
- ETS 42
- EVR 41
- Extended rapid virological response 42
- Extrahepatic manifestations
  - hepatitis C 91
- Faldaprevir 42, 63, 93, 99, 115, 121, 125
- Filibuvir 94
- Genotypes 23
- Genotyping 33
- Glomerulonephritis 146
- GS-5816 93
- GS-5885 93, 109
- GS-9190 93
- GS-9256 93, 115
- GS-938 94
- GS-9451 93, 124
- GS-9669 93
- HAART 153
- HBV/HCV Coinfection 162
- HCV
  - assembly 28, 29
  - genome organization 24
  - lifecycle 26
  - nucleic acid testing 31
  - proteins 25
  - RNA replication 28
  - structure 23
  - translation 27
  - viral entry 26
- HCV genotype 1 50
- HCV genotypes 2 and 3 71
- HCV genotypes 4, 5, and 6 77
- HCV life cycle 95
- HCV/HIV coinfection 149
  - liver transplantation 159
- HCV-796 94
- Hemodialysis 89
- Hemophilia 90
- Hepatic decompensation 20
- Hepatitis C
  - treatment 37
- HIV 18, 149
- Host targeting agents 93
- Hypothyroidism 146
- IDX184 94
- IDX320 93
- IDX375 94
- Infergen 44
- Interferon lambda 1 126
- Interferon  $\alpha$ -2a 44
- Interferon  $\alpha$ -2b 44
- Intron 44
- Lead-In 42
- Ledipasvir 93, 115, 120
- Liver cirrhosis
  - compensated 87
- Liver transplantation 88
- Lymphoproliferative disorders 141
- MALT lymphoma 144
- MELD score 21
- Mericitabine 93, 105, 115, 119
- Miravirsen 93, 112, 115
- MK-3281 94
- MK-5172 93
- MK-7009 93
- MK-8742 93
- Narlaprevir 94

- Natural history
  - acute hepatitis 19
  - chronic hepatitis 19
- NIM811 94
- Nitazoxanide 112
- NM283 94
- Nonresponse 42
- NS3/4A protease inhibitors 93, 97
- NS5A inhibitors 93, 108
- NS5B inhibitors 93, 104
- Null response 42
- NULR 42
  
- Partial response 42
- Pegasys 44
- PEG-IFN maintenance therapy 70
- PEG-Intron 44
- PF-00868554 94
- PHX1766 94
- PPI-461 93, 109
- PPI-668 93
- PSI-7977 107
  
- Quadruple therapy 116
- Qualitative HCV RNA test 31
  
- R1626 94
- R7227 93
- Rapid virological response 41
- Real-time PCR 32
- Rebetol 44
- Relapse 42
- Ribavirin 44, 153
- Roferon 44
- RVR 41
  
- SCH503034 93
- SCY-635 93
- Serologic assays 30
- Setrobovir 93
- Side effects 128
  - asthenia 129
  - flu-like symptoms 129
  - hypothyroidism 129
  - management 81
  - psychiatric 129
  - weight loss 129
- Signal amplification technique 32
- Silibinin 112
- Simeprevir 42, 53, 60, 93, 99, 115
- Sofosbuvir 53, 62, 72, 115, 118, 120
- Sustained virological response 41
- SVR 41
- SVR-12 41
  
- Target amplification technique 32
- Taxonomy 23
- Tegobuvir 93, 115, 122, 124
- Telaprevir 42, 44, 57, 93, 98, 113, 122
- Thrombocytopenia 145
- TMC435 93
- TMC647055 93
- Transmission 18
- Treatment failure 65
- Treatment response 44
- TruGene 34
  
- Valopicitabine 94
- Versant HCV RNA Qualitative Assay 31
- Virological response 35

VX-222 93, 115

VX-759 94

VX-916 94

VX-950 93



Download Free PDF



*the Flying Publisher*

## Short Guide to Hepatitis C / 2014

*edited by*

Mauss, Berg, Rockstroh, Sarrazin, Wedemeyer

# #14



Exciting new treatment approaches make the management of hepatitis C one of the most rapidly developing areas of medicine.

The *2014 Flying Publisher Short Guide to Hepatitis C* is an up-to-date source of information for physicians, residents and advanced medical students.

*[www.flyingpublisher.com](http://www.flyingpublisher.com)*

ISBN 978-3-942687-15-7



9 783942 687157 >