Viral Hepatitis: Chronic Hepatitis C

Resat Ozaras
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Editors

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Dr. Resat Ozaras dedicates this book to Nihal, Emre, and Omer

and

Dr. Dominique Salmon-Ceron dedicates this book to Pierre Guillaume, Alexandre, Ariane, and Vincent

Foreword

Hepatology is a rapidly evolving field that will continue to grow and maintain excitement over the next decades. In the treatment of hepatitis C we have witnessed a revolution, making a very hard to cure disease to an infection which can be successfully treated in almost all patients without major side effects. Some subpopulations still require special attention, e.g., HCV/HIV-coinfected patients, patients with extrahepatic manifestations, patients who previously failed an antiviral regimen, patients with decompensated cirrhosis, those after organ transplantation, and last but certainly not least patients who inject drugs (PWIDs).

In the last decade, HCV treatment guidelines had to be revised on at least an annual basis. Now, with the development of pangenotypic therapies, management and treatment guidelines have consolidated. With the easy algorithms the challenges have moved away from treatment optimization to issues of screening, case finding, linkage to care and elimination of HCV according to the aims proposed by the WHO.

In a rapidly evolving field, is a book format the right medium to gather and summarize current knowledge? For the field of hepatitis C it is an excellent time point. Numerous studies have been published in the last 5 years that need to be meta-analyzed and integrated into a bigger picture. No new drugs are anymore in clinical development and therefore clear recommendations for treatment can be provided, which will certainly be maintained for some years to come.

The book edited by Prof. Dominique Salmon-Ceron and Prof. Resat Ozaras is well written and provides in-depth information without being lengthy or redundant. All experts involved in the various chapters provide an excellent overview in the respective hot topics. The book will be valuable for both specialists who wish to update themselves and for generalists who plan to manage and treat patients with hepatitis C in the future.

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Preface

Dear Reader Friends Hepatitis C has had a revolution in recent years.

From a complex and severe chronic disease, 30 years ago, called non-A, non-B hepatitis, which has long been the leading cause of liver-related deaths, hepatitis C has become the first chronic curable infection.

The virus has been identified in 1989, the stages of the viral cycle specified, and its pathology precisely described. Antiviral therapeutic strategies have undergone enormous changes. From complex injectable and badly tolerated therapies relying on interferon, they have evolved towards direct antiviral treatments able to eradicate the virus in more than 95% of the patients, whatever the severity of their disease. Those treatments greatly simplified are now widely prescribed by specialist physicians as well as nonspecialists.

All these progresses have been made over several years and are the result of a great deal of work carried out by many teams of researchers.

Those spectacular improvements have led the World Health Organization to adopt in 2016 the ambitious target of eliminating hepatitis C by 2030. This target commits the 194 WHO Member States to reduce the number of deaths by 65% and the number of new infections by 80% in 2030.

In order to reach these targets, the benefits observed at the individual level should be transposed into a significant reduction of hepatitis C at the collective level, and hepatitis C should no longer stay a disease managed by specialists but become a disease known, screened, and managed by all specialists as well as general practitioners.

In this book, our wish has been to synthesize most clearly as possible the recent advances in the field of clinical management of hepatitis C and provide clinicians with all the tools available and necessary to optimally take care of hepatitis C.

We asked the best experts in their field and are very grateful to them that all agreed writing the different chapters.

This book is cut into different chapters addressing the evaluation of the disease, the available therapies, and the most recent recommendations, and then describing several situations requiring special attention such as renal insufficiency, patients living with HIV, patients in therapeutic failure, acute infection, and so on.

We recognize that the knowledge and advances in this field have been spectacular in the five past years but think that the management strategies have now stabilized so that these data will remain relevant for several years.

We hope, dear reader friends, that this modest book will be useful for your practice, easy to read, and will answer to the questions you may have on the clinical management of patients with hepatitis C.

Paris, Istanbul, June 2019.

Paris, France — Dominique Salmon-Ceron
Istanbul, Turkey — Resat Ozaras

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Resat Ozaras and Hakan Leblebicioglu

1.1 Introduction

Chronic hepatitis C (CHC) is a major health problem all over the world. It is a main cause of liver failure, cirrhosis, and hepatocellular carcinoma. Besides hepatic complications of cirrhosis and liver cancer, HCV causes additional comorbidities that are directly attributable to HCV, referred to as extrahepatic manifestations. These manifestations are likely to be affected by HCV treatment.

Global prevalence of chronic HCV infection estimate dropped from 180 million in 2012 [1] to 150–130 million in 2015 [2]. Finally, the World Health Organization estimated that, in 2015, 71 million persons were living with chronic HCV infection worldwide with a global prevalence of 1% and that 399,000 had died from cirrhosis or hepatocellular carcinoma (HCC) [3]. These dramatic changes however are unlikely to be the consequence of the effect of the global attempts to decrease the HCV burden. Instead it is primarily due to the increasing awareness that previous estimates were severely biased. The epidemiological studies mostly screen antibodies against HCV. Since antibodies against HCV are positive in spontaneously healed and successfully treated persons, the prevalence of antibodies against HCV clearly overestimates the prevalence of chronic HCV infection.

The incidence of HCV infection tended to decrease in the developed world; however mortality secondary related to HCV infection is estimated to continue to increase over the next 20 years [4]. With the effective use of diagnostic strategies and direct-acting antiviral drugs, HCV infection could be eliminated in the next 15–20 years. However there are millions of new infections and a good understanding of HCV

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infections should be required to develop strategies to prevent new infections. The WHO estimated that, in 2015, 1.75 million new HCV infections occurred and the main ways of transmission were injecting drug use and unsafe health care [3].

Epidemiology of HCV infection differs across geographical areas in the world and the burden of disease is high in certain risk groups. The highest HCV prevalence is among people who inject drugs, reaching up to 8% globally [2]. Current records suggest that CHC prevalence is the highest in North Africa and Middle East: (>2%), the lowest (<1%) in Western Europe [5]. However there are significant differences within a region and even within the same country, especially in risk groups. The epidemiological studies from the same country may provide significantly different results. Some studies provide the prevalence in certain risk groups including people who inject drugs, hemodialysis patients, and people with HIV infection. In certain studies, results of blood donor screening are given to represent the general population. However blood donors who are male in majority, healthy, and in certain age groups (mostly 20–55 years) are not representative of the general population epidemiology.

In addition to HCV prevalence, the genotype of the virus is critical. Genotype distribution in fact provides a better understanding of HCV epidemiology. It is also important for the management. Although pangenotypic direct-acting antivirals have been developed, they are not readily available in most of the countries. DAAs effective for certain genotypes and pegylated interferon in combination with ribavirin or DAAs are dependent on genotype information. Regional genotype distribution may contribute to the development of country-specific treatment strategies. Worldwide, HCV infection may be caused by one of six major HCV genotypes [6]. However, in many countries, the genotype distribution remains unknown [7].

Global estimates of HCV epidemiology depend on regional prevalence studies. There are still gaps of information in some countries. Although recent efforts of HCV epidemiology have used published data as well as expert opinions to provide a better coverage of countries which lack information [8–11], there is still a need for standardized epidemiological studies for HCV prevalence in the general population in many regions.

In this chapter, we reviewed regional and global epidemiology of HCV infection. We have used the data from published literature for the general population where available. We generally used anti-HCV prevalence since studies depending on detection of HCV-RNA are very limited. We described genotypes in the region. We further described genotypes at county level when it is significantly different from those of the region.

1.2 Epidemiology of HCV by Regions

1.2.1 Africa

The estimated anti-HCV prevalence in Africa is 2.9% corresponding to a population of 27 million, second highest HCV burden following Asia [5]. The central sub-Saharan Africa has the highest prevalence of anti-HCV prevalence among the

regions in the world, 6%. North Africa and Middle East have a prevalence of 2.7%. In both East sub-Saharan and West sub-Saharan Africa, anti-HCV prevalence is 2.4%. The lowest prevalence in Africa is in southern sub-Saharan Africa: 0.9%.

1.2.1.1 The Central Sub-Saharan Africa

This region having the highest prevalence of anti-HCV positivity includes Burundi, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of Congo (DRC), Equatorial Guinea, Gabon, Rwanda, Sudan, and Uganda.

Cameroon has been reported to have very high anti-HCV prevalence of 6–14%. A recent study testing anti-HCV in 14,150 individuals showed that nationwide HCV prevalence was 0.81% for the 15–49 years group and 2.51% for all individuals aged ≥15 years. Only 0.2% of individuals aged 15–19 were seropositive. In age group of 15–44 years, HCV was associated with age, rural residence, and, for males, with ritual circumcision. For 45–59 years age group, HCV was associated with age and access to medical care in the late 1950s [12].

The prevalence study of HCV from Congo was derived from blood donors who are male in majority and it has been reported 4.7% in 2014 [13].

Burundi has one of the highest prevalence of HCV: it is estimated as 8.2% [14].

In Gabon, it is 6.5–22% [15, 16], Uganda 4.1–12%, Chad 4.8%, Rwanda 2.5–5.7%, Central African Republic 2.8–4.72%, and Democratic Republic of Congo (DRC) 0.2–3.8% [17–19]. In Sudan, pooled HCV antibody prevalence in the general population seemed comparatively low: 1.0% (95% CI: 0.3–1.9%) and 1.9% (95% CI: 1.4–2.6%) in Sudan [20]. In high-risk populations (e.g., hemodialysis and hemophilia patients), pooled HCV prevalence was 17.3%. Equatorial Guinea has a prevalence of 3.7–13.4% among blood donors [21].

Genotypes: In this region, the prevalent genotype is G4 (83%) followed by G1 (12%), G2 (4%), and G3 (1%). In DRC, Burundi, and Gabon, G4 is highly predominant (97%, 92.7%, and 92%, respectively). In Equatorial Guinea, there has been an increase in the rate of G1 of 35% [5].

1.2.1.2 East Sub-Saharan Africa

This region includes Eritrea, Ethiopia, Kenya, Madagascar, Mozambique, Somalia, and Tanzania. The average HCV prevalence in this region is 2.4%. The highest prevalence is in Tanzania (3.2%) followed by Mozambique (2.8%).

In Somalia and Kenya the prevalence is relatively lower (0.9% and 0.5%, respectively).

Pooled HCV antibody prevalence in the general population in Somalia was 0.9% and in intermediate-risk populations (e.g., healthcare workers, in patients, and men who have sex with men), pooled HCV prevalence was 1.7% [22].

The prevalence is 0.6–1.2% in Ethiopia [23], and 1.2–1.7% in Madagascar [24, 25]. Information of HCV prevalence in the general population in Eritrea is lacking. Studies from blood donors report it is 0.5–0.7% [26, 27].

Genotypes: In Ethiopia, G4 was reported in about half of the genotypes. In Madagascar, two genotypes were detected: G1 (53%) and G4 (47%). In Mozambique, G1 (53%), G5 (26%), and G3 (21%) were the reported genotypes.

1.2.1.3 Southern Sub-Saharan Africa

This region includes Malawi, South Africa, Swaziland, Zambia, and Zimbabwe and represents the lowest HCV prevalence among African regions. An average of anti-HCV prevalence is 0.9%. Malawi, Zimbabwe, and Swaziland have higher prevalence, 3.9%, 2.0%, and 1.5% respectively. South Africa (0.1–1.1%) and Zambia (0.2–1.1%) have the lowest prevalence [28, 29].

Genotypes: Genotype prevalence was reported only from South Africa where G5 (39%) is the leading one, followed by G1 (33%), G2 (14%), G3 (8%), and G4 (2%) [30].

1.2.1.4 North Africa and Middle East

This region includes Algeria, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Syria, Tunisia, United Arab Emirates, and Yemen. The overall prevalence of HCV in the general population in this region is 2.7%. In this region, among anti-HCV positives, the overall pooled mean viremic rate was reported at 67.6% [31].

Egypt has the highest prevalence in this region. In the general population, very high rates up to 51% have been reported. A recent analysis of 259 prevalence studies reported that pooled mean HCV prevalence was 11.9% among the general population, 55.6% among populations at high risk, 14.3% among populations at intermediate risk, 56.0% among populations with liver-related conditions, and 35.0% among special clinical populations [32]. Mean HCV viremic rate was reported at 66.7%. There is a trend of decreasing HCV prevalence in Egypt; a metaregression analysis indicated 6% lower odds for HCV prevalence for each one-year increment in publication year [32].

In Iran, a recent meta-analysis reported HCV prevalence at 0.3% among the general population, 6.2% among intermediate risk populations, 32.1% among high-risk populations, and 4.6% among special clinical populations [33]. This meta-analysis estimated HCV prevalence at 52.2% among people who inject drugs, 20.0% among populations at high risk of healthcare-related exposures, and 7.5% among populations with liver-related conditions. Iraq has a prevalence of 3.2%. Pooled HCV antibody prevalence in the general population in Yemen was reported at 0.9%. Three studies of hemodialysis patients reported HCV prevalence between 40.0% and 62.7% [20].

HCV prevalence was 2.8% in Syria, 0.6–2.9% in Lebanon, 2% in Algeria, 1.8% in Tunisia, 1.2–1.8% in Libya, 1.6% in Morocco, 1.5% in Saudi Arabia, 0.9% in Yemen, 0.9% in Qatar, 0.1–0.8% in Iraq, 0.8% in Kuwait, 0.5% in Oman, and 0.1% in United Arab Emirates [22].

No data available for HCV prevalence in the general population in Israel, Jordan, and Palestine. In blood donors it is 0.1–0.9% in Jordan and 0.2–0.3% in Palestine [22]. In Israel, the best estimate of prevalence came from unpublished data from the health service provider; among 789,689 individuals tested, 1.96% were HCV antibody positive in 2001–2010 [34].

Genotypes: G4 is the predominant one in the region corresponding to 65%, followed by G1 (27%) and G3 (6%). G2 and G5 are rare. Genotype 4 accounted for

94.1% of infections in Egypt [32], followed by G1 (4%), G2 (1.2%), and G3 (0.8%). Iraq, Kuwait, Palestine, Saudi Arabia, and Syria have predominantly G4 (50–60%), while Tunisia, Jordan, and Morocco have G1 (75–85%). In Iran, a recent meta-analysis reported G1 as the most frequent circulating strain at 58.2%, followed by genotype 3 at 39.0% [33]. In United Arab Emirates, 49.2% had genotype 1, 34.6% had 3, 14.5% had 4, and 1.6% patients had genotype 2 [35]. In Israel, G1 is most prevalent: 70%, followed by G3, 20%; and G2, 8%.

1.2.1.5 West Sub-Saharan Africa

This region includes Benin, Burkina Faso, Cote d'Ivoire, Gambia, Ghana, Guinea Bissau, Mauritania, Niger, Nigeria, Senegal, and Togo. The prevalence in the region is 2.4% [5].

Guinea Bissau and Burkina Faso have higher prevalence (5.5% and 4.9% respectively), while Benin (1.6%) and Mauritania (1.1%) have relatively lower prevalence.

Genotypes: The predominant genotype in the region is G2, which corresponds to 63% of the genotypes, followed by G1 (26%) and G3 (4%). However the distribution is heterogeneous. Nearly all genotypes (98.2%) in Guinea Bissau and the vast majority (87%) in Ghana are G2. In Nigeria, G1 is prevalent (85%) [5].

1.2.2 Asia

The prevalence of anti-HCV in Asia is 2.8%. Considering the population of the continent, this figure accounts for 60% of the cases worldwide. Prevalent genotype is G1 (47%), followed by G3 (22%), G2 (19%), and G6 (7%). G4 and G5 are reported in small percentages.

1.2.2.1 Asia Pacific

In this region, the prevalence in Japan and South Korea is reported 1.5% and 0.8, respectively. In Japan, a significant number of patients with HCV infection are over the age of 65. While the prevalence is 0.35% among 40–44 years group, it is 1.09% in 65–69 and 1.67% in 70–74 years group [36].

In Japan, 70% of patients are infected with HCV genotype 1b, 20% with genotype 2a, and 10% with genotype 2b [37]. In South Korea, the prevalent genotypes are genotype 1b (45%) and genotype 2 (45%) [38].

1.2.2.2 Central Asia

This region includes Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Mongolia, Tajikistan, Turkmenistan, and Uzbekistan. In this region, the prevalence of HCV is high: 5.8% in the general population. Anti-HCV prevalence has been reported at 11.3% in Uzbekistan, 9.8% in Mongolia, 6.7% in Georgia, 5.6 in Turkmenistan, 3–5% in Armenia, 2.9–3.9% in Kazakhstan, 3.1% in Azerbaijan, 2.5–3.1% in Kyrgyzstan, and 0.5% in Tajikistan [5].

Uzbekistan has the highest prevalence in the region. The viremic rate is relatively low (39.2%) [39]. HCV prevalence was reported very high in Mongolia up to 15.6% in previous studies. A recent review of studies from Mongolia reported that the prevalence of HCV has decreased from 15.6% to 9.8% among the general population during the last decade [40]. HCV is the most common etiology for HCC in Mongolia (46%) followed by HBV infection (34%), coinfection of HBV and HCV (14%), and alcohol (5.6%).

Genotype: The predominant genotype is 1b in Mongolia (99.8%), Tajikistan (82.7%), Uzbekistan (64.2%), Georgia (59%), and Kazakhstan (59%). In Armenia, G3 (37%) and G1b (36%) are the main genotypes [39].

1.2.2.3 East Asia

This region includes China and Taiwan. The overall HCV prevalence is 2.8%. It was reported at 3.3% in Taiwan and 1.3–1.6% in China.

In China, although the number of studies reporting the prevalence of HCV is small, studies conducted in specific populations, and large population-based studies are lacking, a review of HCV prevalence studies showed that HCV prevalence in the general population was 1.6% [41]. There are regions with higher prevalence: In Putian County, HCV prevalence was found to increase significantly with age, ranging from 12% in those 20–29 years of age to 69% in those aged 60–69 years. More than half of residents over the age of 40 years were infected with HCV, and this finding was due to the lack of sterilization of medical equipment that was common practice in this region until the 1990s [42].

In Taiwan, a national surveillance study reported anti-HCV prevalence as 3.3% (2.5–8.6%) [43]. The viremic rate was found to be 74%. Significant geographic variations, a slightly higher prevalence rate among males, and increasing prevalence as age increases were noted [44].

In China, 1b (62.78%) and 2a (17.39%) are the two predominant subtypes [45]. Genotypes and subtypes exhibit significant regional differences: In North, Northwest, Northeast, East (except Jiangxi province) and Central China (except Hunan province), G1b and 2a were reported as the two predominant subtypes. In South China, 14 subtypes were found [45]. In Taiwan, the predominant genotype was 1b (45.5%), followed by 2a/2c (30.9%) and 2b (6.9%).

1.2.2.4 South Asia

This large area includes Afghanistan, Bangladesh, India, and Pakistan and the prevalence of anti-HCV in the general population is 2.5%.

It is 6.2% in Pakistan, 0.84% in Bangladesh, 0.5–1.5% in India, and 0.7% in Afghanistan.

In Pakistan, a recent meta-analysis reported the pooled mean HCV prevalence at 6.2% among the general population, 34.5% among high-risk clinical populations, 12.8% among populations at intermediate risk, 16.9% among special clinical populations, 55.9% among populations with liver-related conditions, and 53.6% among

people who inject drugs. Most reported risk factors in analytical epidemiologic studies related to healthcare procedures [46].

In Bangladesh, main risk factors for the transmission of HCV were reported as treatment from quacks, shaving and haircut in barber shops, body piercing, as well as vaccination against small pox, cholera, dental procedure, intravenous infusion [47]. There is a male predominance with males accounting for more than 70% HCV infections, and more than 60% HCV-infected people in Bangladesh are between 30 and 50 years of age [47].

In India, the prevalence shows significant differences among regions; for example, in the northern state of Punjab, it is 5.6%, while it is 0.87% in the eastern state of West Bengal [48]. In the whole country, it has been estimated that the prevalence of HCV is between 0.5% and 1.5% [49].

In this area, the most common genotype is G3 (66.7%), followed by G1 (15.5%) and G4 (3.7%). G2, G5, and G6 are reported in low rates. In Bangladesh, predominant genotype is G3 (50–89%), followed by G1 (8–29%). In India and Pakistan, G3 counts more than half of all the genotypes (54.4% and 79.0%).

Genotypes distribution of HCV in Afghanistan comes from 71 HCV RNA positive injection drug user patients: G3a (62%, $n=44$), G1a (35.2%, $n=25$), and G1b (2.8%, $n=2$) [50].

1.2.2.5 Southeast Asia

This area includes Cambodia, Indonesia, Laos, Myanmar, Malaysia, the Philippines, Sri Lanka, Thailand, and Vietnam. The prevalence of anti-HCV in the general population is 1.6%.

In Cambodia the prevalence is 2.3–14.7%; it has been reported at 5.8% in a recent study [51]. It is 2.7% in Thailand, 2.5% in Malaysia, 2% in Myanmar, 0.8% in Indonesia, and 1.06% in Sri Lanka [52, 53].

In Vietnam, it is 1% for the country [54]. However the prevalence differs among the regions: it is 1.0% in North Vietnam [55] and 3.3% in Binh Thuan province [56].

No general population HCV prevalence data are available from Laos and the Philippines. In Laos, its prevalence among blood donors is 1.1% [57] and in the Philippines, it is 0.3–0.9% in blood donors and overseas worker candidates [58].

In the region, G1 and G6 represent over 60% of all the genotypes identified (35.2% and 30.8%, respectively), followed by G3 (19.9%) and G2 (11.1%). G4 and G5 have been seen in small percentages. G6 is seen in the vast majority (95.6%) in Laos and is predominant in Cambodia, Myanmar, and Vietnam (56.0%, 49.0%, and 54.4%, respectively). G1 is seen in higher than 60% in Indonesia. G3 is seen in Malaysia and Thailand in significant percentages (58.6% and 44.2%)

1.2.3 Europe

The estimated anti-HCV prevalence in all Europe is 1.8%, accounting over 13 million of cases.

1.2.3.1 Central Europe

This area includes Albania, Bulgaria, Bosnia and Herzegovina, Czech Republic, Croatia, Hungary, Macedonia, Montenegro, Poland, Romania, Serbia, Slovakia, and Slovenia. The overall anti-HCV prevalence is 1.3%, ranging from 0.4% in Macedonia to 1.4% in Slovakia. The prevalence is around 1% in most of the countries in the region: Albania (1%), Bosnia and Herzegovina (1%), Croatia (<1%), Macedonia (0.4), Serbia (1%), and Slovenia (<1%) [59]. It is 0.7% in Czechia. No data for Montenegro are reported.

G1 (70%) is the predominant genotype, followed by G3 (21%), G4 (4.9%), and G2 (3.2%). Only a small percentage of mixed genotypes and G6 has been found in Poland, whereas no G5 cases are reported.

G1 is the predominant genotype in Romania, Hungary, Slovakia, and Bulgaria (98%, 94.1%, 89.9%, and 82.4%, respectively). G3 is reported in considerable rates from Macedonia (44.6%), Slovenia (37.8%), and Croatia (35.6%), G2 from Albania (20%), and G4 from Montenegro (19.6%) and Albania (16%) [5].

1.2.3.2 Eastern Europe

This region includes Belarus, Estonia, Lithuania, Latvia, Moldova, Russia, Turkey, and Ukraine, and overall anti-HCV prevalence is 3.1%, ranging between 12.3% in Ukraine and 1.26% in Belarus.

In Ukraine, the prevalence of HCV in the general population was reported as 12.3%, having one of the highest rates in the world. Relatively high prevalence (1.3%) in healthy blood donors also suggests a very high prevalence in the country (Hope). The prevalence is higher compared to other parts of Europe: Moldova (4.5%), Russia (4.1%), Latvia (2.4%), Lithuania (1.96–2.85%), Estonia (1.5–2.4%), Belarus (1.26%), and Turkey (0.95%).

The predominant genotype in this region is G1 (68.1%), followed by G3 (26.6%) and G2 (4.3%). A small percentage of mixed genotypes and G4 (2.6% in Belarus) are reported, while no G5 and G6 cases have been described. A considerable percentage of G3 was described in Belarus (38.5%), Russia (35.1%), Estonia (24%), and Lithuania (19%). In Turkey, 87.5% of genotypes is G1 [60]. No genotypes distribution data are available from Ukraine.

1.2.3.3 Western Europe

The countries in this area include Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and the United Kingdom.

The overall prevalence of HCV in the general population is 0.9%, ranging from 2.0% in Italy to 0.2% in the Netherlands. The prevalence is relatively low compared to other parts of Europe and to other parts of the world.

Anti-HCV positivity prevalence in Switzerland is 1.6%, Greece 1.5%, Portugal 1.5%, Spain 1.5%, Ireland 0.9%, Belgium 0.7%, France 0.7%, Luxembourg 0.7%, Denmark 0.6%, Norway 0.6%, Sweden 0.6%, Finland 0.5%, Germany 0.5%, Iceland 0.4%, the United Kingdom 0.4%, and Austria 0.3% [5–12].

The predominant genotype is G1 (55.1%), followed by G3 (29%), G2 (8.9%), and G4 (5.8%). Only small percentages of G5 (2% in Belgium), G6 (0.2% in France), and mixed genotypes are reported. G1 is more than 60% in Austria, Spain, Germany, and Italy.

A considerable percentage of G3 was described in some of the countries of the Northern Europe, such as Iceland (55%), Finland (46%), the United Kingdom (43.8%), Denmark (43%), Portugal (28%), Germany (27%), France (20%), Austria (19%), and Belgium (19%) while only Italy has a significant percentage of G2 (26%).

1.2.4 Australasia

This area contains Australia and New Zealand, with an overall prevalence of HCV of 1.8%. It ranges between 1.9% in New Zealand and 1.7% in Australia and accounts for 0.5 millions of cases [5].

The leading genotype is G1 (55%) followed by G3 (36%) and G2 (6.6%). Only a small percentage of G4 and G5 has been reported.

1.2.5 Americas

Three areas are analyzed in the American continent: North America, Caribbean, and Latin America.

The prevalence of anti-HCV in the whole American continent is 1.3%, corresponding to more than 12 million of estimated cases. The most prevalent genotype is G1 in the continent (74.5%), followed by G3 (10.6%), G2 (10.2%), and G4 (1.7%). G5 and G6 are reported in small rates.

1.2.5.1 North America

This area includes Canada and the United States. The average prevalence of HCV in the general population is 1.2%: 1.1% in Canada and 1.3% in the United States.

The predominant genotype is G1 (60% in Canada and 72.5% in the United States), followed by G3 (22.3% in Canada and 8.9% in the United States), G2 (13.1%), and G4 (4.3%). Small percentages of G5 (from Canada) and G6 (Southeast Asian immigrants from the United States) have been reported [61].

In the United States, HCV is the most common blood-borne infection. The best estimates of HCV prevalence derive from analysis of serum specimens taken from participants in the National Health and Nutrition Examination Survey (NHANES) including data from 2003 to 2010 and estimated a prevalence of 1.0% [62]. However, the survey did not sample certain populations, including the incarcerated, homeless, nursing home residents, persons on active military duty, and immigrants. The HCV prevalence is highest among persons born during 1945–1965 [63]. The Center for Disease Control (CDC) estimates that approximately three-fourths of all persons living with HCV infection in the United States were born during 1945–1965. The higher prevalence of HCV infection among persons born during 1945–1965 corresponds

with the high HCV incidence that occurred among young adults in the 1970s and 1980s [64]. Injection drug use is the most common risk factor for acquiring HCV in the United States, accounting for more than 60% of all cases of HCV [65].

Based on national 2011 hepatitis C estimates, HCV prevalence in Canada is 1.0% [66]. People who inject drugs comprised 42.6% of all antibody-positive cases and people born in a country outside of Canada comprised an additional 35.0% of all antibody-positive cases. Chronic hepatitis C was most prevalent among people born in 1955–1959 (1.5%), followed by those born in 1950–1954 (1.25%), 1960–1964 (1.2%), 1965–1969 (1.1%), and 1970–1974 (0.8%).

In the United States, 75% of chronic HCV infections are caused by hepatitis C G1, 15–20% by genotype 2 or 3, and less than 5% by genotypes 4, 5, or 6. Among the G1 infections, G1a is more common than G1b (Manos). In Canada, G1 is the most prominent genotype (60%), followed by G3 (22.3%) and G2 (15.4%) respectively [34].

1.2.5.2 Caribbean

This area includes Cuba, Dominican Republic, and Puerto Rico. The overall prevalence of HCV is 1.5%: 0.8% in Cuba, 1% in Dominican Republic, and 2.3% in Puerto Rico [5].

The predominant genotype in the region is G1: 98% in Cuba, 62.6% in Dominican Republic, and 82.1% in Puerto Rico. G2 (7.2%) and G3 (2.1%) are seen in small percentages. No cases of G5 and a very small percentage of G4 and G6 are reported.

1.2.5.3 Latin America

Latin America is further divided in four different areas: Andean which includes Bolivia and Peru; Central includes Colombia, Mexico, and Venezuela; Southern includes Argentina, Chile, and Uruguay; and Tropical includes only Brazil.

The HCV prevalence in the area is 1.4%. It is 1.2% in the Andean area and 1.6% in the Tropical zone. The countries in the area have comparable HCV prevalence: Brazil (1.6%), Argentina and Venezuela (1.5%), Mexico (1.4%), Peru (1.2%), Chile (1.15%), and Colombia (1.1%).

The predominant genotype in the region is G1 (74.3%), followed by G3 (14.2%) and G2 (10.4%). Only a small percentage of G4, G5, G6, and mixed genotypes are reported.

In some of the countries in the region (Peru, Colombia, Chile, and Uruguay) G1 is almost the only observed (86%, 88.5%, 80.6%, and 74%, respectively), whereas in others (Venezuela, Mexico, and Argentina) G2 shows a significant percentage (34.4%, 21.8%, and 24.7%). Brazil and Uruguay are countries where G3 has a considerable percentage (30.2% and 26%, respectively) [67]. No genotypes distribution data are available from Bolivia.

HCV epidemiology of the countries according to the region and income status is given in Table 1.1 [5, 6, 8–11, 39, 68–72]. Figures 1.1 and 1.2 show the map of countries according to the prevalence of HCV and genotypes, respectively [73, 74].

Table 1.1 HCV epidemiology of the countries according to the region and income status [5, 6, 8–11, 39, 68–71]

Country	Income[a]	HCV prevalence %	Viremic prevalence %	Viremic rate %	Viremic diagnostic rate %	The most common genotype
Asia						
Asia, Central						
Azerbaijan	Upper-middle-income	3.1				1
Georgia	Lower-middle-income	6.7	4.2			1
Kazakhstan	Upper-middle-income	2.9–3.9	2.2	80	17	1
Kyrgyzstan	Lower-middle-income	2.5–3.1				
Mongolia	Lower-middle-income	9.8	6.8	70	30	1
Tajikistan	Low-income	0.5	4.3			1
Turkmenistan	Upper-middle-income	5.6				
Uzbekistan	Lower-middle-income	11.3	4.4	39.2		1
Asia, East						
China	Upper-middle-income	1.6	0.9	60		1
Hong Kong	High-income	0.3	0.2	78	22	1
Taiwan	No data	3.3	2.4	74	43	1
Asia, Pacific						
Japan	High-income	1.5	1.0	70	73	1
South Korea	High-income	0.8	0.5	56	39	1
Asia, South						
Afghanistan	Low-income	0.7	0.4	58.1		3
Bangladesh	Lower-middle-income	0.84	0.6	77.8		3
India	Lower-middle-income	0.5–1.5	0.7	81	5	3
Pakistan	Lower-middle-income	4.8–6.2	4.2	87	15	3

(continued)

Table 1.1 (continued)

Country	Income[a]	HCV prevalence %	Viremic prevalence %	Viremic rate %	Viremic diagnostic rate %	The most common genotype
Asia, Southeast						
Cambodia	Lower-middle-income	2.3–14.7	1.7	75.8		6
Indonesia	Lower-middle-income	0.8	0.5	66	10	1
Malaysia	Upper-middle-income	2.5	1.7	74	8	3
Myanmar	Lower-middle-income	2.0	1.1	55.6		6, 3
Philippines	Lower-middle-income	0.3–0.9	0.6			1
Thailand	Lower-middle-income	2.7	1.7	62.7		3
Australasia						
Australia	High-income	1.7	1.2	74.6		1
New Zealand	High-income	1.9	1.1	76	40	1
Europe						
Europe, Central						
Bulgaria	Upper-middle-income	1.5	1.3	87	19	1
Czech Republic	High-income	0.7	0.5	70		1
Croatia	High-income	0.9	0.9	70	25	1, 3
Hungary	High-income	0.7	0.5	75	47	1
Poland	High-income	0.8	0.5	70	15	1
Romania	Upper-middle-income	3.3	2.8	85	16	1
Slovak Republic	High-income	1.4	0.7	49	10	1
Slovenia	High-income	0.4	0.3	78	51	1, 3
European, Eastern						
Belarus	Upper-middle-income	1.26	0.9	69		1, 3
Estonia	High-income	1.5–2.4	1.5	76	51	1

Table 1.1 (continued)

Country	Income[a]	HCV prevalence %	Viremic prevalence %	Viremic rate %	Viremic diagnostic rate %	The most common genotype
Latvia	High-income	2.4	1.8	71	45	1
Lithuania	High-income	1.9–2.9	1.1	66	17	1
Moldova	Lower-middle-income	4.5				
Russia	Upper-middle-income	4.1	2.9	71	40	1
Turkey	Upper-middle-income	0.95	0.8	82		1
Ukraine	Lower-middle-income	3.6				3
Europe, Western						
Austria	High-income	0.3	0.2	73.4		1
Belgium	High-income	0.7	0.5	80		1
Germany	High-income	0.5	0.4	66.7		1
Denmark	High-income	0.6	0.4	62.2		1, 3
Finland	High-income	0.5	0.4	80	75	3
France	High-income	0.7	0.4	65		1
Greece	High-income	1.5	1.2	80	26	1
Iceland	High-income	0.4	0.3	80	83	3, 1
Ireland	High-income	0.9	0.7	75	38	1
Italy	High-income	2.0	1.5	73.3		1
Luxembourg	High-income	0.7	0.6	77	84	1
Netherland	High-income	0.18	0.13	74	61	1, 3
Norway	High-income	0.6	0.4	80	57	3
Spain	High-income	1.5	1.2	68.6		1
Sweden	High-income	0.6	0.5	77		1
Switzerland	High-income	1.6	1.0			1

(continued)

Table 1.1 (continued)

Country	Income[a]	HCV prevalence %	Viremic prevalence %	Viremic rate %	Viremic diagnostic rate %	The most common genotype
United Kingdom	High-income	0.4	0.3	68.5		3
America						
Caribbean						
Dominican Republic	Upper-middle-income	1.0	0.6	65	10	1
Puerto Rico	No data	2.3	1.0	68		1
Latin America, Andean						
Peru	Upper-middle-income	1.2	0.5			1
Latin America, Central						
Colombia	Upper-middle-income	1.1	0.9	80	13	1
Mexico	Upper-middle-income	1.4	0.8	65	30	1
Venezuela	No data	1.5	0.4			1
Latin America						
Argentina	High-income	1.5	1.2	80	34	1
Brazil	Upper-middle-income	1.6	1.3	80.5		1
North America						
Canada	High-income	1.0	0.8	74		1
United States	High-income	1.0	0.8	76.9		1
Africa						
North Africa and Middle East						
Algeria	Upper-middle-income	2	1.0			1
Bahrain	High-income	1.7	1.3	77	17	1
Egypt	Lower-middle-income	11.9	7.9	66.7		4
Iran	Upper-middle-income	0.3	0.2	62	33	1
Iraq	Upper-middle-income	0.1–0.8				4
Israel	High-income	1.96	1.5	76	24	1

Table 1.1 (continued)

Country	Income[a]	HCV prevalence %	Viremic prevalence %	Viremic rate %	Viremic diagnostic rate %	The most common genotype
Jordan	High-income	0.1–0.9	0.4	85	21	1, 4
Kuwait	High-income	0.8				4
Lebanon	Upper-middle-income	0.6–2.9	0.2	85	20	4
Libya	Upper-middle-income	1.2–1.8	0.7			4
Morocco	Lower-middle-income	1.6	0.9	75	10	1
Oman	High-income	0.5	0.4	75	20	1
Palestine	Lower-middle-income	0.2–0.3				4
Qatar	High-income	0.9	0.5	90	46	1
Saudi Arabia	High-income	1.5	0.5	70	21	4
Syria	Low-income	2.8				4
United Arab Emirates	High-income	0.1	0.1	68	40	1
Yemen	No data	0.9	0.8			4
Sub-Saharan Africa, South						
South Africa	Upper-middle-income	0.1–1.1	0.9	77	14	5
Zimbabwe	Low-income	2				
Sub-Saharan Africa, West						
Benin	Low-income	1.6				2
Gambia	Low-income	2.1	0.8			
Ghana	Lower-middle-income	2.0	1.5	74	7	2
Mauritania	Upper-middle-income	1.1				
Nigeria	Low-income	2.2	1.5	68	4	1

[a]World Bank Country classification [72]

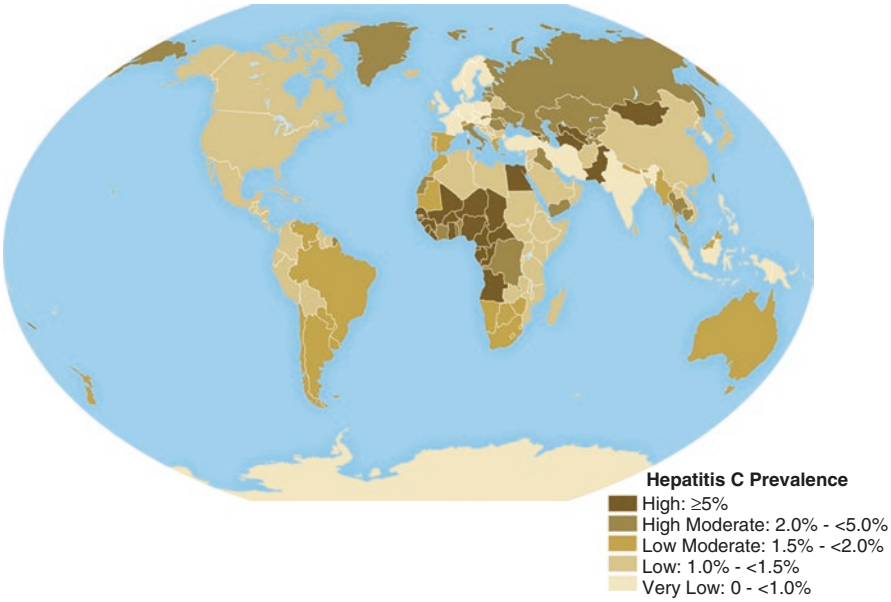

Fig. 1.1 Prevalence of hepatitis C virus infection [73]

1.3 Discussion

The recent and realistic estimates show that global HCV prevalence is about 1% with significant regional changes. In high-income countries HCV prevalence is usually below 2%, while it reaches higher than 5% in several low to middle-income countries [6]. Especially in Asia and Central Africa, some countries have insufficient data on the epidemiology of HCV, and in large countries, information from some region may not reflect the other parts.

Changing risk factors over time seem to change the incidence of HCV infection and cause significant prevalence differences among age groups. In Egypt, unsafe medical practices in the past have caused a significant increase in HCV infection. This effect shows itself as high percentage of HCV infection in the elderly; however young population has very low prevalence [32]. In Japan, most of HCV infections were transmitted through contaminated blood products and unsafe medical procedure during the first half of the twentieth century [36, 75]. In Italy, HCV infection burden was associated with unsafe injections practices between the 1940s and the early 1960s [76], in addition to injection drug use between the 1970s and the early 1980s [77].

The incidence of new HCV infections has changed over time by different exposure to key risk factors. Injection drug use, blood transfusion, and iatrogenic infections appear as the current risk factors (Table 1.2) [78]. In the USA, about 75% of total hepatitis C infection cases are those born between 1945 and 1964, the so-called

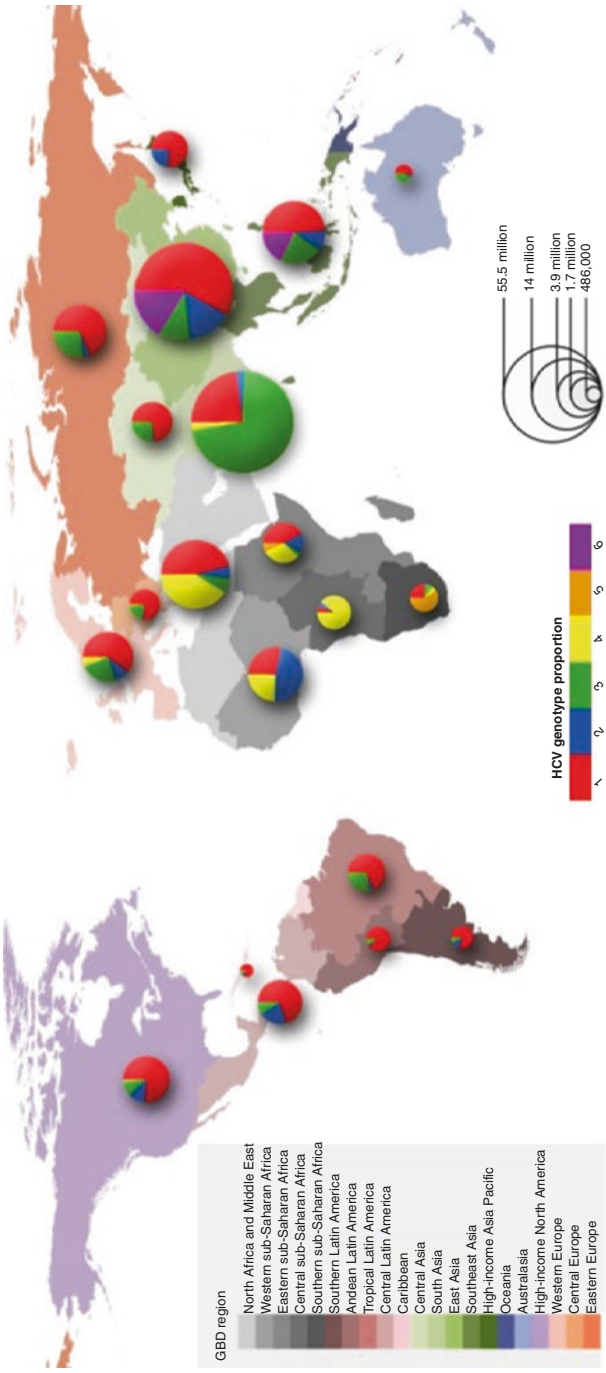

Fig. 1.2 Global distribution of HCV genotypes [74] (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4303918/bin/hep0061-0077-f1.jpg)

Table 1.2 Populations at increased risk of HCV infection [78]

Risky populations	Remarks
1. Person who inject drugs (PWID)	• The prevalence of HCV in this group is 67%
2. Blood transfusion receivers or patients who undergo invasive processes in hospital	• In case of not complying with infection control precautions
3. Infants born from mothers infected with HCV	• Infection rate without coinfection with HIV 4–8% • Infection rate with coinfection with HIV 17–25%
4. Person who has a sex partner infected with HCV	• Especially in MSM population, risk increases with having unprotected sex
5. Person who used intranasal drug (drugs which are not injectable)	• Like cocaine
6. Cosmetic procedure	• Like tattoo or piercing

baby boomers [79]. The reason baby boomers have high rates of hepatitis C is not completely understood; they are believed to be infected in the 1960s through the 1980s when transmission of hepatitis C was very high. They could have been infected from medical equipment or procedures before universal preventive measures and infection control procedures were used, or from contaminated blood and blood products before widespread screening eliminated HCV transmission from the blood supply by 1992. Sharing needles or equipment used to prepare or inject drugs is another way that the virus can be transmitted.

In the Russian Federation, new infections have dramatically increased between the late 1990s and 2000s. Injection drug use has been reported as playing a major role in the spread of HCV in addition to the probable role of an increase in iatrogenic infections [80]. Cameroon, Gabon, Georgia, Mongolia, and Uzbekistan have a high prevalence (>5%) of HCV infection in the adult population. The regional risk factors are iatrogenic infections, including unsafe medical practices and suboptimal blood screening [81, 82].

There have been HCV outbreaks in the developed world. The US Centers for Disease Control and Prevention (CDC) reported 22 HCV outbreaks associated with medical practice leading to 239 new acute HCV cases and more than 90,400 at-risk persons between 2008 and 2014 [83]. HCV outbreaks at hospital settings are also reported in Europe [84, 85]. Injection drug use is another way of transmission supporting the HCV burden. The United Kingdom reported a high HCV incidence of 42 cases per 100 person-years among injection drug users aged less than 30 years [86].

The CDC reported that the annual incidence rate of acute HCV infection in the USA increased more than twofold (from 0.3 to 0.7 cases/100,000) from 2004 to 2014. The increase was especially noted among select demographic subgroups. Admissions to medical care for disorders attributed to injection drug use increased significantly, with an almost fourfold increase in prescription opioid analgesic injection. These increases in opioid injection use were parallel to those for reported cases of acute HCV infection among demographic subgroups [87]. Even HCV reinfection rates remain elevated after DAA therapy among injection drug users because of ongoing exposure risk [88].

Heterosexual transmission has a very limited role in the transmission of the virus [89]. However, HCV prevalence and incidence are significantly higher in men having sex with men, suggesting a role in transmission [90, 91].

Mother-to-child vertical transmission of HCV is an important contributor to the HCV infection burden and is the commonest HCV transmission route in children. Transmission rates of HCV from mother to child ranges from 6% to 11% in different populations globally [92]. In previous studies, many factors have been suggested to be associated with vertical transmission [93]. A recent systematic review showed that nonpharmacological intervention (mode of delivery, labor management strategies, and breastfeeding practices) has not been clearly demonstrated to reduce the risk for mother-to-infant HCV transmission. The risk of transmission of HCV through breast milk is very low [94].

Immigration from Eastern Europe, Middle East, and African countries to Western European countries has increased due to the social, economic, and political conflicts in the region. Immigration from Syria increased dramatically during the last decade [95]. Immigration causes interruption of the health care and the immigrant can carry the infectious agent to the other countries. European data show that HCV prevalence among immigrants is close to the prevalence of country of birth [96]. Immigrants are not expected to contribute to the host country's HCV prevalence significantly; however a nonprevalent genotype may be transmitted.

1.4 Conclusion

The prevalence of HCV infection, depending on detection of HCV antibodies, is around 1% with significant regional differences. There is still limited information of its prevalence and genotype distribution in some parts of the world.

There is no effective vaccine against HCV. However, with the use of DAAs, it is a treatable disease. Treating currently infected individuals is an effective way of transmission. The vast majority of the infected individuals are not aware of the disease and remain undiagnosed. Among diagnosed patients, reach of DAAs is limited in several regions. The strict application of standard preventive measures and screening of blood/blood products before transfusion are main ways for controlling HCV transmission. Needle and syringe programs and opioid substitution therapy are effective in reducing blood-borne infection among injection drug users. Besides increasing diagnostic rate and extending use of effective therapy, public health programs aiming to prevent emergence of new infections by raising awareness of and education on HCV and conducting screening activities are essential to eliminate HCV at the global level.

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Laboratory and Molecular Diagnosis of Hepatitis C and Resistance Testing

2

Maliha Naseer, Harleen Chela, and Alhareth AlJuboori

2.1 Introduction

Hepatitis C infection is a global epidemic. It is currently one of the major public health problems with a significant economic burden. According to World Health Organization (WHO) the most commonly affected regions are Eastern Mediterranean and Europe with a prevalence of 2.3% and 1.5%, respectively. In other regions of the WHO, the prevalence of infection ranges from 0.5 to 1.0%. It has been estimated that globally there are 23.7 new HCV infections per 100,000 people [1]. According to the CDC, estimated prevalence of chronic hepatitis C infection in the United States is 3.5 million [2].

Primary mode of transmission of hepatitis C infection includes intravenous drug use. Other common causes include exposure to contaminated blood and blood products in the healthcare setting such as transfusion before 1992, hemodialysis, occupational exposure to contaminated needles, and patient-to-patient transmission of HCV due to poor infection control policies. Vertical transmission from infected mother to infant at the time of delivery, tattoos from unlicensed parlors, and men who have sex with men (MSM) are relatively uncommon modes of hepatitis C transmission [3].

The natural history of the chronic hepatitis C infection is not completely defined. Acute hepatitis C infection is commonly unrecognized. Most of the patients with acute hepatitis C infection are asymptomatic or may have mild nonspecific flu-like symptoms such as fatigue, malaise, nausea, or jaundice. It has been shown from the

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available literature that approximately 18–34% of the patients are able to spontaneously clear infection. Several genetic factors such as the presence of DQB1∗0301 allele of the MHC class II (major histocompatibility complex) and IL28B inheritance are found to be associated with spontaneous resolution of acute hepatitis C infection. Hepatitis C is a slowly progressing disease and approximately 80% of the acute HCV patients develop chronic hepatitis C infection. Progression from acute to chronic infection is usually subclinical. Persistent inflammation of the hepatocytes leads to the development of liver cirrhosis in about 15–20% of the patients with annual 1–4% risk of development of hepatocellular carcinoma and a 3–6% annual risk of hepatic decompensation. Decompensated liver cirrhosis and hepatocellular cancer due to chronic hepatitis C are the major causes of liver transplantation in the developed countries [4, 5].

Serological immunoassays and confirmatory virological tests are needed to diagnose, manage hepatitis C infection, and assess response to treatment and prevention of transmission. Rapid, inexpensive, sensitive, and specific tests are approved by FDA and include HCV antibody test, HCV viral load, genotyping, and less commonly liver biopsy. This chapter focuses on the laboratory molecular diagnosis of hepatitis C infection and resistance testing.

2.2 Indications for HCV Testing and Linkage to Care

According to World Health Organization (WHO), American Association for the Study of Liver Disease (AASLD), and European Association for the Study of the Liver (EASL) guidelines one-time screening test is needed in the following population [6–8].

2.2.1 Recommendations for One-Time HCV Testing

Persons born between 1945 and 1965, without prior ascertainment of risk (Grade 1b).

Other persons should be screened for risk factors for HCV infection, and one-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection (Grade 1b).

1. *Risk behaviors*: Such as intravenous drug use and intranasal drug use.
2. *Risk exposures*: Which include people on long-term hemodialysis, percutaneous/parenteral exposures in an unregulated setting, people with occupation exposure in healthcare setting for example needlestick injury, children born to HCV-infected mother, recipient of blood transfusion before 1992 or clotting factor concentrate before 1987, solid-organ recipient, and people who were ever incarcerated.

3. *Other consideration includes*: People who are HIV positive, sexually active people about to start pre-exposure prophylaxis (PreP) for HIV, unexplained cirrhosis, or elevated liver enzymes in asymptomatic patients and solid-organ donors.

2.2.2 Recommendation for HCV Testing in Those with Ongoing Risk Factors (Grade IIa, C)

1. Periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV. Annual HCV testing is recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men.

2.3 Laboratory and Molecular Diagnosis of Hepatitis C and Resistance Testing

Screening test: This includes serological test for the HCV antibody (Ab).

Confirmatory test: Positive anti-HCV test requires confirmation with the presence of HCV RNA (quantitative and qualitative test). Initial HCV-RNA testing is also recommended among people at risk of reinfection after previous spontaneous or treatment-related viral clearance, because an anti-HCV test is expected to be positive (Grade I, C) and prior to the initiation of antiviral therapy to document the baseline level of viremia (i.e., baseline viral load) (Grade I, A) [6].

Genotype: After confirmatory testing, specific genotype of the HCV and its subtype should be determined using genotype test.

Drug resistance: Mutations of some proteins in HCV can allow the virus to have resistance to direct-acting antivirals (DAAs), commonly referred to as resistance-associated variants (RAVs) or resistance-associated polymorphisms (RAPs).

2.4 Recommended Testing Sequence

The Centers for Disease Control and Prevention published the testing sequence for diagnosis of chronic HCV infection in May 2013 (Fig. 2.1). According to the new recommended sequence, the initial screening test for hepatitis C infection is HCV antibody (using either a rapid or laboratory-conducted assay), followed by HCV RNA testing for all positive HCV antibody tests. No further diagnostic tests are necessary if a person has a negative screening HCV antibody test and is considered as noninfected. However, high-risk individuals such as acute HCV infection, chronic hemodialysis, or an immunocompromised host need further evaluation to rule out false-negative result. On the other hand, individuals with a positive HCV antibody test and HCV RNA are considered to have current (active) HCV infection. An individual who has a positive HCV antibody test and a negative HCV RNA assay is considered not infected; further testing with different immunoassay is required to differentiate a false-positive result from infection [9].

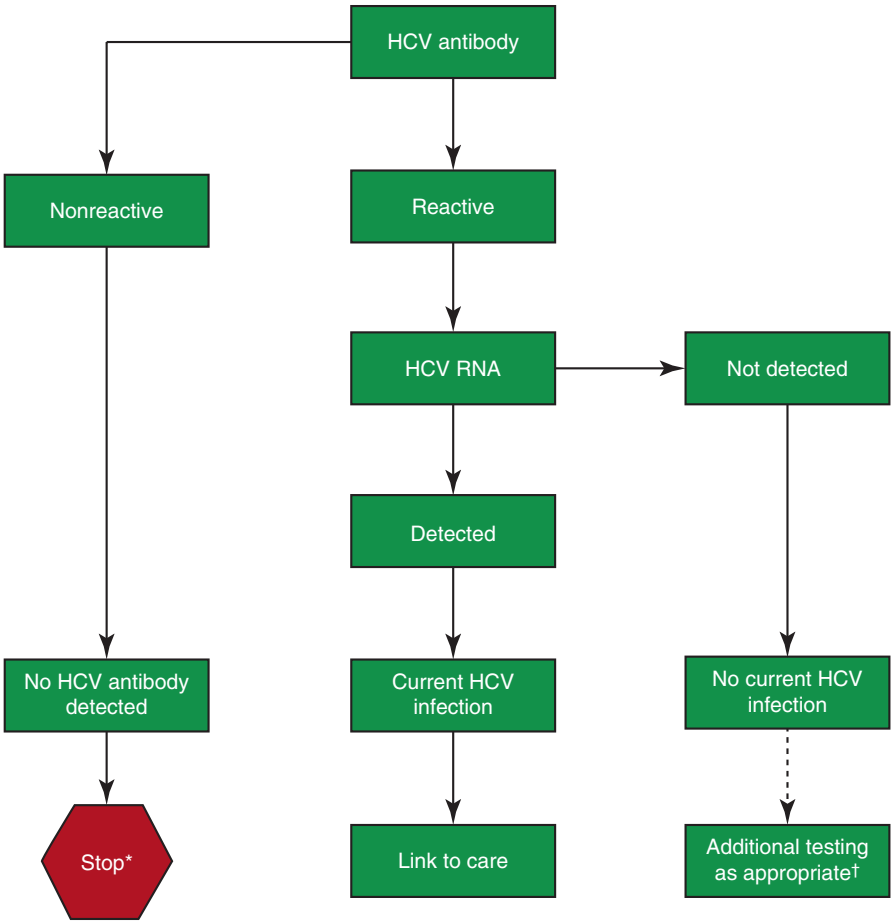

Fig. 2.1 HCV testing sequence for identifying current HCV infection (adopted from 2013 CDC guideline on the testing sequence of hepatitis C infection diagnosis)

*For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or followup testing for HCV antibody should be performed. For persons who are immunocompromised, testing for HCV RNA should be performed

†To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV-antibody assay can be considered. Repeat HCV-RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen

2.4.1 HCV Genome

First identified in 1989, hepatitis C virus is a single-stranded RNA, small (approximately 55–65 nm) in size, and an enveloped virus that belongs to the Hepacivirus genus in the family Flaviviridae. The HCV genome has structural (S) and nonstructural (NS) regions that encode 3011- to 3033-amino-acid polypeptides that translate

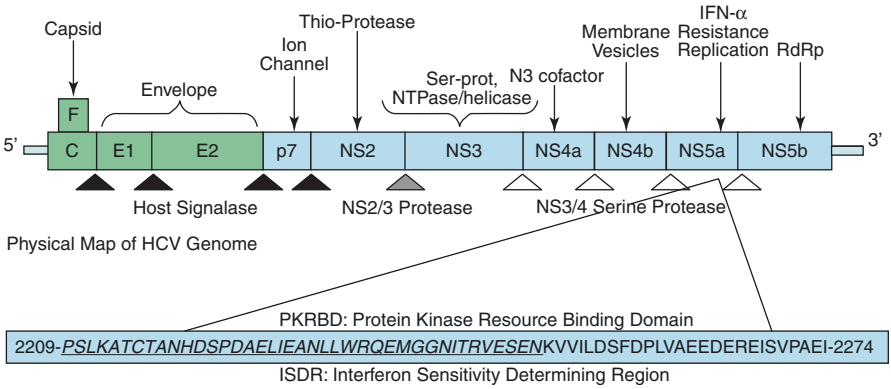

Fig. 2.2 Hepatitis C virus genomic map. The proteins are arranged as N terminal-core-envelope (E1)–E2–p7-nonstructural protein 2 (NS2)–NS3–NS4A–NS4B–NS5A–NS5B–C terminal

into ten structural and nonstructural proteins. The nonstructural (NS) proteins are classified as protease (NS2, NS3, and NS4A), RNA-dependent RNA polymerase (NS5B), and helicase (NS3). On the other hand, the structural region contains two envelope proteins (E1 and E2) and the core protein [10]. Genomic structure of the hepatitis C virus is illustrated in Fig. 2.2.

As shown in the figure the untranslated region (UTR) of hepatitis C virus mRNA consists of 5′ and 3′ ends which are important to the translation and replication of the viral RNA. At the 5′ untranslated region ribosome binds through the ribosome-binding site (IRES—internal ribosome entry site). HCV genome and protein form the basis of laboratory and molecular diagnostic tests for HCV and play a vital role in the emergence of resistant strain.

2.4.2 Hepatitis C Proteins

The hepatitis C genome can give rise to different proteins that are required for replication and these include [11–19]:

1. Structural proteins
   (a) Core protein: highly conserved and is part of the viral nucleocapsid. It consists of three domains and impacts functions of the host cell such as metabolism of lipids, transcription of genes, signaling pathways, and apoptosis.
   (b) Envelope proteins: are two types of highly glycosylated proteins called E1 and E2 and are key mediators in cell entry.
   (c) P7 protein: is a membrane-spanning polypeptide that consists of 63 amino acids and is found within the endoplasmic reticulum. It is required for assembly of the virus particle assembly and also mediates the release of these infectious particles by a process that is noted to be genotype specific.

2. Nonstructural proteins
   (a) NS2: is a transmembrane protein that is required for completion of the cycle of viral replication both in vivo and in vitro.
   (b) NS3: is a 63 kDa protein that serves numerous functions with its N-terminal having serine protease activity and the C-terminal carrying the NTPase/helicase activity for RNA replication.
   (c) NS4A: essentially serves as a cofactor for the NS3 protein.
   (d) NS4B: plays an important role of helping other viral proteins localize to a site in the endoplasmic reticulum referred to as the membranous web (formed by structural change in the endoplasmic reticulum induced by the NS4B protein itself). This site is where the replication complex is thought to form as all the viral proteins confine here.
   (e) NS5A: a hydrophilic phosphoprotein that is a crucial mediator of viral replication, affects signaling pathways and response to interferon.
   (f) NS5B: is a 65 kDa protein that is an RNA-dependent RNA polymerase and is involved in the formation of a new RNA genome.

2.5 Laboratory Diagnosis of HCV

2.5.1 Serological Immunoassays for HCV Detection

Serological assays for HCV detection are the preliminary tests to be performed when HCV infection is suspected and in select populations. Serological test aims at detecting anti-HCV antibodies after exposure to hepatitis C virus. A positive anti-HCV test indicates HCV infection at some point in time. However, it does not differentiate between current and resolved HCV infection and further confirmatory tests are required to make diagnosis of HCV and to guide appropriate treatment [20]. Below is the description of FDA-approved immunoassays.

2.5.1.1 Immunoassays

Enzyme Immunoassay (EIA)

Enzyme immunoassay was introduced in the 1970s and is among the first FDA-approved test which uses HCV recombinant antigens to identify the presence of anti-HCV antibodies. Enzyme immunoassay has been developed to detect antibodies to proteins expressed by structural (HC-34) and nonstructural (HC-31, c100-3) regions on the HCV genome. Solid-phase EIAs utilize immobilization of antigens or antibodies coated on a surface using solid support. After this step, the detection of antibodies or antigen is added, to form an antigen-antibody complex. The detection antibody can be covalently linked to an enzyme, or can itself be detected by a secondary antibody that is linked to an enzyme through bio-conjugation. The plate is usually washed with a mild detergent solution between each step to remove any antigens or antibodies that are not specifically bound to HCV proteins. The ultimate step during this process is the addition of an acid or an enzymatic substrate to

quantify the amount of antigen or antibody in the sample, which is read with a spectrophotometer [21].

According to available evidence single-antigen enzyme immunoassay for anti-HCV antibody detection is not as sensitive and specific as compared to multiple-antigen immunoassays. Hence, there is development of more sensitive and specific second- and third-generation assays [22].

- *First-generation EIA*: First-generation immunoassay was first developed in 1989 and involves identification of c100-3 epitope from the nonstructural NS4 regions of HCV genome. The major disadvantage of the test is low sensitivity, i.e., approximately 80%, leading to the high number of false negatives in the high-prevalence population. Also, the negative predictive value of the first-generation EIA is as low as 70% in the low-risk population such as in blood donors [23].
- *Second-generation EIA*: Developed in 1992 and included recombinant/synthetic antigens from the core and nonstructural NS3 and NS4 regions of the HCV genome. Second-generation EIAs have proved to be more effective as a screening test in individuals who are at high risk for chronic hepatitis C because of improved sensitivity and specificity. In acute HCV infection, second-generation EIAs can detect HCV antibodies in 20% more patients and 10% more patients with chronic HCV infection, i.e., increased sensitivity from 80% to 92–95% as compared to first generation and detect HCV antibodies 30–90 days earlier. The mean window of seroconversion was reduced from 16 weeks with EIAs 1.0 to 10 weeks with EIAs 2.0. The sensitivity of EIAs 2.0 in a high-prevalence population is approximately 95% (based on HCV RNA detection by PCR) [24].
- *Third-generation EIA*: FDA approved a third-generation EIA (EIA 3.0) in 1996 and currently Abbott HCV EIA (version 2.0; Abbott Laboratories, Abbott Park, IL) is used in the United States. The third-generation EIA detects antibodies that bind to recombinant antigens derived from four viral regions: core, NS3 (nonstructural 3), NS4 (nonstructural 4), and NS5 (nonstructural 5). The sensitivity of third generation of EIA is as high as 97% in a high-prevalence population and the mean time to seroconversion reduced from 10 weeks with second-generation EIAs to 5 weeks. The specificity of the anti-HCV assay (third generation) was found to be 99.5% for blood donor samples and 99.83% in volunteer blood donors and 99.79% in plasmapheresis donations based on an assumed zero prevalence of HCV antibody [25, 26].

Interpretation of the Test [27]

According to the ABBOTT HCV EIA 2.0 criteria the interpretation of the results is as follows:

1. Serum specimen with absorbance values ≥0.005 but less than the cutoff value is considered negative.
2. Specimen results having absorbance values less than 0.005 must be retested using the same product and test method. If the specimen still shows absorbance value <0.005 than the cutoff value, the specimen may be considered negative for anti-HCV antibodies.

3. Specimens with absorbance values greater than or equal to the cutoff value are considered initially positive. Original sample must be retested using the same product and test method. If the retested specimen still shows absorbance values greater than the cutoff value the test is interpreted as positive. However, if the retested specimen shows absorbance value less than cutoff value then the test is interpreted as negative.
4. Positive result, i.e., presence of HCV IgG antibodies in the patient serum, is not able to differentiate between current or past infection and exposures. To confirm the presence of viremia a positive antibody test result should be followed by confirmatory test such as HCV RNA.

ORTHO HCV Version 3.0 ELISA Test System

ORTHO HCV Version 3.0 is an enzyme-linked immunosorbent assay with the main purpose to detect antibody to hepatitis C (anti-HCV) in the human serum, plasma, and cadaveric specimen. Recombinant HCV-encoded antigens used in ORTHO HCV Version 3.0 ELISA Test system are c22-3, c200, and NS5 which cover 60% of the HCV genome. The test has high sensitivity and specificity, i.e., >99% [28, 29].

Principle of the Procedure

ORTHO HCV Version 3.0 ELISA Test System is a three-stage test, i.e., performed in a microwell coated with HCV recombinant antigens (c22-3, c200, and NS5).

- *Stage One*: In this stage human serum, plasma, or cadaveric specimen is diluted and then incubated in the test well for a specified length of time. Antigen-antibody complexes will be formed on the microwell surface if the sample has antibodies reactive to any of these above-mentioned antigens.
- *Stage Two*: During this stage, murine monoclonal antibody conjugated to horseradish peroxidase is added to the microwell which would subsequently bind to the human IgG portion of the antigen-antibody complexes.
- *Stage Three*: In this final stage, *o*-phenylenediamine (OPD) and hydrogen peroxide are added to the microwell. The OPD will be oxidized if antigen-antibody conjugate is present leading to a colored product which is detected by a spectrophotometer.

Interpretation of Results

Results of ORTHO ELISA are interpreted as follows [30]:

1. If the tested specimen is with absorbance values <−0.025, the specimen should be retested in the single microwell. If the retest absorbance value is less than the cutoff value, the specimen should be considered nonreactive.
2. Further testing is not required for specimens with absorbance values less than the cutoff value but greater than or equal to −0.025 and these specimens are considered nonreactive.
3. Specimens with absorbance values greater than the cutoff value are initially considered reactive and should be retested in duplicate before final interpretation. Retested specimen is considered repeatedly reactive, if either or both duplicate determination(s) have absorbance values greater than the cutoff value.

False-Negative and False-Positive HCV Ab Results

False-negative and -positive results with immunoassay are possible despite high sensitivity and specificity and HCV RNA should be ordered to confirm viremia in those situations.

False-Negative HCV Antibody

False-negative enzyme immunoassay should be suspected in the following situations [31]:

Serological Window Period: The average time for "serological window" period which is defined as the period after acute HCV infection but before seroconversion of negative to positive IgG HCV antibodies is 8 weeks in hepatitis C infection. It is the time during which EIA is often reported as false negative. It is appropriate to order HCV RNA if acute infection is suspected to happen within the past 8 weeks.

Immunocompromised patients: For example patients with diagnosis of HIV, recipients of organ transplantation, patients on long-term hemodialysis, patients with mixed cryoglobulinemia, and immunosuppressed patients. In these patients if HCV EIA is negative but there is strong suspicion of infection, HCV RNA testing should be performed.

False-Positive HCV Antibody

False-positive HCV antibody test may occur due to cross-reactivity of EIA HCV polyprotein with other viral antigens or secondary to the presence of certain autoimmune disease such as lupus arthritis or psoriasis [32].

Chemiluminescence Immunoassay (CLIA)

Chemiluminescence immunoassay (CIA) detects anti-HCV antibodies in human serum or plasma specimens by emitting light when a chemical reaction occurs between hepatitis C virus antigen and antibody. Like ELISA, antigens are initially immobilized during solid phase on monoclonal antibody-coated well. This step is followed by the addition of horseradish peroxidase (HRP)-labeled antibody or antigen [33]. After incubation for a shorter period, i.e., 1 h at 37 °C, unbound enzyme-labeled Ab is removed and chemiluminescence reagent added (Fig. 2.3).

The concentration of anti-HCV is expressed as a signal-to-cutoff (S/CO) ratio, and S/CO levels correspond to the antibody concentration. CLIA analyzers are fully automated, commercially available, and widely used, particularly in high-volume clinical settings. They are optimized for efficiency and throughput. Chemiluminescence immunoassays are reliable, reproducible, and technically simple to perform. For the diagnosis of chronic hepatitis C infection, the CLIA has much better sensitivity and specificity as compared to third-generation EIA. However, skilled personnel and suitable lab infrastructure are required to run these analyzers in the low-income countries [34]. The characteristics of the different CLIA analyzers are presented in Table 2.1.

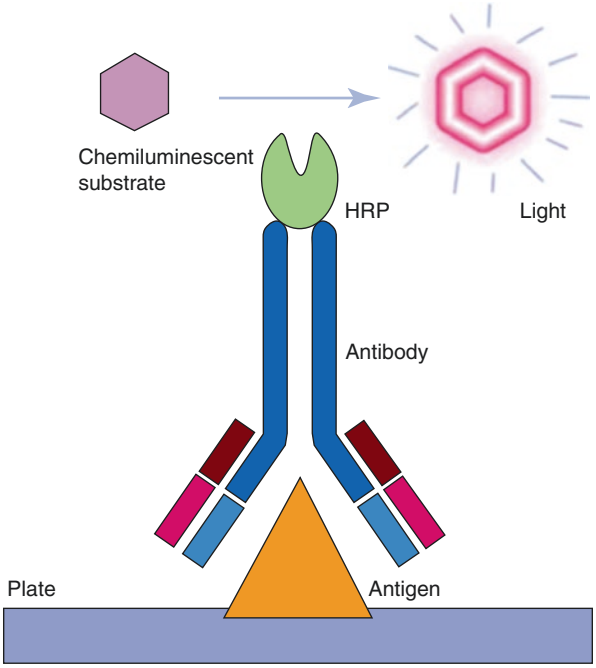

Fig. 2.3 Schematic presentation of CLIA for detection of anti-HCV antibodies

Table 2.1 Comparison of accuracy of commonly used point-of-care rapid diagnostic tests

Chemiluminescence immunoassay (CLIA)	Manufacturer	Method	Sensitivity	Specificity	Signal-to-cutoff ratio
ARCHITECT	Abbott	CMIA	90%	100%	≥5.0
Advia Centaur	Siemens	CIA	100%	99.9%	≥11.0
VITROS immunoanalyzers	Ortho	CIA	100%	99.7%	≥8.0
AxSYM anti-HCV	Abbott	MEIA	99.84%	98.9%	≥10.0

2.5.1.2 Point-of-Care Rapid Immunoassays/Rapid Diagnostic Tests (RDTs)

Though Centers for Disease Control and Prevention (CDC) recommends the use of enzyme immunoassay for the screening and recombinant immunoblot assay or HCV nucleic acid testing for RNA, these tests are expensive, require high-technology laboratories, and have long turnaround times. Rapid immunoassay tests detect HCV antigens from core, NS3, NS4, and NS5 regions of the hepatitis C virus [35]. RDTs are simple to perform, acceptable to patients, and cost-effective tests with an excellent turnaround time [36]. For the abovementioned reasons, this has the potential to substantially improve the access to HCV testing in hard-to-reach rural populations,

in limited resource settings, and can be used in outreach programs such as prison services, and substance use/treatment services. There is substantial evidence to suggest that rapid diagnostic tests improve linkage to care as the test can be performed by well-trained lay providers and hence reduce loss to follow-up [37]. According to the results of the study published by Morano et al., patients with HCV infection who had the rapid test were more likely to be linked to care as compared to those with conventional testing (93.8% compared with 18.2%). Patient and staff preference surveys showed strong support to use the rapid diagnostic tests at point of care [38].

Point-of-care rapid diagnostic tests can be run on the oral fluid, capillary, or venous whole-blood specimens and have high sensitivity (99%) and specificity (100%) in different populations and a wide range of settings based on the findings of the systematic review [39, 40]. An oral fluid-based point-of-care test has several advantages. They are noninvasive and simple to perform and do not require expert staff to carry out the test. However, the sensitivity of the oral RDTs is much lower than blood-based tests possibly due to lower concentration of anti-HCV antibodies in human saliva than blood specimens. According to the study published by Shivkumar et al. POCTs of blood (serum, plasma, or whole blood) have the highest accuracy, followed by RDTs of serum or plasma and POCTs of oral fluids [41].

Cost analysis showed that the average cost of RDTs for detection of HCV antibodies for capillary and whole-blood assay specimens ranges from $0.50 to $2.00 and $10 for oral fluid [42]. Although there are several rapid diagnostic tests available commercially, OraQuick is the only one approved by FDA from June 2010. The characteristics of the commercially available RDTs are compared in Table 2.2.

OraQuick HCV Rapid Antibody Test

The OraQuick HCV Rapid Antibody Test is approved by FDA for the qualitative detection of anti-HCV in individuals 15 years or older. Basic principle of the OraQuick HCV RDA test is to detect antibodies to both structural and nonstructural HCV proteins by utilizing the synthetic peptides and recombinant antigens from the core, NS3, and NS4 regions of the HCV genome that are immobilized as a single test line on the assay strip [43]. Specimens with positive anti-HCV antibodies produce a visible line in the test zone and are visualized by colloidal gold labeled with protein A. The OraQuick is very accurate, reproducible with sensitivity and specificity performance similar to third-generation EIAs. Though rapid kits have been extensively used for surveillance purposes, OraQuick HCV test has not been approved for general screening of hepatitis C infection. Furthermore, it is not well

Table 2.2 Comparison of accuracy of most commonly used point-of-care rapid diagnostic tests

Test	Sample	Sensitivity	Specificity	Positive LR	Negative LR
OraQuick	Whole blood, plasma, and serum	99.5%	99.8%	445.84	0.004
TriDot	Serum	98.2	98.4	61.22	0.009
Chembio	Whole blood and serum	95.1	98.6	68.45	0.065
Spot	Whole blood and serum	75.4	95.2	14.38	0.072

suited for high-risk groups and immunocompromised patients for detection of HCV infection [44]. World Health Organization recommends rapid diagnostic assays in the low- and middle-income countries and where there is limited access to the high-technology laboratory and immunoassay testing such as EIA and CIA.

2.6 Confirmatory Test

2.6.1 Recombinant Immunoblot Assay (RIBA)

The hepatitis C recombinant immunoblot assay (RIBA) is an in vitro qualitative enzyme immunoblot assay for the detection of HCV antibodies. It is one of the confirmatory tests for the hepatitis C infection and performed on the specimens found to be repeatedly positive for anti-HCV antibodies using anti-HCV screening procedure.

2.6.1.1 CHIRON' RIBA' HCV 3.0 SIA

The CHIRON' RIBA' HCV 3.0 SIA is an in vitro qualitative assay based on strip immunoblot assay methodology. It utilizes recombinant HCV-encoded antigens (c33c and NSS) and synthetic HCV-encoded peptides (C 100p and 5- 1- 1 p) immobilized as individual bands onto test strips. Detection of anti-HCV antibodies is facilitated by the addition of calorimetric enzyme detection system composed of hydrogen peroxide and 4-chloro-1-naphthol. The visual band pattern is produced when antigen reacts with specimen antibodies on the strip.

Advantages of the RIBA include provision of additional information in humans who had positive HCV immunoassay and a negative HCV RNA test. In this circumstance, the RIBA could differentiate whether the patient had resolved HCV infection or had a false-positive EIA. One of the advantages of RIBA is its high specificity (99.5%). However, CHIRON' RIBA' HCV 3.0 SIA is no longer used in the United States because of low sensitivity, high cost of the test, long duration to perform procedure, and hands-on complexity [45].

2.6.1.2 Interpretation of RIBA Results

Test is interpreted as positive if two or more antigens are present in the specimens, indeterminate if 1 antigen is identified, and negative for no antigen [46].

True-positive RIBA results indicate the presence of anti-HCV and do not differentiate past infection with spontaneous clearance from active infection; in this situation testing for HCV RNA is required to confirm active hepatitis C infection.

Indeterminate results: In acute HCV infection, assays are usually indeterminate during the first week of infection and it takes 1–6 months for the test to be positive. Moreover, presence of cross-reacting antibodies in specimen may result in indeterminate RIBA assay.

False-negative RIBA: RIBA may be false negative in immunocompromised patients or individuals with resolving hepatitis C infection because of waning level of anti-HCV antibodies.

2.7 Molecular Diagnosis of HCV Infection

As mentioned above, serological assays detect whether the person is infected with HCV or not and do not differentiate between current and resolved infection. Molecular diagnostic tests are required to confirm infection and identify current (active) hepatitis C infection status after the initial serological assays positive for anti-HCV antibodies. Molecular diagnostic tests serve important function of detection of HCV RNA, its quantification, and determination of genotype. HCV RNA can be detected in approximately 1–2 weeks after initial HCV infection with nucleic acid amplification test [25]. Several FDA-approved HCV nucleic acid amplification tests (HCV-NAAT) are available commercially and vary based on their accuracy, efficiency, and cost per test.

For the detection of HCV viremia FDA has approved both qualitative and quantitative tests. Qualitative HCV RNA nucleic amplification test is reported as positive and negative based on the presence or absence of detectable HCV RNA. In contrast, quantitative NAAT detects the quantity of HCV RNA in serum as viral load and provides information regarding specific genotype. Results of quantitative tests are important in making decision regarding treatment and response to therapy [47].

2.7.1 Sample Preparation

It is the first step in nucleic acid amplification test and involves extraction of HCV RNA from plasma using silica-based solid-phase and probe-based capture for RNA extraction. Silica-based solid-phase extraction is used in Cobas AmpliPrep (Roche), m2000 (Abbott Molecular, Abbott Park, IL), and VERSANT kinetic polymerase chain reaction (kPCR) sample prep system (Siemens) and involves reversible adsorption of nucleic acids to silica-coated magnetic beads in the presence of chaotropic salts and organic solvents. Probe-based capture for RNA extraction is used by direct tube sampling (DST) system, TIGRIS, and PANTHER platforms (Hologic, Bedford, MA) [48].

While Hologic TIGRIS is a fully automated system, the Siemens VERSANT kPCR Sample Prep system, Abbott m2000sp platform, and Qiagen Qiasymphony SP/AS (Qiagen, Venlo, the Netherlands) use semiautomated extraction system and assay setup. Manual transfer of eluted DNA is required in the final step of HCV RNA extraction. The Hologic TIGRIS system is currently incorporated in Procleix Ultrio Assay and APTIMA HCV RNA assay [49].

2.7.2 Amplification and Detection

Amplification and detection after RNA extraction entail polymerase-based target amplification via reverse transcription PCR or isothermal methods, coupled with endpoint or real-time detection formats. Assays based on real-time detection of virus such as Cobas TaqMan RT-qPCR HCV Assay are favored over endpoint

detection because of low risk of contamination. Other RT-qPCR assays commercially available are the Abbott RealTime and Siemens VERSANT kPCR HCV viral load assays, which use a similar principle [50].

2.7.3 Use of Quantitative or Qualitative NAT Assays

According to 2016 World Health Organization guidelines, either qualitative or quantitative NAAT is acceptable for the detection of HCV. However, the preferred strategy depends on resources of the healthcare system and laboratory infrastructure. Qualitative assays are preferred in resource-limited settings because these assays have the potential to be cheaper and more accessible. The cost of quantitative NAAT is high, ranging from $30 to $200 [51, 52]. According to the results of a systematic review that was conducted to determine the accuracy of qualitative versus quantitative NAT methods, the sensitivity of quantitative assays was 87–100% with lower limit of detection of 10–15 IU/mL as compared to qualitative assays (600–1100 IU/mL). However, with the advent of new quantitative HCV RNA assay the lower limit of detection of HCV has improved to 15 IU/mL (range: 12–108 IU/mL). Since 95% of chronic infection has a viral load >10,000 IU/mL most of the qualitative or quantitative NAT assays can detect HCV infection [53].

2.8 HCV Genotyping Assays

HCV genotyping is necessary to determine appropriate treatment selection, response to treatment, duration of treatment, and dose of ribavirin. Genotype is determined by analyzing genotype-specific sequences of the viral genome. Methods by which HCV genotyping can be done are as follows:

1. Direct Sequencing
   Direct sequencing for HCV genotyping is mainly used in epidemiological studies and currently considered a gold standard test. It involves direct sequencing of specific regions in viral genome (NS5, core, E1, and 5′ UTR) followed by alignment and phylogenic analysis. Examples of direct sequencing tests are HCV DupliType assay which is offered by Quest Diagnostics (New York, NY) and TRUGENE HCV Genotyping Assay by Siemens. TRUGENE HCV Genotyping Assay is an FDA-approved test. However, it is used solely for research purpose. Basic principle of the test is to use 244 base pair fragments of the 5′ UTR of the HCV viral genome. This fragment of HCV genome is then amplified via real-time PCR and sequencing using bidirectional cross-linking immunoprecipitation [54].
2. RT-qPCR
   Real-time PCR (RT-PCR) is a widely used and commercially available FDA-approved test for the purpose of genotyping of hepatitis C virus. It uses RT-qPCR technology with Taqman probes to detect and differentiate the HCV genotypes.

Sample is analyzed using three different RT-qPCR reactions. During each reaction primer, internal control-specific and genotype-specific probes conjugated to different fluorophores are used to allow detection of HCV genotype. RT-PCR assay involves four different primer sets used for different purpose. First primer set amplifies a sequence in the 5′ UTR, and second and third primer sets amplify sequences in the NS5B regions present in genotypes 1a and 1b. Fourth primer set added to the assay has the function to amplify IAC in the form of an armored RNA. During the process of amplification, the target RNA is initially converted into complementary DNA (cDNA) by rTth DNA polymerase (thermostable). After the process of denaturation, i.e., raising the temperature of the process above the melting point of the double-stranded cDNA, RNA and double-stranded DNA product are formed. During each round of thermal cycling, annealing of the primer and extension is allowed by dissociation of amplification into single strand at high temperature. Real-time PCR is >99% accurate in identifying HCV genotypes 1, 2, and 4. The test is 100% accurate for genotypes 3, 5, and 6. Shortcomings of the RT-PCR are long run time of the test (120 min), risk of contamination of the specimen, and need of high-technology laboratory facility [55, 56].

3. Hybridization-based line probe assays
   The VERSANT HCV Genotype 2.0 test (Siemens) is an FDA-approved test to commercially use in the United States for the genotyping of HCV. In Europe, the approved tests are LINEAR ARRAY Hepatitis C Virus Genotyping Test (Roche) and VERSANT HCV Genotype 2.0 test (Siemens). Principle of VERSANT HCV Genotype 2.0 test involves the amplification of 119 sequences in the 5′ UTR and core regions of the HCV genome using biotinylated primers by RT-PCR methodology. The biotinylated amplicons are immobilized on strips of nitrocellulose membrane and hybridized to genotype-specific oligonucleotide probes. Then conjugate composed of streptavidin–alkaline phosphatase is added to the sample which binds to the biotinylated captured amplicons. The last step involves addition of chromogenic substrate (BCIP–nitro blue tetrazolium) which produces a colored product on the membrane. Results are interpreted on LiPA HCV Scan software [57, 58].

2.9 Hepatitis C Ag Testing

The HCV core protein protects HCV by forming a capsid shell. HCV core protein can serve as a diagnostic marker for the diagnosis of viral hepatitis due to its antigenic characteristics. The HCV core antigen test was developed as an alternative to NAT, as access to and affordability of HCV confirmatory RNA NAT assays remain a challenge in resource-limited settings. Levels of hepatitis C virus (HCV) core antigen (Ag) can serve as a test to diagnose infection and to monitor response to treatment [59].

The ARCHITECT HCV Ag assay is a twostep chemiluminescent microparticle immunoassay (CMIA) technology based on flexible assay protocols referred to as

Chemiflex, for the quantitative determination of core antigen of hepatitis C virus. It's a fully automated test in which antigen-antibody reaction takes place between microparticle-coated monoclonal antibody and the HCV core antigen which is later detected by chemiluminescence technology [60]. The Architect HCV Antigen assay is now commercially available in Europe but not approved for use by FDA in the United States.

The sensitivity and specificity of ARCHITECT HCV antigen assay were found to be 97.2% and 100%, respectively. The sensitivity for detection of genotype 1 is found to be slightly better than genotype 3. The HCV Ag assay showed good correlation and excellent linearity with HCV RNA level. The HCV core antigen assay is an immunoassay that does not require sample processing as in molecular assay sampler, and a positive result confirms active infection. Hence it proved to be more cost effective, has better turnaround time, and does not require sophisticated laboratory structure. The lower limit of detection of HCV viremia with HCV antigen test is approximately 1000 IU/mL resulting in lower sensitivity as compared to NAAT [61].

2.9.1 Interpretation of Results

Results of ARCHITECT HCV Ag assay are interpreted as follows [62]:

1. Specimens with concentration values <3.00 fmol/L are considered nonreactive for HCV Ag.
2. Specimens with concentration values ≥3.00 fmol/L are considered reactive for HCV Ag.
3. Specimens with concentration values ≥3.00 fmol/L to <10.00 fmol/L should be retested in duplicate.
4. If both retest values are nonreactive, the specimen must be considered nonreactive for HCV Ag.
5. If one or both of the duplicates is (are) ≥3.00 fmol/L, the specimen must be considered repeatedly reactive for HCV Ag, and the initial value is used as the final reported value.

2.10 Resistance Testing

With the development of newer drugs, there has been the simultaneous emergence of drug-resistant viral variants of hepatitis C over the years. It is extremely important to be cognizant of the fact that the hepatitis C virus has the ability to develop resistance to antiviral therapies. Therapy for chronic hepatitis C has advanced significantly over the years from the combination treatment regimen of pegylated interferon and ribavirin combination to the powerful direct-acting antiviral agents (DAAs) [33]. These DAAs are categorized according to their mechanism of action and their molecular target and they impact different phases of the HCV life cycle

[63]. There are predominantly four main groups of DAAs and include the NS5A inhibitors, NS3/4A protease inhibitors, nucleotide analogue inhibitors of NS5B RNA-dependent RNA polymerase (RdRp), and non-nucleoside inhibitors of RdRp [33]. Treatment with DAAs is highly effective and results in high rates of sustained virological response (SVR). However approximately 10–15% of cases result in failure of therapy and this is due to the emergence of resistant viral variants [64]. These arise secondary to mutational changes that occur due to alterations in the amino acid sequences in the target protein of the virus, hence decreasing the susceptibility to the antiviral agent [64]. As the genomic sequences of HCV are so variable the resistance-associated variants (RAVs) can exist (at a low quantity) even prior to the initiation of therapy with DAAs [64]. Of note, the genotype 3 virus has been shown to have decreased rates of SVR to DAAs as compared to the other genotypes [65].

The hepatitis C virus is a 9.5 kb RNA virus that has the ability to replicate quickly by the action of an enzyme that can lead to several transcription errors per cycle [66]. The resultant transcription errors can lead to modification of coding regions causing the antivirals to become ineffective, hence leading to development of resistance to therapy [66]. The RNA-dependent RNA polymerase (RdRp) is deficient in the ability to proofread and this combined with the fact that the hepatitis C virus is highly replicative makes it prone to develop resistance to the direct-acting antiviral agents [67]. Due to the process of natural selection, there is formation of a "quasispecies" within an individual infected with HCV that consists of genetically distinct viral isolates [67]. The production of these variants tends to occur when levels of antiviral drugs are below the therapeutic level [66]. The resistant viruses then continue to proliferate as the drugs are no longer effective against them. The minor variants with polymorphisms that render them drug resistant can become the dominant isolates resulting in a virological breakthrough causing treatment failure or relapse after completion of therapy [68]. It is possible to detect known resistant variants prior to selection of antiviral therapy and this is especially valuable in cases of treatment regimens that include NS5A inhibitors as this can lead to an unfavorable outcome with therapy [66]. These alterations in the virus structure that attribute to resistance are known as baseline resistance-associated substitutions (RASs) [66]. Another form of resistant variants arises due to treatment failure with direct-acting antivirals and are known as treatment-emergent or treatment-selected RASs [66]. NS5A and NS3 resistance-associated substitutions are known to commonly emerge when there is treatment failure with regimens that include NS5A or NS3 inhibitors [66]. This is opposed to NS5B nucleotide resistance-associated substitutions that seldom emerge from treatment failure [69]. This phenomenon is referred to as a high barrier to resistance as the area to which the nucleotides attach is extremely conserved, hence minimal chances of producing resistant substitutions [66]. It is also believed that if such a substitution were to occur then it would also impede replication of the virus [66]. Another dilemma that is associated with the NS5A RASs is that they can continue to replicate even without the stress of selection from drugs in contrast to NS3 protease or NS5B nucleotide polymerase inhibitor RASs [66].

The clinical effect of resistance-associated substitutions (baseline and selected) on the results of therapy depends not only on the RASs but also on the choice of the antiviral regimen and patient-related attributes as well [66]. Hence merely testing for resistance-associated substitutions only will not help to guide the choice of antiviral therapy as other factors also need to be accounted for and an antiviral with known decrease in efficacy for a particular RAS can be utilized in certain scenarios [66]. Therefore, resistance testing needs to be performed but other factors also help to choose the appropriate antiviral regimen.

2.10.1 Polymorphisms (Also Called Substitutions)

For each genotype of the hepatitis C virus there is a consensus or reference nucleotide (an amino acid sequence) that exists [66]. A polymorphism (also referred to as substitution) is a change in the amino acid sequence that occurs at a particular location of the HCV protein resulting in a modification of the protein in the patient as compared to the reference protein [66]. Though substitution is the term that is more widely employed by most, the US Food and Drug Administration utilizes the term polymorphism to describe this alteration [66].

To delineate a substitution, one has to first describe the HCV genotype, the subtype, the HCV protein, as well as the location of the amino acid in the sequence [66]. Substitutions are defined as letter-number-letter [66]. The letter at the beginning denotes the amino acid that is normally present in that location in the reference protein [66]. The numerical value defines the position of the amino acid and the last letter describes the amino acid that is present in the patient's HCV protein [66]. For example, NS5A Y93M denotes that the amino acid at location 93 of the NS5A protein is typically tyrosine and the amino acid in the patient is methionine at this location [66]. It is also possible to have numerous variants and hence various amino acids can be seen at a particular location [66].

Naturally occurring polymorphisms can exist in treatment-naïve patients and they can confer resistance to NS5A, NS5B, and NS3/4A NS5B inhibitors [70]. Their occurrence is variable according to the genotype and subtype of HCV [70]. These can be then selected during direct-acting antiviral therapy and become the predominant variant leading to failure of therapy [70–72]. An example of such a substitution is the presence of the NS3/4A Q80K which predominantly occurs in those inflicted with the HCV genotype 1a leading to reduced rates of SVR in patients that receive treatment with the combination of simeprevir (protease inhibitor) and PEG-INF/RBV in contrast to those lacking the Q80K substitution [73, 74].

2.10.2 Resistance-Associated Substitutions (RASs)

This refers to any changes in the amino acid from the reference sequence at a location that is related to decreased susceptibility of the virus to a single or even multiple antiviral agent [66]. They can be categorized as:

1. Drug-Class RASs
   These are amino acid polymorphisms that decrease the vulnerability of a virus to any antiviral in a particular class (at least to one drug in the class) [66]. Though the act on a specific drug class this does not imply that all drugs within that class have emergence of resistance [66].
2. Drug-Specific RASs
   These are amino acid polymorphisms that decrease the vulnerability of a virus to a particular drug [66]. This is the category of RASs that needs to be addressed when evaluating the effect of a resistance-associated substitution on a treatment regimen [66]. In a treatment-naïve population that is inflicted with HCV infection, the drug-specific resistance-associated substitutions will be much less as compared to the class resistance-associated substitutions [66].

2.11 Methods of Resistance Testing

The methods for resistance testing can be categorized into genotypic and phenotypic analytical methods. The genotypic assays that are used to detect the resistance-associated substitutions are the population sequencing (also referred to as Sanger sequencing) and deep sequencing (also known as next-generation sequencing [NGS]) [66]. Both of these are based on the process of sequencing the RNA of the hepatitis C virus followed by deciphering of the sequence of amino acids and then analyzing as to whether there are any resistance-associated substitutions present [66]. Both of these vary in their sensitivity towards spotting the presence of RASs [66]. Either of these methods can be used and will be considered comparable if a cutoff of $\geq$15% is employed for detection of RASs by the method of next-generation sequencing [66]. Some of the latest research reveals that when next-generation sequencing is at 1% sensitivity then this leads to the detection of extra RASs that do not lead to treatment failure and may not necessarily carry clinical relevance [75–77]. Clonal sequencing is another form of genotypic analysis that is not commonly employed these days [67]. Phenotypic methods assess the degree of resistance to antivirals along with the replicative ability that is conferred as a result of amino acid substitutions [66].

2.11.1 Genotypic Methods

1. Population-Based Sequencing (or Sanger sequencing)
   This form of sequencing can be carried out on the targeted coding region using reverse transcription polymerase chain reaction (PCR) as well as by sequencing of the entire PCR product [66]. This method has a sensitivity rate that ranges from 15 to 25% for detecting resistance-associated substitutions [66]. The detected substitutions are then evaluated in comparison to a genotype-specific wild strain [66]. It reveals the predominant viral variants that are present within a quasispecies [67]. PCR primers that are genotype specific have to be utilized to allow for effective amplification of a particular gene given the vast diversity of the genotype

and subtypes of the virus [67]. With this approach however there is a potential for missing some potential minority RASs that have a clinical bearing [78].

2. Clonal Sequencing
   This involves the isolation of individual variants by the method of genetic cloning or by a process known as end-point limiting dilution [67]. The viral variants are introduced into a plasmid vector and then introduced into a bacterial host following which Sanger sequencing is performed on the individual clones [67]. Every clone signifies a variant within the quasispecies [67]. This method is extremely cumbersome as well as costly and with a restricted quantity of clones that can be examined [67]. This is not commonly used nowadays since the availability of next-generation sequencing which is preferred instead [67].
3. Deep Sequencing or Next-Generation Sequencing (NGS)
   Next-generation sequencing techniques (or deep sequencing) employ one of the two techniques: quasispecies assessment of a target gene or sequencing of the whole genome [67]. It leads to increased rates of sensitivity for detecting less frequently occurring substitutions [56]. Once the targeted HCV coding regions are sequenced using the PCR approach, the sequences are then analyzed and sorted to isolate the substitutions detected at a particular level. This threshold can be variable and can be set to >1% but the level is usually fixed at ≥10% so that the results from NGS are comparable to those attained from population sequencing [66]. Variants that account for <0.5% of the total are typically not counted due to the high changes of false-positive results that can occur during the process of amplification and sequencing [67].

2.11.2 Phenotypic Methods

These methods analyze the extent of drug resistance that occurs when an amino acid substitution or polymorphism occurs [66]. These techniques also analyze the ability of an individual RAS to replicate in the presence of a consensus strain [66]. To analyze the degree of resistance, the RASs are inserted as point mutations into a HCV genome that is present in a cell culture or even an enzyme-based system [66]. The variants that have the RASs are subjected to antivirals at increasing amounts and monitored for decline in replicative activity or decrease in enzymatic activity [66]. This is analyzed in reference to the wild strain [66]. Fitness can be assessed when the replicative capacity of the variants is compared to the wild strain without the presence of the drug [66]. However these methods are not commonly used clinically and more often employed for research purposes [66].

2.11.3 Clinical Correlation

As progress is being made to develop new direct-acting antiviral agents, the hepatitis C virus itself is making advances and is evolving to give rise to resistant variants. Being aware of drug resistance is important in order to help choose appropriate

treatment regimens containing the DAAs and to prevent failure of therapy and to optimize the success rates [68]. Resistance testing for antiviral agents can be carried out by either the population sequencing or the next-generation sequencing to evaluate for resistance-associated substitutions in NS5A, NS3, and NS5B [66]. Clinically when either the population sequencing or the deep sequencing methods are utilized the resistance-associated substitutions should be prevalent at a minimum of 15% and this is the advised threshold [66]. Below this threshold the RASs are not believed to have a substantial impact [66]. Apart from that when evaluating the clinical impact of resistance-associated substitutions, one should look at the drug-specific ones [66]. Hence the drug-specific resistance-associated substitutions need to be prevalent in at least 15% of a patient's virions to negatively impact the rates of sustained virological response [79].

Research studies and clinical trials reveal that resistance-associated substitutions are not always detected when failure of therapy occurs [66]. Some viral variants are less fit as compared to others; hence their life span is limited. Those that exhibit resistance to NS3/4A protease inhibitors are less resilient (can survive for only weeks or months) as compared to the viruses that are resistant to NS5A inhibitors (survive for years) and this carries clinical significance for treatment [66].

The RASs that are under close clinical scrutiny and carry substantial importance are those predominantly in relation to genotypes 1 and 3 [66, 78]. The RASs are less relevant for genotype 2 due to the restricted clinical impact [78]. The impact of a RAS depends on the antiviral drug class, effect on replicative capacity due to the RAS, genotype of the virus, and patient-related factors (whether patient is treatment naïve or not and if cirrhosis is present) [78]. For cases of HCV genotype 1, the subtype has a pivotal role in determining the presence of baseline (prior to antiviral exposure) nonstructural protein 5A (NS5A) resistance-associated substitutions along with their significance [78].

2.11.3.1 Key RASs by HCV Genotype and DAA Regimen (AASLD/IDSA, HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C)

Elbasvir/grazoprevir

- Genotype 1a: M28A/T, Y93C/H/N, L31M/V, and Q30H/R
- Genotype 1b: Y93H
- Genotype 3: None

Ledipasvir/sofosbuvir

- Genotype 1a: Y93C/H/N, Q30H/R, and L31M/V
- Genotype 1b: L31V, Y93H
- Genotype 3: None

Sofosbuvir/velpatasvir

- Genotype 1a: None
- Genotype 1b: None
- Genotype 3: Y93H

Paritaprevir/ritonavir/ombitasvir with dasabuvir ± ribavirin

- Genotype 1a: None
- Genotype 1b: None
- Genotype 3: None

The resistance-associated substitutions that affect the NS5A inhibitors carry the most clinical importance [78]. The RASs that affect NS5B nucleotide inhibitor sofosbuvir are not present in treatment-naïve individuals and only occur rarely (about 1%) or in those with treatment failure [69, 80]. The NS5B mutation known as S282T gives some resistance to the variant but is not beneficial for replication [69]. Hence this mutation does not carry a clinical significance as it does not alter the overall effect of sofosbuvir and therefore NS5B resistance testing is not recommended routinely for patients that are treatment naïve or exposed to treatment in the past [78].

RASs to NS3 protease inhibitors that would bear importance are uncommon in those that are treatment naïve to this antiviral class [78]. For HCV genotype 1a the testing of Q80K polymorphism is recommended only in cases of cirrhotic patients who are treatment experienced and not recommended routinely anymore when combination therapy of simeprevir and sofosbuvir is administered for the appropriate duration [81]. There is no effect of the Q80K polymorphism on the other NS3 inhibitors such as grazoprevir- or the ritonavir-boosted paritaprevir [78]. NS3 RASs occur in about 50% cases of treatment failure of a regimen that contains a protease inhibitor [82, 83]. Of the three main RASs, the R155K variant is seen in genotype 1a HCV and has no effect on the efficacy of grazoprevir [84]. However the D168 and A156 variants are seen in infections with both genotypes 1a and 1b [78]. They both occur more commonly and have an effect on the efficacy of all the protease inhibitors that are used in the treatment of HCV [78]. On the other hand they have meager replicative activity and hence disappear quickly once the antiviral agent is withdrawn (along with the stimulus to promote their selection) [82, 83]. Once variants disappear and are undetectable, it is unclear as to whether they will affect the follow-up treatments [78].

The most crucial resistance-associated substitutions are those that are in the nonstructural protein 5A (NS5A) [78]. Preexisting NS5A RASs are common with a prevalence rate of 13% in genotype 1a and 18% in genotype 1b [77]. The prevalence in genotype 3 infection is 12–17% [85, 86]. The effect of preexisting NS5A RASs depends on the genotype and subtype of the hepatitis C virus and has the most effect on the genotypes 1a and 3 [78]. Patient-related factors also play a role and increase the effect of NS5A RASs and these include patients inflicted with cirrhosis and treatment-experienced patients (not with an NS5A inhibitor) [78]. Once therapeutic failure occurs with a regimen containing NS5A inhibitor, the outcome is that most patients will then be infected with these NS5A RASs (noted from 75 to 90%) [80, 82, 83]. These NS5A RASs are very resilient and have significant amount of replicative fitness. In the majority of cases once they emerge in an individual they are detectable for over 2 years [82, 87]. There is also a significant degree of cross resistance that occurs among the NS5A inhibitors [78]. In genotype

1a, particularly the RASs at certain positions [80, 82, 83, 85] lead to cross resistance among the early-generation NS5A inhibitors [78]. By extending the duration of treatment and by combining ribavirin to the treatment regimen, one can dampen the effect of NS5A RAS [76].

2.11.3.2 Recommendations as per AASLD/IDSA Guidelines on Indications of RAS Testing According to Treatment Regimens

Antiviral combinations in which NS5A RAS testing is recommended (AASLD/IDSA, HCV guidance: recommendations for testing, managing, and treating hepatitis C).

Elbasvir/grazoprevir

1. Perform testing for genotype 1a: both treatment-naïve and -experienced individuals.
2. If RAS present: add ribavirin (weight based) and lengthen duration of therapy to 16 weeks.

Sofosbuvir/velpatasvir

1. Perform testing for genotype 3 cases that are treatment experienced, with or without the presence of cirrhosis.
2. Perform testing for genotype 3 treatment-naïve cases in the setting of cirrhosis if treatment for 12 weeks' duration is planned.
3. If Y93H detected: add ribavirin (weight based).

Ledipasvir/sofosbuvir

1. Perform testing for genotype 1a cases that are not cirrhotic and are treatment-experienced patients.
   (a) >100-fold resistance detected: add ribavirin (weight based) + duration of therapy should be 12 weeks (or alternative therapy).
2. Perform testing for genotype 1a cases that are cirrhotic and treatment experienced.
   (a) >100-fold resistance detected: add ribavirin (weight based) + duration of therapy should be 24 weeks (or alternative therapy).

Daclatasvir plus sofosbuvir

1. Perform testing for genotype 3 cases that are not cirrhotic and are treatment experienced in whom 12 weeks of treatment is planned.
   (a) If Y93H detected: add ribavirin (weight based).
2. Perform testing for genotype 3 cirrhotic cases that are treatment naïve in whom 24 weeks of treatment is planned.
   (a) If Y93H detected: add ribavirin (weight based) or alternative therapy.

Antiviral combinations in which NS5A RAS testing is not recommended (AASLD/IDSA, HCV guidance: recommendations for testing, managing, and treating hepatitis C).

Elbasvir/grazoprevir
Do not test in cases of genotype 1b.

Ledipasvir/sofosbuvir
NS5A RAS testing is not indicated in the following cases:

1. Genotype 1b cases.
2. Genotype 1a cases that are treatment naïve.
3. Genotype 1a or 1b non-cirrhotic cases that are treatment naive that have a viral load <6 million IU/mL in whom 8 weeks of therapy is planned.

Sofosbuvir/velpatasvir
Do not test in cases of genotype 1, 2, 4, 5, or 6 infections in whom 12 weeks of therapy is planned.

Glecaprevir/pibrentasvir
Do not test in cases of genotype 1, 2, 3, 4, 5, or 6 infections in whom 8, 12, or 16 weeks of therapy is planned.

Sofosbuvir/velpatasvir/voxilaprevir
Do not test in cases of genotype 1, 2, 3, 4, 5, or 6 infections in whom 12 weeks of therapy is planned.

Paritaprevir/ritonavir/ombitasvir with dasabuvir ± weight-based ribavirin, or paritaprevir/ritonavir/ombitasvir + weight-based ribavirin
Do not test in cases of genotype 1 or 4 that are treatment naive or treatment experienced in whom either therapeutic regimen will be used.

2.12 Tackling Resistance

The therapy for hepatitis C continues to make advancements. However, until more therapeutic options become available through clinical trials, there are some factors that can be modified to achieve better treatment outcomes in the setting of resistance to antivirals. These factors include those that are patient related and virus related and those in relation to the antiviral therapy itself [68].

1. Patient-related factors
   It is important to be aware whether the patient has fibrotic changes in the liver and if the patient is treatment naïve or treatment experienced [68]. These attributes will help guide therapy choices.
2. Virus-related factors
   The characteristics of the HCV virus that play a role in therapy are the genotype and subtype as well as the presence of any preexisting resistance-associated substitutions [66].

3. Therapy-related factors
   Duration of therapy can significantly impact the probability of an occurrence of a relapse [66]. Though shorter courses are more commonly linked to more replaces, allocating the appropriate patient population for them can reduce expenses and decreases chances of relapse [66]. However extended treatment with the combination of ribavirin can be used in certain cases as well to increase the rates of sustained virological response [66]. This tactic can especially be used in patients who had therapeutic failure with prior antiviral therapy even if there are preexisting RASs [66, 88, 89]. Combining ribavirin to the DAA regimens aids in improving the rates of SVR in patient populations that are more prone to failure of therapy, in cases of preexisting NS5A RASs and with previous failure of therapy with DAAs [66].

2.13 Emerging Technologies for HCV Detection

There have been recent promising advances in the molecular diagnostic technologies for the improved assays to diagnose hepatitis C infection. Few of the technologies are described here.

1. Isothermal amplification
   Isothermal amplification assay has the ability to develop into a point-of-care (PoC) HCV RNA detection and potentially can be used at laboratory or in the field. This technique has been successfully used to diagnose various infectious organisms such as mycobacterium tuberculosis and trypanosoma [90].
   (a) Loop-mediated isothermal amplification of DNA (LAMP)
   LAMP is developed recently and based on autocycling of DNA and its synthesis using DNA polymerase under isothermal conditions (63–65 °C). Large amount of pyrophosphate ion produced during LAMP reaction reacts with magnesium ions to form magnesium pyrophosphate which allows rapid visualization of amplified DNA. LAMP is a highly sensitive and specific DNA amplification technique suitable for diagnosis of an infectious disease. Though LAMP reaction is efficient as it synthesizes 10–20 μg of target DNA within 30–60 min and cost effective further evaluation is required for these novel modalities [90].
   (b) Simultaneous Amplification Test (SAT)
   Simultaneous amplification and testing (SAT) assay is also based on isothermal amplification of RNA followed by real-time fluorescence detection of amplified DNA. SAT assays have the potential to detect as few as ten copies of HCV RNA transcripts in 60 min. The sensitivity and specificity of SAT-HCV assay were 99.6% and 100%, respectively, when compared to the results from real-time PCR [91]. SAT assays are faster because T7 RNA polymerase which is used in SAT assays can produce 10–103 copies of RNA per copy of DNA template and for this reason, e.g., results of SAT assays are available in 60 min as compared to 120 min for real-time PCR with low risk

of contamination. Moreover, the SAT assays are cost effective as it requires only isothermal incubator and does not need PCR thermal cycler [92].

2. Aptamers
   One of the promising novel technologies to provide efficient, accurate, and cost-effective diagnostic modality of HCV infection is the use of aptamers as capture molecules. Aptamers are single-stranded oligonucleotides that bind to specific target molecule and in case of HCV detection they bind to hepatitis core protein. Aptamers are isolated using selective evolution of ligands by the exponential enrichment approach (SELEX) approach and displays high display and high affinity and specificity for HCV core protein. One of the major advantages of aptamers over serological test for anti-HCV antibodies is their convenient synthesis, easy modification with dependability, accuracy, and lack of immunogenicity. Furthermore, different HCV genotypes can be detected by core-specific aptamers [93].
3. Prototype nanoparticle-based diagnostic assays
   They have been developed for the detection of biomarkers in hepatitis C infection and are based on the principle of immunosensors. Immunosensors are solid-state affinity ligand-based biosensing devices that couple immunochemical reactions to appropriate transducers and have been studied extensively for clinical diagnosis of various infectious disease including HCV infection [94]. Immunosensors usually consist of sensing element which is formed by the immobilization of antigens or antibodies and transducers which measure signal produced by this binding event.
   Commonly used nanoparticles include quantum dots (QDs) and gold nanoparticles:
   (a) *Quantum dots*: These are the nanoparticles used in semiconductor material which emits light when antigen-antibody reaction takes place. These assays are found to be highly sensitive and specific.
   (b) *Gold nanoparticles*: These are small-size molecules (2–50 nM) and successfully used to detect anti-HCV and HCV RNA.

2.14 Technological Advances and Innovations to Improve Access to Hepatitis C Testing

Early diagnosis and management are needed to prevent complications associated with chronic infection such as chronic liver disease, decompensated liver disease, and hepatocellular carcinoma (HCC). Recent data suggests that current burden of HCV infection is just tip of the iceberg. It has been estimated that approximately 40–85% of the HCV-infected patients are unaware of their HCV status globally [95]. According to the data published by NHANES from 2001 to 2008, approximately 50.3% of the persons infected by HCV are unaware of their infection status in the United States. The situation is worse in middle- and low-income countries with only small fraction of people with HCV having access to screening and diagnostic tests for viral hepatitis [96]. Key barriers to HCV screening and diagnostic tests are listed in Table 2.3.

Table 2.3 Key barriers for the screening and diagnostic testing of HCV in low- and middle-income countries (LMIC)

Lack of awareness and understanding among the general population and healthcare workers about hepatitis C infection, its disease progression, and treatment.
High levels of stigma, discrimination, and social marginalization of those with or at risk of viral hepatitis, especially among persons who inject drugs (PWID), men who have sex with men (MSM), prisoners, and sex workers.
Few facilities and limited healthcare infrastructure for viral hepatitis testing.
Weak hepatitis surveillance programs and therefore limited data on the epidemiological situation to guide country-specific viral hepatitis testing approaches.
Lack of testing guidance for LMICs, and limited evidence base to guide hepatitis testing approaches. There have been few large studies or randomized controlled trials that have evaluated the impact or cost-effectiveness of different testing approaches to support the development of guideline recommendations.
Few LMICs have national viral hepatitis strategies or plans, and even fewer have designated units and budgets within their health ministries to lead, guide, and coordinate their hepatitis responses.
Poor laboratory capacity and infrastructure with inconsistent supplies of test kits and reagents due to poor logistics, shortages of trained staff, and poor-quality assurance and management systems.
Limited access to reliable and low-cost HCV diagnostics, including rapid serological tests and molecular viral load tests that are quality-assured by stringent regulatory authorities, leading to the use of poor-quality test kits and reagents.

Diagnostic innovations and interventions are needed to improve the access and increase the uptake of hepatitis C screening tests especially in low- and middle-income countries. In 2016–2017 World Health Organization proposed diagnostic innovations and future developments for the chronic hepatitis C infection which are as follows:

1. Simplification of testing algorithms
   As mentioned above, current diagnostic algorithm for hepatitis C infection includes screening test with serological test followed by confirmatory tests for viremia which can lead to loss to follow-up and increased cost on healthcare system. Rationale for simplification of testing algorithms is to increase affordability and so in turn uptake of testing. It includes considerations for one-step diagnostic approaches using either HCV core antigen or HCV RNA assays especially in high-risk population. This can be achieved with starting patients on pangenotypic direct antiretroviral drugs (DAA), which eliminates the need for costly genotyping which is largely unavailable in resource-limited settings. Also, on treatment monitoring with HCV viral load is not required while patient is on DAA [97].
2. Dried blood spots (DBS)
   DBS sampling approach has been successfully used in expanding access and care for HIV in many low-resource settings due to its low cost, simplicity of sample collection, more acceptability to patients, ease of DBS sample transportation, stability over time, and ability to withstand extremes of environmental condition with easier storage options. The 2017 WHO Guidelines Development

Group recognized the high diagnostic accuracy and impact of DBS for serological and nucleic amplification testing (NAT) for HCV. Though implementation of DBS sampling methodology can simplify the diagnostic algorithm for HCV diagnosis (serological and NAT testing can be done on single DBS sample) further validation studies are required to assess their performance in different populations and settings [98, 99].

3. Oral fluid RDTs

Oral fluid rapid diagnostic assays are acceptable to the patients for HCV testing because of their simplicity and flexibility. The use of oral fluid RDTs has already been established in the field of HIV because of its potential to reach community and increasing access for hard-to-reach population and is especially successful in men who have sex with men (MSM). As discussed above, OraQuick® HCV Rapid Antibody Test is approved by FDA for HCV testing (oral fluid, venous blood, finger-stick capillary blood, serum, and plasma).

Recently point-of-care NAT assays to detect HCV RNA are commercially available, and are expected to improve access to diagnosis, treatment, and linkage to care with health system by reducing the loss to follow-ups. Instrument to perform point-of-care NAT does not need electricity and uses reagents that are stable at 2–30 °C. Moreover, phlebotomy or precision pipetting is also not required to run the test and results are usually available within 2 h. HCVcAg portable point-of-care device is still under development and when available would have the potential to significantly improve the access and limit the cost of healthcare system by same-day diagnosis of infection [100, 101]. Characteristics of commonly used RDTs are as follows (Table 2.4).

4. Multiplex and multi-analyte testing

It involves diagnosis of hepatitis C infection along with other infections of public health concerns such as HIV, syphilis, and hepatitis B and can be done by testing of one specimen in the same test device or reagent cartridge at the same time for multiple infections. As most of the countries are facing the overlapping epidemics of HIV-HBV and HIV-HCV coinfection, implementation of multiplex testing would improve the efficiency of screening program. Multiplex and multi-analyte testing is found to be cost effective (by lowering cost per pathogen) and efficient (less time required per pathogen per visit). Also, it is more acceptable to patients and providers as fewer needlesticks are required and less specimen volume is needed to run the test [102]. Despite all these advantages further data is required on their diagnostic accuracy. In 2014, Fisher et al. compared the accuracy of different rapid point-of-care test in terms of sensitivity, specificity, true positivity, and false negativity [103]. The MedMira rapid human immunodeficiency virus (HIV)/HCV antibody test, MedMira hepatitis B (HBV)/HIV/HCV antibody test,

Table 2.4 Comparison of accuracy of most commonly used oral fluid RDTs

Test	Sample	Sensitivity	Specificity	Positive LR	Negative LR
OraQuick	Oral fluid	95.9	99.4	147.98	0.037
Chembio	Oral fluid	88	94	14.93	0.141

Chembio HCV Screen Assay used with both whole blood and oral specimens, Chembio HIV-HCV Assay also used with both whole blood and oral specimens, Chembio HIV-HCV-Syphilis Assay, and OraSure HCV Rapid Antibody Test used with whole blood were compared. The results of the study showed that OraSure had the highest sensitivity and specificity at 92.7% and 99.8%, respectively, followed closely by Chembio. The sensitivities of MedMira HIV/HCV and MedMira HIV/HCV/HBV tests were the lowest, at 79.1% (95% CI = 72.6–85.5%) and 81.5% (95% CI = 75.2–87.8%), respectively [104].

5. Self-testing

   As the name indicates it's a test which is performed and interpreted in private by the individual, who wants to know his or her hepatitis C infection status. However, further confirmatory tests are required if the individual is tested positive for viral hepatitis. Currently, self-testing is an active area of research in HIV diagnosis and access to management. Several studies have been conducted to evaluate the effectiveness of self-testing in HIV care (HIVST). Results of these studies showed that HIV self-testing is acceptable in different high-risk population in different settings [105]. From the available studies, self-testing is a promising methodology for diagnosis of HIV but it's still not clear whether self-testing can promote the uptake of the viral hepatitis testing among marginalized population. One of the several advantages of self-testing is the simplicity and flexibility to perform test conveniently in private setting [106].

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Pretherapeutic Evaluation of the Patients with HCV Infection

3

T. Asselah and Dominique Salmon-Ceron

The advent of oral direct-acting antiviral agents (DAAs) has dramatically improved hepatitis C treatment landscape in the last 4 years, providing cure rates over 95% with shorter duration of treatment and a very good safety profile [1]. This allowed giving access to treatment in nearly all hepatitis C virus (HCV) infected patients. We however need to make a rigorous pretherapeutic evaluation of patient characteristics, such as stage of liver disease, kidney function, and extrahepatic manifestations as well as consider viral characteristics, such as HCV genotype and viral load (Fig. 3.1).

This assessment has been described in an extensive manner in the last recommendations of the European Association for the Study of the Liver (EASL) for the treatment of chronic hepatitis C [2, 3].

3.1 Assessment of Comorbidities, Extra Hepatic Manifestations, and Renal Function

The contribution of comorbidities to the progression of liver disease must be evaluated and appropriate corrective measures should be implemented.

- HBV and HAV coinfection: HBV and HAV vaccination should be proposed to patients who are not protected. Delta coinfection in case of HBV coinfection.
- HIV coinfection.
- Alcohol consumption: Advice for abstinence or at least reduction.

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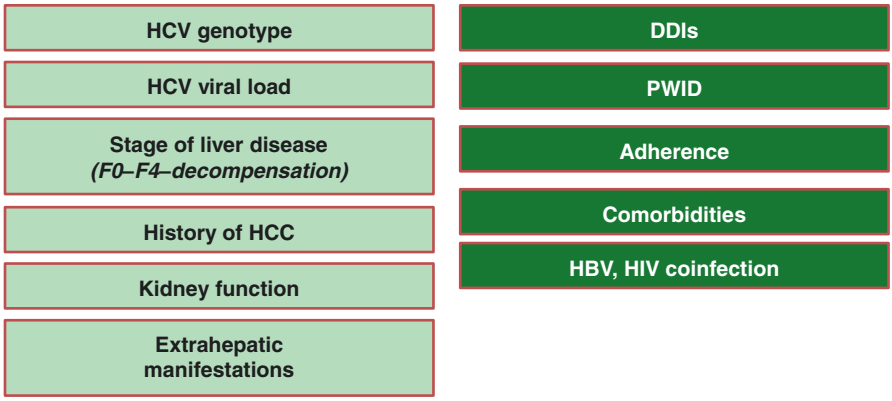

HCV = hepatitis C virus; F0-F4 = fibrosis stage 0–4; DDI = drug-drug interaction; PWID = people who inject drugs; HBV = hepatitis B virus; HCC = hepatocellular carcinoma.

Fig. 3.1 Pretherapeutic evaluation of the patients with HCV infection

- Diabetes, overweight/obesity: Advice for diet and physical activity.
- Dyslipidaemia, autoimmunity disorder, metabolic diseases, cholestasis, and haemochromatosis.
- Renal function (creatinine/estimated glomerular filtration rate [eGFR]) should be ascertained in order to adapt and select DAAs accordingly.
- Cardiac diseases.
- Other medications (prescribed and self-medication): Drug–drug interactions can easily be assessed in the following website https://www.hep-druginteractions.org/

Extra-hepatic manifestations of HCV infection should be identified in case of symptoms.

3.2 Assessment of Liver Disease Severity

Liver disease severity must be assessed prior to therapy in order to inform treatment decisions including HCV treatment duration and need for continued HCC screening.

Identifying patients with cirrhosis (METAVIR score F4) or advanced (bridging) fibrosis (METAVIR score F3) prior to therapy is of particular importance. Since significant fibrosis may be present in patients with repeatedly normal ALT, evaluation of disease severity should be performed regardless of ALT levels (Fig. 3.2).

Assessment of the stage of fibrosis is not required in patients with clinical evidence of cirrhosis.

Patients with cirrhosis need to be assessed for portal hypertension, including oesophageal varices.

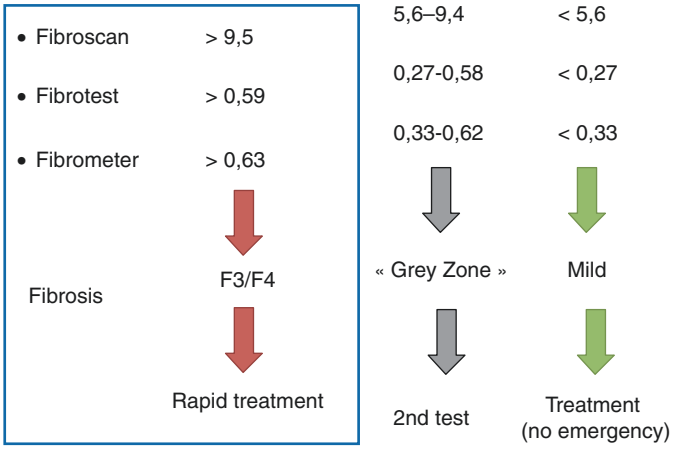

Fig. 3.2 Fibrosis evaluation

Non-invasive methods should be used instead of liver biopsy to assess liver disease severity prior to therapy.

- Liver stiffness measurement can be used to assess liver fibrosis and the presence of portal hypertension in patients with chronic hepatitis C. Consideration must be given to factors that may adversely affect its performance, such as obesity, high ALT levels, or post-prandial testing. Well-established panels of fibrosis biomarkers can also be applied.
- Non-invasive markers including APRI may be used to assess for cirrhosis prior to HCV treatment according to current EASL and WHO guidelines (FibroTest, FibroMeter, Hepascore, APRI, FIB-4, etc.)

Both liver stiffness measurement and biomarkers perform well in the identification of cirrhosis or no fibrosis, but they perform less well in resolving intermediate degrees of fibrosis [2]. Cut-offs used with common non-invasive markers to establish the different stages of fibrosis in patients with chronic hepatitis C prior to therapy are shown in Table 3.1 of [2, 4–9]. In low- and middle-income countries, as well as in settings where treatment expands outside of specialty clinics, aspartate aminotransferase to platelet ratio index (APRI) and fibrosis-4 (FIB-4) are generally available, simple and cheap, and the information they provide is reliable.

The APRI formula is the following:

$$\text{APRI} = \text{AST}\left(\text{IU}/\text{L}\right)/\ \text{AST upper normal limit}\left(\text{IU}/\text{L}\right)/\ \text{Platelet count}\left(109/\text{L}\right)\times 100.$$

The formula for FIB-4 is:

$$\left(\text{Age}\times\text{AST}\right)/\left(\text{Platelets}\times\left(\text{sqr}\left(\text{ALT}\right)\right)\right).$$

Table 3.1 Non-invasive marker cut-offs for prediction of stages of fibrosis, including F3 (advanced fibrosis) and F4 (cirrhosis) [2]

	Stage of fibrosis	Number of patients	Cutoff	AUROC	Sensitivity	Specificity	PPV	NPV	Ref.
FibroScan®	F3	560 HCV-positive	10 kPa[a]	0.83	72%	80%	62%	89%	[4]
	F4	1855 HCV-positive	13 kPa[a]	0.90–0.93	72–77%	85–90%	42–56%	95–98%	[4, 6, 9]
ARFI (VTQ®)	F3	2691 (including 1428 HCV-positive)	1.60–2.17 m/s	0.94 (95% CI 0.91–0.95)	84% (95% CI 80–88%)	90% (95% CI 86–92%)	n.a.	n.a.	[8]
	F4	2691 (including 1428 HCV-positive)	2.19–2.67 m/s	0.91 (95% CI 0.89–0.94)	86% (95% CI 80–91%)	84% (95% CI 80–88%)	n.a.	n.a.	[8]
Aixplorer®	F3	379 HCV-positive	9 kPa[a]	0.91	90% (95% CI 72–100%)	77% (95% CI 78–92%)	n.a.	n.a.	[7]
	F4	379 HCV-positive	13 kPa[a]	0.93	86% (95% CI 74–95%)	88% (95% CI 72–98%)	n.a.	n.a.	[7]
Fibrotest®	F4	1579 (including 1295 HCV-positive)	0.74	0.82–0.87	63–71%	81–84%	39–40	93–94	[6, 9]
FIB-4	F4	2297 HCV-positive	1–45[b] 3.25[b]	0.87[c] (0.83–0.92)	90% 55%	58% 92%	n.a.	n.a.	[5]
APRI	F4	16,694 HCV-positive	1.0[b] 2.0[b]	0.84[c] (0.54–0.97)	77% 48%	75% 94%	n.a.	n.a.	[5]

APRI aspartate aminotransferase to platelet ratio index, *ARFI* acoustic radiation force impulse, *AUROC* area under the receiver operating characteristic curve, *FIB-4* fibrosis-4, *n.a.* not applicable, *NPV* negative predictive value, *PPV* positive predictive value

[a]Scales for liver stiffness cut-offs (in kPa) are different between FibroScan® and Aixplorer®

[b]Two cut-offs are provided for FIB-4 and for APRI, respectively, with their own sensitivities and specificities

[c]Median (range)

3.3 HCV RNA or HCV Core Antigen Detection/Quantification

HCV RNA detection and quantification in serum or plasma should be made by a sensitive assay with a lower limit of detection of ≤15 IU/mL. In low- and middle-income countries and in specific settings in high-income countries, a qualitative HCV RNA assay with a lower limit of detection of ≤1000 IU/mL can be used if more sensitive quantitative assays are not available and/or not affordable.

If HCV RNA testing is not available and/or not affordable, HCV core antigen detection and quantification by EIA can be used as a surrogate marker of HCV replication.

3.4 HCV Genotype Determination

The HCV genotype and genotype 1 subtype (1a or 1b) must be assessed prior to treatment initiation to determine the choice of therapy and its duration, among other parameters.

With pan-genotypic HCV drug regimens, it is possible to treat individuals without identifying their HCV genotype and subtype. This may be particularly useful in regions where virological tests are not available or their cost exceeds that of antiviral treatment, or to simplify therapy in other regions, in order to improve access to care.

3.5 HCV Resistance Testing

The current EASL recommendations suggest treatment regimens that do not necessitate any resistance testing prior to first-line therapy.

3.6 Contraindications to Therapy

Contraindications to treatment with a DAA are few.

The use of certain cytochrome P450 (CYP)/P-glycoprotein (P-gp) inducing agents (such as carbamazepine and phenytoin) is contraindicated with all regimens, due to the risk of significantly reduced concentrations of DAA.

Treatment regimens comprising a protease inhibitor must not be used in patients with Child–Pugh B or C decompensated cirrhosis or in patients with previous episodes of decompensation.

In patients with an eGFR <30 mL/min/1.73 m^2, sofosbuvir should only be used if no alternative treatment is approved.

3.7 Indications for Treatment: Who Should Be Treated

All patients with HCV infection must be considered for therapy, including treatment-naïve patients and individuals who failed to achieve SVR after prior treatment.

Treatment should be considered without delay in patients with significant fibrosis or cirrhosis (METAVIR score F2, F3 or F4), including compensated (Child–Pugh A) and decompensated (Child–Pugh B or C) cirrhosis, in patients with clinically significant extra-hepatic manifestations (e.g. symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia, HCV immune complex-related nephropathy, and non-Hodgkin B-cell lymphoma), in patients with HCV recurrence after liver transplantation, in patients at risk of a rapid evolution of liver disease because of concurrent comorbidities (non-liver solid organ or stem cell transplant recipients, HBV coinfection, and diabetes), and in individuals at risk of transmitting HCV (PWID, men who have sex with men with high-risk sexual practices, women of childbearing age who wish to get pregnant, haemodialysis patients, and incarcerated individuals). *Patients with decompensated (Child–Pugh B or C) cirrhosis and an indication for liver transplantation with a MELD score ≥18–20 should be transplanted first and treated after transplantation.

If the waiting time on a liver transplant list is more than 6 months, patients with decompensated (Child–Pugh B or C) cirrhosis with a MELD score ≥18–20 can be treated before transplantation, although the clinical benefit for these patients is not well established (B2).

3.8 Conclusion

Direct-acting antivirals provide cure rates over 95% with shorter duration of treatment from 8 to 12 weeks and a favorable safety profile. These treatments allow to treat all patients, also those with rare genotypes [10].

All patients with HCV infection are candidates for therapy. Although treatment is easy and "friendly," a careful pretherapeutic evaluation of patient characteristics is needed. In particular, stage of liver disease, kidney function, and extrahepatic manifestations, drug-drug interactions, have to be assessed.

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D. Salmon has been invited to conferences and speaker for AbbVie, Bristol-Myers Squibb, and Gilead Sciences.

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Current Therapy of Chronic Hepatitis C Virus in Treatment-Naive Patients

4

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4.1 Introduction

Hepatitis C virus (HCV) is one of the most commonly transmitted blood-borne diseases in the United States, with chronic cases ranging from 2.7 to 3.9 million in the United States and 130–170 million worldwide [1]. As reported by Denniston et al., the actual number of cases in the United States is underestimated because the survey precluded high-risk populations such as prisoners and homeless population [2]. Roughly 95% of the worlds and 50% of the United States' HCV-infected population are unaware of their infectious status [3]. It can be transmitted by blood transfusions, intravenous drug administration, intranasal drug administration, sexual intercourse, and vertical transmission [1].

The progression from acute hepatitis C to chronic HCV infection is poorly defined. About 15–45% will clear an acute infection with estimates of time to clearance ranging from 1 to 2 weeks up to 1–3 years [1, 4]. Of the patients who fail to clear they go on to develop chronic HCV and after 2–3 decades of untreated chronic HCV, 10–20% of these patients are expected to develop cirrhosis [4]. HCV is the leading case of chronic liver disease, cirrhosis, and hepatocellular carcinoma, and the main indication for liver transplantation in the Western countries [5]. Chronic HCV is a major public health concern with total healthcare costs associated with HCV disease and its complications, excluding treatment expenses, estimated to be $6.5 billion in 2011, with a projected increase to $9.1 billion by 2024 [6].

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Since early diagnosis and revolutionary advancements in current treatment options can prevent cirrhosis and HCC, the CDC recommends a general screening strategy with a one-time testing without prior ascertainment of HCV risk for baby boomers—persons born during 1945–1965 [7].

Treatment of chronic HCV with the new direct-acting antivirals (DAAs) has shown increased SVR rates, simpler regimens, and less severe side effect profiles, making it ideal to start treatment earlier. We will discuss current available chronic hepatitis C treatment regimens with DAAs, and the supporting trials from which the recommendations are made.

4.2 Hepatitis C Virus and Its Proteins

Hepatitis C virus was first identified by Choo et al. in 1989, as an enveloped single-stranded RNA virus, belonging to Flaviviridae family [8]. The virus can circulate through the human body but has a strong affinity towards the liver and invades the hepatocytes by endocytosis. The hepatitis C virus contains a single-stranded RNA that is translated to a large polyprotein that cleaves into ten mature proteins using either host or viral proteases inside endoplasmic reticulum, yielding structural (core, E1, E2, and p7) and nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) [9].

Structural proteins are involved in forming viral particles. HCV core is the viral nucleocapsid protein, and E1/E2 are glycosylated envelope glycoproteins that surround the viral particles [9]. The structural proteins are separated from the nonstructural proteins by the short membrane peptide p7 [9].

Nonstructural proteins are components of the replication complex. NS2 is a non-glycosylated membrane protein that participates in proteolytic cleavage at the NS2-NS3 junction [9]. NS3 consists of the N-terminal HCV serine protease and the C-terminal RNA helicase domain [9]. NS3 proteinase domain associates with NS4A and is a cofactor for NS3 protease which plays a critical role in HCV processing by cleaving downstream of NS3 at four sites (between NS3/NS4A, NS4A/NS4B, NS4B/NS5A, NS5A/NS5B) [10]. NS4B is an integral membrane protein that cotranslationally associates with the endoplasmic reticulum (ER) membrane inducing the formation of a seemingly ER-derived membranous web that harbors all HCV structural and nonstructural proteins as well as replicating viral RNA [9, 11]. NS5A binds the viral RNA and various host factors in close proximity to HCV core and lipid droplets [12]. NS5A protein lacks enzymatic activity, and appears to have multiple roles in establishing the replication complex, in viral assembly, and in inhibiting apoptosis. NS5A is also involved in mediating resistance of the hepatitis C virus to the action of interferon [13]. NS5B is the RNA-dependent RNA polymerase [12].

4.3 Hepatitis C Genotyping

HCV is a very heterogeneous virus, and has substantial genetic variability. Currently there are seven different genotypes (GT) of HCV 1–7 [1]. HCV genotypes differ from each other at 30–35% of nucleotide sites, and each GT is further classified as

67 confirmed and 20 provisional subtypes [14]. The most commonly demonstrated subtypes are GT1a and GT1b.

Globally, GT1 is estimated to account for 46.2%, GT2 9.1%, GT3 30.1%, GT4 8.3%, GT5 <1%, and GT6 5.4% [15]. In the United States, approximately 70% of chronic HCV infections are caused by hepatitis C GT1, 15–20% by GT2, 10–12% GT3, 1% GT4, and less than 1% GT5 or -6 [16].

Over one-third of GT1 cases are located in East Asia, whereas three-quarters of the global estimate of GT3 cases occur in south Asia [15]. GT2 and GT6 were seen mostly in East Asia, GT4 in North Africa and Middle Eastern region, and the majority of GT5 cases occur in Southern and Eastern sub-Saharan Africa [15].

4.4 Historical Interferon Era in HCV Therapy

Before advancements in chronic hepatitis C therapy the standard of care for treatment consisted of pegylated interferon (PegIFN) and weight-based ribavirin. The regimen depended on genotype, viral load at baseline, and treatment, with the duration of treatment being driven by HCV RNA quantification and sustained virologic response (SVR). For GT1, GT4, GT5, or GT6 the recommended duration of treatment was 48 weeks, and for GT2 and GT3 it was 24 weeks. These recommendations were based on data that supported GT2 and GT3 being more responsive to this regimen with SVRs of 80%, compared to SVR rates of 40–50% with GT1 [17].

For GT1 early virological response was determined at week 12 in hopes of not overtreating patients with low changes of achieving SVR. Viral load was measured and if it dropped ≥ 2 $\log_{10}$ from baseline with or without detection of the HCV RNA treatment was continued for 48 weeks. If HCV RNA continued to be detectable at week 24 then treatment was stopped as the likelihood of an SVR was virtually zero, but it could be continued with the aim to slow liver disease progression in patients with a severe prognosis [18]. For GT2 or GT3, no monitoring of HCV RNA during therapy was recommended because clear majority became HCV RNA negative early in treatment, but it was measured at the end of therapy to assess whether the virologic response was sustained [19]. As more data and research became available it was determined that regimens could be shortened to 24 weeks for GT1 and 16 weeks for GT2 if the patient showed rapid virological response (RVR) which was defined as an undetectable viral load at week 4 [18, 19].

In general, the concluded SVR response using these regimens was limited and the adverse effect profile was intolerable due to hematological toxicities, psychiatric disruptions, fatigue, and flu-like symptoms.

4.5 The Four Classes of Direct-Acting Antivirals (DAAs)

The four classes of DAAs include NS3/4A protease inhibitors, NS5A inhibitors, non-nucleoside NS5B polymerase inhibitors, and nucleoside and nucleotide NS5B polymerase inhibitors.

NS3/4A protease inhibitors—prevent cleavage of the nonstructural proteins and inhibit the ability of the virus to evade the immune response [20]. Current protease inhibitors include simeprevir, paritaprevir, and grazoprevir which have been approved in combination with NS5A/B inhibitors for GT 1 and/or 4 disease [1].

The first breakthrough in direct-acting antiviral era was in 2011 when telaprevir and boceprevir were approved to be used to treat chronic hepatitis C. Both are considered first-generation NS3/4A protease inhibitor, and were used in triple therapy along with PegIFN/ribavirin. The SVR rates showed improvement with triple therapy and in patients with GT1 SVR rate went from 50% to greater than 70% [20]. However, along with the improved SVR rates there was also a higher frequency of adverse events noted. Boceprevir triple therapy is associated with increased risk of neutropenia, dysgeusia, anemia, thrombocytopenia, and telaprevir triple therapy is associated with increased frequency of anemia, pruritus, and rash in up to 50% of patients, and associated with severe events in up to 5–10% of patients [20, 21].

The second class of the first generation of protease inhibitor was simeprevir with activity against genotypes 1, 2, 4, 5, and 6. Along with PegIFN/ribavirin, simeprevir was used for 12 weeks with subsequent additional 12–36 weeks of PegIFN/ribavirin depending on patient's treatment history. This regimen increased SVR rates from 50% up to almost 80%, except in GT1a population with Q80K resistance-associated substitution (RAS), in which case patients were seen to have SVR12 rates of 46.7% [20, 22].

NS5A inhibitors—work by inhibiting hyperphosphorylation, which is required for viral replication, and binding to NS5A domain 1 and preventing RNA binding without affecting NS5A dimerization [23]. Examples include ledipasvir, daclatasvir, elbasvir, ombitasvir, and velpatasvir [1]. Daclatasvir was coupled with PegIFN/ribavirin for 24 weeks for genotype 4 populations in Europe and showed evidence of improving SVR rates [24].

Polymerase inhibitors interfere with viral replication by binding to the NS5B RNA-dependent RNA polymerase. There are two types of polymerase inhibitors—nucleoside and non-nucleoside inhibitors.

Nucleoside analogue polymerase inhibitors—require conversion to an active triphosphate form and once active it inhibits the RdRp active site and causes chain termination [20]. Sofosbuvir was the first approved IFN free therapy for GT2 or -3, but research showed that it was not as successful in those with GT1 [1].

Non-nucleoside analogue polymerase inhibitors—suppress RdRp activity by binding to several discrete sites on HCV polymerase in a noncompetitive fashion to arrest HCV viral replication [20]. This class is only active against GT1. Dasabuvir is an example of this class.

4.6 Indications and Goals of Therapy

Major goal of therapy is to prevent HCV-related complications including advanced fibrosis, cirrhosis, and extrahepatic complications. Extrahepatic complications of chronic hepatitis C include diabetes mellitus, cardiovascular disease, lymphomas,

and renal disease [25]. Treatment-naive patients represent a group of patients who are infected with chronic hepatitis C without any previous experience with treatment including interferon, ribavirin, or any direct-acting antiviral. Treatment-experienced patients are those who previously underwent treatment with one of the above agents and failed to cure HCV infection. Both groups need to be treated regardless of their liver status. All patients without cirrhosis, but significant or advanced fibrosis (METAVIR score F2-F3), need to be considered for treatment without delay [26]. Extrahepatic complications are considered an indication for initiating therapy including HCV related nephropathy, cryoglobulinemia, B-cell lymphomas, and vasculitis [25]. Treatment also needs to be considered in patients with coinfection with HIV or hepatitis B to prevent further progression of hepatic fibrosis [7]. For decompensated cirrhosis with high MELD score >18–20, treatment needs to be considered after liver transplantation due to the risk of treatment failure and lack of evidence of significant liver function improvement and eventual delisting [7, 26]. For all liver-transplanted patients, treatment is indicated after transplant. IV drug abusers, incarcerated persons, and patients on hemodialysis also need to be treated, as it has been shown that treating this population will reduce disease transmission in the future [7, 26].

4.7 Pretreatment Patient's Evaluation

The most pivotal assessment for a patient with chronic hepatitis C is to identify patient's fibrosis stage as it has a great impact on patient's prognosis and disease outcome. Early detection and prevention is the most effective approach to substantially impact the prognosis as treatment can be started earlier, and the biomarkers could also improve early HCC detection.

Liver biopsy is the gold standard for fibrosis staging; however limiting factors include sampling error and observer variability. Also of note is the possibility of discordance between fibrosis stages in the different lobes. Given the invasive nature of the procedure minor and rare major complication can occur, and for that reason noninvasive methods should be used for initial fibrosis assessment.

Noninvasive methods include both serum biomarkers and imaging techniques. Noninvasive imaging techniques however outperform the serum-scoring systems but most biomarkers are accurate for advanced-stage disease.

Serum biomarkers are categorized as either direct or indirect. Indirect markers include bilirubin, aminotransferase levels, gamma-glutamyl transpeptidase, prothrombin time, albumin, and platelet count. These markers are used in algorithms to form the following tests: APRI test, FIB-4, FibroSure, and NAFLD-fibrosis score. FibroSure has a high accuracy for predicting the presence of fibrosis, and reducing the need for biopsy. The European Liver Fibrosis (ELF) panel incorporates only direct markers of fibrosis such as hyaluronic acid, procollagen III amino terminal peptide, and TIMP-1, and can also be used for assessing fibrosis [27, 28]. The other less sensitive tests noted above could be useful if FibroSure and FibroScan are not available locally [28].

A noninvasive imaging method called vibration-controlled transient elastography (FibroScan) is currently being used to evaluate liver stiffness. Studies are evaluating combinations of serum biomarkers and imaging to increase diagnostic accuracy so ideally FibroScan should be used in conjunction with a serologic marker. Other imaging modalities include acoustic radiation force impulse, supersonic shear imaging, magnetic resonance elastography, and magnetic resonance imaging.

A liver biopsy should be performed if there is a discrepancy between the two testing modalities. For patients with clear evidence of cirrhosis on imaging and biochemical tests, fibrosis staging is not indicated.

It is crucial to identify risk factors in patients with chronic hepatitis C which can lead to progression of hepatic fibrosis. Factors include male sex, duration of the infection, and infection at older age. Concomitant hepatic insults like alcoholism, nonalcoholic fatty liver disease, coinfection with HIV, or chronic hepatitis B are known factors in faster progression of fibrosis in patients with chronic hepatitis C. Solid-organ transplant and immunosuppression status can also yield to rapid hepatic fibrosis progression and treatment of chronic hepatitis C is recommended [29].

4.8 Chronic Hepatitis C Therapy in Treatment-Naive Genotype 1

Genotype 1 is the most common genotype in the world, and the most difficult genotype to treat with genotype 1a having higher failure rate than genotype 1b. This is believed to be due to the incidence of baseline NS5A resistance-associated substitutions (RASs), which can be found in up to 15% of patients prior to treatment [30]. NS5A RASs negatively impact treatment outcomes by decreasing efficacy of some NS5A inhibitor-containing regimens. It is highly recommended to test for RASs in patients with genotype 1a before starting certain DAA regimens to choose the best regimen to maximize achieving SVR [7].

Four highly potent DAA oral combination regimens are recommended for patients with genotype 1 infection, although there are differences in the recommended regimens based on the HCV subtype, presence or absence of baseline NS5A resistance-associated substitutions (RASs), and presence or absence of compensated cirrhosis.

4.9 Treatment of Genotype 1a with or Without Cirrhosis

4.9.1 Elbasvir/Grazoprevir

This is a combination of NS5A inhibitor (elbasvir) and NS3/4A protease inhibitor (grazoprevir). It comes in a fixed daily-dose tablet containing 50 mg of elbasvir and 100 mg of grazoprevir. The 2016 AASLD/IDSA guidelines list 12 weeks of

elbasvir/grazoprevir treatment as a Class 1, Level A recommendation for treatment-naive patients with GT 1a with or without cirrhosis [7]. In patients who demonstrate a baseline high-fold change NS5A RAS, treatment duration should be extended to 16 weeks and weight-based ribavirin should be added (AASLD/IDSA Class IIa, Level B recommendation) (Tables 4.1 and 4.2).

Recommendations for patients without cirrhosis are based on data generated in the phase 3 C-EDGE trial, and phase 2 C-WORTHY trial [31–33]. The C-EDGE trial was a randomized, placebo-controlled, parallel-group phase 3 trial that used a

Table 4.1 Initial regimens for genotype 1a treatment naive of chronic hepatitis C with no cirrhosis [7, 26]

Genotype	Treatment	Duration	Dose	Rating of recommendation
1a	Glecaprevir 300 mg/pibrentasvir 120 mg	8 weeks	Daily fixed	IA
	Ledipasvir 90 mg/sofosbuvir 400 mg	12 weeks	Daily fixed	IA
	Ledipasvir 90 mg/sofosbuvir 400 mg	8 weeks	Daily fixed	IB
	Elbasvir 50 mg/grazoprevir 100 mg	12 weeks	Daily fixed	IA
	Sofosbuvir 400 mg/velpatasvir 100 mg	12 weeks	Daily fixed	IA
	Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg/ dasabuvir 250 mg and weight-based ribavirin	12 weeks	Daily fixed except for dasabuvir twice daily	IA
	Simeprevir 150 mg/sofosbuvir 400 mg	12 weeks	Daily	IA
	Daclatasvir 60 mg/sofosbuvir 400 mg	12 weeks	Daily	IB
	Elbasvir 50 mg/grazoprevir 100 mg (positive baseline RASs)	16 weeks	Daily fixed	IIA,B

Table 4.2 Initial regimens for genotype 1a treatment naive of chronic hepatitis C with cirrhosis [7, 26]

Genotype	Treatment	Duration	Dose	Rating of recommendation
1a	Glecaprevir 300 mg/pibrentasvir 120 mg	12 weeks	Daily fixed	IA
	Ledipasvir 90 mg/sofosbuvir 400 mg	12 weeks	Daily fixed	IA
	Elbasvir 50 mg/grazoprevir 100 mg	12 weeks	Daily fixed	IA
	Sofosbuvir 400 mg/velpatasvir 100 mg	12 weeks	Daily fixed	IA
	Elbasvir 50 mg/grazoprevir 100 mg (positive baseline RASs)	16 weeks	Daily fixed	IIA, B

fixed-dose combination of elbasvir-grazoprevir for 12 weeks in treatment-naive patients with GT1, -4, or -6 chronic HCV in 60 centers around the world. Out of the 421 patients enrolled 382 patients were identified as monoinfected chronically with GT1, 50% (211) had GT1a and 41% (171) GT1b [31]. The data by Zeuzem et al. shows the SVR12 to be 92% (144/157) for the genotype 1a cohort that was assigned to the immediate arm of the study. Twelve percent of genotype 1a patients were identified with baseline NS5A RASs, and only 58% of these patients achieved SVR12 compared to 99% without the NS5A RAS [31]. Data from the C-EDGE TE open-label trial suggests extending the course of treatment with elbasvir/grazoprevir to 16 weeks with ribavirin in patients with baseline NS5A RASs, as they saw no virologic failures in the treatment-experienced patients [32]. Based on known inferior response in patients with baseline NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients who are being considered for elbasvir/grazoprevir therapy.

Recommendations for patients with compensated cirrhosis are based on C-EDGE and C-WORTHY trial [31–33]. C-WORTHY trial was a randomized, open-label, phase 2 trial examining the safety and efficacy of elbasvir plus grazoprevir with or without ribavirin for 12 or 18 weeks with cohort 1 being treatment-naive patients with cirrhosis, and cohort 2 being patients with a previous null response to PegIFN/ribavirin combo. A 97% (28/29) SVR12 rate had been demonstrated in genotype 1 cirrhotic treatment-naive patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin in the open-label phase 2 C-WORTHY trial, which enrolled both HCV-monoinfected and HIV/HCV-coinfected patients [33]. Findings from the phase 3 C-EDGE trial supported the earlier findings from this phase 2 study. In the C-EDGE trial 92 patients (22% with Metavir F4 disease) were seen having had a 97% SVR12 with elbasvir/grazoprevir. Presence or absence of cirrhosis does not appear to alter the efficacy of the elbasvir/grazoprevir regimen.

No dosage adjustments are recommended in patients with renal dysfunction or mild hepatic impairment; however it should not be used in patients with moderate-to-severe hepatic impairment (decompensated cirrhosis) [31].

4.9.2 Glecaprevir/Pibrentasvir

This is a combination of NS3/4A protease inhibitor (glecaprevir) and NS5A inhibitor (pibrentasvir). It was recently approved by FDA as a pan-genotypic DAA for patients with chronic hepatitis C. It comes in a fixed daily dose with three tablets of glecaprevir 100 mg and pibrentasvir 40 mg. The 2016 AASLD/IDSA guidelines list 8 weeks of glecaprevir/pibrentasvir treatment as a Class 1, Level A recommendation for treatment-naive patients with GT1a without cirrhosis, and 12 weeks with compensated cirrhosis [7] (Tables 4.1 and 4.2).

Recommendations for patients without cirrhosis are derived from phase II SURVEYOR 1 and ENDURANCE-1 trial [34, 35]. SURVEYOR-1 is an ongoing phase 2, two-part study designed to evaluate the safety and efficacy of this combination pill with or without RBV, for 8–12 weeks, in cirrhotic and non-cirrhotic adult

GT1 patients. Data for the non-cirrhotic group showed 97% (33/34) SVR12, and SVR12 was achieved in 98% (49/50) of treatment-naive patients [34, 35]. The ENDURANCE-1 trial is a randomized, open-labeled, phase 3 trial that evaluated the safety and efficacy of this fixed-dose combination for 8 versus 12 weeks in treatment-naive or treatment-experienced adults with GT1 chronic HCV infection without cirrhosis. SVR12 was achieved at 99.1% in 8-week arm and 99.7% in 12-week arm and it was concluded that 8 weeks of therapy was none inferior to 12 weeks [36].

Recommendations for patients with compensated cirrhosis are based on EXPEDITION-1 and EXPEDITION-2. EXPEDITION-1 is an open-label phase 3 trial to evaluate the safety and efficacy of the fixed-dose combination for 12 weeks in treatment-naive and treatment-experienced adults with GT1, -2, -4, -5, or chronic HCV infection and compensated cirrhosis. Out of the total 146 patients enrolled 48 patients were identified to have been infected with GT1a and SVR12 was noted to be 98% (47/48), with one patient experiencing viral relapse [37]. EXPEDITION-2 looks at HIV/HCV-coinfected adults with GT1, -2, -3, -4, -5, or -6 using the glecaprevir/pibrentasvir for 8 weeks in noncirrhotic patients and 12 weeks in cirrhotic patients [38].

No dosage adjustments are recommended in patients with renal dysfunction or mild hepatic impairment; however it should not be used in patients with moderate-to-severe hepatic impairment (Child-Pugh B and C).

Most common side effects included headache (12%) and fatigue (11%).

4.9.3 Sofosbuvir/Velpatasvir

This is a combination of NS5B polymerase inhibitor (sofosbuvir) and NS5A inhibitor (velpatasvir). It comes in a daily fixed-dose pill containing sofosbuvir (400 mg) and velpatasvir (100 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of sofosbuvir/velpatasvir treatment as a Class 1, Level A recommendation for treatment-naive GT1a patients with or without cirrhosis [7] (Tables 4.1 and 4.2).

Recommendations for this fixed-dose combination are based on the ASTRAL-1 trial and POLARIS-2 [39, 40]. ASTRAL-1 is a randomized, placebo-controlled, phase 3 trial using fixed-dose combination of sofosbuvir-velpatasvir for 12 weeks in treatment-naive and treatment-experienced patients with GT1, -2, -4, -5, or -6 chronic HCV. Total number of patients enrolled were 624 with 210 (34%) being identified as GT1a. In this group SVR12 was achieved in 98% (206/210) with virologic failure being very rare. One patient out of the GT1a group who failed the regimen was detected to have RAVs. This study also compared treatment results by cirrhosis and results showed that SVR12 was achieved 99% of the time in both noncirrhotics (496/501) and cirrhotics (120/121) [39].

POLARIS-2 is a phase 3 trial comparing efficacy of a fixed-dose combination of sofosbuvir-velpatasvir-voxilaprevir (SOF-VEL-VOX) for 8 weeks versus sofosbuvir-velpatasvir (SOF-VEL) for 12 weeks in treatment-naive patient with GT1–6 chronic HCV infection. Study had 941 patients enrolled, of which 465 were identified as

GT1, and 341 as GT1a. The SOF-VEL-VOX × 8 weeks cohort achieved a 95% (477/501) SVR12 and the SOF-VEL × 12 weeks cohort achieved a 98% (432/440) SVR12. When looking at data on the GT1a group treated with SOF-VEL-VOX × 8 weeks 92% (155/169) achieved SVR12 whereas 99% (170/172) of the SOF-VEL × 12 weeks achieved SVR12 [40]. There were 14 relapses observed in the SOF-VEL-VOX × 8 weeks group compared to 1 relapse in the SOF-VEL × 12 weeks group. The two combinations were also compared in cirrhotics versus noncirrhotics and the following results were obtained. In the SOF-VEL-VOX × 8 weeks cohort 96% (394/411) SVR12 was achieved in the noncirrhotic cohort, whereas 91% (82/90) SVR12 was achieved in the cirrhotic cohort. There were also observed to be 14 and 7 relapses, respectively. In the SOF-VEL × 12 weeks 98% (349/356) of SVR12 was achieved in the noncirrhotic cohort and 99% (83/84) in the cirrhotic cohort. The observed relapses in this group were 2 and 1, respectively [40].

In patients who are genotype 1a with or without cirrhosis, 12 weeks of sofosbuvir/velpatasvir should suffice to achieve SVR 12.

This combination has very tolerable side effect profile, with mild gastrointestinal adverse events associated with regimens including voxilaprevir. Most common side effects included headache, fatigue, diarrhea, and nausea.

4.9.4 Ledipasvir/Sofosbuvir

This is a combination of NS5A inhibitor (ledipasvir) and NS5B polymerase inhibitor (sofosbuvir). It comes in a daily fixed-dose pill containing ledipasvir (90 mg) and sofosbuvir (400 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of ledipasvir/sofosbuvir treatment as a Class 1, Level A recommendation for treatment-naive GT1a patients with or without cirrhosis. These guidelines also list 8 weeks of ledipasvir/sofosbuvir treatment as a Class 1, Level B recommendation for noncirrhotic, HIV-uninfected, non-African-American whose baseline HCV RNA is less than <6 million IU/ml [7] (Tables 4.1 and 4.2).

Treatment regimen has been approved by the FDA based on two major trials, ION-1 and ION-3 [41, 42]. ION-1 open-label, randomized phase 3 trial used fixed-dose combination of ledipasvir-sofosbuvir (LDV-SOF) ± ribavirin (RBV) for 12 or 24 weeks in treatment-naive patients with GT1 chronic HCV infection. In this study by Afdhal et al., 865 patients were recruited, of which 67% (581/865) were identified as having GT1a and 16% (136/865) had cirrhosis. Data on the treatment duration and regimen choice shows that LDV-SOF ± RBV for 12 or 24 weeks achieved SVR12 of 97–99% in all arms of the trial with no notable difference in sustained virologic response in regard of genotype 1, length of the treatment, or ribavirin use. Data for treatment duration and liver disease status also showed no difference between both groups who achieved SVR12 97% in cirrhotics versus 98% in noncirrhotics [41].

ION-3 is an open-label, randomized, phase 3 trial comparing ledipasvir-sofosbuvir (LDV-SOF) with or without ribavirin (RBV) for 8 weeks and ledipasvir-sofosbuvir (LDV-SOF) for 12 weeks in treatment-naive, noncirrhotic patients

with GTI HCV. The purpose of this study was to investigate reducing the course of treatment from 12 to 8 weeks with exclusion of cirrhotic population. They recruited 647 treatment-naive patients and randomized them to three treatment groups. Treatment group one consisted of 215 patients and received LDV-SOF for 8 weeks, treatment group two consisted of 216 patients and received LDV-SOF + RBV for 8 weeks, and treatment group three consisted of 216 patients receiving LDV-SOF for 12 weeks. Kowdley et al. reported data that showed SVR12 ranging between 93 and 95% throughout all treatment arms [42]. Based on these findings no additional benefit was achieved by adding ribavirin or extending the duration of treatment. Higher level of relapse was noted in patients with high baseline HCV RNA ≥6 million. In regard to resistance data, 116 (18%) of 647 patients had baseline NS5A resistance. SVR12 was noted to be 90% (104/116) in this patient population [42].

4.10 Alternative Regimens for Genotype 1a with or Without Cirrhosis

4.10.1 Simeprevir/Sofosbuvir

This is a combination of NS3/4A protease inhibitor (simeprevir) and NS5B polymerase inhibitor (sofosbuvir). It comes in a daily pill containing simeprevir (150 mg) plus sofosbuvir (400 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of simeprevir/sofosbuvir as an alternative treatment with a Class 1, Level A recommendation and can be used in patients without cirrhosis [7] (Tables 4.1 and 4.2).

OPTIMIST- I trial is a randomized phase 3 open-label trial evaluating the safety and efficacy of sofosbuvir plus simeprevir for 8 or 12 weeks in treatment-naive or treatment-experienced HCV GT1 patients without cirrhosis [43]. Three hundred and ten patients were randomized into 8- or 12-week groups. We will focus on the data for the treatment-naive patients which account for 218 of the 310 (70%) patients. SVR12 was achieved in 97% of the patients with 12 weeks of treatment, whereas 85% achieved SVR12 in the 8-week arm. There was also no difference in SVR12 based on genotype 1 subtype or presence of the baseline Q80K resistance substitution [43].

4.10.2 Daclatasvir/Sofosbuvir

This is a combination of NS5A inhibitor (daclatasvir) and NS5B polymerase inhibitor (sofosbuvir). It comes in a daily pill containing daclatasvir (60 mg) plus sofosbuvir (400 mg). The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. The 2016 AASLD/IDSA guidelines list 12 weeks of daclatasvir/sofosbuvir as an alternative treatment with a Class 1, Level B recommendation and can be used in patients without cirrhosis [7] (Tables 4.1 and 4.2).

The recommendations are based on ALLY-2 phase 3 trial which assessed the efficacy and safety of daclatasvir (DCV) and sofosbuvir (SOF) for 12 weeks in treatment-naive or -experienced patients coinfected with HIV and HCV (genotypes 1, 2, 3, or 4) [44]. Total number of patients enrolled in the study was 395, of which 106 (27%) were identified as having GT1a, and being treatment naive. We will discuss the results for the treatment-naive GT1a patients here. SVR12 was achieved in 96% (68/71) of the patients with DCV + SOF × 12-week arm, compared to 80% (28/35) in the DCV + SOF × 8-week arm. Next, we will compare the date for all GT1 patients with or without cirrhosis. For noncirrhotics SVR12 was achieved in 97% of the patients in the DCV + SOF × 12-week arm compared to 78% in the DCV + SOF × 8-week arm. For the cirrhotic patients SVR12 was achieved in 89% in the DCV + SOF × 12-week arm in contrast to 50% in the DCV + SOF × 8-week arm [44].

4.10.3 Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir and Ribavirin

This is a fixed daily-dose combination of paritaprevir (150 mg), ritonavir (100 mg), ombitasvir (25 mg) plus a twice-daily dose of dasabuvir (25 mg) with weight-based ribavirin which was approved for treatment of treatment-naive GT1a chronic HCV infection without cirrhosis. Per the 2016 AASLD/IDSA guidelines this is listed as an alternative 12-week regimen with a Class 1, Level A rating [7] (Tables 4.1 and 4.2).

The recommendations are based on three major clinical trials for all GT1a patients without cirrhosis, including the SAPPHIRE-I trial, PEARL-IV trial, and TURQUOISE-II [45–47].

SAPPHIRE-I trial is a randomized, phase 3, double-blind, placebo-controlled trial evaluating the safety and efficacy of combination for 12 weeks in treatment-naive patients with chronic HCV GT1 infection. In the GT1a subgroup 95.3% (307/322) of the patients achieved SVR12 using the multitargeted regimen for 12 weeks [45].

PEARL-IV trial is a randomized, phase 3, open-label trial evaluating the safety and efficacy of ombitasvir-paritaprevir-ritonavir+dasabuvir (3D) ± ribavirin (RBV) for 12 weeks in treatment-naive patients with chronic HCV GT1a infection. SVR12 was noted to be higher in the 3D + RBV arm, 97% (97/100) compared to 90% (185/205) in the 3D arm, which elucidated to the need for ribavirin with this regimen to ensure higher SVR rates in GT1a infection [46].

TURQUOISE-II trial is a randomized, phase 3, open-label trial evaluating the safety and efficacy of 3D + RBV for 12 or 24 weeks in treatment-naive and -experienced patients with chronic HCV GT1 and compensated cirrhosis. A total of 380 patients were enrolled and 261 were identified to have GT1a infection. In the 3D + RBV × 12 weeks' arm SVR12 was achieved in 89% (124/140) of the patients and in the 3D + RBV × 24 weeks' arm SVR12 was achieved in 94% (114/121) of the patients, but this included data for treatment-naive and -experienced patients.

When looking at the data for patients with no prior treatment there were a total of 120 patients out of the 261 with GT1a infection and SVR12 was achieved in roughly 92–93% in both arms [47].

Common side effects include headache, fatigue, pruritus, nausea, insomnia, and diarrhea.

4.11 Treatment of Genotype 1b with or Without Cirrhosis

4.11.1 Elbasvir/Grazoprevir

This is a combination of NS5A inhibitor (elbasvir) and NS3/4A protease inhibitor (grazoprevir). It comes in a fixed daily-dose tablet containing 50 mg of elbasvir and 100 mg of grazoprevir. The 2016 AASLD/IDSA guidelines list 12 weeks of elbasvir/grazoprevir treatment as a Class 1, Level A recommendation for treatment-naive patients with GT1b with or without cirrhosis [7] (Tables 4.3 and 4.4).

Recommendations for patients without cirrhosis are based on data from the phase 3 C-EDGE trial and phase 2 C-WORTHY trial [31–33]. Phase 3 C-EDGE trial assessed the efficacy and safety of this regimen for 12 weeks in treatment-naive adults with genotypes 1, 4, and 6. Out of the 421 total patients enrolled 171 were identified as chronically infected with GT1b. SVR12 was achieved in 99% (129/131) of the patients assigned to the immediate arm. 14% of genotype 1b patients were identified with baseline NS5A RAVs, and 94% of these patients achieved SVR12 compared to 100% without the NS5A RAVs [31]. In contrast to genotype 1a, the presence of baseline substitutions associated with NS5A resistance did not appear

Table 4.3 Initial regimens for genotype 1b treatment naive of chronic hepatitis C with no cirrhosis [7, 26]

Genotype	Treatment	Duration	Dose	Rating of recommendation
1b	Glecaprevir 300 mg/pibrentasvir 120 mg	8 weeks	Daily fixed	IA
	Ledipasvir 90 mg/sofosbuvir 400 mg	12 weeks	Daily fixed	IA
	Ledipasvir 90 mg/sofosbuvir 400 mg	8 weeks	Daily fixed	IB
	Elbasvir 50 mg/grazoprevir 100 mg	12 weeks	Daily fixed	IA
	Sofosbuvir 400 mg/velpatasvir 100 mg	12 weeks	Daily fixed	IA
	Simeprevir 150 mg/sofosbuvir 400 mg	12 weeks	Daily fixed	IA
	Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg/ dasabuvir 250 mg and weight-based ribavirin	12 weeks	Daily fixed except for dasabuvir twice daily	IA

Table 4.4 Initial regimens for genotype 1b treatment naive of chronic hepatitis C with cirrhosis [7, 26]

Genotype	Treatment	Duration	Dose	Rating of recommendation
1b	Glecaprevir 300 mg/pibrentasvir 120 mg	12 weeks	Daily fixed	IA
	Ledipasvir 90 mg/sofosbuvir 400 mg	12 weeks	Daily fixed	IA
	Elbasvir 50 mg/grazoprevir 100 mg	12 weeks	Daily fixed	IA
	Sofosbuvir 400 mg/velpatasvir 100 mg	12 weeks	Daily fixed	IA
	Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg/ dasabuvir 250 mg and weight-based ribavirin	12 weeks	Daily fixed except for dasabuvir twice daily	IA

to affect genotype 1b response to elbasvir/grazoprevir. Thus, current data do not support extending the treatment duration or adding ribavirin in genotype 1b patients with NS5A RASs [31].

Recommendations for patients with compensated cirrhosis are based on C-EDGE and C-WORTHY trial [31–33]. C-WORTHY trial was a randomized, open-label, phase 2 trial examining the safety and efficacy of elbasvir plus grazoprevir with or without ribavirin for 12 or 18 weeks with cohort 1 being treatment-naive patients with cirrhosis, and cohort 2 being patients with a previous null response to PegINF/ribavirin combo. A 97% (28/29) SVR12 rate had been demonstrated in genotype 1 cirrhotic treatment-naive patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin in the open-label phase 2 C-WORTHY trial, which enrolled both HCV-monoinfected and HIV/HCV-coinfected patients [33]. Findings from the phase 3 C-EDGE trial supported the earlier findings from this phase 2 study. In the C-EDGE trial 92 patients (22% with Metavir F4 disease) were seen having had a 97% SVR12 with elbasvir/grazoprevir. Presence or absence of cirrhosis does not appear to alter the efficacy of the elbasvir/grazoprevir regimen [31].

4.11.2 Glecaprevir/Pibrentasvir

This is a combination of NS3/4A protease inhibitor (glecaprevir) and NS5A inhibitor (pibrentasvir). It was recently approved by FDA as a pan-genotypic DAA for patients with chronic hepatitis C. It comes in a fixed daily dose with three tablets of glecaprevir 100 mg and pibrentasvir 40 mg. The 2016 AASLD/IDSA guidelines list 8 weeks of glecaprevir/pibrentasvir treatment as a Class 1, Level A recommendation for treatment-naive patients with GT1b without cirrhosis, and 12 weeks with compensated cirrhosis [7] (Tables 4.3 and 4.4).

Recommendations for patients without cirrhosis are derived from phase 2 SURVEYOR 1 and ENDURANCE-1 trials [34, 35]. SURVEYOR-1 data for the non-cirrhotic group showed 97% (33/34) SVR12 [34].

The ENDURANCE-1 trial is a randomized, open-labeled, phase 3 trial that evaluated the safety and efficacy of this fixed-dose combination for 8 versus 12 weeks in treatment-naive or treatment-experienced adults with GT1 chronic HCV infection without cirrhosis. SVR12 was achieved at 99.1% in 8-week arm and 99.7% in 12-week arm and it was concluded that 8 weeks of therapy was none inferior to 12 weeks [34].

In the SURVEYOR 1 trial 50 out of the 79 patients enrolled were treatment naive, and a SVR12 of 98% (49/50) was achieved [35].

Recommendations for patients with compensated cirrhosis are based on EXPEDITION-1 and EXPEDITION-2 [37, 38]. EXPEDITION-1 is an open-label phase 3 trial to evaluate the safety and efficacy of the fixed-dose combination for 12 weeks in treatment-naive and treatment-experienced adults with GT1, -2, -4, -5, or chronic HCV infection and compensated cirrhosis. Out of the total 146 patients enrolled 39 patients were identified to have been infected with GT1b and SVR12 was noted to be 100% (39/39) [37]. EXPEDITION-2 looks at HIV/HCV-coinfected adults with GT1, -2, -3, -4, -5, or -6 using the glecaprevir/pibrentasvir for 8 weeks in noncirrhotic patients and 12 weeks in cirrhotic patients [38]. There was (5/16) cirrhotic patients were enrolled with chronic HCV GT1b treated in the 12-week arm. In this arm (14/15) patients had achieved SVR12 (98%) with one breakthrough and 1 patient who discontinued therapy [38].

4.11.3 Sofosbuvir/Velpatasvir

This is a combination of NS5B polymerase inhibitor (sofosbuvir) and NS5A inhibitor (velpatasvir). It comes in a daily fixed-dose pill containing sofosbuvir (400 mg) and velpatasvir (100 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of sofosbuvir/velpatasvir treatment as a Class 1, Level A recommendation for treatment-naive GT1b patients with or without cirrhosis [7] (Tables 4.3 and 4.4).

Recommendations for this fixed-dose combination are based on the ASTRAL-1 trial and POLARIS-2. ASTRAL-1 trial enrolled 624 participants with 118 (19%) being identified as GT1b. In this group SVR12 was achieved in 99% (117/118) with virologic failure being very rare. There was no difference noted in the rate of SVR12 achieved in cirrhotic versus noncirrhotic patients [39].

POLARIS-2 study had 941 patients enrolled, of which 122 were identified as GT1b. SVR12 for both treatment arms SOF-VEL-VOX × 8 weeks and SOF-VEL × 12 weeks was 97%, with a single relapse observed [40].

4.11.4 Ledipasvir/Sofosbuvir

This is a combination of NS5A inhibitor (ledipasvir) and NS5B polymerase inhibitor (sofosbuvir). It comes in a daily fixed-dose pill containing ledipasvir (90 mg) and sofosbuvir (400 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of ledipasvir/sofosbuvir treatment as a Class 1, Level A recommendation for treatment-naive GT1b patients with or without cirrhosis [7] (Tables 4.3 and 4.4).

Treatment regimen has been approved by the FDA based on two major trials, ION-1 and ION-3 [41, 42]. ION-1 enrolled 865 patients, of which 32% (273/865) were identified as having GT1b and 16% (136/865) had cirrhosis. Data on the treatment duration and regimen choice shows that LDV-SOF ± RBV for 12 or 24 weeks achieved SVR12 of 97–99% in all arms of the trial with no notable difference in sustained virologic response in regard to genotype 1, length of the treatment, or ribavirin use [41]. Data for treatment duration and liver disease status also showed no difference between both groups who achieved SVR12 97% in cirrhotics versus 98% in noncirrhotics [41].

In ION-3 trial, they recruited 647 treatment-naive patients and randomized them to three treatment groups. Treatment group one consisted of 215 patients and received LDV-SOF for 8 weeks, treatment group two consisted of 216 patients and received LDV-SOF + RBV for 8 weeks, and treatment group three consisted of 216 patients receiving LDV-SOF for 12 weeks. Kowdley et al. reported data that showed SVR12 97.7% (42/43) among patients with GT1b who were treated for 8 weeks versus 95.5% SVR 12 among patients who were treated with LDV/DOF + RBV for 8 weeks [42]. Based on these findings no additional benefit was achieved by adding ribavirin or extending the duration of treatment. Higher level of relapse was noted in patients with high baseline HCV RNA ≥6 million. In regard to resistance data, 116 (18%) of 647 patients had baseline NS5A resistance. SVR12 was noted to be 90% (104/116) in this patient population [42].

4.12 Alternative Regimens for Genotype 1b with or Without Cirrhosis

4.12.1 Simeprevir/Sofosbuvir

This is a combination of NS3/4A protease inhibitor (simeprevir) and NS5B polymerase inhibitor (sofosbuvir). It comes in a daily pill containing simeprevir (150 mg) plus sofosbuvir (400 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of simeprevir/sofosbuvir as an alternative treatment with a Class 1, Level A recommendation and can be used in patients without cirrhosis [7] (Tables 4.3 and 4.4).

Recommendations are based on OPTIMIST-I which enrolled 310 patients which were randomized into 8- or 12-week groups. Focusing on the data for the treatment-naive patients, which accounted for 218 of the 310 (70%) patients, showed that SVR12 was achieved in 97% of the patients with 12 weeks of treatment versus 85% in the 8-week arm. There was also no difference in SVR12 based on genotype 1 subtype or presence of the baseline Q80K resistance substitution [43].

4.12.2 Daclatasvir/Sofosbuvir

This is a combination of NS5A inhibitor (daclatasvir) and NS5B polymerase inhibitor (sofosbuvir). It comes in a daily pill containing daclatasvir (60 mg) plus sofosbuvir (400 mg). The dose of daclatasvir may need to increase or decrease when used

concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. The 2016 AASLD/IDSA guidelines list 12 weeks of daclatasvir/sofosbuvir as an alternative treatment with a Class 1, Level B recommendation and can be used in patients without cirrhosis [7] (Tables 4.3 and 4.4).

The recommendations are based on ALLY-2 phase 3 trial which had 395 patients enrolled, of which 18 (5%) were identified as having GT1b, and being treatment naive. We will discuss the results for the treatment-naive GT1b patients here. SVR12 was achieved in 100% (12/12) of the patients in the 12-week arm, compared to 50% (3/6) in the 8-week arm. For noncirrhotics SVR12 was achieved in 97% (70/72) of the patients in the 12-week arm compared to 78% (28/36) in the 8-week arm. For the cirrhotic patients SVR12 was achieved in 89% (8/9) in the 12-week arm in contrast to 50% (2/4) in the 8-week arm for treatment-naive patients [44].

4.12.3 Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

This is a fixed daily-dose combination of paritaprevir (150 mg), ritonavir (100 mg), ombitasvir (25 mg) plus a twice-daily dose of dasabuvir (25 mg) with weight-based ribavirin which was approved for treatment of treatment-naive GT1b chronic HCV infection with or without cirrhosis. Per the 2016 AASLD/IDSA guidelines this is listed as an alternative 12-week regimen with a Class 1, Level A rating [7] (Tables 4.3 and 4.4).

The recommendations are based on three major clinical trials for all GT1a patients without cirrhosis, including the SAPPHIRE-I trial, PEARL-IV trial, and TURQUOISE-II [45–47].

SAPPHIRE-I trial showed that in GT1b subgroup 98% (148/151) of the patients achieved SVR12 using the multitargeted regimen for 12 weeks [45].

In the PEARL-IV trial SVR12 for GT1b infection was noted to be similar in the 3D + RBV arm 99.5% (209/210) and 99% (207/209) in the 3D arm. Rates of virologic failure were higher without ribavirin than with ribavirin among patients with genotype 1a infection but not among those with genotype 1b infection [46].

In the TURQUOISE-II trial a total of 380 patients were enrolled and 119 were identified to have GT1b infection. In both the 12-week and 24-week arms SVR was similar (99% and 100%, respectively) in patients with GT1b infection [47].

4.13 Treatment of Genotype 2 with or Without Cirrhosis

4.13.1 Glecaprevir/Pibrentasvir

This is a combination of NS3/4A protease inhibitor (glecaprevir 300 mg) and NS5A inhibitor (pibrentasvir 120 mg). Per the 2016 AASLD/IDSA guidelines this is listed as an 8-week regimen for patients without cirrhosis with a Class 1, Level A rating. For patients with compensated cirrhosis it is recommended to treat for a 12 weeks' duration with a Class 1, Level B rating [7] (Tables 4.5 and 4.6).

Table 4.5 Initial regimens for genotypes 2, 3, 4, 5, and 6 treatment naive of chronic hepatitis C with no cirrhosis [7, 26]

Genotype 2	Genotype 3	Genotype 4	Genotypes 5 and 6
Glecaprevir 300 mg/ pibrentasvir 120 mg, daily dose for 8 weeks	Glecaprevir 300 mg/ pibrentasvir 120 mg daily dose for 8 weeks	Glecaprevir 300 mg/ pibrentasvir 120 mg daily for 8 weeks	Glecaprevir 300 mg/ pibrentasvir 120 mg daily for 8 weeks
Sofosbuvir 400 mg/ velpatasvir 100 mg, daily dose for 12 weeks	Sofosbuvir 400 mg/ velpatasvir 100 mg, daily dose for 12 weeks	Sofosbuvir 400 mg/ velpatasvir 100 mg, daily dose for 12 weeks	Sofosbuvir 400 mg/ velpatasvir 100 mg, daily dose for 12 weeks
Daclatasvir 60 mg/ sofosbuvir 400 mg, daily dose for 12 weeks	Daclatasvir 60 mg/ sofosbuvir 400 mg, daily dose for 12 weeks	Ledipasvir 90 mg/ sofosbuvir 400 mg, daily dose for 12 weeks	Ledipasvir 90 mg/ sofosbuvir 400 mg, daily dose for 12 weeks
		Elbasvir 50 mg/ grazoprevir 100 mg, daily dose for 12 weeks	
		Paritaprevir 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg and weight-based ribavirin for 12 weeks	

Table 4.6 Initial regimens for genotypes 2, 3, 4, 5, and 6 treatment naive of chronic hepatitis C with cirrhosis [7, 26]

Genotype 2	Genotype 3	Genotype 4	Genotypes 5 and 6
Glecaprevir 300 mg/ pibrentasvir 120 mg, daily dose for 12 weeks	Glecaprevir 300 mg/ pibrentasvir 120 mg daily dose for 12 weeks	Glecaprevir 300 mg/ pibrentasvir 120 mg daily for 8 weeks	Glecaprevir 300 mg/pibrentasvir 120 mg daily for 12 weeks
Sofosbuvir 400 mg/ velpatasvir 100 mg, daily dose for 12 weeks	Sofosbuvir 400 mg/ velpatasvir 100 mg, daily dose for 12 weeks	Sofosbuvir 400 mg/ velpatasvir 100 mg, daily dose for 12 weeks	Sofosbuvir 400 mg/ velpatasvir 100 mg, daily dose for 12 weeks
Daclatasvir 60 mg/ sofosbuvir 400 mg, daily dose for 16–24 weeks	Sofosbuvir 400 mg/ velpatasvir 100 mg/ voxilaprevir 100 mg, daily dose for 12 weeks	Ledipasvir 90 mg/ sofosbuvir 400 mg, daily dose for 12 weeks	Ledipasvir 90 mg/ sofosbuvir 400 mg, daily dose for 12 weeks
	Daclatasvir 60 mg/ sofosbuvir 400 mg with weight-based ribavirin daily for 24 weeks	Elbasvir 50 mg/ grazoprevir 100 mg, daily dose for 12 weeks	
		Paritaprevir 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg and weight-based ribavirin for 12 weeks	

Kowdley et al. presented their data from ENDURANCE-2 trial at AASLD 2016 about the use of glecaprevir/pibrentasvir [48]. They had 302 patients recruited for the study cohort infected with genotype 2 and 202 of them were randomized for placebo-controlled groups. There was 70% of the cohort population treatment naive with no cirrhosis. They were all treated with glecaprevir 300 mg/pibrentasvir 120 mg daily for 12 weeks and the SVR 12 rate was achieved in 99% of the cohort. It is worth to mention that one patient of the study achieved SVR 4 who was lost for follow-up [48].

Glecaprevir/pibrentasvir was actually investigated for shorter course of therapy at 8 weeks. In phase 2, single-arm study, Hassanein et al. examined in SURVEYOR-2 trial 203 patients with no cirrhosis infected with genotypes 2, 4, 5, and 6. There were 142 (70%) patients with genotype 2 and 137 (96%) of them were treatment naive. All of them received 8 weeks of daily fixed dose of glecaprevir 300 mg/pibrentasvir 120 mg and the SVR rate was 99% achieved in 135/137 of treatment-naive patients [49].

From both trials mentioned above, it was elucidated that both regimens are clearly highly effective in the treatment of chronic hepatitis C in patients infected with genotype 2 without cirrhosis using 8 or 12 weeks' regimens [48, 49].

In compensated cirrhosis, EXPEDITION-1, a phase 3 open-label single-arm trial, had investigated glecaprevir/pibrentasvir in 146 patients with compensated cirrhosis infected with genotypes 1, 2, 4, 5, and 6. All of the patients had received 12 weeks of daily fixed dose of glecaprevir 300 mg/pibrentasvir 120 mg and SVR 12 was achieved in 99% of participants from all genotypes [37]. On the other hand, in EXPEDITION-2, the cohort was smaller where they enrolled 31 patients infected with a genotype 2; between naive and experienced all 31 patients achieved SVR 12 successfully [38].

Recommendations for patients without cirrhosis are derived from phase 2 SURVEYOR 1 and ENDURANCE-2 trial. SURVEYOR-1 data for the noncirrhotic group showed 97% (33/34) SVR12.

ENDURANCE-2 trial is a randomized, double-blinded, phase 3 trial to evaluate the safety and efficacy of this fixed-dose regimen for 12 weeks in treatment-naïve or treatment-experienced adults with GT2 chronic HCV infection without cirrhosis. Out of the 202 patients enrolled into the treatment arm 141 (70%) were treatment naive. Overall SVR12 was noted to be 99% in this group.

4.13.2 Sofosbuvir/Velpatasvir

This is a combination of NS5B polymerase inhibitor (sofosbuvir) and NS5A inhibitor (velpatasvir). It comes in a daily fixed-dose pill containing sofosbuvir (400 mg) and velpatasvir (100 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of sofosbuvir/velpatasvir treatment as a Class 1, Level A recommendation for treatment-naive GT2 patients with or without cirrhosis [7] (Tables 4.5 and 4.6).

Recommendations for this fixed-dose combination are based on the ASTRAL-1, ASTRAL-2, and POLARIS-2 trials. ASTRAL-1 trial enrolled 624 participants with 104 (17%) being identified as GT2. In this group SVR12 was achieved in 100% of the patients. There was no difference noted in the rate of SVR12 achieved in cirrhotic versus noncirrhotic patients [39].

ASTRAL-2 trail is a randomized, placebo-controlled, phase 3 trial using a fixed-dose combination of sofosbuvir-velpatasvir (SOF-VEL) for 12 weeks compared with sofosbuvir plus ribavirin (SOF + RBV) in treatment-naive and treatment-experienced patients with GT2 chronic HCV. A total of 266 patients were randomized into either SOF-VEL arm or SOF + RBV arm. There were roughly 14% cirrhotics and treatment-experienced patients in both arms. SVR 12 rates were found to be higher in SOF-VEL compared to SOF + RBV, 99% vs. 94%, respectively [50]. Patients with cirrhosis were all successfully able to achieve SVR12 with 12 weeks of sofosbuvir/velpatasvir. Similar findings were seen in patients with prior virologic failure. The treatment was well tolerated and there was not any reported case of anemia [50].

POLARIS-2 study had 941 patients enrolled, of which 116 were identified as infected with GT2. SVR12 for SOF-VEL-VOX × 8 weeks was 97% (61/63) and SOF-VEL × 12 (53/53) weeks was 100% [41].

4.14 Alternative Regimens for Genotype 2 with or Without Cirrhosis

4.14.1 Daclatasvir/Sofosbuvir

Daclatasvir NS5A inhibitor (60 mg) and sofosbuvir (400 mg) was not approved for treatment of genotype 2 infection, but since daclatasvir maintains adequate activity against genotype 2 and in association with sofosbuvir has shown high SVR rates in treatment-naive patients it has been recommended as an alternative regimen. The 2016 AASLD/IDSA guidelines list 12 weeks of daclatasvir/sofosbuvir as an alternative treatment with a Class IIa, Level B rating in patients without cirrhosis, and in compensated cirrhosis they recommend therapy duration to range from 16 to 24 weeks with Class IIa, Level B rating [7] (Tables 4.5 and 4.6).

In ALLY-2 trial, Wyles et al. had treated 13 patients with no cirrhosis; 2 of them were treatment experienced, with daily combination of daclatasvir 60 mg/sofosbuvir 400 mg for 12 weeks. SVR 12 was achieved in 100% of the group [44]. Sulkowski et al. also published good evidence of 24 weeks of daclatasvir/sofosbuvir used for genotype 2 with SVR12 rate at 92% of 26 patients enrolled in this trial. For patients who develop intolerance to prior recommended regimens, daclatasvir/sofosbuvir can be used for 12 or 24 weeks depending on disease staging and prior virologic failure [51].

4.15 Treatment of Genotype 3 with or Without Cirrhosis

4.15.1 Glecaprevir/Pibrentasvir

This is a combination of NS3/4A protease inhibitor (glecaprevir 300 mg) and NS5A inhibitor (pibrentasvir 120 mg). Per the 2016 AASLD/IDSA guidelines this is listed as an 8-week regimen for patients without cirrhosis with a Class 1, Level A rating. For patients with compensated cirrhosis it is recommended to treat for a 12 weeks' duration with a Class 1, Level A rating [7] (Tables 4.5 and 4.6).

In ENDURANCE-3 trial, Foster et al. had compared the efficacy of glecaprevir/pibrentasvir in patients with genotype 3 at 8 and 12 weeks. The study recruited 348 patients infected with genotype 3 treatment naive without cirrhosis and randomized first into two groups, glecaprevir 300 mg/pibrentasvir 120 mg (233) versus sofosbuvir 400 mg/daclatasvir 60 mg (115). Later on it was decided to add another arm of the study to investigate the efficacy of glecaprevir/pibrentasvir for 8 weeks (157) [52]. SVR12 rate was reached successfully at 95% of the both arms (222/233, 149/157). SVR12 rate in 8 weeks arm was found none inferior to 12 weeks' arm of glecaprevir/pibrentasvir. Both of these arms were eventually found non-inferior to the other arm of sofosbuvir and daclatasvir which considered the standard of treatment (SVR12 rate 97%). Virologic failure of 8 weeks' arm was noted in six subjects (one virologic breakthrough and five relapses), meanwhile four virologic failures were recorded among 12 weeks' arm (one virologic breakthrough and three relapses) [52].

In SURVEYOR II phase 2 trial, 48 patients with compensated cirrhosis treatment naive infected with genotype 3 were randomized into 2 groups with 24 patients each. First group received 12 weeks of glecaprevir 300 mg/pibrentasvir 120 mg versus 12 weeks of glecaprevir 300 mg/pibrentasvir 120 mg with weight-based ribavirin [49]. All patients in both arms achieved SVR12 and baseline RAVs appeared to have no impact on SVR12. It was concluded for those GT3 treatment-naive patients with compensated cirrhosis that treatment with 12 weeks of glecaprevir 300 mg/pibrentasvir 120 mg suffices to achieve SVR12 regardless of the use of ribavirin [49].

4.15.2 Sofosbuvir/Velpatasvir

This is a combination of NS5B polymerase inhibitor (sofosbuvir 400 mg) and NS5A inhibitor (velpatasvir 100 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of sofosbuvir/velpatasvir treatment as a Class 1, Level A recommendation for treatment-naive GT3 patients with or without cirrhosis [5]. RAS testing for Y93H is recommended for cirrhotic patients and if present it is recommended that ribavirin should be included in the regimen or sofosbuvir/velpatasvir/voxilaprevir should be considered [7] (Tables 4.5 and 4.6).

Foster et al. in ASTRAL 3 trial screened 652 patients infected with genotype 3 [50]. Out of those, 558 patients were randomized into 2 groups and 552 patients received treatment. 277 patients received 12 weeks of daily fixed dose of sofosbuvir 400 mg/velpatasvir 100 mg while 275 patients received 24 weeks of sofosbuvir 400 mg and weight-based ribavirin (1000 mg < 75 kg and 1200 mg > 75 kg). The SVR12 rate was 95% with sofosbuvir/velpatasvir arm in comparison to 80% SVR12 among those who received sofosbuvir and ribavirin for 24 weeks. For treatment-naive patients without cirrhosis, the SVR rate was 98% (16/163) and 93% (40/43) for treatment-naive patients with compensated cirrhosis versus 73.5% (33/45) for those with compensated cirrhosis who were treated with sofosbuvir and ribavirin. It's worth mentioning that SVR12 was 88% for those who had NS5A RAVs at the baseline and 84% (21/25) was noted in subjects with detected Y93H variants at the baseline. It is recommended to add ribavirin for those patients with compensated cirrhosis who do have detectable level of the aforementioned variant [50].

In POLARIS 2 and 3, Jacobson et al. have looked into 12-week treatment with sofosbuvir/velpatasvir versus 8 weeks of sofosbuvir/velpatasvir/voxilaprevir in patients infected with genotype 3 with or without cirrhosis [40]. In Polaris 2 phase 3 study 89 patients infected with genotype 3 were treated with sofosbuvir/velpatasvir for 12 weeks and 97% (86/89) achieved SVR12 with no virologic failure and this adds another strong evidence for this regimen's efficacy in treating genotype 3 chronic HCV in noncirrhotic population [40].

In POLARIS 3 study, the cohort included 229 patients infected with genotype 3 and compensated cirrhotics were randomized into 2 groups. 109 patients received 12 weeks of daily fixed dose of sofosbuvir 400 mg/velpatasvir 100 mg and 110 patients received 8 weeks of sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg. The SVR rate achieved was 96% in both arms of the study (105/109) and (106/110), respectively. All patients with detected Y93H at baseline had achieved SVR in the sofosbuvir/velpatasvir arm [53].

4.16 Alternative Regimens for Genotype 3 with or Without Cirrhosis

4.16.1 Daclatasvir/Sofosbuvir

Daclatasvir NS5A inhibitor (60 mg) and sofosbuvir (400 mg) is approved for the treatment of genotype 3 infection. The 2016 AASLD/IDSA guidelines list 12 weeks of daclatasvir/sofosbuvir as an alternative treatment with a Class I, Level A rating in patients without cirrhosis, and in compensated cirrhosis they recommend therapy duration of 24 weeks with or without weight-based ribavirin with Class IIa, Level B rating [7] (Tables 4.5 and 4.6).

In ALLY-3 phase 3 trial, Nelson et al. had evaluated the use of 12 weeks' regimen of daclatasvir 60 mg (DCV)/sofosbuvir 400 mg (SOF) in noncirrhotic and cirrhotic patients infected with genotype 3 [54]. There were 152 patients enrolled with 101

patients being treatment naive and 51 patients being treatment experienced; both groups received 12 weeks of the aforementioned treatment; however we will focus on the data for the treatment-naive group. 19% (19/101) of the treatment-naive patients had compensated cirrhosis. The SVR12 rate was 90% (90/101) among all treatment-naive patients; patients without cirrhosis achieved 97% (73/75) SVR12 whereas cirrhotic patients who were treated with same regimen for the same length of therapy achieved an SVR12 of 58% (11/19) only [54].

In the follow-up, ALLY 3+ trial was a phase 3 open-label randomized trial of DCV + SOF + RBV for 12 versus 16 weeks in both treatment-naive or -experienced chronic HCV GT3 with advanced fibrosis or compensated cirrhosis. SVR12 was achieved in 88% (21/24) of patients in the 12 weeks' arm, and 92% (24/26) in the 16 weeks' arm. In regard to patients with cirrhosis 83% achieved SVR12 in the 12 weeks' arm and 89% in the 16 weeks' arm [54].

The results from the ALLY-3+ study suggested that compensated cirrhotic patients with genotype 3 would benefit from treatment extension, and this hypothesis was confirmed by data from the real-world cohort DCV European compassionate-use program [56]. This analysis included 102 genotype 3 chronic hepatitis C patients considered at high risk of hepatic decompensation or death within 12 months if left untreated. Participants were treated with DCV + SOF ± RBV × 24 weeks; however providers could opt for a shorter course, or addition of ribavirin. In treatment-naive patients on DCV + SOF 92% achieved SVR12 whereas 100% achieved SVR12 with DCV + SOF + RBV. For cirrhotic patients 89% achieved SVR12 on DCV + SOF and 88% on DCV + SOF + RBV. 85% of the GT3-infected patients had cirrhosis and there were some notable variations with SVR12 rate and liver disease severity. SVR12 rates were higher among patients with Child-Pugh A cirrhosis compared to those with Child-Pugh B and C (80–100% vs. 70%) [55]. Between both arms which were treated with or without ribavirin, it was concluded that SVR12 was comparable independently from ribavirin use (95.9% vs. 81.3%). As it was mentioned earlier in ENDURANCE-3 trial, gravida 15 patients were randomized in the sofosbuvir 400 mg/daclatasvir 60 mg arm for 12 weeks. SVR rate achieved in this cohort was 97% and 95% (20/21) with baseline NS5A RASs [55].

The presence of NS5A RAS baseline was associated dramatically with reduced SVR12 rates among patients infected with genotype 3. The presence of NS5A Y93H was found to be related to decreased SVR12 in 7/13 (54%) with baseline NS5A Y93H who were treated in ALLY-3 [54]. On the other hand, in those who did not have NS5A Y93H the SVR12 was 92% (149/162). Also, cirrhosis felt to be a factor contributed to less SVR12 rate in those with baseline NS5A RASs. Another RAS detected was associated with lower SVR12 like A30K. In ALLY-3 trial, patients without cirrhosis who did have detectable level of this RAS all achieved SV2 12 (9/9). However, among those with compensated cirrhosis, 1/5 only achieved SVR12 but 2/5 were NS5A Y93H positive and it felt to be hard to differentiate the real reason for not achieving SVR12 in those patients [54].

4.16.2 Sofosbuvir/Velpatasvir/Voxilaprevir

NS5B polymerase inhibitor (sofosbuvir 400 mg), NS5A inhibitor (velpatasvir 100 mg), and NS3/4A protease inhibitor (voxilaprevir 100 mg) are new 12-week regimen approved by FDA recently to treat DAA-experienced patients with cirrhosis and Y93H [7] (Table 4.6).

In POLARIS-3 trial this combination was used to examine 8-week non-inferiority in comparison to 12 weeks of sofosbuvir and velpatasvir. It included patients infected with genotype 3 and compensated cirrhosis. 229 were randomized into 2 groups. 109 patients received 12 weeks of daily fixed dose of sofosbuvir 400 mg/velpatasvir 100 mg and 110 patients received 8 weeks of sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg. The SVR rate achieved was 96% in both arms of the study (105/109) and (106/110), respectively. All patients with detected Y93H at baseline had achieved SVR6 in 8-week SOF-VEL-VOX arm and 4 in 12-week SOF-VEL arm [53].

4.17 Treatment of Genotype 4 with or Without Cirrhosis

4.17.1 Glecaprevir/Pibrentasvir

This is a combination of NS3/4A protease inhibitor (glecaprevir 300 mg) and NS5A inhibitor (pibrentasvir 120 mg). Per the updated 2016 AASLD/IDSA guidelines this is listed as an 8-week regimen for patients without cirrhosis with a Class 1, Level A rating [7] (Tables 4.5 and 4.6).

In part 4 SURVEYOR-2 study, 22 patients with genotype 4 were treated with 12 weeks of glecaprevir 300 mg and pibrentasvir 120 mg. SVR12 rate was achieved in 100% of the patients [49]. In ENDURANCE-4, Asselah et al. recruited 121 patients with genotypes 4, 5, and 6, noncirrhotic (majority F0-1), treatment naive or experienced with interferon or PegIFN with ribavirin, or sofosbuvir with ribavirin or without PegIFN. They were treated with 12 weeks of glecaprevir 300 mg and pibrentasvir 120 mg with 99% (75/76) achieving SVR12 in genotype 4 [56].

In an open-label, single-arm, multicenter study (SURVEYOR-2 part 4) phase 2 trial the use of 8 weeks of glecaprevir 300 mg and pibrentasvir 120 mg was investigated. There were 46 patients (23%) infected with genotype 4 who achieved SVR12 rates of 93% (43/46), with 1 discontinuation and 2 missing SVR12 data [49].

For patients with compensated cirrhosis it is recommended to treat for a 12 weeks' duration with a Class 1, Level B rating [7]. In EXPEDITION-1, Forns et al. looked at using glecaprevir 300 mg/pibrentasvir 120 mg for patients with compensated cirrhosis. They enrolled 146 patients with compensated cirrhosis secondary to chronic hepatitis C; 11% of the cohort was infected with genotype 4. Their results show that 100% of the patients enrolled achieved SVR with this regimen [37].

4.17.2 Elbasvir/Grazoprevir

This is a combination of NS5A inhibitor (elbasvir) and NS3/4A protease inhibitor (grazoprevir). It comes in a fixed daily-dose tablet containing 50 mg of elbasvir and 100 mg of grazoprevir. The 2016 AASLD/IDSA guidelines list 12 weeks of elbasvir/grazoprevir treatment as a Class 2a, Level B recommendation for treatment-naive patients with GT 4 with or without cirrhosis [7] (Tables 4.5 and 4.6).

Based on data from pooled analysis from phase 2/3 trials presented by Asselah et al. at AASLD 2015, 103 patients were enrolled with 66 of them being treatment naive and 6 patients being cirrhotic. 56 patients were treated with 12 weeks of daily dose of elbasvir/grazoprevir and 10 patients were treated with elbasvir/grazoprevir and ribavirin. Results showed that 97% (64/66) achieved SVR12 including all 10 patients who received ribavirin. 6/6 treatment naive with compensated cirrhosis also achieved SVR12 [58].

4.17.3 Sofosbuvir/Velpatasvir

This is a combination of NS5B polymerase inhibitor (sofosbuvir 400 mg) and NS5A inhibitor (velpatasvir 100 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of sofosbuvir/velpatasvir treatment as a Class 1, Level A recommendation for treatment-naive GT4 patients with or without cirrhosis [7] (Tables 4.5 and 4.6).

Favorable data generated from ASRTRAL-1 and POLARIS-2 trial strongly supports the use of sofosbuvir 400 mg/velpatasvir 100 mg for 12 weeks to treat genotype 4 HCV infection with or without cirrhosis [39, 40]. In ASTRA-1 trial, 116 (19%) patients infected with genotype 4 were treated with 12 weeks of sofosbuvir 400 mg/velpatasvir 100 mg; 27 of them had compensated cirrhosis. The SVR12 rate was achieved at 100% in all genotype 4 patients [39].

In POLARIS-2 trial, 57 patients with genotype 4 were treated with 12-week sofosbuvir 400 mg/velpatasvir 100 mg and showed that SVR12 rate was achieved in 98% with one recorded relapse and no virologic failure [40].

4.17.4 Ledipasvir/Sofosbuvir

This is a combination of NS5A inhibitor (ledipasvir) and NS5B polymerase inhibitor (sofosbuvir). It comes in a daily fixed-dose pill containing ledipasvir (90 mg) and sofosbuvir (400 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of ledipasvir/sofosbuvir treatment as a Class 2a, Level B recommendation for treatment-naive GT 4 patients with or without cirrhosis [7] (Tables 4.5 and 4.6).

Kohli et al. reported in the SYNERGY trial (single-center open-label trial) promising data regarding treatment of genotype 4 patients. They recruited 21 patients infected with genotype 4; 7 of them were cirrhotic. One patient did not complete treatment and the rest all successfully achieved SVR12 (95%), with intention-to-treat analysis SVR12 rate of 100% including all patients with compensated cirrhosis

[58]. Also, data from Abergel et al. reported SVR12 95% in their cohort, 21/22 treated with 12 weeks of ledipasvir/sofosbuvir [59].

4.18 Alternative Regimens for Genotype 4 with or Without Cirrhosis

4.18.1 Paritaprevir/Ritonavir/Ombitasvir and Ribavirin

This is a fixed daily-dose combination of paritaprevir (150 mg), ritonavir (100 mg), ombitasvir (25 mg) plus weight-based ribavirin used for the treatment of genotype 4 HCV infection with or without compensated cirrhosis. According to AASLD/IDSA guidelines these recommendations are Class 1, Level A [7] (Tables 4.5 and 4.6).

In PEARL-I trial Hézode et al. had tested the efficacy of this combination with and without ribavirin on patients infected with genotype 4. In this multicenter, randomized, phase 2b trial, 135 noncirrhotic patients were enrolled infected with genotype 4 who were randomized to be treated with paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) with or without weight-based ribavirin. 86 patients were treatment naïve; 42 of them received paritaprevir (150 mg), ritonavir (100 mg), ombitasvir (25 mg) plus weight-based ribavirin daily and 44 of them received paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) without ribavirin daily. SVR12 rate was achieved in 100% among ribavirin group and 90.9% among other group which did not receive ribavirin [60].

In AGATE-II trial, Esmat et al. treated 100 noncirrhotic, treatment-naive and -experienced (with interferon-based regimen) patients infected with genotype 4 with daily combination of paritaprevir (150 mg), ritonavir (100 mg), ombitasvir (25 mg), and weight-based ribavirin which resulted in SVR12 rate of 94%.

In AGATE-1 trial, Asselah et al. evaluated the efficacy of this combination with ribavirin in the treatment of genotype 4 patients with compensated cirrhosis. 120 patients with compensated cirrhosis were randomized into two groups, 12 weeks versus 16 weeks of therapy with paritaprevir (150 mg), ritonavir (100 mg), ombitasvir (25 mg) plus weight-based ribavirin; 51% of the patients in the 12-week arm and 48% in 16-week arm were treatment naive. The SVR12 rate was 96% in 12-week arm versus 100% in 16-week arm [61].

Based on the excellent data from trials mentioned above 12 weeks of paritaprevir (150 mg), ritonavir (100 mg), ombitasvir (25 mg) plus weight-based ribavirin would suffice and serve a as good alternative therapy to first-line regimens for the treatment of genotype 4 with or without cirrhosis.

4.19 Treatment of Genotype 5–6 HCV Infection

4.19.1 Glecaprevir/Pibrentasvir

This is a combination of NS3/4A protease inhibitor (glecaprevir 300 mg) and NS5A inhibitor (pibrentasvir 120 mg). Per the updated 2016 AASLD/IDSA guidelines this

is listed as an 8- or 12-week regimens for patients without or with cirrhosis, respectively, with a Class 1, Level A rating [7] (Tables 4.5 and 4.6).

In ENDURANCE-4, Asselah et al. recruited 121 patients with genotype 4, 5, and 6, noncirrhotic (majority F0-1), treatment naive or experienced with interferon or PegIFN with ribavirin, or sofosbuvir with ribavirin or without PegIFN. They were treated with 12 weeks of glecaprevir 300 mg and pibrentasvir 120 mg. The SVR12 rate was 100% among patients with genotypes 5 (26/26) and 6 (19/19) [56]. Kwo et al. in SURVOYER-2 study treated 12 patients with genotypes 5 and 6 with 12 weeks of glecaprevir 300 mg and pibrentasvir 120 mg and the SVR12 rate was achieved in 100% [34].

In an open-label, single-arm, multicenter study (SURVYOR-2 part 4) phase 2 trial, 8-week glecaprevir 300 mg and pibrentasvir 120 mg was investigated. There were 46 patients (23%) infected with genotype 5 treated with 8 weeks of glecaprevir 300 mg/pibrentasvir 120 mg. The SVR rate achieved was 100% (2/2) in genotype 5 and 90% (9/10) in genotype 6 with 1 patient missing SVR12 data testing; intention to treat SVR12 was 100% [50]. For patients with compensated cirrhosis it is recommended to treat for a 12 weeks' duration with a Class 1, Level A rating [7].

In EXPEDITION-1, Forns et al. looked into using glecaprevir 300 mg/pibrentasvir 120 mg for patients with compensated cirrhosis. They enrolled 146 patients with compensated cirrhosis secondary to chronic hepatitis C; 7 of them were infected with genotypes 5 and 6. They received 12 weeks of glecaprevir 300 mg/pibrentasvir 120 mg and the SVR12 rate was achieved at 100% in both genotypes [37].

4.19.2 Sofosbuvir/Velpatasvir

This is a combination of NS5B polymerase inhibitor (sofosbuvir 400 mg) and NS5A inhibitor (velpatasvir 100 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of sofosbuvir/velpatasvir treatment as a Class 1, Level B recommendation for treatment-naive GT 5–6 patients with or without cirrhosis [7] (Tables 4.5 and 4.6).

In ASTRAL-I trial, Feld et al. had investigated sofosbuvir 400 mg/velpatasvir 100 mg for 12 weeks for infected patients with genotypes 5 and 6. There were 35 patients with genotype 5 (5 of them were with compensated cirrhosis) and 41 patients with genotype 6 (6 of them were with compensated cirrhosis) who were treated with 12 weeks of sofosbuvir 400 mg/velpatasvir 100 mg. The SVR12 rate was achieved in 96% with genotype 5 and 100% among those with genotype 6. All patients with compensated cirrhosis had achieved SVR12 among both genotypes [40].

4.19.3 Ledipasvir/Sofosbuvir

This is a combination of NS5A inhibitor (ledipasvir) and NS5B polymerase inhibitor (sofosbuvir). It comes in a daily fixed-dose pill containing ledipasvir (90 mg) and sofosbuvir (400 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of

Table 4.7 IFN-free treatment regimens available for treatment-naïve and treatment-experienced patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis, recommended for each HCV genotype/subtype [26][a]

	Pan-genotypic			Genotype-specific		
Genotype	SOF/VEL	GLE/PIB	SOF/VEL/VOX	SOF/LDV	GZR/EBR	OBV/PTV/r + DSV
1a	Yes	Yes	No[b]	Yes	Yes	No
1b	Yes	Yes	No[b]	Yes	Yes	Yes
2	Yes	Yes	No[b]	No	No	No
3	Yes	Yes	Yes	No	No	No
4	Yes	Yes	No[b]	Yes	Yes	No
5	Yes	Yes	No[b]	Yes	No	No
6	Yes	Yes	No[b]	No	Yes	No

DSV dasabuvir, *EBR* elbasvir, *GLE* glecaprevir, *GZR* grazoprevir, *IFN* interferon, *LDV* ledipasvir, *OBV* ombitasvir, *PIB* pibrentasvir, *PTV* paritaprevir, *r* ritonavir, *SOF* sofosbuvir, *VEL* velpatasvir, *VOX* voxilaprevir

[a]Recommendations can be specific to certain subgroups; please see the text

[b]Triple combination therapy is efficacious in these genotypes; however it is not useful due to the efficacy of double combination regimens

ledipasvir/sofosbuvir treatment as a Class 2a, Level B recommendation for treatment-naive GT5–6 patients [7] (Tables 4.5 and 4.6).

In a small study from New Zealand, Gane et al. had used ledipasvir (90 mg) and sofosbuvir (400 mg) for 12 weeks in the treatment of genotype 6-infected patients; 25 patients (2 with cirrhosis) were treated with 12 weeks of ledipasvir (90 mg) and sofosbuvir (400 mg) and 24 of them achieved SVR12 (96%). The one patient who did not achieve SVR12 withdrew treatment at week 8 after relapsing post-week 4 [62]. It was reported that ledipasvir does not have good in vitro activity against genotype 6 subtype e; otherwise it holds good in vitro activity against all other genotype 6 subtypes [62].

Abergel et al. had reported treating 41 patients with genotype 5; 39 of them had achieved SVR12 (95%). Data still limited on treating patients with genotype 5 using ledipasvir (90 mg) and sofosbuvir (400 mg) [59]. A summary of IFN-free treatment regimens available for treatment-naïve and treatment-experienced patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis, recommended for each HCV genotype/subtype is given in Table 4.7.

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Treatment of Hepatitis C Virus-Infected Patients with Renal Failure

5

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5.1 Hepatitis C Virus and the Kidney

The prevalence of hepatitis C virus (HCV) infection in patients with renal diseases is higher compared to the general population [1]. Anti-HCV antibody positivity is higher among hemodialysis patients suggesting that dialysis may be a risk factor in transmission of HCV infection [2]. On the other hand chronic HCV infection is independently associated with the development of chronic kidney disease. Fabrizi et al. in their meta-analysis demonstrated that chronic HCV infection was associated with a 43% increase in the incidence of chronic kidney disease [3]. The deposition of immune complexes (anti-HCV and HCV RNA) in the glomeruli appears to be responsible of the pathogenesis. The most common types are membranoproliferative glomerulonephritis usually associated with essential mixed cryoglobulinemia and less frequently membranous nephropathy [4, 5]. The risk of progression to end-stage renal disease (ESRD) in patients with chronic HCV and chronic kidney disease is also higher compared to general population [3]. According to the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines, patients having chronic HCV infection diagnosis should be screened for kidney disease and then followed up annually thereafter with urinalysis and serum creatinine level [3, 6].

Since HCV infection in ESRD patients may lead to increased risk of all-cause and liver-related mortality, HCV-infected patients with renal impairment should be considered for antiviral therapy [7].

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5.2 Patient Selection for Treatment

American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) guidelines recommend treatment for all patients with chronic HCV infection except those with short life expectancies (<1 year) due to underlying comorbidities [8]. Although AASLD no longer recommends prioritization of antiviral treatment in specific populations, treatment should be primarily considered in some specified groups such as patients with advanced fibrosis and persons at greater risk for rapidly progressive fibrosis and cirrhosis, persons who have undergone liver transplantation, patients with extrahepatic manifestations including significant HCV-related kidney disease (mixed cryoglobulinemic vasculitis and HCV-related glomerulonephritis), and HCV-infected persons at greatest risk for transmission. Treatment of chronic HCV infection may reverse proteinuria and nephrotic syndrome and may lead to resolution of cryoglobulinemia in most patients with extrahepatic manifestations. Therefore treatment of HCV-infected patients with especially mixed cryoglobulinemic vasculitis and HCV-related glomerulonephritis may be crucial in terms of resolution of renal involvement [8].

5.2.1 Treatment Options

The selection of the most appropriate regimen depends on genotype, presence or absence of cirrhosis, prior treatment history, and, in patients with renal failure, degree of renal impairment [8, 9].

Chronic kidney diseases (CKD) can be classified into five stages according to the estimated glomerular filtration rate (eGFR) level:

- *CKD stage 1* = normal (eGFR >90 mL/min per 1.73 m^2)
- *CKD stage 2* = mild CKD (eGFR 60–89 mL/min per 1.73 m^2)
- *CKD stage 3* = moderate CKD (eGFR 30–59 mL/min per 1.73 m^2)
- *CKD stage 4* = severe CKD (eGFR 15–29 mL/min per 1.73 m^2)
- *CKD stage 5* = end-stage CKD (eGFR <15 mL/min per 1.73 m^2)

CKD stages listed above determine the dose adjustment and the selection of appropriate treatment regimen [8–10].

– *Patients with mild-to-moderate renal impairment (eGFR ≥ 30 mL/min per 1.73 m^2)*: No dosage adjustments are necessary for directly acting antiviral (DAA) agents in patients with mild-to-moderate renal impairment. These group of patients should be treated according to the general recommendations [10].
– *Patients with severe renal impairment (eGFR <30 mL/min per 1.73 m^2) or on dialysis*: Antiviral treatment should be evaluated on a case-by-case basis since some drugs are not safe in patients with severe renal failure [10].

Combination therapy composed of pegylated interferon and ribavirin was previously the standard regimen for treatment of chronic HCV infection. Sustained virological response (SVR) rates were generally suboptimal (62–64%) in patients with renal disease or on dialysis and the toxicity rate was higher compared to the general population. Severe anemia rates (hemoglobin <8 g/dL) were significantly higher in the combination therapy group [11, 12]. With the advent of DAA agents having higher rate of SVR and lesser toxicity profile, interferon-based standard therapy has been replaced by new antiviral regimens. But still, pegylated interferon and ribavirin may be the only alternatives for treatment in some regions of the world until drug costs decline and access is provided [10].

5.3 Safety of Antiviral Drugs in Renal Impairment

Although sofosbuvir and ribavirin are mainly eliminated by the kidneys, principal elimination route of the remaining DAA agents is biliary and does not require dose adjustments in case of renal impairment [8, 9].

5.3.1 Sofosbuvir

In patients with severe renal impairment the exposure to nucleoside metabolite of sofosbuvir is increased [9, 13]. Whereas levels of the drug and its metabolite among patients with eGFR ≥30 mL/min per 1.73 m^2 are comparable to patients with normal renal function, drug levels are higher among patients with eGFR <30 mL/min per 1.73 m^2 or with ERDS. Due to high exposure to the metabolite and safety concern, sofosbuvir currently is not recommended in patients with severe renal impairment (eGFR <30 mL/min per 1.73 m^2) [8, 9].

5.3.2 Pegylated Interferon

Since half-life of the pegylated interferon increases in patients under hemodialysis this may lead to higher rate of adverse events [14, 15]. Pegylated interferon when used for treatment of chronic HCV infection in patients with renal impairment may lead to development or exacerbation of glomerulonephritis or vasculitis [16, 17]. Therefore dose reduction is required in case of renal failure and varies according to the formulation prescribed as stated below:

Pegylated interferon alfa-2a:

- If CrCl <30 mL/min: The dose should be reduced to 135 mcg once weekly, and the patient should be monitored for side effects.
- In case of ESRD requiring hemodialysis: The dose should be reduced to 135 mcg once weekly, and the patient should be monitored for side effects. If severe

adverse reactions or laboratory abnormalities develop, the dose should be reduced to 90 mcg once weekly until adverse reactions resolve [18].

Pegylated interferon alfa-2b:
- If CrCl <50 mL/min: Dual therapy of pegylated interferon alfa-2b and ribavirin is not recommended.
- If CrCl is 30–50 mL/min: Pegylated interferon alfa-2b is recommended as monotherapy and the dose should be reduced by 25%.
- If CrCl is 10–29 mL/min or the patient is on hemodialysis: The dose should be reduced by 50%.

If renal function declines during treatment, the drug should be discontinued [19].

5.3.3 Ribavirin

In case of renal insufficiency, accumulation of ribavirin may lead to severe anemia even at lower doses. Although it was contraindicated in ESRD due to the risk of anemia, low doses of ribavirin increase SVR rates. Therefore dose adjustment is required in patients with severe renal insufficiency or ESRD [7, 20]. But the dose reduction recommendations differ according to the manufacturer:

- The manufacturer of Rebetol contraindicated the use of ribavirin in patients with creatinine clearance of <50 mL/min. However the other manufacturer (Copegus) is approved in the United States for patients with ESRD and for those on hemodialysis as reduced doses [21, 22]. If the hemoglobin level decreases to <8.5 g/dL, ribavirin should be interrupted temporarily [7, 21, 22].

5.4 Efficacy of Antiviral Drugs in Renal Impairment

5.4.1 Pegylated Interferon and Ribavirin Combination Therapy

Pegylated interferon and ribavirin combination therapy was until recently the only treatment modality of chronic HCV infection but has been replaced currently by regimens including DAAs. But in resource-limited areas where DAAs are not available pegylated interferon and ribavirin may still be the only alternatives for treatment.

Fabrizi et al., in their meta-analysis of 24 prospective studies including 529 HCV-infected patients on hemodialysis, analyzed the efficacy of interferon-alpha monotherapy. SVR-48 rate was achieved in only 39% of cases [23]. However, studies evaluating the efficacy of pegylated interferon and reduced-dose ribavirin treatment in Asian population revealed that SVR-24 rate was approximately 60% [11, 12]. On the other hand, Rendina et al. in their study evaluating SVR-24 rate in 35

patients receiving pegylated interferon and ribavirin revealed that 97% of the patients achieved SVR at 24th week [24]. But it's noteworthy that 54% of the patients were infected with genotypes other than genotype 1 and this may be the reason of the very high SVR rate.

Furthermore, it is well known from the clinical studies that patients with HCV genotype 2 or 3 infection usually have higher SVR rates than those with genotype 1 or 4 infection [25].

Duration of treatment is 48 weeks for genotypes 1 and 4, and 24 weeks for genotypes 2 and 3 [24, 25].

5.4.1.1 Sofosbuvir-Based Regimens

In patients with mild-to-moderate renal impairment (eGFR ≥30 mL/min per 1.73 m^2) no dose adjustments are required for sofosbuvir-based regimens. But in case of severe renal failure (eGFR <30 mL/min per 1.73 m^2) data on the safety and efficacy of sofosbuvir-based regimens are limited [8, 9].

In an international prospective observational cohort study (TARGET), safety and efficacy of sofosbuvir-containing regimens in patients with mild-to-severe renal dysfunction (eGFRs <30, 31–45, 46–60, and >60 mL/min per 1.73 m^2) have been evaluated in real-world settings. A total of 1789 patients were enrolled in the study; 73 with eGFR ≤45 mL/min per 1.73 m^2 (18 with eGFR ≤30 mL/min per 1.73 m^2, 5 on dialysis) were compared to 1716 with eGFR >45 mL/min per 1.73 m^2. Antiviral regimens included in this study were sofosbuvir + pegylated interferon + ribavirin, sofosbuvir + simeprevir, sofosbuvir with or without ribavirin, or sofosbuvir + ribavirin. SVR rates were similar, ranging from 82 to 83% among all patients with different eGFR ranges. SVR was achieved in 83% of patients with renal impairment (eGFR ≤45 mL/min per 1.73 m^2) treated with sofosbuvir-containing regimens. The number of individuals with eGFR ≤30 mL/min was small, but worsening of renal function and renal adverse events was more frequently reported among these group of patients [8, 26].

Aggarval et al. in their study evaluated 14 patients with chronic HCV infection and ESRD who received sofosbuvir-based regimens retrospectively. Most patients were on chronic renal replacement therapy. All treatment regimens included sofosbuvir, and 4 out of 14 treatment courses included ribavirin. The first 7 out of 14 treatment courses used half-dose of sofosbuvir. Two patients were switched to full-dose sofosbuvir dosing at 4–6 weeks after initiation of the antiviral treatment. SVR-12 was reached in 13 out of 14 patients (92.8%). Patient who had relapsed was retreated for 24 weeks with full dose of sofosbuvir plus ledipasvir and SVR-12 was achieved. Minor adverse effects were headache in one, acid reflux in one, and fatigue in one patient. Two patients developed anemia and transfusion was required in one of them who was receiving ribavirin and developed sepsis [27].

Food and Drug Administration (FDA) approved this drug for patients with eGFR >30 mL/min per 1.73 m^2 [7]. Although some studies demonstrated that full-dose sofosbuvir may be safe, safe and effective doses of sofosbuvir have to be established in patients with eGFR <30 mL/min per 1.73 m^2 [28, 29]. If sofosbuvir-containing regimens have to be administered in patients with severe renal impairment it should only be prescribed by or in consultation with an expert in this field.

5.4.1.2 Daclatasvir-Based Regimens

Daclatasvir is primarily metabolized by the liver and renal elimination is minor. Although it is not among the recommended regimens according to the AASLD or European Association for the Study of the Liver (EASL) guidelines, in countries where daclatasvir plus asunaprevir is a recommended combination, this regimen is safe in patients with severe renal impairment, including HCV genotype 1 patients with hemodialysis [30].

5.4.2 Paritaprevir, Ritonavir, Ombitasvir, Dasabuvir (PrOD) with or Without Ribavirin

RUBY-1 clinical trial evaluated the efficacy of PrOD in 20 patients without cirrhosis infected with genotype 1 HCV, with stage 4 or stage 5 CKD (13 on dialysis). Enrolled patients were treated for 12 weeks with PrOD. Patients infected with genotype 1b were treated without ribavirin, whereas ribavirin (200 mg/day) was added to the treatment in 13 patients infected with genotype 1a. The SVR-12 rate was 95% (18/19) with only one patient relapsing and one patient died from a cause not attributed to the drug. Most adverse events were mild or moderate. Patients infected with genotype 1a had more frequent side effects related to ribavirin, including anemia, fatigue, and nausea, and ribavirin was interrupted in 69% of the patients. Erythropoietin treatment was required in four patients and only three patients restarted ribavirin [8, 9, 31]. Based on these findings, EASL guidelines recommend PrOD as an option for the treatment of HCV genotype 1 infection in patients with mild-to-moderate or severely compromised renal function and in ESRD whereas AASLD guidelines do not recommend as a first-line agent [8, 9].

5.4.2.1 Elbasvir-Grazoprevir

In a study (C-SURFER) evaluating the safety and efficacy of 12 weeks of elbasvir-grazoprevir therapy versus placebo, 122 HCV genotype 1-infected patients with CKD stages 4/5 were included. Seventy-five percent of the patients were on dialysis and only 6% had cirrhosis. The SVR-12 rates (intention-to-treat and modified intention-to-treat analysis) were 94% and 99%, respectively. The most common adverse events were headache, nausea, and fatigue, occurring at similar frequencies in patients receiving placebo. None of the patients discontinued therapy due to adverse effects, but one case of congestive heart failure was attributed to elbasvir-grazoprevir [32].

Based on these data, the fixed-dose combination elbasvir/grazoprevir is recommended for the treatment of HCV genotype 1 infection in patients with severely compromised renal function. Although genotype 4-infected persons were not evaluated in C-SURFER trial, results of the studies in with normal renal function can also be adapted to genotype 4-infected persons with CKD stage 4/5 [8].

Genotype 1a-infected patients harboring preexisting NS5A resistance-associated substitutions have a lower SVR12 rate with the 12-week regimen in studies

enrolling patients with normal renal function. Although extending the duration to 16 weeks and adding weight-based ribavirin may overcome this issue, these require further study [8–10].

5.4.2.2 Glecaprevir-Pibrentasvir

Approved in August 2017 by FDA, this pangenotypic drug is a fixed-dose combination of glecaprevir, an NS3/4A protease inhibitor, and pibrentasvir an NS5A inhibitor [33]. It is contraindicated in patients with decompensated cirrhosis (Child-Pugh class B or C). EXPEDITION-4 trial including 104 patients with genotype 1–6 infection and with stage 4 or 5 CKD, 82% of whom were on dialysis, revealed that treatment with glecaprevir-pibrentasvir for 12 weeks led to 98% SVR-12. Four percent of the participants discontinued the drug because of adverse events [34]. These results are promising in terms of treatment safety and efficacy.

5.4.3 Recommended Regimens

Patients with mild-to-moderate renal impairment (eGFR ≥30 mL/min per 1.73 m^2) can be treated according to the general recommendations since no dose adjustments for DAAs are necessary [8, 9].

According to AASLD guidelines, in patients with severe renal impairment (eGFR <30 mL/min per 1.73 m^2) daily fixed-dose combination of glecaprevir/pibrentasvir is the recommended regimen for all genotypes (genotypes 1–6) for 8–16 weeks. Fixed-dose combination of elbasvir/grazoprevir is recommended for genotypes 1a–b and genotype 4 for 12 weeks [8].

According to the EASL guidelines patients with severe renal impairment (eGFR <30 mL/min per 1.73 m^2) or with end-stage renal disease on hemodialysis infected with genotype 1a or genotype 4 should be treated with PrOD or with elbasvir/grazoprevir plus ribavirin (daily 200 mg) if Hgb level is >10 g/dL for 12 weeks. In patients infected with genotype 1b the treatment regimen is the same but ribavirin is not required. In case of urgent therapy, patients with severe renal impairment (eGFR <30 mL/min per 1.73 m^2) or with end-stage renal disease on hemodialysis infected with genotype 2 or genotype 3 should receive fixed-dose combination of sofosbuvir and velpatasvir, or combination of sofosbuvir and daclatasvir for 12 weeks. In genotype 3-infected patients if Hgb level is >10 g/dL, ribavirin (daily 200 mg) should be added; if not, the treatment duration should be prolonged to 24 weeks. Since renal function may worsen under these treatment regimens the patient should be closely monitored and interrupted if required [9].

In many countries, the access to new DAAs may be limited and the combination of pegylated interferon-alpha and ribavirin may still be the standard treatment modality in these group of patients. Recommended regimens according to different major guidelines are summarized in Table 5.1.

Table 5.1 Recommended regimens in patients with chronic kidney disease stage 4 or 5 or end-stage renal disease in treatment-naive and experienced kidney-transplant patients with or without compensated cirrhosis [8, 9]

AASLD				EASL		
	Genotype	Duration	Rating	Genotype	Duration	Rating
Daily fixed-dose combination of glecaprevir (300 mg)/ pibrentasvir (120 mg)	1–6	8 weeks[a] 12 weeks[b,c] 16 weeks[d]	I, B			
Daily fixed-dose combination of elbasvir (50 mg)/ grazoprevir (100 mg)	1a, 1b, 4	12 weeks	I, B	1a[e], 1b, 4[e]	12 weeks	B1, A1, B1
Paritaprevir (75 mg), ritonavir (50 mg), ombitasvir (12.5 mg), dasabuvir (250 mg)				1a[e], 1b, 4[e]	12 weeks	B1, A1, B1

[a]Without cirrhosis
[b]Compensated cirrhosis except genotypes 5 and 6
[c]NS3 or NS5A experienced
[d]Genotype 3 treatment experienced
[e]Plus ribavirin (daily 200 mg) if Hgb level is >10 g/dL for 12 weeks

5.5 Kidney-Transplant Patients

Since interferon is associated with an increased risk of acute rejection of the allograft interferon-based regimens are contraindicated in patients having had kidney transplantation [35]. Therefore interferon-free regimens are preferred in the setting of kidney transplantation.

Recommended antiviral regimens are the same as for the general population in kidney-transplant recipients with eGFR >30 mL/min per 1.73 m^2. But due to the limited experience, velpatasvir is not yet recommended for use in transplant patients. However, EASL guidelines recommend velpatasvir as an option in transplant recipients but warn against the possible drug interactions with immunosuppressive agents [9, 10].

In patients with eGFR <30 mL/min per 1.73 m^2 glecaprevir/pibrentasvir ranks among the recommended regimens. It is contraindicated in Child-Pugh class B and C cirrhosis, and it should be cautious against the possible drug interactions with immunosuppressive agents. For patients with genotype 1 or 4 infection, elbasvir/grazoprevir or PrOD may be alternative regimens, but the drug-drug interactions should be evaluated very carefully [10].

Various clinical trials have been designed to evaluate the efficacy of DAAs in transplanted patients:

The safety and efficacy of the combination of ledipasvir/sofosbuvir were evaluated in 114 kidney-transplant recipients in a phase 2 trial. Patients included in the study had been transplanted for longer than 6 months. Ninety-one percent of the patients had genotype 1 or 4. SVR-12 was achieved in all of the patients. In four patients with an eGFR >40 mL/min at screening eGFR decreased to <30 mL/min and increased to >30 mL/min in three of these patients during the treatment [36].

Table 5.2 Recommended and alternative regimens in treatment-naive and experienced kidney-transplant patients with or without compensated cirrhosis [8]

Recommended	Genotype	Duration	Rating
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)	1–6	12 weeks	I, A[a] IIa, C[b]
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	1, 4	12 weeks	I, A
Alternative			
Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) plus low initial dose of ribavirin (600 mg; increase as tolerated)	2, 3, 5, 6	12 weeks	II, A

[a]Genotypes 2, 3, and 6
[b]Genotype 5

In two other studies enrolling totally 45 kidney-transplanted patients efficacy of sofosbuvir-based regimens was evaluated. Ledipasvir, ribavirin, simeprevir, and daclatasvir were the antivirals combined with full-dose sofosbuvir. Sawinski et al. discussed treatment of patients with an eGFR <30 mL/min with their nephrologist whereas in the study of Kamar et al. all patients had eGFR of 30 mL/min or greater. Majority of the patients included in these studies had genotype 1 and advanced fibrosis. SVR-12 was achieved in all of the patients in both studies [37, 38].

Efficacy of the recently approved glecaprevir/pibrentasvir was evaluated in a phase 3 study (MAGELLAN-2) including 80 liver and 20 kidney-transplant patients. SVR-12 rate was 99% and the safety profile was very good [39].

Based on the above studies' data, recommended regimens in kidney-transplant patients according to AASLD/IDSA guidelines are summarized in Table 5.2.

In conclusion, with the advent of the directly acting antivirals SVR-12 rate is over 95% and near to 100% in HCV-infected patients with renal failure. Glecaprevir/pibrentasvir is recommended in all genotypes whereas elbasvir-grazoprevir is effective against genotypes 1a, 1b, and 4 in patients with renal impairment without dose adjustments. Paritaprevir, ritonavir, ombitasvir, and dasabuvir with or without ribavirin are other alternatives in patients infected with genotypes 1a, 1b, and 4 with SVR-12 rate of 95%. But in resource-limited areas where directly acting antivirals are not available pegylated interferon and reduced-dose ribavirin may still be the only alternatives for treatment.

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Treatment of Hepatitis C Virus in Special Populations (HBV Coinfection, Drug Users, and Prisoners)

6

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6.1 Hepatitis C Virus (HCV) and Hepatitis B Virus (HBV) Coinfection, Their Peculiar Interaction, and Treatment

6.1.1 Introduction

HBV and HCV are responsible for most cases of chronic hepatitis, liver cirrhosis, and HCC in all countries although nonalcoholic steatohepatitis (NASH) is becoming the leading cause in the West after the advent of treatment for HCV [1, 2]. Geographical areas, which have intermediate or high HBV and HCV endemicity, favor occurrence of dual infection. In areas like Spain, Italy, Japan, Taiwan, and Iran, 5–40% of patients with HBV are coinfected with HCV whereas 2–25% of patients with HCV are positive for hepatitis B surface antigen (HbsAg) [3–8]. The high-risk population reported to have high likelihood of the coinfection are intravenous drug users (IVDU), hemodialysis patients, patients undergoing organ transplantation, HIV-infected subjects, men having sex with men, and thalassemic patients.

The viruses have a reciprocal inhibition of viral genomes [1, 6, 9–12]. It results in a dynamic fluctuation of HBV and HCV viremia and also spontaneous clearance of one or both viruses as observed in a 1-year longitudinal study [13]. Sheen et al. reported that HBsAg clearance was 2.5 times higher in HBsAg/anti-HCV-positive cases as against HBV-positive/anti-HCV-negative cases [14].

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However, HBV and HCV coinfection is a serious virological condition associated with more severe forms of liver disease and increased incidence of HCC [15–19]. The advent of second-generation DAAs has changed the face of HCV therapy. With eradication rates reaching 95%, the discussion has now shifted to the behavior of HBV when HCV is eradicated [20–25]. HBV reactivation in dual infections where HBV is inactive is infrequent and this was found in a recent study from the USA, which showed that this could be prevented by HBV screening and adequate HBV treatment [25].

6.1.2 Epidemiology

The incidence of HBV/HCV coinfection is primarily calculated from clinical studies with scarce population-based studies. Clinical studies have shown that 2–10% of patients with chronic HCV have circulating HBsAg [26, 27] and 5–20% of patients with chronic hepatitis B are anti-HCV positive [5]. Occult HBV is observed in patients with chronic HCV where there is no measurable S antigen but there is positive HBV DNA so just measuring HBsAg will miss this diagnosis. In a study from India, 16% of chronic HBV-related liver disease patients had HBV and HCV coinfection at a much higher rate than that reported in a retrospective study from Egypt (0.7% of 3300 patients) [28]. This prevalence was 2.6% in 1950 chronic carriers examined in Turkey [29], and ranged from 7 to 15% in studies performed in Spain [3], Italy [4, 30], Japan, Taiwan [31, 32], and Iran [33]. The rate of HBV/HCV coinfection in HCV chronic carriers was 1.4% in two large surveys performed in the USA whereas in a third US study this rate reached 5.8% [8, 34, 35]. In two large Italian surveys the rate of HBV/HCV coinfection was 1.3% in 2001 and 1.2% in 2014 [36–38].

HBV/HCV coinfection is found frequently in several high-risk population such as IVDU/people who inject drugs (PWID), patients on hemodialysis, patients undergoing organ transplantation, HIV-positive individuals, and beta thalassemia patients [4, 34, 39–41]. The same risk factors were found in a US study where younger age, drug abuse, HIV coinfection, male sex, and comorbidities requiring blood transfusion or blood transfusions were independent risk factors for this coinfection [4].

In a study from New York on the incidence and prevalence of HBV and HCV coinfection, of the 1257 subjects with chronic HCV infection, 773 (61.5%; 95% CI, 58.8–64.2%) had evidence of prior exposure to HBV (HBcAb positive), whereas 73 (5.8%; 95% CI, 4.5–7.1%) had dual infection with HBV (HBsAg positive) [8].

All of the HBcAb-positive subjects were positive for total antibody against the HBV core antigen, but none were HBc immunoglobulin M positive. The prevalence of HBV dual infection was significantly higher in patients enrolled at the VA New York Harbor Healthcare System than those subjects seen at Bellevue Hospital Center (6.5% vs. 3.3% [$P = 0.04$]). Among the 73 patients with HBV/HCV dual infection, 54 (74.0%; 95% CI, 63.7–84.3%) were HBeAg positive. The prevalence of HBV infection was strongly associated with injection drug use and increased as

the number of lifetime sexual partners increased. The prevalence of HBV dual infection differed significantly according to age, race/ethnicity, injection drug use, and number of lifetime sexual partners. HBV dual infection was highest in those 40 years of age, whereas it was lowest in those who were 50–59 years of age. Asians had the highest prevalence of HBV dual infection followed by blacks [8].

6.1.3 Viral Interactions

HBV and HCV interactions have been studied in both in vitro studies and clinical scenarios. In vitro studies have demonstrated that liver cells replicating HBV may be infected by HCV [42] and that HBV and HCV can replicate in the same hepatocytes with no evidence of interference [43], observations confirmed by in vitro co-transfectional studies using full-length HBV genomes and HCV replicons [44]. The coexistence of HBV and HCV in the same hepatocytes has also been observed in liver biopsies of patients with HBV/HCV dual infection [45]. Other in vitro studies provided data in favor of a reciprocal suppression or of viral interference [15, 46] and demonstrated that the HCV "core" protein strongly inhibits HBV replication [47].

It has also been shown that the HCV NS5A protein may influence HBV activity. However, due to contrasting data in terms of inhibition or enhancement of HBV replication at present there is no concrete evidence to arrive at that conclusion [48].

The inverse relationship between the replicative levels of the two viruses suggests direct or indirect viral interference, which has been confirmed in clinical studies [49, 50]. Most cross-sectional studies evaluated the viral load of both viruses at a single checkpoint and reported a dominant role of HCV (high HCV-RNA and low or undetectable HBV-DNA levels), whereas reciprocal interference or even a dominant effect of HBV is described less frequently [5, 46, 51, 52].

Patients with HCV predominance have higher serum IFN γ-induced protein 10 (IP-10) levels and lower HBsAg levels than those with HBV predominance, suggesting that in dual-HBV/HCV infection, HCV suppresses both HBV-DNA and HBsAg synthesis by immune mechanisms [53].

Accordingly, in chimpanzees with HBV chronic infection, acute HCV superinfection suppresses HBV replication, resulting in reduced HBsAg serum values [5, 9, 54, 55] and increased IP-10 values [14]. HBV and HCV interact differently in the innate immune system. HCV activates the IFN type I genes, whereas HBV is unable to activate the antiviral innate immune response within infected hepatocytes since it inhibits the signaling pathways inducing IFN production. As HBV is sensitive to the antiviral effect of type I IFN response, drug-induced HCV eradication in patients with dual-HBV/HCV infection may be followed by a transient HBV reactivation.

Cellular and humoral adaptive immune responses play a central role for the control of both viruses. In HBV infection, major histocompatibility complex (MHC) class II-restricted CD4+ helper T cells generate antibodies to clear circulating virus particles and MHC class I-restricted CD8+ T lymphocytes eliminate the infected cells.

Both innate and adaptive immune responses drive the spontaneous clearance of HCV infection. Innate immunity includes the release of antiviral cytokines and the activation of innate immune cells and the adaptive immune response, which play a crucial role in HCV clearance through HCV-specific CD4 and CD8 T-cell responses. Patients who spontaneously resolve acute HCV infection develop long-lived memory T cells, whereas in persistent infection the number of virus-specific T cells tends to decrease and to have an exhausted phenotype [56, 57].

Bellecave et al. analyzed HBV and HCV replication in the same in vitro model and concluded that the reciprocal replicative suppression observed in coinfected patients was not attributable to direct antiviral interference but, as both viruses are susceptible to the effects of innate and/or adaptive immune responses, it was more likely attributable to cytokines produced by infected cells or by infiltrating T cells present in the in vitro model [44].

Ethnic differences have also been suggested as factors influencing the dominant role of one virus over the other [31], a suggestion that still awaits confirmation. In the middle of the last decade, an Italian multicenter study longitudinally examined a large series of HBsAg/anti-HCV-positive patients [58] where the analysis of HBV-DNA in the liver extracts and observing an increase of serological IgM anti-HBc titer at the time of the abrupt elevation of the aminotransferase levels seem to be the most useful tools in revealing HBV activation as a cause of acute hepatitis in chronic HBsAg carriers; overall the phase of viremia is transient, indicating wide fluctuations in the HBV-DNA and HCV-RNA levels.

6.1.4 Clinical Features and Scenarios

6.1.4.1 Hepatitis C Superinfection

In areas of high prevalence of HBV infection, such as Asia Pacific countries, HCV superinfection in individuals with chronic hepatitis B (CHB) infection is the most common scenario of HBV/HCV coinfection [55, 59]. Two studies from Taiwan showed that a significant proportion of instances of fulminant/sub-fulminant hepatitis in those with CHB infection (HBsAg carriers) could be attributed to HCV superinfection [60, 61]. A recent study by Liaw et al. found that acute HCV infection in patients with CHB infection could be associated with more severe symptoms during the acute phase [59, 62]. More importantly, long-term follow-up analyses showed that those with HCV superinfection had higher cumulative rates of liver cirrhosis (48% at 10 years) and hepatocellular carcinoma (HCC) (32% at 20 years). In a prospective study on Taiwanese patients admitted with acute HCV, the occurrence of fulminant hepatic failure was significantly higher among those with underlying HBV infection than those without (23% vs. 3%, $P < 0.01$) [62].

6.1.4.2 Hepatitis B Superinfection

Superinfection with HBV in patients with chronic hepatitis C (CHC) is less common. Previous case reports indicated that HBV superinfection was associated with acute deterioration of liver function resulting in fulminant hepatitis [63, 64]. In one

study they found that anti-HCV can disappear during HBV superinfection. A small study showed that the incidence of hepatic encephalopathy or ascites formation was higher in HCV patients with HBV superinfection as compared to monoinfection with HBV infection alone (29% vs. 0%, $P < 0.05$) [6, 64].

HBV superinfection in patients with chronic HCV infection was responsible for a strong inhibition of HCV replication, which led to the eradication of HCV in a quarter of the patients. In fact, 6 out of 24 patients who were still HCV-RNA negative 3 years after HBV superinfection remained so even at the 4th year, and at the 5th and 6th years for those tested. At the time of HBV superinfection, the differences distinguishing patients who subsequently eradicated HCV infection from those showing only a temporary inhibition of HCV were a higher prevalence of cases with severe acute hepatitis B and a higher level of serum aminotransferases in the first subgroup, differences that were statistically significant and of clinical relevance. Thus, even though extensive acute hepatocellular necrosis can be life threatening, it may lead to a clearance of chronic HCV infection. The inhibition exerted by HBV superinfection on HCV chronic replication was really impressive in one patient who became HCV-RNA negative. In two studies on patients with fulminant and sub-fulminant hepatitis, HBV/HCV coinfection was responsible for nearly 10% of cases [27, 65]. Apart from acute HBV/HCV coinfection, both HCV superinfection in HBsAg chronic carriers [59] and HBV superinfection in HCV chronic carriers [66] may be followed by chronic HBV/HCV dual infection, a complete recovery from one or both infections, or, less frequently, progression to a fulminant or subfulminant form. A self-limiting, benign course with a complete recovery from one or both infections occurs more frequently in the simultaneous acquisition of HBV/HCV dual infection [67] than HBV or HCV superinfections of HCV or HBV chronic carriers, respectively, who, due to preexisting liver damage, frequently develop significant histological injury. If anti-HCV becomes negative, it is a predictor of HCV eradication soon after acute hepatitis B.

6.1.4.3 Occult HBV Infection in Patients with HCV Infection

Occult HBV infection has frequently been identified in patients with CHC infection. The prevalence of "occult" HBV infection among HCV-infected persons is unknown, but has been detected in as many as 50% of patients in some series [68–70]. From the available evidence we can conclude that occult HBV infection might aggravate the clinical outcome of CHC and contribute to the development of liver cirrhosis and HCC [71–73]. The prevalence of anti-HBc is high among HCV-positive individuals. HCV-positive individuals who are anti-HBc positive have (1) a higher prevalence of cirrhosis; (2) lower HCV-RNA levels; and (3) an impaired ability to respond to interferon treatment [73].

AASLD suggests that all HCV patients who are about to initiate DAA therapy should be assessed for HBV coinfection by checking for the presence of HBsAg, anti-HBs, and anti-HBc. In addition, patients with positive HBsAg should be tested for HBV DNA viral load prior to the initiation of DAA therapy [22].

EASL guidelines suggest that patients should be tested for HB antigen, anti-HBc, and anti-HB antibodies before the initiation of DAA therapy [21]. If HB

antigen is present, or if HBV DNA is detectable in HB antigen-negative, anti-HBc antibody-positive patients ("occult" hepatitis B), then concurrent anti-HBV nucleotide therapy is indicated [21].

6.1.4.4 Fibrosis Progression in HBV/HCV Coinfection

Several studies have compared the histological findings between HBV/HCV coinfection with single viral infection. Zarski et al. found that liver injury was more severe in dual infection than in HCV single infection, piecemeal necrosis and fibrosis, and incidence of liver cirrhosis [46]. Several cross-sectional studies found that HBV/HCV coinfection is associated with a higher prevalence of liver cirrhosis and hepatic decompensation as compared with monoinfection alone. This is yet to be proven in longitudinal studies with sequential liver biopsies to evaluate the rate of fibrosis progression in coinfected subjects [3, 5, 46, 67].

The median necro-inflammatory score was significantly higher in HBV/HCV-coinfected patients than in those with HCV monoinfection (8.0 [IQR, 6.0–10.0] vs. 5.0 [IQR, 4.0–7.0]; (P<0.001). Bini and Perumalswami found that HBV/HCV-coinfected patients had more advanced fibrosis than those with HCV monoinfection in their review of 1245 patients with HCV infection. Stage 3 or 4 fibrosis was present in 84.6% of patients with HBV/HCV infection and 29.9% of those with HCV monoinfection (P<0.001) [8].

6.1.4.5 Impact of HBV/HCV Coinfection on Development of HCC

Coinfection with HBV and HCV has been shown in many case–control studies to correlate with an increased risk of developing HCC [16, 74–76]. Benvegnu et al. conducted a prospective study of 290 cirrhotic patients and found that coinfection (detectable anti-HCV and HBsAg) was an independent predictor for development of HCC by both univariate and multivariate analyses. In this longitudinal study, the incidence of HCC (per 100 person years) was 6.4 in coinfected patients, compared to 2.0 in HBV and 3.7 in HCV-monoinfected patients, while the cumulative risk of developing HCC at 10 years was 45% in coinfected patients, compared with 16% and 28% in HBV- and HCV-monoinfected disease controls [77].

A meta-analysis conducted by Donato et al. enrolled 32 case–control studies to investigate the impact of HBV/HCV coinfection on the development of HCC. This study showed that the relative risk of HCC in coinfected patients (odds ratio [OR] = 165) was significantly higher than HBV (OR = 22.5) and HCV (OR = 17.3) infection alone [17].

6.1.4.6 Chronic Hepatitis B Treatment

The treatment strategies include IFN-alpha-based immunomodulation and nucleos(t)ide analog (NUC)-based inhibition of viral replication [21, 78, 79]. IFN-alpha is a cytokine with direct antiviral, immunomodulatory, and antiproliferative effects, while NUCs suppress HBV synthesis by inhibiting DNA elongation and HBV reverse transcription. These treatments, however, do not eradicate HBV infection since the covalently closed circular DNA (cccDNA) persists in infected hepatocytes and seroconversion to anti-HBs is infrequent [80].

Seven drugs are available for the treatment of CHB in Europe and in the USA:

1. Two formulations of alpha-IFN, conventional and pegylated (Peg-IFN)
2. Three NUCs, lamivudine (LAM), adefovir dipivoxil, and telbivudine, which have lost popularity due to their low genetic barrier
3. Two NUCs with a high genetic barrier, entecavir (ETV) and tenofovir disoproxil fumarate (TDF), which are now widely used and provide long-term virological suppression

In addition, a new formulation of TDF, tenofovir alafenamide (TAF), has been approved in Europe and the USA. This formulation is better tolerated than TDF because of a lower frequency of adverse bone and renal reactions in long-term treatment.

PEG-IFN has the advantage of a finite duration of treatment and of a higher rate of seroconversion to e antigen neg and s antigen neg status, but its use is limited in practice to the HBeAg-positive patients with normal immune reactivity. Both ETV and TDF monotherapies have shown great efficacy, since they obtain long-term viral suppression in 95% of patients, with a regression of liver fibrosis and prevention of cirrhosis [16–19]; however, conversion to HBsAg negative is infrequent and the onset of HCC seems to be preventable only for some treated patients [48, 49].

6.1.4.7 Chronic Hepatitis C Therapy

The treatment of chronic HCV infection has undergone significant changes over the past 25 years. Alpha-IFN was the first pan-genotypic option [21, 81–83], used in combination with ribavirin (RBV) from 1998 to improve treatment efficacy. In 2001–2002, Peg-IFN replaced conventional IFN and, in combination with RBV, further raised the HCV-genotype 1 sustained virological response (SVR) rate to 43% [21]. The SVR rate improved to approximately 70% in 2011 by combining Peg-IFN and RBV with a first-generation DAA, an NS3/4A protease inhibitor telaprevir or boceprevir. Subsequently, simeprevir, a potent inhibitor targeting HCV NS3/4A of HCV-genotype 1 or 4, and sofosbuvir, an NS5B polymerase, was the first all-oral regimen.

At present, IFN-free DAA treatment regimen comprises NS3/4A protease inhibitors, NS5A inhibitors (nucleotides and non-nucleotide analogs), and NS5B polymerase inhibitors, acting, respectively, on different strategic points of HCV replication: self-cleavage, viral replication and assembly, and synthesis of RNA polymerase.

The combination regimens ledipasvir/sofosbuvir and the “3D” regimen (ombitasvir/paritaprevir/ritonavir plus dasabuvir) were approved in 2014 and the combinations daclatasvir plus sofosbuvir and elbasvir/grazoprevir in 2015 and 2016, respectively [84]. The combination therapy with sofosbuvir/velpatasvir is a pan-genotypic DAA treatment approved in June 2016; sofosbuvir/velpatasvir/voxilaprevir in June 2017, and glecaprevir and pibrentasvir in August 2017, provides SVR12 rates in 95–100% for all HCV genotypes [85, 86]. Worthy of note, all DAA combination treatments provided SVR12 rates around or over 95% after an 8–12-week administration both for chronic hepatitis and compensated cirrhotic patients.

6.1.4.8 IFN-Based and DAA-Based Therapy of HCV/HBV Dual Infection

The management of patients with HCV/HBV dual infection includes the eradication of HCV, permanent suppression of HBV replication, resolution of hepatic necroinflammation, prevention of cirrhosis and HCC, and ultimately improved survival [87].

The treatment of HCV/HBV dual infection is complex and should be individualized according to the HBV and HCV loads and liver histology or, in the absence of liver biopsy, the ALT serum concentration or with noninvasive surrogate methods to assess liver fibrosis (Fig. 6.1).

A contemporary active replication of HBV DNA and HCV RNA is infrequent in patients with HBV/HCV dual infection, because in most cases reciprocal viral interference leads to a dominant productive virus that should be identified before deciding treatment.

In cases of both HBV and HCV being active, both infections should be treated with a high genetic barrier NUC for the HBV and with a combination of two or more second-generation DAAs for the HCV infection (Fig. 6.1).

This combination therapy should also be used to treat HBV/HCV cirrhotic patients, independently of the extent of viral production. For patients with HBV/HCV dual infection without cirrhosis, HBV treatment should be applied when HBV infection is in a productive phase, whereas in a nonproductive phase only monitoring for HBV reactivation up to 1 year after the end of DAA therapy (Fig. 6.2).

Anti-HCV treatment is a priority for HBV/HCV patients with HCV predominance (high HCV RNA and absent HBV DNA or below the threshold of treatment), but close monitoring of HBV replication is mandatory for an early diagnosis of HBV reactivation, a phenomenon interpreted as an unbalanced HBV replication due to the eradication of HCV with DAA-based treatment [12, 46, 88, 89]. In this

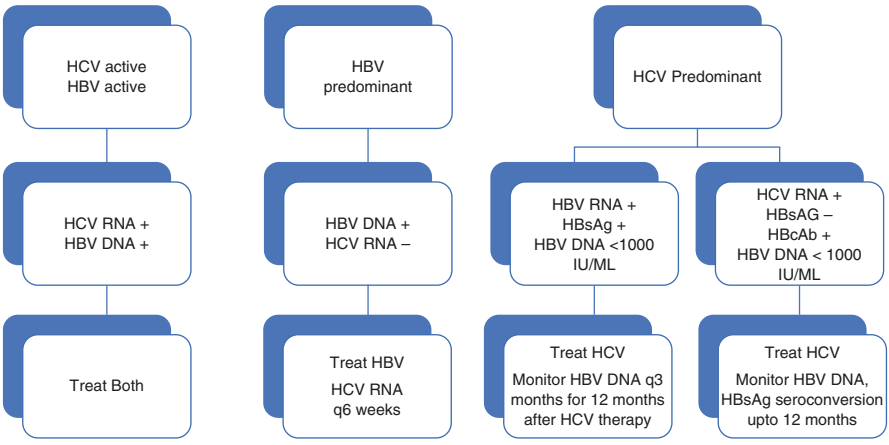

Fig. 6.1 Treatment algorithm based on active HCV and HBV infection and predominance of HCV versus HBV infections

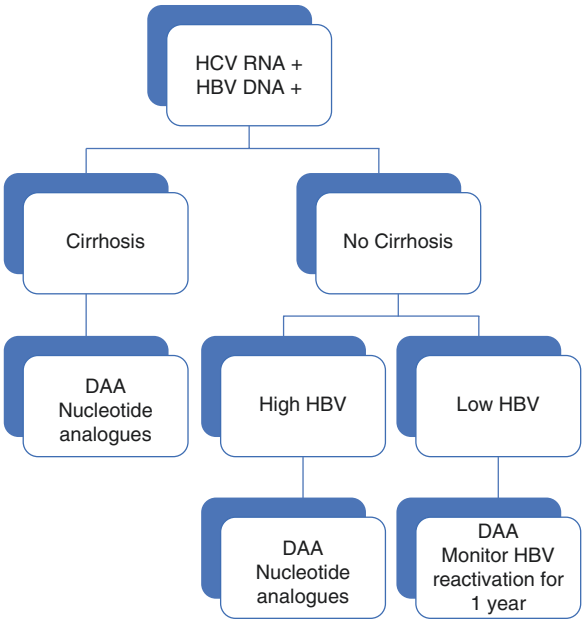

Fig. 6.2 Treatment algorithm for patients who are positive for both HCV RNA and HBV DNA

prospective study, the combination of ledipasvir and sofosbuvir for 12 weeks produced a SVR in 100% of patients with HCV infection who were coinfected with HBV. Most patients had an increase in the level of HBV DNA not associated with signs or symptoms (Fig. 6.3).

Potthoff et al. described HBV reactivation in 31% of 13 HBsAg-positive/HBV DNA-negative patients after anti-HCV treatment with Peg-IFN and RBV observed for up to 48 months [90]. In a study by Liu et al., 36.4% of 77 HBV/HCV patients with undetectable serum HBV DNA at baseline became positive on Peg-IFN/RBV treatment administered to eradicate HCV infection. HBV reactivation was more frequent in patients who achieved SVR (33.3%) than in nonresponders (8.7%) [91].

Belperio et al. retrospectively evaluated 377 HBsAg-positive patients and 7295 with isolated anti-HCV treated with a DAA regimen among 62,920 veterans treated in the USA. An increase in the HBV load of more than 3 log was observed in nine patients, eight known to be HBsAg positive (2.1%) and one with isolated anti-HBc before treatment. An HBV DNA increase of less than 3 log was observed in 12 (3.1%) subjects known to be HBsAg positive before treatment, while a concomitant biochemical reactivation occurred only in three cases [25]. In addition, Chen et al. carried out a systematic review and meta-analysis to compare the rates of HBV reactivation in HBV/HCV-coinfected patients treated with either an IFN-based therapy or a DAA regimen [92]. Of the 779 patients with dual-HBV/HCV infection, the incidence rate of HBV reactivation was similar in those treated with IFN-based treatments (14.5%) or with DAA regimens (12.2%), but it occurred much earlier (within 4–8 weeks of treatment) and was more frequently associated with clinical and/or biochemical abnormalities in those treated with DAAs (12.2% vs. 0%) [26].

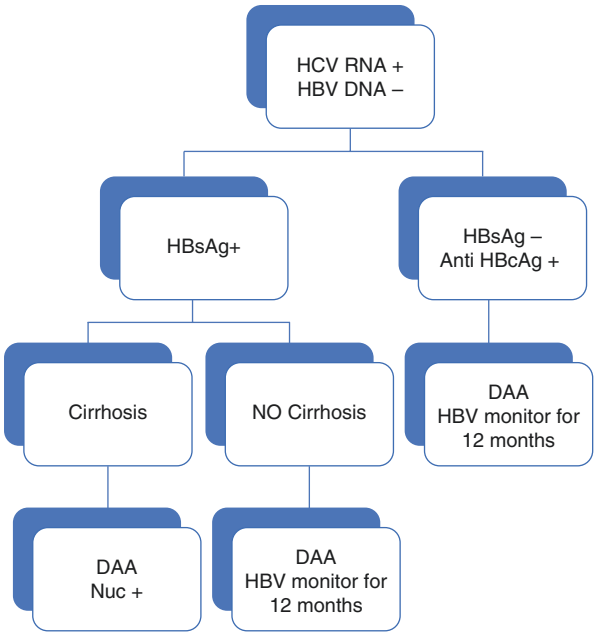

Fig. 6.3 Treatment algorithm for patients with positive hepatitis C RNA but negative HBV DNA

A cohort of 137 consecutive HCV patients treated with IFN-free regimens in routine clinical practice was evaluated. From this cohort, plasma samples of 44 subjects with positive serology for HBV (anti-HBc positive) were tested for HBV DNA levels at baseline and 24 weeks after the end of the treatment. Two of them were HBsAg positive, while the others had signs of a past HBV exposure (HBsAg negative ± HBsAb positive). No reactivation was found in HBcAb-positive and HBsAg-negative subjects. Of the two HBsAg positive, one experienced an increase in HBV DNA levels of ≥2 log10 IU/mL during treatment. However, the reactivation was without clinical impact and, most important, was followed by HBsAg loss [93].

In the US FDA Adverse Event Reporting System (FAERS) on 29 cases of severe HBV reactivation occurring from November 2013 to October 2016 in different countries, predominantly after 4–8 weeks of DAA treatment, the mean age was 60.7 years; 13 were males and 16 females [92]. Of these 29, 2 died of liver failure, 1 underwent liver transplantation, 8 developed clinical symptoms requiring hospitalization in 6, and 10 discontinued DAA treatment. This FAERS report underlines the need to screen for HBsAg, HBsAb, and HBcAb in all patients undergoing treatment for HCV eradication [92].

Eight (28%) of the patients were reported to have a clinical illness that accompanied the increase in HBV DNA levels; of these, 6 (75%) were hospitalized. Reported symptoms included malaise, fatigue, abdominal pain, jaundice, and encephalopathy. Among the 19 patients with minimal information, 5 discontinued DAA treatment because of HBV-R, 2 were hospitalized, and at least 7 were started on

medication to treat HBV infection. More than half of the patients (15 of 29, 52%) eventually received HBV antiviral therapy (tenofovir or entecavir); 8 were specifically noted to have received no treatment for HBV infection. No reports of treatment were found for the remaining 6 patients.

Among the 15 patients who received HBV therapy, treatment was delayed by 7 days or more after diagnosis in at least 7 (47%), 1 of whom died. In addition, a possible delay occurred in at least 7 other patients, 1 of whom required a liver transplant. All patients in the current series were receiving treatment for HCV infection and therefore were presumed to be undergoing monitoring for liver events. Despite provider knowledge of relevant baseline HBV status in these cases, diagnosis and treatment of HBV-R were delayed after an increase in transaminase or HBV DNA levels was noted, with delays ranging from 7 to 60 days to treatment. This indicating close follow-up and initiation of HBV therapy at the earliest can save lives and reduce morbidity [92].

HBsAg-negative/HBcAb-positive patients with HCV infection should also be monitored for HBV reactivation during DAA treatment [82]. In a retrospective study, 5 (5.9%) of 84 patients with a productive HCV infection and previously resolved HBV infection developed HBV reactivation under IFN-free DAA treatment (sofosbuvir/ledipasvir or sofosbuvir/RBV or daclatasvir/asunaprevir) [92], whereas Sulkowski et al. did not find any HBV reactivation in 103 HBsAg-negative/HBcAb-positive patients with HCV infection treated with sofosbuvir/ledipasvir [94].

Patients with HBV predominance (HBV DNA level more than 2000 IU/ml and low or absent HCV RNA) should first be considered for anti-HBV treatment, but monitoring for HCV reactivation consequent to HBV suppression is highly recommended. HBV therapy is highly recommended in patients with cirrhosis regardless of the HBV viral load. HCV reactivation, defined as an increase in viral load to at least 1 log10 IU/mL above the baseline value, is relatively infrequent in NUC treatment for HBV suppression and is usually limited to an asymptomatic virological abnormality associated only in a minority of cases with an abnormal enzymatic profile without.

When tenofovir is the antiviral choice for HBV therapy, the co-administration with ledipasvir/sofosbuvir or with velpatasvir/sofosbuvir should be carefully monitored because of a possible increase in tenofovir serum concentration.

Treatment of anti-HIV-positive patients with chronic hepatitis due to HBV/HCV dual infection is essential to prevent the development of cirrhosis, life-threatening liver failure, and HCC. Early antiretroviral treatment including drugs with anti-HBV and anti-HIV activity is recommended, and tenofovir combined with LAM or emtricitabine should be used to suppress HBV replication.

The DAA-based combination treatments with second- or third-generation DAAs bring about HCV eradication in about 95% of patients both in HCV monoinfection and in dual-HBV/HCV infection, whether anti-HIV positive or anti-HIV negative, with a strong warning to consider the potential drug-to-drug interaction with HIV antiretrovirals.

6.1.5 Conclusions

Treatment of dual-HCV/HBV infection is complex, since it has several aims, such as the eradication of HCV infection, suppression of HBV replication, a reduction in liver damage, and prevention of cirrhosis and HCC. Further complexities come from the numerous virological profiles we can observe in patients with dual-HBV/HCV infection, which reflect alternate phases in viral replication, due in part to the natural course of each infection and in part to reciprocal viral interference.

These complexities oblige us to make individual therapeutic choices based on the HBV and HCV loads and the severity of liver disease, to prevent viral reactivation and disease deterioration.

The favorable news for HBV/HCV-coinfected patients, as well as for HCV-monoinfected patients is that a combination of second-generation DAAs obtains HCV eradication in about 95% of cases and that this treatment is well tolerated and rarely associated with serious adverse reactions. IFN-based treatments are now obsolete as they are inferior to DAA regimens in eradicating HCV infection and have poor tolerability.

HCV eradication, long-term HBV suppression, and consequent prevention of viral reactivation are highly recommended for cirrhotic patients, independently of the viral production, the contemporary administration of a second-generation DAA regimen, and a high genetic barrier NUC being the treatment of choice. The choice of therapy is dictated by careful evaluation of disease progression, HBV and HCV loads, and comorbidities. Several virological profiles can be observed in dual-HBV/HCV chronic infection, which reflect alternate phases in viral replication, due in part to the natural course of each viral infection and in part to the inhibitory effect exerted by one virus on the replication of the other.

A combination therapy with a high genetic barrier NUC and DAA should be administered also to non-cirrhotic patients with both viruses in a productive phase, because treatment of one infection may induce a reactivation of the other.

In cirrhotic patients with HCV predominance, treatment entails the combination of second-generation DAAs associated with high genetic barrier anti-HBV NUCs starting before or together with the DAA regimen regardless of the HBV load because in these cases HBV reactivation may be serious or life threatening even in patients with a low or an absent HBV load. For patients with chronic hepatitis with HCV predominance, treatment with the combination of second-generation DAAs should be associated with close monitoring of the HBV load for an early diagnosis of HBV reactivation. However, in these cases, the range of the rates of HBV reactivation in retrospective or small prospective studies is wide (from 5 to 63%), suggesting the need for multicenter prospective investigations.

How to manage any single case of HBV reactivation is still controversial, since the current international guidelines are of little use in single cases, and as contrasting information comes from case reports [92]. Whatever the clinical presentation of HBV reactivation in patients with dual-HBV/HCV infection treated with DAAs, treatment with high genetic barrier anti-HBV NUCs, close monitoring of the clinical condition, and HBV DNA and ALT serum levels are strongly recommended up

to 1 year after the end of DAA treatment; clinicians should always bear in mind the recent FDA report on the extremely detrimental effect of HBV reactivation in some patients treated with DAAs [92].

Even HBsAg-negative/HBcAb-positive patients with HCV infection may be at risk of HBV reactivation during DAA treatment [82], since ccc DNA persists in the liver after HBsAg clearance and even after seroconversion to anti-HBs. HBV reactivation occurs infrequently in these patients, but monitoring during DAA treatment is advisable with viral loads every 4 weeks during treatment and every 3 months after completion for 1 year [92, 94].

Patients with HBV predominance (HBV DNA serum level more than 2000 IU/ml and low or absent HCV RNA) should be considered for anti-HBV treatment and monitoring for HCV reactivation.

Due to the high potency and high genetic barrier of ETV and tenofovir, they have been used successfully for years to inhibit HBV replication and, consequently, they should be used to impair HBV synthesis in dual-HBV/HCV infection with HBV dominance. Due to the high sensitivity of the modern HCV RNA assays, the possibility that a negative HCV RNA could reflect a previous HCV eradication cannot be excluded and an HBV DNA-positive/HCV RNA-negative pattern might be an HBV monoinfection with serological evidence of a past HCV infection rather than dual-HBV/HCV infection with HBV predominance.

There is little information on HCV reactivation under NUC treatment, an unlikely event that is asymptomatic in most cases; however, monitoring for HCV replication seems appropriate mainly to extend our knowledge in this setting and possibly for treatment decisions to be made.

Combination treatments with two or more second-generation DAAs of different classes achieve HCV eradication in about 95% of patients with HCV monoinfection or dual-HBV/HCV infection; they are well tolerated and rarely responsible for serious adverse effects. Because of reciprocal viral interference, a contemporary HBV and HCV production is infrequent in patients with HBV/HCV dual infection. For patients with both viruses in a productive phase and for patients with cirrhosis, treatment should include a DAA regimen and a high genetic barrier NUC.

In cases with HCV predominance (Fig. 6.3) (HCV RNA positive, HBV DNA negative, or under the treatment threshold), a combination of two or more DAAs should be used to eradicate HCV infection, obtain a reduction in liver damage, and prevent progression to cirrhosis and HCC, unfavorable events more frequent in dual than in single HBV or HCV infection. In patients with a mild or moderate liver disease, close monitoring of the HBV load during DAA treatment is highly recommended for an early diagnosis of HBV reactivation, identifiable by an increase in the HBV load associated with an increase in ALT serum levels in a minority of cases. Instead, in patients with liver cirrhosis, a NUC regimen should be started before or together with DAA treatment because in these cases HBV reactivation may be a serious event.

Overall, close monitoring of the clinical events and the HBV DNA and serum ALT concentration is necessary even in these cases for an early diagnosis of HBV reactivation and to establish the relative therapeutic decisions to be made. Little

information is available on HCV reactivation in HBV/HCV patients with HBV predominance treated with ETV or tenofovir. Fortunately, this reactivation seems to be infrequent and usually limited to an asymptomatic virological abnormality, but monitoring of HCV replication seems appropriate both to extend our knowledge on this point and to intervene without delay. The cost of DAA treatments has limited their use in the past, but the reduction in prices in Western countries, the use of generics, and the sharp decline in prices in developing countries now make a long-term project of global eradication of HCV infection possible.

6.2 HCV Treatment in Injection Drug Users (IDUs)

6.2.1 Introduction

According to the United Nations Office on Drugs and Crime (UNODC), about 275 million people worldwide that is about 5.6% of the global population aged 15–64 years used drugs at least once during 2016 and approximately 450,000 people died as a result of drug used in 2015 [95].

The joint UNODC/WHO/UNAIDS/World Bank estimates the number of IDUs/people who inject drugs (PWID) for 2013 to be 12.19 million (range: 8.48–21.46 million). This corresponds to 0.26% (range 0.18–0.46%) of the adult population aged 15–64. This estimate is based on reports from 93 countries covering 84% of the global population aged 15–64. The highest prevalence of PWID continues to be in Eastern and South-Eastern Europe, where 1.27% of the general population aged 15–64 is estimated to be injecting drugs, which is nearly five times the global average. In terms of actual numbers, the largest proportion resides in East and Southeast Asia, with an estimated 3.15 million PWID. In North America, this number is 2.07 million comprising 17% of the global total number of PWID [95] (Fig. 6.4).

6.2.2 Epidemiology of Hepatitis C in IVDU

Injecting drugs poses the strongest risk for HCV infection in the USA and Europe, with an estimated HCV seroprevalence of 10–70% [96, 97]. While globally about 2.2% of the total population is affected with hepatitis C, this number was remarkably high at 52% in PWID (6.3 million PWID) worldwide in the year 2013 [95]. Countries with large PWID populations have considerably higher number of hepatitis C-infected individuals with 1.93 million PWID in China (2012) and 1.52 million PWID in the USA (2007) [98, 99] (Fig. 6.5).

To add to the woes, a systematic review showed that a high proportion of PWID are unaware of their hepatitis C diagnosis and even among those known to be infected have low chances of getting antiviral treatment. This study reported high level of undiagnosed hepatitis C among PWID with a median of 49% (range: 24–76%) and low proportion of PWID with hepatitis C who started antiviral treatment with a median of 9.5% (range: 1–19%) [100].

Region	Subregion	People who inject drugs					
		Estimated number			Prevalence (percentage)		
		low	best	high	low	best	high
Africa		**330,000**	**1,000,000**	**5,590,000**	**0.05**	**0.16**	**0.91**
America		**2,150,000**	**2,820,000**	**3,970,000**	**0.34**	**0.44**	**0.62**
	North America	1,780,000	2,070,000	2,380,000	0.56	0.65	0.75
	Latin America and the Caribbean	370,000	750,000	1,590,000	0.11	0.23	0.49
Asia		**3,380,000**	**4,560,000**	**6,110,000**	**0.12**	**0.16**	**0.21**
	Central Asia and Transcaucasia	360,000	410,000	470,000	0.66	0.75	0.87
	East and South-East Asia	2,330,000	3,150,000	4,300,000	0.15	0.20	0.27
	South-West Asia	400,000	670,000	940,000	0.22	0.37	0.51
	Near and Middle East	30,000	70,000	130,000	0.03	0.08	0.13
	South Asia	250,000	260,000	260,000	0.03	0.03	0.03
Europe		**2,500,000**	**3,680,000**	**5,630,000**	**0.45**	**0.67**	**1.02**
	Eastern and South-Eastern Europe	1,790,000	2,910,000	4,780,000	0.78	1.27	2.09
	Western and Central Europe	710,000	770,000	850,000	0.22	0.24	0.26
Oceania		**120,000**	**130,000**	**160,000**	**0.49**	**0.53**	**0.66**
GLOBAL		**8,480,000**	**12,190,000**	**21,460,000**	**0.18**	**0.26**	**0.46**

Fig. 6.4 Estimated number and prevalence (percentage) of people who currently inject drugs among the general population aged 15–64, 2013 (source courtesy: www.unodc.org)

6.2.3 Initial Testing in IVDU

Both Centers for Disease Control (CDC) and United States Preventive Services Task Force (USPSTF) recommend a one-time testing in people with a history of injecting drugs and annual HCV testing for persons who inject drugs and following a high-risk episode. These recommendations are also endorsed by American association for the study of liver diseases (AASLD) and European association for the study of the liver (EASL) [21, 22, 101]. An HCV antibody test is recommended for initial HCV testing and if the result is positive active (current) infection should be confirmed by a sensitive HCV RNA test. Among persons at risk of reinfection after previous spontaneous or treatment-related viral clearance, initial HCV RNA testing is recommended, as HCV-antibody test will likely be positive. Quantitative HCV RNA testing and HCV genotype testing are recommended before initiation of antiviral regimen. CDC recommends using an FDA-approved quantitative or qualitative nuclear amplification test (NAT) with detection level of 25 IU/mL or lower to detect HCV RNA [22].

It is of utmost importance to educate PWID regarding precautions needed to avoid exposing others to infected blood since persons who use injection drugs are at risk of sharing needles and other contaminated drug injection equipment.

6.2.4 Goal of HCV Treatment in IVDU

The goal of HCV treatment in PWID is similar to general population infected with hepatitis C, which is to reduce all-cause mortality and complications from chronic hepatitis C infection such as end-stage liver disease and hepatocellular carcinoma.

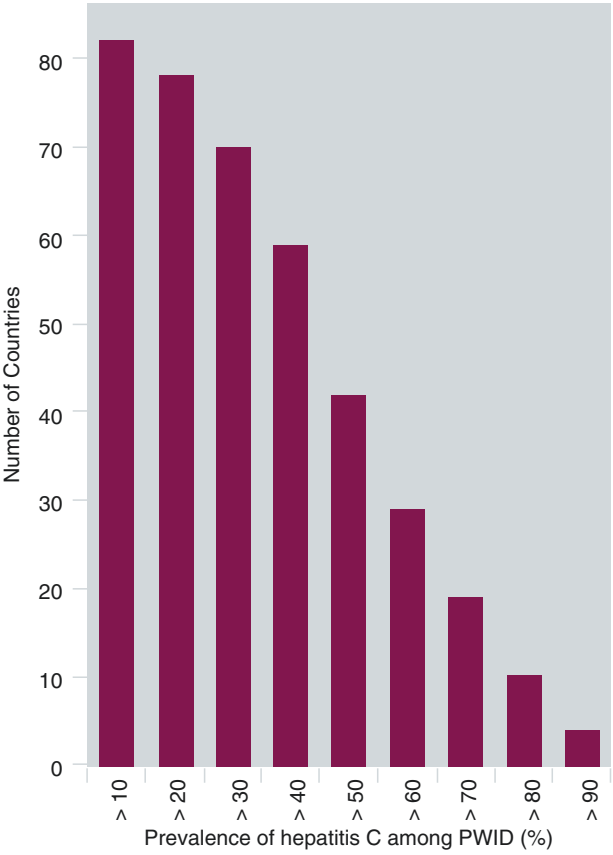

Fig. 6.5 Prevalence of hepatitis C in patients who inject drugs. Courtesy: UNODC. Number of countries, by prevalence of hepatitis C among people who inject drugs. (*Note: Total number of countries with data on hepatitis C prevalence among PWID is 88*)

Treatment is recommended for all with chronic HCV infection, except those with a short life expectancy. The end point of HCV therapy is achieving SVR defined as undetectable viral load at least 12 weeks after completion of therapy. Studies have shown that patients who achieve SVR (cured of HCV) have decrease in liver inflammation and rate of liver fibrosis and necrosis progression [102]. An upward of 70% reduction in the risk of HCC and a 90% reduction in the risk of liver-related mortality and liver transplantation has been reported in patients who achieve SVR [103–105]. In addition, an improvement in portal hypertension and splenomegaly has been reported as well. Apart from liver-related improvements, patients who achieve SVR have several extrahepatic advantages such as reduction in symptoms and mortality from cryoglobulinemic vasculitis, lymphoproliferative disorders, and non-Hodgkin's lymphoma [106–108].

A number of studies have shown that the benefit of SVR is highest when achieved in early stages of fibrosis preferably before Metavir F3. Treatment delay can lead to rapid progression of fibrosis with one study showing survival rate of 92% for those with SVR compared to 88% for those not treated and 82% with failed treatment at 15 years [109]. Another Swiss study showed that there is two and five times higher rates of liver-related mortality for Metavir fibrosis stages F3 and F4, respectively, compared with treating at Metavir stage F2 [110].

6.2.5 Management Strategies

Theoretically, testing and linkage to care combined with treatment of HCV infection in PWID with hepatitis C infection hold great potential in decreasing HCV incidence and prevalence, although there is still lack of strategies to integrate hepatitis C treatment with risk reduction techniques such as opiate substitution therapy, and needle and syringe exchange programs [111].

In an ideal world, treatment of hepatitis C in IVDU should be delivered in a multidisciplinary setting with involvement of social workers and psychotherapist to reduce the risk of reinfection and manage common social and psychiatric comorbidities in this patient population [112–114].

Currently there is strong evidence in support of treating hepatitis C in IVDU by their ability to show adherence to treatment and low rate of reinfection countering arguments that proposed treating IDU with hepatitis C as an absolute contraindication [115–117]. Combining HCV treatment with needle exchange and opioid agonist therapy can help significantly decrease the HCV disease burden [111].

6.2.6 Treatment Strategies

6.2.6.1 Interferon Era

Prior to 2011, pegylated interferon in combination with ribavirin was used for treatment of hepatitis C. Depending on genotype, treatment duration varied from 24 to 48 weeks [118]. The combined treatment of pegylated interferon and ribavirin has been found to be modestly effective in PWID with reported median SVR of 54.3% [119] and ranging from 45 to 70% for genotypes 1 and 4, and 70–80% for genotypes 2 and 3. Unfortunately, it was associated with high rates of adverse effects wherein about half of patients experience flu-like symptoms leading to discontinuation in several patients [118, 120].

A 10-year retrospective study from Ireland showed no significant difference in treatment nonadherence between PWID and nondrug users who were treated with Peg-IFN alpha/RBV (8.4% in PWID vs. 6.8% in non-PWIDs; RR 1.23, CI 0.76–1.99). Additionally, SVR in PWID was similar to non-PWID (64.2% vs. 60.9%, RR 1.05, 95% CI 0.95–1.17) [121]. The multicenter clinical trial (ACTIVATE) assessed adherence and response to directly observed Peg-IFN alpha-2a plus self-administered RBV for 12 (undetectable HCV RNA at 4 weeks) or 24 (detectable HCV RNA at

4 weeks) in patients with genotype 2 and 3 hepatitis C virus infection. Study results showed that overall 76% completed treatment although much higher rate of treatment completion was observed among patients receiving 12 weeks versus 24 weeks of therapy (97% vs. 46%, $P < 0.001$) [122]. These were important findings showing that shortening the duration of therapy can increase treatment completion of PWID. A randomized, open-label, parallel group trial from Canada investigated the efficacy and safety of directly observed Peg-IFN alpha-2a plus self-administered ribavirin for the treatment of hepatitis C virus (HCV) among people with active drug use and found that in patients actively using drugs treated with directly observed therapy SVR is comparable to that seen in clinical trials of nondrug users, and the rate of HCV reinfection is low [123]. A number of other retrospective and prospective studies have now shown comparable adherence of interferon-based regimens and efficacy in persons who inject drugs and those who do not use injected drugs with a meta-analysis of treatment with Peg-IFN, with or without ribavirin showing SVR rates of 37% and 67% for genotypes 1 or 4 and 2 or 3, respectively, in active or recent drug users [115, 119].

6.2.6.2 Follow-Up Studies for Hepatitis C Virus Treated with Peg-IFN/Ribavirin Among IVDU

Traditionally, clinicians have swayed away from treating hepatitis C in active injection drug users. However, as mentioned above several studies have now shown comparable adherence to treatment among PWID and nondrug users. The other concern has been reinfection after successful treatment. In a 5-year follow-up study of 116 patients, 45 patients achieved SVR, of which 27 were IVDU. Of these 27, HCV RNA reappeared in 1 patient compared to 0 of 18 nondrug users ($P = 0.41$) [124]. Aspinall et al. in their systematic review and meta-analysis showed pooled risk of 2.4 (95% CI, 0.9–6.1) per 100 person-years across 5 studies (comprising 131 drug users) examining reinfection [115].

6.2.6.3 DAA Era

With the introduction of direct-acting antivirals (DAAs) in the last few years, the treatment of hepatitis C infection has been revolutionized. Even though DAAs can achieve greater than 90% SVR rates, their efficacy depends primarily on adherence to the treatment raising concerns especially in underprivileged patients such as PWID [125]. Most of our information about the use of DAAs in PWID is based on post hoc analysis of clinical trials on DAAs in the treatment of hepatitis C although data have been conflicting where some studies report poor adherence in active drug users and high rate of reinfection while others show no difference between drug use and adherence.

Petersen et al. found that recent drug abuse was a risk factor for nonadherence [126]. The C-Edge CO-STAR trial estimated the incidence of reinfection after treatment with elbasvir and grazoprevir in patients on opioid substitution therapy and found it to be 10.6 (95% CI 3.42–24.6) per 100 person years from the end of therapy to follow-up week 12 [127]. Other clinical trials have not found the same

association between drug use and nonadherence. Grebely et al. in their post hoc analysis of the phase 3 ION-1 study showed no relation between nonadherence and drug use [128]. In the D3FEAT study, patients with HCV genotype 1 on OST and/or recent injection drug use received a combination of ombitasvir, ritonavir-boosted paritaprevir, and dasabuvir with or without ribavirin for 12 weeks in 87 participants and found that 94% completed 12 weeks of therapy and 91% achieved SVR with no virological failure with no impact of injecting drug use on SVR [129]. The SIMLIFY study that included only IDUs receiving or not receiving OST treated with fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks found adherence of 94% and SVR12 of 94% with one reinfection [130].

More recently there has been few real-world studies that confirmed high treatment completion rates (93–100%) and high SVR rates (80–96%) in patients receiving OST treated with DAAs [131–134]. A retrospective cohort study from 15 hospitals in Belgium consisting of 579 patients (19.9% PWID) found that PWID especially active users are underserved by DAAs. PWID were more infected with genotypes 1a and 3 ($P = 0.001$). There were equal rates of side effects (44.7% vs. 46.6%; $P = 0.847$), similar rates of treatment completion (95.7% vs. 98.1%; $P = 0.244$), and SVR (93.0% vs. 94.8%; $P = 0.430$) between PWID and non-PWID, respectively. Treatment adherence is similar in PWID and the general population, even in patients with active abuse. This study concluded that DAAs were safe and effective in PWID despite the higher prevalence of difficult-to-treat genotypes [135].

A study from Canada in 74 patients on DAAs showed that strong adherence and SVR with DAAs are achievable, with appropriate supports, even in the context of substance use, and complex health/social issues [132]. A recent study by Schitz et al. showed their results of treating 15 IDUs with DAAs under direct observation of a physician or nurse. In this study every patient completed treatment with 100% SVR [136]. The RISE II Study, which evaluated real-world adherence to DAAs among 61 patients receiving OST, found that adherence was comparable to registration trial [137]. Several other prospective studies have shown that DAA treatment of PWID with hepatitis C is safe and effective showing high HCV cure rates regardless of active drug use or opioid agonist therapy [134, 138].

Based on this data, it is recommended that treatment of hepatitis C in drug users with DAAs should be on a case-to-case basis and mere active drug use should not be an absolution contraindication to treatment. These recommendations are also endorsed by EASL guidelines on treatment of hepatitis C [21].

6.2.7 Hepatitis C Prevention Strategies in PWID

Apart from treating hepatitis C in PWID, it is extremely important to prevent transmission of hepatitis C in PWID, which in turn will help decrease the disease burden. Programs such as needle and syringe program and opiate substitution therapy are currently in place to achieve this goal.

6.2.8 Needle and Syringe Program (NSP)

Also known as needle exchange program (NEP) or syringe-exchange program (SEP), this is a service that allows IDUs to obtain hypodermic needles at minimal cost or for free. The primary basis for this is harm reduction that attempts to reduce the risk factors for diseases such as hepatitis and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). An important part of the exchange programs requires users to return used syringes to receive an equal number of new syringes. A study by the WHO found that NSPs substantially reduce the spread of HIV among IDUs in a cost-effective manner [139].

6.2.9 Opiate Substitution Therapy (OST)

Opioid substitution therapy is another program where IDUs who commonly inject an opiate derivative such as heroin are supplied with a replacement drug, a prescribed medicine such as methadone or buprenorphine, which is usually administered orally in a supervised clinical setting. The effectiveness of this therapy is recognized in developed countries although more data is needed from developing countries [139].

The role that NSP and OST play in preventing hepatitis C transmission is controversial. Van der Meer et al. and Turner et al. showed that NSP and OST are key primary interventions that can greatly reduce an individual's HCV risk [104, 140]. However, Vickerman et al. in their model predictions showed that OST and high-coverage NSP are unlikely to achieve meaningful reductions in HCV prevalence among PWID [141]. Model projections have suggested that HCV prevention can be achieved by HCV treatment among PWID. Martin et al. have proposed that it is more cost effective to treat PWID with ongoing transmission risk compared to former PWID [142]. A multicenter UK study that collected data on PWID who were treated and achieved SVR reported that current treatment rates among PWID are unlikely to achieve observable reductions in HCV prevalence over the next 10 years. However, scaling up treatment to 26/1000 PWID annually with IFN-free direct-acting antivirals (DAAs) can achieve an observable absolute reduction in HCV chronic prevalence of at least 15% among PWID [143].

These findings are similar to a previous study by the same author in which mathematical models suggested that upscaling of HCV treatment is required to achieve a reduction in HCV prevalence of more than 40% among PWID over the next decade [111].

Dimova et al. in their systematic review and meta-analysis found that the treatment completion rate among drug users was 83.4% (95% confidence interval [CI], 77.1–88.9%). Among studies that included addiction-treated and -untreated patients during HCV therapy, the higher the proportion of addiction-treated patients, the higher the HCV treatment completion rate ($P < 0.0001$) [144].

6.2.10 Conclusion

Treatment of hepatitis C in IV drug users is a complex phenomenon and best served in a multidisciplinary approach. There is robust data showing evidence in favor of treatment of PWID with comparable rates of adherence and reinfection compared to nondrug users. Even though this data has been for Peg-IFN alpha and ribavirin, there are increasing number of studies showing similar results with newer direct-acting antivirals. DAAs are highly active agents against hepatitis C, which are expected to eradicate hepatitis C in most patients with excellent side effect profile. DAAs in combination with programs such as needle syringe program and opiate substitution therapy will help not only in treatment of affected patients but also in preventing transmission of the virus. PWID during the year preceding treatment should be offered ideally biannual, at least annual testing for reinfection after DAA-induced SVR.

6.3 Treatment of HCV in Prisoners

6.3.1 Epidemiology of HCV in Prisoners

The population of prisoners is growing at a rapid rate compared to general population growth in the world and is currently estimated at about 10.35 million with a large number cycling through this on a yearly basis [145]. There is a high prevalence of viral hepatitis in prisoners compared with the corresponding non-prisoner population particularly among those in prison with a history of injecting drug use with a recent systematic review estimating prevalence of 15.5% for HCV among prisoners in Western Europe and 20.2% in Eastern Europe [146]. Another study from Australia among 253 inmates reported incidence of hepatitis C at 34.2 per 100 person years [147]. An updated study from US prisons reported prevalence of hepatitis C at 17.4% with chronic infection estimated to be between 12 and 35%. A more recent review of hepatitis C infection in prisoners found the prevalence ranging from 3.1 to 38% [148].

6.3.2 Risk Factors for HCV in Prisoners

The high prevalence is likely due to high incidence of psychiatric and social issues, unsafe lifestyle, IVDU, tattooing, promiscuous behavior, violence, and overcrowding that prisoners experience before and during incarceration [149]. The main risk factor in prisoners is IVDU with some studies showing continued use of injection drugs after imprisonment and widespread sharing of infected equipment [150]. The other risk factors for HCV infection were older age and previous incarceration with one study showing HCV prevalence to be 58.5% in inmates over 45 years with an odds ratio of 13.1 [151].

6.3.3 Barriers to Treatment

Unfortunately, there are several barriers in the treatment of hepatitis C in prisoners. Most incarcerated individuals are unaware of their diagnosis. Social taboo, fear of the diagnosis, discrimination, lack of awareness, and lack of medical personal to treat hepatitis C are some of the obstacles that prisoners with hepatitis C face. There is strong evidence now that inmates with chronic hepatitis C can achieve SVR with the same rate as non-incarcerated patients [152]. However, this can only be achieved with collaborative efforts of prison authorities and physicians by implementing strategies for regular screening of prisoners with anti-HCV antibody. According to one study from Australia, approximately 8000 individuals were HCV antibody positive of the 50,000 individuals in custody; however only 313 prisoners received antiviral treatment. This study reported fear of side effects and stigma of being identified to custodial authorities as HCV infected being the common barriers [153].

6.3.4 Treatment

It is highly important to provide HCV testing, treatment, and linkage to care services to people who are incarcerated since over 90% of prisoners will be released back to their communities within a few years of sentencing [154]. Most of the information on treatment of hepatitis C in prisoners comes from cross-sectional studies. A range of 28–69% has been reported regarding SVR with Peg-IFN plus ribavirin combination treatment in prisoners with hepatitis C [155–157]. SVRs were 74% for those not released or transferred, 59% for those transferred and 45% for those released during treatment. This study confirmed that HCV treatment in prison is both feasible and effective with the caveat of poorer outcomes for prisoners who were either released or transferred during therapy [158].

More recently there is highly encouraging data on the use of DAAs in prisoners. This option is attractive for its short duration and possibility of directly observed treatment or supervision. Marco et al. studied all patients treated at the ten prisons of Catalonia and at three public hospitals in the Barcelona area over a 15-month period. Prisoners were significantly younger than non-prisoners, with higher proportions of men drug users. Overall, 98.4% of patients completed treatment with low discontinuation rate although higher in inmates (3.7% vs. 1.2%, $P = 0.003$). SVR was 93.1% in inmates versus 96.5% in noninmates ($P = 0.08$). Virologic failure rates were similar (3.8% vs. 3% in noninmates; $P = 0.60$) [159]. Bartlett et al. recently reported excellent results on their study of 119 patients with chronic HCV infection treated with DAA therapy in an Australian prison with HCV in-prison viremic prevalence declining from 12 to 1% [160]. Apart from high adherence rates and SVR, research has shown that HCV treatment with DAAs is cost effective in prison settings [161].

6.4 Conclusion

Treatment of hepatitis C in prisoners is a multistep approach. Ideally a dedicated team of specialists, diagnostic tests, and treatment procedures should be established at every prison. Due to high effectiveness of DAAs, it should be initiated as early as possible in all eligible patients with the goal of curing and preventing transmission.

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HIV/HCV Coinfection: Current Challenges

7

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7.1 Introduction

Both human immunodeficiency virus (HIV) infections and hepatitis C virus (HCV) infections rank high among global causes of death [1]. Due to shared routes of transmission, prevalence of coinfection with both viruses is high and therefore an area of concern as progression of liver disease was known to be accelerated by HIV. However, due to a number of important changes in the management of HIV and HCV, our beliefs have radically changed. In this chapter the changing dynamics in the field of HIV/HCV coinfection is discussed.

7.2 Changes in Epidemiology of Hepatitis C in HIV Infection

At a global level, there are 37 million people infected with HIV and 115 million people with antibodies to hepatitis C virus (HCV) [2]. Worldwide, there are approximately 2,278,400 HIV/HCV coinfections (IQR 1,271,300–4,417,000), of which

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1,362,700 (847,700–1,381,800) are in people who inject drugs (PWID), equaling an overall coinfection prevalence in HIV-infected individuals of 6.2% (3.4–11.9) [3]. This estimation comes from a recent systematic review and meta-analysis of 783 epidemiological studies published between January 1st 2002 and January 28th 2015 [2]. In this study, odds ratios of HCV infection were six times higher in people living with HIV (5.8, 95% CI: 4.5–7.4) than their HIV-negative counterparts. The study also showed a wide variation in the mode of transmission: from a low seroprevalence within pregnant or heterosexually exposed individual (4.0%, 95% CI: 1.2–8.4) to 6.4% (3.2–10.0) in men who have sex with men (MSM), up to even 82.4% (55.2–88.5) in people who inject drugs (PWID).

Since injecting drug use was popular in most European countries in the late twentieth century, the number of PWID that were coinfected with both HIV and HCV in Europe was relatively high between 15 and 30% [4]. In those countries that reacted upon this IV drug epidemic with adequate harm reduction strategies, prevalence rates remained low like in the Netherlands with about 10% coinfection rate. However, seroprevalence rates have also declined in countries that have introduced preventive strategies for PWID more recently, as was shown for Spain, where prevalence of HIV/HCV coinfection has decreased from 25.3% (95% CI: 23.1–27.5) in 2004–2005 to 8.2% (95% CI: 6.9–9.5) in 2010–2011 [5].

7.3 Pathophysiology of Liver Fibrosis Progression in Patients with HIV and Recent Changes in Natural History

7.3.1 The Pre-highly Active Antiretroviral Therapies (HAART) Era

It was widely observed that HIV/HCV-coinfected patients suffered from faster progression of liver fibrosis (LF) compared to HCV-mono-infected patients, resulting in increased rates of cirrhosis and decompensation of liver disease [6, 7]. This was well established from several large observational studies and further meta-analyses [8, 9]. In 2001, Graham et al. performed a meta-analysis of eight studies to assess the risk of cirrhosis and end-stage liver disease (ESLD) in HIV/HCV-coinfected patients compared to HCV-mono-infected patients, and found that the risk of progression to cirrhosis and ESLD was twofold and sixfold higher, respectively, in coinfected patients than those with HCV mono-infection [8]. This was confirmed in a meta-analysis by Deng et al. that involved 16,750 patients from 29 trials, to quantify the effect of HIV coinfection on progression in liver disease in patients with HCV infection [9]. In this study, the overall OR for histological cirrhosis or decompensated liver disease or liver cancer or death was 3.40 (95% CI: 2.45–4.73) for HIV/HCV-coinfected as compared to HCV-infected patients. In subgroup analysis, the authors found that there was a substantial increased risk for decompensated liver disease and death, 5.45 (95% CI:

2.54–11.71), and 3.60 (95% CI: 3.12–4.15), respectively, but smaller difference regarding the development of cirrhosis or liver cancer, 1.47 (95% CI: 1.27–1.70) and 0.76 (95% CI: 0.50–1.14), respectively [9].

The pathophysiology of liver fibrosis progression in patients with HIV results from a multifactorial process (Fig. 7.1). The viral replication of HCV is generally higher in HIV/HCV-coinfected than in mono-infected subjects [10]. Besides this high viral replication, chronic immune activation, and inflammation due both to HIV and bacterial translocation [11], mitochondrial toxicity and steatosis triggered by some older nucleos(t)ide reverse transcriptase inhibitors (NRTI) such as stavudine and didanosine [12, 13] have contributed in the past to more severe intrahepatic damage in HIV/HCV-coinfected compared to mono-infected subjects [13].

7.3.2 Recent Changes in Natural History

The natural history of chronic HCV infection has dramatically changed over the past decade. Three steps have markedly changed the landscape:

First, from the early twenty-first century onwards, with the introduction of safe and effective antiretroviral drugs, the cutoff at which initiation of cART was recommended has increased gradually, from 200 to 350 cells/mm^3 until since 2015 to systematic initiation of cART in all HIV-positive persons, irrespectively of their CD4 count [14]. This major shift in HIV treatment guidelines has resulted in a

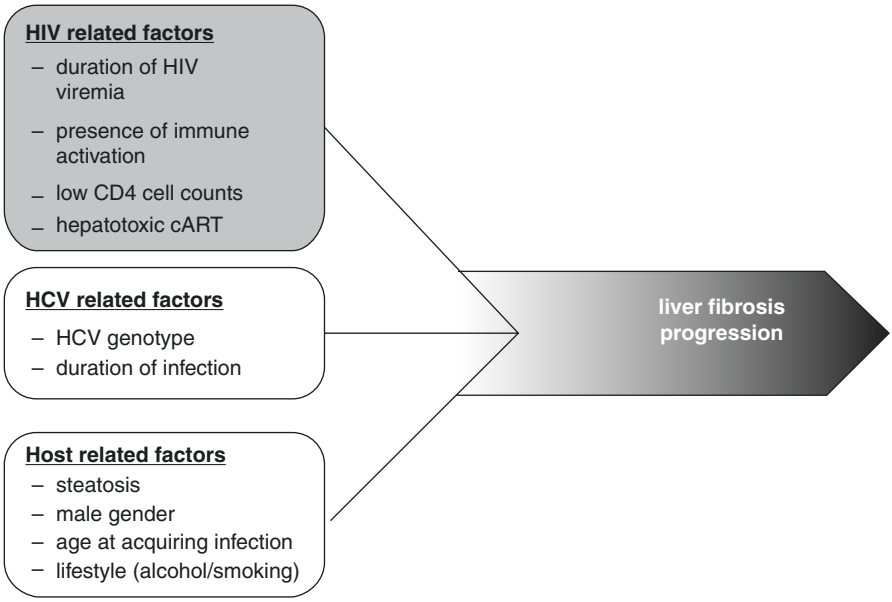

Fig. 7.1 Pathophysiology of liver fibrosis progression in patients with HIV (from Arends et al. [17])

corrected immune deficit in most patients. It is well known that higher CD4+ T-cell recovery protects HIV-coinfected individuals from HCV-related clinical events, and that undetectable plasma HIV-RNA and high CD4+ T cell appeared to protect from progression of liver fibrosis as was shown by FIB-4 transitions to worse stage [15]. The second major change was withdrawal of NRTI with mitochondrial toxicity such as didanosine and stavudine from the cART armamentarium [16] and introduction of safer antiretroviral drugs without liver toxicity. The third and last important change was the development of all-oral direct-acting antiviral (DAA) regimens, leading to HCV cure in more than 95% of the patients.

With all these changes, it is generally accepted that HIV-infected patients, especially those who newly acquire HCV, have the same liver fibrosis progression rate as HCV-mono-infected individuals [17, 18]. A recent French study performed in cirrhotic patients confirmed this fact showing that HIV/HCV-coinfected patients have now a similar risk of liver decompensation and of hepatocellular carcinoma compared to HCV-mono-infected patients with cirrhosis [18]. HIV/HCV-coinfected patients however keep an increased risk of overall mortality than HCV-mono-infected patients, mainly due to death from extrahepatic causes such as infections, cancers, and cardiovascular events [18].

7.4 Specificities of HCV Treatments in HIV Infection and Drug–Drug Interactions (DDIs)

In the pre-HAART era, sustained virological response (SVR) rates to interferon-based therapy were lower in HIV/HCV-coinfected people than in those who were not and did not exceed 50% overall and 15% in patients with cirrhosis [19, 20]. This has been well described in the literature [21].

With the development of all-oral direct-acting antiviral (DAA) drug regimens, the treatment of chronic hepatitis C has dramatically improved [22]. Up to 93–98% of patients obtain an SVR at 12 weeks (SVR12) in clinical trials, whatever the combinations and the fibrosis stage [23–28]. And the response rate in HIV/HCV-coinfected individuals has become similar to that of HCV-mono-infected ones [29–34] (Fig. 7.2). Furthermore, in real-life settings, several cohorts in France, Italy, and Spain have shown that this high efficacy and safety of DAA were similar as in clinical trials [35–37]. It is now firmly established that coinfected patients treated with all oral DAAs have comparable, if not equivalent, SVR rates to mono-infected patients treated with the same regimen and thus appear to be no longer a "hard-to-treat population."

Potential explanations for the improved, and now equivalent, SVR rates in coinfected and mono-infected patients are likely to rest with the differing mechanism of action of the different anti-HCV therapies. With the introduction of DAAs, the pharmacological mechanism of action of HCV therapies has shifted from immune regulation by peg-IFN-alfa/RBV to (predominately) direct viral inhibition. It is conceivable that with peg-IFN-alfa/RBV therapy even minor defects in the host cellular responsiveness might impact efficacy, while such minor deficits have little

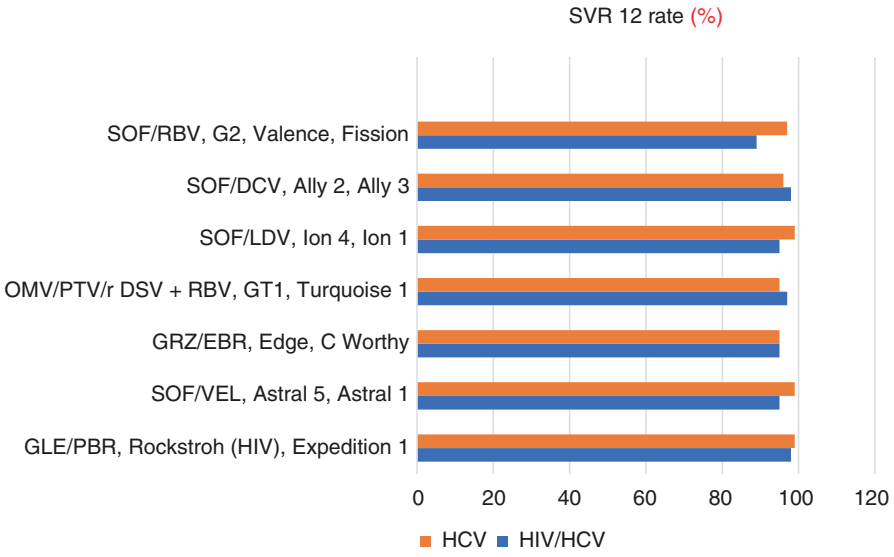

Fig. 7.2 Comparison of SVR rate after DAA treatment in clinical trials performed in HCV-mono-infected and HIV/HCV-coinfected populations

or negligible influence when the main activity is direct viral targeting. This view however may prove too simplistic [17].

The main particularity of the treatment of HCV in HIV infection remains in the fact that DAAs can cause drug–drug interactions (DDIs) with antiretrovirals and non-cART co-medication [38]. The ability of HCV protease inhibitors to inhibit cytochrome 450-3A4 (CYP3A4) and transporters (hepatic and/or intestinal and/or renal) can have significant clinical consequences [38].

Mainly throughout an induction or an inhibition of CYP3A4, most of the antiretroviral drugs can affect the metabolism of DAA and lead to abnormal drug exposures. But HCV DAA may also inhibit CYP3A4 and/or transporters leading to an increased exposure of several antiretrovirals (Table 7.1).

7.4.1 Effect of HIV Drugs on the Metabolism of HCV DAAs

HIV boosted protease inhibitors, and most HIV non-nucleoside reverse transcriptase inhibitors (NNRTI), interact via this mechanism of induction or inhibition of CYP3A4. In contrast, HIV integrase inhibitors (e.g., dolutegravir) do not or only marginally affect CYP3A4, and therefore are relatively free of DDI. Exposure to some HIV and HCV nucleos(t)ide analogues (e.g., tenofovir and sofosbuvir, respectively) is subject to competition on drug transporters (e.g., P-glycoprotein) and requires special attention in patients with renal insufficiency.

Table 7.1 Main interactions between antiretrovirals (ARV) and direct-acting antivirals (DAA)

Effect on antiretroviral drugs		Effect on anti-HCV drugs									
		Ribavirin (RBV)	Simeprévir (SMV)	Daclatasvir (DCV)	Sofosbuvir (SOF)	Sofosbuvir (SOF)/ ledipasvir (LDV)	Sofosbuvir (SOF)/ velpatasvir (VEL)	Sofosbuvir (SOF)/ velpatasvir (VEL)/ voxilaprevir (VOX)	Grazoprevir (GZR)/elbasvir (EBR)	Glecaprévir (GLE)/ pibrentasvir (PIB)	Paripatrevir/ ritonavir (PTV/r)/ ombitasvir (OBV) ± dasabuvir (DSV)
Nucleos(t)ide reverse transcriptase inhibitors (NRTI)	Zidovudine (ZDV)	Not recommended	Not recommended if RBV associated	Not recommended if RBV associated	Not recommended if RBV associated	Not recommended if RBV associated	Not recommended if RBV associated	Not recommended if RBV associated	Not recommended if RBV associated	Not recommended if RBV associated	Not recommended if RBV associated
	Tenofovir disoproxil fumarate (TDF)	Possible	Possible	Possible	Possible	Possible TDM + renal monitoring Avoid if eGFR <60 mL/mm	Possible TDM + renal monitoring	Possible TDM + renal monitoring	Possible	Possible	Possible
	Tenofovir alafénamide (TAF)	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible
	Emtricitabine (FTC)	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible
	Lamivudine (3TC)	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible
	Abacavir (ABC)	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible

Nonnucleoside reverse transcriptase inhibitors (NNRTI)	Efavirenz (EFV)	Possible	Not recommended	Possible DCV 90 mg qd + TDM	Possible	Possible	Not recommended	Contraindicated	Contraindicated	Contraindicated	Contraindicated
	Nevirapine (NVP)	Possible	Not recommended	Possible DCV 90 mg qd + TDM	Possible	Possible	Not recommended	Contraindicated	Contraindicated	Contraindicated	Contraindicated
	Etravirine (ETR)	Possible	Not recommended	Possible DCV 90 mg qd + TDM	Possible	Possible	Not recommended	Contraindicated	Contraindicated	Contraindicated	Not recommended
	Doravirine (DOR)	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible TDM DOR
	Rilpivirine (RPV)	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible TDM RPV + ECG monitoring	Possible TDM RPV + ECG monitoring
Protease inhibitors (PI)	Atazanavir/r (ATV/r)	Possible	Not recommended	Possible DCV 30 mg qd + TDM	Possible	Possible TDM ATV + bilirubin monitoring	Possible TDM ATV + bilirubin monitoring	Contraindicated	Contraindicated	Contraindicated	Possible ATV 300 mg *without RTV* administered at the same time + TDM
	Darunavir/r (DRV/r)	Possible	Not recommended	Possible DVC 60 mg qd + TDM	Possible	Possible	Possible	Contraindicated	Contraindicated	Contraindicated	Possible DRV 800 mg qd *without RTV* administered at the same time + TDM Absence of extensive PI resistance
	Lopinavir/r (LPV/r)	Possible	Not recommended	Possible DVC 60 mg qd + TDM	Possible	Possible	Possible	Contraindicated	Contraindicated	Contraindicated	Contraindicated
	Fosamprenavir/r (FPV/r)	Possible	Not recommended	Not recommended	Possible	Possible	Not recommended	Contraindicated	Contraindicated	Contraindicated	Contraindicated
	Tipranavir/r (TPV/r)	Possible	Not recommended	Possible DVC 60 mg qd + TDM	Possible +TDM SOF	Possible +TDM SOF/ LDV	Not recommended	Contraindicated	Contraindicated	Contraindicated	Contraindicated

(continued)

Table 2.1 (continued)

Effect on antiretroviral drugs		Effect on anti-HCV drugs									
		Ribavirin (RBV)	Simeprévir (SMV)	Daclatasvir (DCV)	Sofosbuvir (SOF)	Sofosbuvir (SOF)/ ledipasvir (LDV)	Sofosbuvir (SOF)/ velpatasvir (VEL)	Sofosbuvir (SOF)/ velpatasvir (VEL)/ voxilaprevir (VOX)	Grazoprevir (GZR)/elbasvir (EBR)	Glecaprévir (GLE)/ pibrentasvir (PIB)	Paripatrevir/ ritonavir (PTV/r)/ ombitasvir (OBV) ± dasabuvir (DSV)
Integrase inhibitors (INI)	Raltegravir (RAL)	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible
	Dolutegravir (DTG)	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible
	Elvitegravir/ cobicistat (EVG/c)	Possible	Not recommended	Possible DVC 30 mg qd + TDM	Possible	Possible	Possible	Contraindicated	Contraindicated	Contraindicated	Contraindicated
Entry/fusion inhibitors	Maraviroc (MVC)	Possible	Possible MVC 150 mg bid + TDM	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible MVC 150 mg bid + TDM
	Enfuvirtide (T20)	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible	Possible

TDM therapeutic drug monitoring

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7.4.2 Effect of HCV DAAs on the Metabolism of HIV Drugs

HCV protease inhibitors have the ability to inhibit cytochrome 450-3A4 (CYP3A4) and transporters (hepatic and/or intestinal and/or renal) and consequently can increase the drug concentrations of HIV proteases [38]. In contrast, HCV polymerase inhibitors, most HCV NS5A inhibitors, do not or only marginally affect CYP3A4, and therefore are relatively free of DDI.

7.4.3 Other Interactions Between DAA et Co-medications

Several other interactions are possible between DAA and co-medications often prescribed in HIV-infected patients such as statins or drug substrates of the CYP450 and/or transporters (e.g., P-glycoprotein, OATP1B1/1B3, BCRP) mainly with the HCV protease inhibitors and to a lesser extent with some HCV NS5A inhibitors.

These drug–drug interactions between DAA and cART should be known by physicians to prevent either toxicity due to drug overexposure or treatment failures due to suboptimal drug concentrations. These interactions can be easily found on the free-access checkers web site www.hcv-druginteractions.org or www.hiv-druginteractions.org. Interactions with cART are described in Table 7.1. Switching cART before DAA treatment can be an option and this was exemplified in a study from the Netherlands, in which category 2 and 3 DDIs were prevented by switching cART in 78 of 147 (53%) and 47 of 49 (98%) patients [39].

7.5 Beneficial Consequences of HCV Cure in HIV-Infected Patients

There have been many advances and changes in the management of both HIV and HCV over the past decade resulting in a decrease in liver fibrosis progression already demonstrated in the pre-DAA era. In addition to the increased SVR rates in coinfected patients treated with DAAs which are now similar to HCV-mono-infected patients, factors responsible for this favorable outcome are improved control of HIV with safer, less hepatotoxic cART and with commencement of HIV therapy at an earlier stage and higher CD4 count—all of which directly influence the degree of immune activation and dysregulation which impacts fibrosis (Fig. 7.3) [40]; the question is how this affects future development of liver-related complications.

7.5.1 Liver Events

Although more evidence has surfaced in mono-infected patients treated with DAAs, already several studies have now evaluated liver-related complications in HIV/HCV-coinfected patients cured of HCV [41–43]. Indeed, a similar reduction in liver decompensation and increased survival were demonstrated [41].

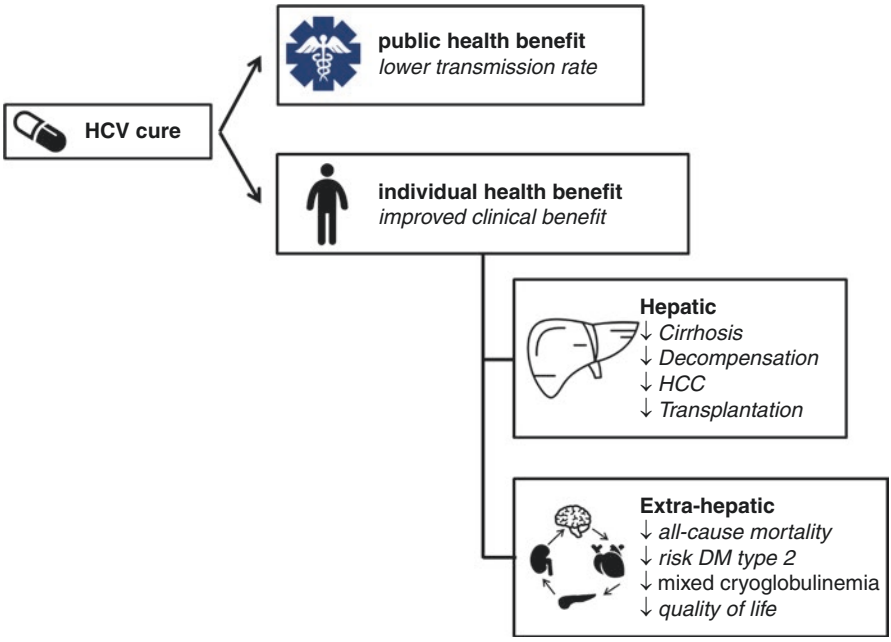

Fig. 7.3 Overview of benefits and challenges after HCV cure (Ref. [40])

It was also recently found that the incidence rates of diabetes mellitus, renal events, and non-AIDS-related infections were significantly lower in responders than in no responders to anti-HCV treatment [43].

7.5.2 Quality of Life

SVR is associated with improved long-term clinical outcomes, economic benefits, and improved health-related quality of life. DAA treatment has demonstrated to have less impairment on patient's quality of life, in terms of physical and mental functioning and social activities. This was mostly observed in pegIFN/RBV-experienced patients who were retreated with a new DAA regimen [44]. A study conducted in Germany suggested that cure of HCV with direct-acting antivirals is associated with positive metabolic effects with weight gain during long-term follow-up of 1 year [45]. Similar conditions were observed in HIV-coinfected patient. During treatment with ledipasvir/sofosbuvir and sofosbuvir/velpatasvir, patients showed an improvement in patient-reported outcome measures (PROMs: activity/energy, physical component, and fatigue score) compared to those treated with sofosbuvir/ribavirin. Those improvements remained present also after treatment cessation [46].

7.6 Residual Risk After Cure?

Despite the numerous demonstrated clinical benefits of HCV cure, the risk of HCC is not abolished in patients with severe fibrosis or cirrhosis before HCV cure. Cirrhosis is the main factor influencing the propensity to develop HCC after SVR, with a risk ranging from 1.0 to 2.2% per year in cirrhotic patients, whereas the risk is very low in patients without cirrhosis [47].

In those patients with cirrhosis or severe fibrosis, specific added risk factors have been identified that increase the risk for HCC occurrence after cure:

- Age is the most important risk factor, patients being older than 55, and especially 65+ being more likely than younger patients to develop HCC after SVR [47, 48]. This role of age among patients with cirrhosis was well demonstrated in a European study, in which the 8-year HCC incidence was 2.6% (95% CI: 0.0–5.5) among patients <45 years, 9.7% (95% CI: 5.8–13.6) among patients 45–60 years, and 12.2% (95% CI: 5.3–19.1) among patients >60 years at the start of therapy (aHR for those >60 years: 8.91; 95% CI: 1.12–70.79) [48].
- Furthermore, the severity of cirrhosis, as assessed by a low albumin blood level and a low platelet count [48], or a high elastometry score (over 20 kPa) [49] increases the risk of events as compared with patients with less severe, compensated cirrhosis.
- Finally, the metabolic syndrome and diabetes [defined by BMI $\geq$25 kg/m^2 and/or diabetes and/or dyslipidemia] carry a much higher risk of HCC occurrence after cure [48, 50]. In one study from France, the HCC incidence among cirrhotic patients cured of HCV but with the metabolic syndrome was around 6% at 6 years, while it was nearly zero in those without the metabolic syndrome [50].

7.7 HCV Reinfections

Modelling studies predict that universal HCV treatment will lead to a decrease in the incidence of new infections [51]. However, HCV is not an infection that confers protective immunity after cure. Reinfection is defined as having detectable plasma HCV-RNA following an undetectable level more than 12 weeks after the end of the treatment (SVR12) with demonstration of different genotype or clade compared with the primary infection.

Risk of reinfection varies according to populations and risk factors. A recent meta-analysis suggested that the rate of HCV reinfection was higher among HIV-coinfected than mono-infected patients, even if there is a great variability among different groups, such as PWID, MSM, and prisoners [52, 53].

7.7.1 Risk of Hepatitis C Reinfection Among MSM

Epidemics of acute hepatitis C have been observed since more than a decade, mostly among MSM with previous HIV infection and with sexual high-risk behaviors in

European countries, Australia, the USA, and Asia [53–55]. In the Swiss cohort, there was between 2014 and 2015 a 67.1% increase of the number of acute cases attributed to transmission among men who have sex with men, while it declined in PWID and remained stable <1 per 100 in heterosexuals [56]. In these populations, the transmission of HCV is linked to blood contacts via these extremely hard sexual behaviors. Several other factors have increased the incidence like increased cheap air travel, rising popularity of Internet, and use of drugs and stimulants for sexual pleasure ("chemsex") (see Chap. 11).

In MSM, the risk of HCV reinfection after a first episode of hepatitis is also very high [57, 58]. Prevention strategies are needed for this high-risk group to reduce morbidity and accelerate diagnosis and treatment to avoid transmission. HIV-positive MSM with a prior HCV infection should then be tested frequently for reinfection (every 3–6 months).

7.7.2 Risk of Hepatitis C Reinfection Among PWID

There is uncertainty about reinfection rates among PWID due to lack of available data for good-quality studies (retrospective designs, exclusion of recent PWID from trials, inability to distinguish reinfection from relapse). A study conducted in Australia estimated an incidence of reinfection of 7.4 per 100 patient-years [59]. Among people who injected drugs, the risk of reinfection was found to be low after successful treatment. Risk of reinfection may vary depending on the local background epidemic among the PWID population of HCV. Therefore, in communities with a higher local background HCV epidemic, treated PWID are likely to have a higher risk of reinfection [60]. In addition, injecting behavior after treatment, as well as implementation of a needle exchange program, influences the risk of reinfection among PWID [61].

This ongoing risk underlines that regular monitoring for reinfection is important following SVR, particularly in persons who continue to engage in IDU and for high-risk MSM. In order to increase the success of HCV treatment, it will be essential to establish a posttreatment surveillance [62].

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Management of Interferon-Free Direct-Acting HCV Antiviral Therapy Failure

8

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8.1 Introduction

Chronic hepatitis C causes a serious global liver disease including liver cirrhosis and hepatocellular carcinoma. An estimate of 71 million people worldwide are chronically infected with the hepatitis C [1]. In the USA, chronic hepatitis C is the leading cause of liver-related mortality and liver transplantation, surpassing human immunodeficiency (HIV) infection [2]. Since the arrival of high response rate of HCV protease inhibitor agents in 2011, the landscape of hepatitis C treatment has evolved rapidly given the introduction of numerous combination therapies over the past few years and many more are expected in near future. The current gold standard for hepatitis C treatment is interferon-free direct-acting antiviral (DAA) combination therapy with or without ribavirin (RBV). Three major DAA drug classes that interfere with HCV replication and posttranslational processing are as follows [3]:

1. NS3/4A protease inhibitors ("-previrs") interfere with the proteolytic processing of the HCV polyprotein by blocking the NS3/4A serine protease. Current FDA approvals are simeprevir (approved in 2013), paritaprevir (approved in 2014), and grazoprevir (in 2016). In 2017, two pan-genotypic protease inhibitors, voxilaprevir and glecaprevir, were approved.
2. NS5B polymerase inhibitors ("-buvirs") target the viral RNA replication by inhibition of the RNA-dependent RNA polymerase (RdRp). Two subgroups are nucleoside/-tide analogue; current agent is sofosbuvir (available in 2013) and non-nucleoside inhibitors; the available agent is dasabuvir (in 2014).
3. NS5A inhibitors ("-asvirs") affect the viral replication and assembly by blocking the NS5A protein. Current agents are ledipasvir and ombitasvir (approved in

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Table 8.1 Current direct-acting antiviral drug classes for hepatitis C treatment

Class	FDA approvals
NS3/4A protease inhibitors	Simeprevir (2013) Paritaprevir (2014) Grazoprevir (2016) Voxilaprevir (2017) Glecaprevir (2017)
NS5B polymerase inhibitors	Sofosbuvir (2013) Dasabuvir (2014)
NS5A inhibitors	Ledipasvir (2014) Daclatasvir (2015) Ombitasvir (2014) Elbasvir (2016) Velpatasvir (2016) Pibrentasvir (2017)

https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm405642.htm

2014), daclatasvir (in 2015), elbasvir and velpatasvir (available in 2016), and pibrentasvir (approved 2017).

A summary of current DAA drug classes is listed in Table 8.1.

The current DAAs broaden the different groups of patients who were not considered for treatment under interferon era such as those with advanced liver disease (Child-Pugh B, C), autoimmune diseases, renal failure, or postorgan transplant patients. In addition, DAA therapies demonstrate high virological response, on average >90%, compared to 40–50% with interferon and ribavirin in genotypes 1 and 4, 60–70% in genotypes 5 and 6, and 80–90% in genotypes 2 and 3 [4].

8.2 Challenges Under DAA Era

Despite the excellent efficacy under current modern all-oral DAA combination therapy, there are still a small percentage, up to about 5%, of patients who fail combination therapy [5]. Failures to DAA regimens are usually related to relapse defined as rebound of HCV RNA to pretreatment levels once therapy is discontinued [6]. There are multiple factors affecting the outcome and hepatitis C resistance including virus-related factors, host-related factors, and drug-related factors [4].

With virus-related factors, hepatitis C has six different genotypes worldwide and the RNA sequence can vary up to 35% between genotypes [4]. Given highly diversified genetic and rapid rate of replication, significant genetic errors occur and affect the treatment outcome. Failure to direct antiviral therapy is often associated with the development of resistance-associated substitutions (RASs). RASs are viral resistance to DAA by selecting viral variants that have amino acid substitution which alters the drug target used in the therapeutic regimen and therefore becomes less susceptible to drug's inhibitory activity [7, 8] but also affects subsequent salvage treatment [5].

Regarding host-related factors, adherence to therapy with proper administration of the drug at the regular time is a key factor to achieve best drug response. In addition, the presence of fibrosis stages as the presence of cirrhosis is negatively associated with achievement of SVR [9], or presence of comorbidities (i.e., HIV, postorgan transplant status, BMI) also affects treatment outcome [4].

One reasonable approach for retreatment after DAA failure in the presence of RASs is to switch DAA class (due to lack of cross-resistance among different DAA classes) [10, 11]. However, retreatment could be challenging when viruses harbor RASs in multiple DAA targets [12] which is a drug-related factor noticeable in post-treatment RASs. The frequent selected RASs are observed in patients that failed NS3/4A or NS5A inhibitor-containing regimens [13]. NS3/4A RASs seems to be less permanent and could disappear from peripheral blood within weeks to months while NS5A RASs tend to linger for years and impact treatment and retreatment [14–17]. Quite contrary, even after exposure to NS5B inhibitor-containing DAA regimen, only 1% of NS5B nucleotide RASs are selected [18, 19]. Both baseline and selected RASs have a variable negative impact on virological response depending on prior DAA regimen, whether ribavirin was included, and the duration of treatment as those factors would shape the retreatment regimen. However, the RASs are not always absolute as the same class of drug that has resistance can be used with modification (adding ribavirin or increasing duration) [13]. Therefore, RAS testing alone does not dictate the optimal DAA regimen and should only be done in a certain patient characteristic and certain DAA regimen [13]. In fact, given the high barrier resistance of the latest DAA therapy, especially the aforementioned new pan-genotypic agents, the presence of RASs has no impact on sustained virological response.

8.3 Retreatment of DAA Failure

There has been a great influx of new direct-acting antiviral combination therapies targeting patient groups that failed prior DAAs. Below is the summary of AASLD guideline on retreatment of patients with or without cirrhosis that failed to achieve sustained virological response to prior non-interferon direct-acting antiviral therapy listed according to genotype. The management of decompensated cirrhotic patients will not be discussed here.

8.3.1 Genotype 1

Even in patients that have no prior exposure to NS5A inhibitors, an estimation of 10–15% of genotype 1 patients have detectable NS5A RASs [13] which have variable clinical impacts depending on DAA regimen and patient characteristics [13]. Therefore, testing for RASs prior to treatment decision is only recommended in a selected population [20].

For genotype 1a, non-cirrhotic patients that failed non-NS5A inhibitor, sofosbuvir-containing regimen-experienced, a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) for 12 weeks was recommended. The overall SVR rate from POLARIS-4 clinical trial was 97% [13]. And for genotype 1b who met similar criteria of prior sofosbuvir-containing regimen failure, sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was recommended [13]. The regimen of daily fixed dose of glecaprevir (300 mg)/pibrentasvir (120 mg) for 12 weeks was for any genotype 1 non-cirrhotic patients that failed non-NS5A inhibitor, sofosbuvir-containing regimen experienced though clinical data was limited [13]. In non-cirrhotic or cirrhotic patients that failed sofosbuvir-containing regimen (excluding simeprevir), a retreatment regimen with a daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks was recommended due to high SVR 12 in one clinical trial [13].

A summary of recommended regimens for non-cirrhotic genotype 1 patients that failed non-NS5A inhibitor, sofosbuvir-containing regimen is listed in Table 8.2.

Retreatment recommended regimens for compensated cirrhotic genotype 1 patients that were non-NS5A inhibitor, sofosbuvir-containing regimen failure are similar to the aforementioned non-cirrhotic patients except that ledipasvir (90 mg)/sofosbuvir (400 mg) + weight-based ribavirin were not recommended.

In non-cirrhotic or compensated cirrhotic, genotype 1 patients who were NS5A inhibitor DAA experienced, there were no approved DAA regimens for this failure group until July 2017 when a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) given for 12 weeks was recommended. The overall SVR12 rate in POLARIS-1 trial was 97%. In addition, the presence of cirrhosis and baseline RASs was not affecting the virological response rate [13]. Followed the sofosbuvir/velpatasvir/voxilaprevir's approval, in August 2017, another daily fixed-dose combination including glecaprevir (300 mg)/pibrentasvir (120 mg) for 16 weeks was approved for genotype 1-infected patients who were experienced with an NS5A inhibitor but not concomitantly treated with an NS3/4A protease inhibitor. The reported SVR12 rate was 94% in MAGELLAN-1 trial [13].

Table 8.2 Current direct-acting antiviral drug classes for hepatitis C treatment [13, 21]

Genotype 1	Regimen	Duration
1a	Sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks
1a/1b	Glecaprevir (300 mg)/pibrentasvir (120 mg)	12 weeks
1b	Sofosbuvir (400 mg)/velpatasvir (100 mg) OR	12 weeks
1a/1b	Ledipasvir (90 mg)/sofosbuvir (400 mg) + weight-based ribavirin unless simeprevir failures	12 weeks

8.3.2 Genotype 2

In genotype 2 patients with or without compensated cirrhosis who experienced sofosbuvir and ribavirin, two daily fixed-dose combination regimens were recommended. One regimen was sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks. The SVR12 rate in POLARIS-4 clinical trial was 97% though one patient in the trial experienced virologic breakthrough and found to have the presence of NS5B RAS [13]. The other daily fixed-dose regimen recommended was glecaprevir (300 mg)/pibrentasvir (120 mg) for 12 weeks. The SVR12 rate was 99–100% in ENDURANCE-2 and EXPEDITION-1 clinical trials [13].

8.3.3 Genotype 3

Genotype 3-infected patients who were treatment experienced had been the most challenging group for retreatment until the arrival of daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) in July 2017. This regimen was approved for 12 weeks in genotype 3, with or without cirrhotic patients who failed DAA regimen but not an NS5A inhibitor. The SVR12 in POLARIS-4 study was 96%. For genotype 3 cirrhotic patients who failed prior DAA regimen containing an NS5A inhibitor, weight-based ribavirin was added to the sofosbuvir/velpatasvir/voxilaprevir combination for 12 weeks due to high rate of relapse noted in cirrhotic patients [22].

8.3.4 Genotype 4

The same combination of sofosbuvir/velpatasvir/voxilaprevir for 12 weeks was also recommended for genotype 4, DAA-experienced (including NS5A inhibitors) patients with or without cirrhosis. The SVR12 rate was 100% in patients that had a history of treatment failure with DAA regimen not containing an NS5A inhibitor compared to 91% in patients that failed prior DAA containing NS5A inhibitor regimen [22].

8.3.5 Genotypes 5 and 6

Regarding genotype 5 or 6 patients with or without cirrhosis who failed prior DAA regimen including NS5A inhibitors, clinical data are limited though the daily fixed-dose combination of sofosbuvir/velpatasvir/voxilaprevir for 12 weeks was also recommended in this group [22].

8.4 Future DAAs

The next DAA combination therapy coming down the pipeline is the fixed-dose combination of grazoprevir/ruzasvir and uprifosbuvir [23]. This regimen was given either 16 weeks with ribavirin or 24 weeks without ribavirin that has shown a high efficacy in genotype 1 patients with cirrhosis who failed prior ledipasvir/sofosbuvir or elbasvir/grazoprevir with baseline NS5A RASs [5].

8.5 Conclusion

The ultimate goal of hepatitis C elimination is to prevent the progression of liver disease, cirrhosis, and hepatocellular carcinoma. The current direct-acting antiviral therapies offer excellent efficacy and with the future arrivals of combination therapies that target antiviral resistance at multiple sites it would not be too long before hepatitis C is completely eradicated.

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Management of HCV Infection in Decompensated Cirrhosis in the Transplantation Setting

9

Michael D. Voigt

9.1 Introduction

Decompensation of cirrhosis is defined to occur when ascites, hepatic encephalopathy, jaundice (bilirubin >3 g/dl), severe coagulopathy, or bleeding from esophageal varices occur [1, 2]; this generally correlates with Child-Turcotte-Pugh Child's B/CTP score ≥7. However, many patients with Child's B cirrhosis have low MELD scores. Patients are usually not listed for transplant (at least in the USA) until their MELD scores are ≥15–20. This chapter focuses on these sicker patients who are in the transplant setting.

Decompensated cirrhosis and hepatocellular cancer caused by hepatitis C are the leading indications for liver transplantation in every country in the world [3, 4], except the United Kingdom, Germany, and Ireland [5]. Decompensation is associated with markedly increased healthcare utilization and costs, compared to compensated cirrhosis. Annual hospitalizations increased to 74% from 27% ($P < 0.001$), and costs per patient per month increased 2.39 times to $4956 from $1735, respectively ($P < 0.001$) after decompensation occurred [6]. Patients with decompensated HCV cirrhosis have high mortality rates [1].

All patients with HCV who decompensate should be managed by a skilled provider with experience in treating decompensated HCV cirrhosis, preferably at a liver transplant center [7, 8]. Liver transplantation is usually the only lifesaving option for these patients. Patients with decompensated HCV cirrhosis that are not transplant candidates or do not have access to a liver transplant program should all be considered for DAA treatment, as this is their only hope for survival. Treatment of decompensated HCV cirrhosis can improve survival and reverse decompensation and reduce the risk of hepatocellular cancer [9–12].

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Further evidence of DAA treatment reducing mortality is that DAA therapy has reduced the number of people requiring a transplant [13]. Adjusted incidences of new patients listed for decompensated cirrhosis due to HCV decreased by 32% in the DAA era ($P < 0.001$) compared to the IFN era [13]. As fewer HCV patients need to be listed, more non-HCV patients can be transplanted, thereby reducing the death rate in non-HCV patients too.

Despite potential benefits of DAA therapy, it is not prudent to treat every patient with decompensated HCV cirrhosis. Treatment is less effective in decompensated cirrhosis than in patients without cirrhosis or with compensated cirrhosis [12, 14–18] and virological failures are associated with selection of resistance-associated variants [19] which can make treatment less effective after transplant. Even if successful, treatment may not result in sufficient improvement to obviate transplant altogether, but may leave the decompensated cirrhotic patient with reduced priority on the list because of lower MELD score (so-called MELD limbo or MELD "purgatory") [11, 12, 20]. Viral clearance prior to transplant also precludes patient receiving an HCV-positive organ. Being eligible for an HCV-positive organ substantially reduces the candidate's time waiting for an organ, because currently only HCV-positive candidates compete for HCV-positive organs. Currently in the USA, many HCV-positive organs are available [21] because of the opioid epidemic, and patients eligible to receive such organs have substantially shorter waiting times on the list. Some patients deteriorate and die after DAA therapy is started; therefore treatment posttransplant may be safer. Patients with high MELD scores have high rates of transplantation or death within 6 months and may not have long enough time to complete therapy. Treatment of decompensated high MELD patients is relatively less effective, but posttransplant is highly effective. For all of these reasons, DAA treatment of patients with decompensated cirrhosis should be offered only to select candidates with mildly decompensated cirrhosis (these patients are usually not on the transplant waiting list in the USA). However, some patients may die waiting for a transplant, if left untreated, and from a societal standpoint it is advantageous to treat all patients on the list, in the hope that some will improve and not need a transplant. Example, Ahmed et al. showed that, compared to initiation of all-oral DAA treatment after liver transplant, HCV treatment of waitlisted patients with decompensated cirrhosis before transplant was cost effective with an estimated incremental cost-effectiveness ratio (ICER) of $28,692 to $36,583, depending on the initial MELD score [22]. These complex issues are discussed in detail below.

The principles of treating HCV in decompensated cirrhosis include the following:

1. All regimens (except in patients with glomerular filtration rates (GFR) <30 ml/min) use sofosbuvir (SOF), an NS5B polymerase inhibitor, as the backbone of therapy.
2. Sofosbuvir is combined with any of the NS5A inhibitors (ledipasvir (LDV), velpatasvir, or daclatasvir (DAC)). If ribavirin is used, 12-week treatment is usually sufficient, but if not 24-week therapy is needed.

3. NS3/4A protease inhibitors (simeprevir, paritaprevir, grazoprevir, glecaprevir, voxilaprevir) cannot be used in decompensated Child's C cirrhosis as these accumulate with potential excess drug exposure and they may cause liver toxicity.
4. Ribavirin should be used, if there are no contraindications. Ribavirin reduces the risk of virological failure/relapse in decompensated cirrhosis. Because ribavirin can cause hemolysis it is usually started at low dose (600 mg) and increased to weight-based maximum doses (1000 mg/day if <75 kg and 1200 mg/day if >75 kg). If ribavirin is contraindicated, treatment should be extended to 24 weeks [7, 23].

Many patients with advanced cirrhosis develop acute kidney injury or chronic kidney injury, often secondary to type I or II hepatorenal syndrome. Sofosbuvir use is not sanctioned by the manufacturer for treating patients with glomerular filtration rates of <30 ml/min, and should be avoided in those that are transplant candidates. However, in patients who are not transplant candidates, sofosbuvir-based treatment can be considered, after informed discussion with the patient. Many studies report safe use of sofosbuvir in renal failure patients [24–28].

9.2 Effects of Treatment on Decompensated Cirrhosis

In deciding on treatment using DAAs in decompensated cirrhotic patients, providers need to know:

1. Is treatment effective (and which treatment for which genotype)?
2. Can treatment cause harm (death or decompensation, and if so in which patients?)
3. Does treatment reverse decompensation and restore health, and if so in which patients?

9.2.1 Recommended Treatment of HCV in Decompensated Cirrhosis?

Table 9.1 summarizes various antiviral regimens currently recommended by guidelines [7, 23] for use in individuals with decompensated cirrhosis. Antiviral therapy with sofosbuvir (NS5B nucleotide polymerase inhibitor) in combination with any of the NS5A inhibitors, ledipasvir, daclatasvir, or velpatasvir, along with concomitant ribavirin for 12 weeks results in SVR in 82–96% of individuals with HCV genotype 1 infection and decompensated cirrhosis [14, 16, 29].

9.2.2 Ledipasvir/Sofosbuvir

In the SOLAR-1 study, patients were assigned to 12- or 24-week daily fixed-dose combination of LDV 90 mg/sofosbuvir 400 mg plus ribavirin initial dose of 600 mg

Table 9.1 Recommended regimens for treatment of decompensated HCV cirrhosis

HCV GT	Regimen First line	Duration (weeks)	AASLD/ IDSA Rating	Recommendation
1, 4, 5, 6	Ledipasvir (90 mg)/sofosbuvir (400 mg) + ribavirin 600 mg/day and increase as tolerated	12	1, A	Preferred
1–6	Sofosbuvir (400 mg)/velpatasvir (100 mg) + weight-based[a] ribavirin daily[11]	12	1, A	Preferred
1, 4 (1–6)	Sofosbuvir (400 mg) + daclatasvir (60 mg) + ribavirin 600 mg daily increase as tolerated	12	1, B	AASLD recommends this only for genotypes 1 and 4
1, 4, 5, 6	Ledipasvir (90 mg) + sofosbuvir (400 mg) daily	24	1, A	If ribavirin intolerant
1–6	Sofosbuvir (400 mg)/velpatasvir (100 mg) daily	24	1, A	If ribavirin intolerant.
1–6	Sofosbuvir (400 mg) + daclatasvir (60 mg) daily	24	II, C	If ribavirin intolerant. AASLD recommends this only for genotypes 1 and 4
1, 4, 5, 6	Ledipasvir (90 mg) + sofosbuvir (400 mg) Ribavirin (600 mg)/ day; increase as tolerated	24	II, c	Prior sofosbuvir failure (not for prior NS5A failure)
1–6	Daily sofosbuvir (400 mg)/ velpatasvir (100 mg) with weight-based ribavirin	24	II, C	Prior sofosbuvir or NS5A failure
2	Daily sofosbuvir (400 mg) and ribavirin	16–20	EASL guideline	Second line. Not recommended by AASLD/ IDSA

AASLD American Association for the Study of Liver Disease, *IDSA* Infectious Disease Society of America

[a]Weight-based ribavirin: 1000 mg < 75 kg, 1200 mg > 75 kg

and increased as tolerated [14] SVR12 was achieved by 96–98% of patients without cirrhosis or with compensated cirrhosis, by 85%–88% of patients with moderate hepatic impairment, and by 60–75% of patients with severe hepatic impairment [14].

In the SOLAR-2 study response rates to 12 or 24-week ledipasvir/sofosbuvir were 90% and 98% in CTP class B patients and 75% and 77% in the CTP class C patients [17]. In a study of 154, GT-1 treatment-experienced patients with compensated cirrhosis, SVR12 rates were 96% for treatment with ledipasvir + sofosbuvir + ribavirin for 12 weeks versus 97% after treatment with ledipasvir and sofosbuvir without ribavirin, for 24 weeks [30]. These data are extrapolated to support the use of ledipasvir/sofosbuvir plus ribavirin for 12 weeks in patients with decompensated cirrhosis [30].

Real-world data from the multicenter, prospective, observational HCV-TARGET study demonstrated SVR12 rates of 90% (263/293) among genotype 1 patients with decompensated cirrhosis, treated with ledipasvir/sofosbuvir treated for 12 or 24 weeks with or without ribavirin [31].

In a subsequent per protocol analysis of the safety and effectiveness of 12- or 24-week treatment with ledipasvir and sofosbuvir, with or without ribavirin in 610 patients, neither treatment duration nor the addition of ribavirin was associated with

SVR12, but response was greater in compensated cirrhosis (odds ratio [OR] compared to decompensated cirrhosis, 2.41; 95% CI, 1.16–5.02), and albumin ≥3.5 g/dL (OR, 3.15; 95% CI 1.46–6.80), or total bilirubin ≤1.2 mg/dL (OR 3.34; 95% CI, 1.59–7.00) [32]. The authors state that ribavirin or extension of ledipasvir and sofosbuvir treatment to 24 weeks is beneficial in decompensated cirrhosis [32].

In summary, efficacy of treatment with ledipasvir with sofosbuvir (with ribavirin unless contraindicated) in patients with decompensated cirrhosis is affected by the severity of the disease. Treatment is relatively less effective in advanced cirrhosis and response rates may be as low as 60% in high-MELD patients [14]. Current data suggest that a high MELD score, serum albumin <3.5, or bilirubin >1.2 is a better predictor of poor response than CTP score alone [32]. In all decompensated cirrhotic patients, ribavirin should be used if possible. In patients with high MELD scores (MELD >20), if the decision is to treat, there may be benefit to treating for 24 weeks with ledipasvir and sofosbuvir with ribavirin [23].

9.2.3 Velpatasvir/Sofosbuvir

In ASTRAL-4 study, 267 decompensated cirrhosis patients were randomized to receive sofosbuvir and velpatasvir for 12 or 24 weeks, with or without ribavirin in the 12-week arm, in a phase 3, open-label, multicenter study [16]. Response rate to 12-week sofosbuvir/velpatasvir was 83%, to 12-week sofosbuvir/velpatasvir plus ribavirin was 94%, and to 24-week sofosbuvir/velpatasvir was 86%. In this study, 55% were treatment experienced, but the presence of baseline resistance substitutions was not associated with virological relapse [16]. However, only 4–5% of the patients had a CTP score of 10 or a MELD ≥15 so this study does not inform us of treatment efficacy in the type of high-MELD patient on the transplant waiting list.

Pooled data on 141 cirrhotic and 283 non-cirrhotic patients from three studies of sofosbuvir/velpatasvir with or without ribavirin [16, 33, 34] showed that the efficacy for cirrhotic and non-cirrhotic patients was similar for genotypes 1, 2, and 4, but responses for genotype 3 were significantly worse in cirrhotic compared to non-cirrhotic patients (SVR in cirrhotic patients vs. non-cirrhotic patients with genotype 3: 90.7% (95% CI [85.2–96.2%]) versus 97% (95% CI [94.9–99.1%] $P < 0.001$) [35]. In patients with Child-B cirrhosis and HCV genotype −3, SVR rates were only 50% (7/14) for 12-week SOF/VEL and 50% (6/12) for 24-week SOF/VEL, but 85% (11/13) for 12-week SOF/VEL + RBV [16]. No data are available for 24-week SOF/VEL + RBV. Thus patients with decompensated cirrhosis and GT3 should receive ribavirin, and should be considered for 24-week treatment.

In summary: Sofosbuvir and velpatasvir are effective in patients with MELD ≤15 for all genotypes but less so for genotype 3. AASLD/IDSA and the international consensus group recommend sofosbuvir and velpatasvir with ribavirin for 12 weeks or sofosbuvir and velpatasvir without ribavirin for 24 weeks in decompensated cirrhosis patients and sofosbuvir/velpatasvir and ribavirin for 24 weeks in decompensated cirrhosis with genotype 3 infections [7, 23]. An important caveat is that only a handful of patients have been studied who had MELD scores >15. Thus we have few data about the treatment of advanced decompensated cirrhosis; hence we have few data on the treatment of the typical patient on the waitlist.

9.2.4 Daclatasvir Plus Sofosbuvir

In the ALLY-1 trial, 12-week daclatasvir 60 mg a day, sofosbuvir 400 mg a day, and ribavirin 600 mg a day with escalating doses given for 12 weeks yielded SVR rates of 92% in CTP-A, 94% in CTP-B, and 56% in CTP-C patients. Among patients with cirrhosis SVR rates were 82% (37/45) for genotype 1; 80% (4/5) for genotype 2; 83% (5/6) for genotype 3; and 100% (4/4) for genotype 4 [29]. In the observational study by Foster et al. SVR rate in genotype 1-infected patients with decompensated cirrhosis treated with daclatasvir/sofosbuvir plus ribavirin was 88% (30/34) but only 50% (2/4) if ribavirin was not given [12]. SVR12 rates are 65% for genotype 3 if ribavirin was given and 40% if ribavirin was not given [12].

Large multicenter observational studies showed better response rates for sofosbuvir, daclatasvir, and ribavirin given for 24 weeks: In cirrhotic patients infected with hepatitis C genotype 3, treated with SOF + DCV ± RBV (80% were treated for 24 weeks) SVR was 94% (123/131). In decompensated patients, SVR12 was 90.5%. Multivariate analysis showed that addition of RBV did not improve SVR (RR: 1.08; $P = 0.919$) but platelet count <75 × 10E9/mL (RR: 3.50, $P = 0.019$) was predictive of nonresponse [36].

In another study of 242 patients with advanced liver disease including 132 (59%) with decompensated cirrhosis SOF + DCV ± RBV for 24 weeks showed 85% SVR rates.

Patients with GT1 had 92% (171/186) and GT3 85% (33/39) response rates and overall decompensated cirrhosis patients had an 85% (126/148) compared to 99% in compensated cirrhosis [37].

SOF/DCV/RBV for 24 weeks has demonstrated high SVR rates in decompensated cirrhosis, including GT3, but shorter duration of treatment and not using ribavirin appears to reduce response rates.

Protease inhibitor-containing regimens have not been studied adequately, and are associated with toxicity in decompensated cirrhotic patients. As a result elbasvir/grazoprevir, paritaprevir/ritonavir/ombitasvir ± dasabuvir, glecaprevir/pibrentasvir, and sofosbuvir/velpatasvir/voxilaprevir combinations are not FDA approved for use in decompensated cirrhosis (CTP B or C).

9.2.5 Does DAA Therapy IMPROVE Hepatic Function in Decompensated Cirrhosis?

Successful treatment of hepatitis C in decompensated cirrhotic patients may result in improved liver function and some patients may avoid liver transplantation altogether, to their advantages as well as to the advantage of the recipient pool. If viral clearance is attained prior to transplant, it is generally maintained after transplant [38]. However, many patients with decompensated cirrhosis may be considered "too far gone" such that treatment does not restore them to health.

Data from the pre-DAA era, where patients with SVR could be compared to those without SVR, provide compelling evidence that an SVR results in substantially reduced mortality, morbidity, and risk of hepatocellular cancer. In a meta-analysis of 31 studies including 33,360 patients, followed for a median of 5.4 years (interquartile range, 4.9–7.5) across all studies, the adjusted hazard ratio of death in patients achieving SVR versus no SVR was 0.26 (95% CI, 0.18–0.74) in cirrhotic patients [39].

MELD score and liver disease generally improve in patients achieving SVR after treatment. In the Astral-4 study, ten Child C patients achieved SVR and five reverted to Child B and one to Child A (40% remained in Child C). Of the 205 Child B patients 34 (17%) reverted to Child A, 167 (81%) remained Child B, whereas 4 (2%) worsened to Child C. In this study, of patients with baseline MELD scores >15 (26 in total), 84% improved but 8% worsened at 12 weeks [29]. Similar short-term improvement was seen in patients who had an SVR after DAA therapy, in multiple other studies of patients with decompensated cirrhosis [11, 14, 16, 17, 29].

The effects of HCV treatment on transplant listing were examined in a European study of 103 patients awaiting liver transplantation, who were treated with DAAs. Belli et al. showed that the cumulative incidence of inactivation (due to improvement of liver function) was 15.5% at 24 weeks and 33.3% at 60 weeks. The cumulative incidence of delisting was 0% at 24 weeks after the start of therapy and 19.2% at 60 weeks. The 25 patients who were inactivated showed immediate improvement of 4 points in their MELD scores ($P < 0.0001$) and a median improvement of 3 points in their CTP score ($P < 0.0001$). A low baseline MELD [16–20] (HR 0.819 p = 0.0004, delta MELD HR 1.311, $P < 0.0001$) and delta albumin (HR 0.419 $P = 0.0041$) at 12 weeks after DAA therapy were predictive of delisting. If the MELD was <16, about 35% were delisted versus <5% if the MELD was >20. Other pretreatment variables that identified responders included low MELD (<20), younger age (<65), and normal sodium [12].

Around 80% remained listed, but because the MELD score had dropped in many patients they were less likely to receive a transplant. The majority had improved symptoms, reduced signs of decompensation, and lower risk of death on the waitlist, but they also had lower priority for transplantation and were less likely to be transplanted due to lower MELD scores [11].

Patients were inactivated at a median of 22.6 weeks (16.4–35.2) from the start of therapy but were only delisted at a median of 44.3 weeks (range: 36.3–53.3) after treatment [11]. These data show that only a small proportion of patients (in this case 20%) achieve delisting after a year and that the predictors of delisting were predominantly related to the extent of improvement in MELD, improvement in albumin, and extent of reduction in bilirubin [11].

In a follow-up study on this cohort, Belli et al. showed that 38 out of 142 patients (26.7%) could be removed from the waiting list because of clinical improvement. After removal, one patient died as a result of hepatocellular cancer and two other patients had to be relisted. Median MELD score at the start of DAA therapy was 14 (IQR: 12–17) and improved to 9 (IQR: 8–11) after 78 weeks. Median CTP score at the start of DAA therapy was 9 (IQR: 8–10) and improved to 6 (IQR: 5–6) after 78 weeks. These data emphasize that the benefit of treatment pretransplant is in patients with MELD scores <20. In the USA, few patients are listed with MELD <20; the patients that were removed from the list after treatment in this study would not have been listed in the USA to start with [40].

The benefit of treating decompensated cirrhosis with low MELD score was also shown in a cohort study of 183 patients with decompensated cirrhosis awaiting transplantation, where DAA therapy was associated with regression to CPT A (fully compensated disease), in 36%. In this cohort, recovery was more likely in patients with low initial MELD scores [41].

In the USA, most listed patients with HCV cirrhosis have MELD scores >20 (unless they are listed with exception points). Patients with high MELD scores do not respond to treatment sufficiently to be delisted [11], and have higher rates of treatment failure [12]. They may not have time to complete treatment prior to transplant.

9.2.6 Is Treatment with DAAs Safe in Decompensated Cirrhosis?

Based on the above studies, it is clear that patients with decompensated cirrhosis, but low MELD scores, can do well and avoid transplantation after successful DAA therapy. However, there is uncertainty whether DAA treatment is safe in more advanced decompensated cirrhosis and whether such treatment will allow patients a meaningful recovery to Child A disease. Antiviral therapy may be futile in these more advanced patients. Ideally, pretreatment variables should be predictive of a clinically meaningful recovery with DAA therapy, to avoid reducing the patient's priority on the waitlist if they do not have an adequate response. While patients may continue to improve the longer they wait after completion of therapy, very sick high-MELD patients do not have long survival.

Treatment with sofosbuvir and daclatasvir, ledipasvir, or velpatasvir has all been associated with worsening liver failure and worsening decompensation [14, 42–45]. Welker et al. reported lactic acidosis in 5 out of 35 patients (34%) with HCV cirrhosis, treated with sofosbuvir plus ribavirin [46]. Decompensation after initiating treatment is not uncommon in patients with advanced liver disease, but this may occur early or late in treatment and even shortly after stopping treatment. The decompensations are characterized by clinical signs of worsening liver failure, new onset or worsening ascites, hepatic encephalopathy or variceal bleeding, increased MELD, and rising bilirubin, but with minimal changes in serum aminotransferase or alkaline phosphatase levels. It is unclear whether the liver failure is truly due to the DAA therapy, coincidental in patients who are at risk of decompensation or acute-on-chronic liver failure due to severe underlying disease, or due to rapid clearance of the virus, causing hepatotoxicity by an as-yet unknown mechanism [14, 41–44].

Worsening of liver disease associated with treatment with DAAs has been reported in decompensated cirrhosis with relatively low MELD scores. There are extremely limited data on using current DAA treatments in high-MELD patients. In SOLAR-1 [16] and SOLAR-2 [17], patients with CTP scores >12 were excluded and there were only three patients in the Ally-1 study with a MELD score >20 [29]. In the UK study, <20% had a MELD score >15, and only 15 patients had a MELD score >20. It is reasonable to expect that treating high-MELD patients would be associated with worsening of liver disease.

In a real-world setting in the UK of 409 decompensated cirrhotic patients with a median baseline MELD score of 11 (range 6–32), patients with high MELD, albumin less than 3.5 g/dL, sodium <135, and age >65 were more likely to deteriorate and less likely to show clinically meaningful improvement. Thus, there may be a point of no return beyond which treatment will not improve outcomes sufficiently [12].

In a study of posttransplant patients treated with sofosbuvir/daclatasvir ± ribavirin, nine with decompensated cirrhosis and three with fibrosing cholestatic hepatitis, three patients died of complications of liver failure and four had severe adverse effects from liver failure. MELD scores improved in the survivors by 24 weeks but they were left with severe disease [47]. This highlights that there is a point where treatment comes too late.

Treatment may actually be harmful in high-MELD patients. Gray et al. reported a 21% on-treatment mortality in Child C patients and a 6% on-treatment mortality in Child B patients. The on-treatment mortality was higher than after-treatment mortality; the authors suggested that the treatment may be responsible for the increased mortality [48]. However, survivorship bias could also account for this finding.

Decompensating events, mostly new-onset or worsening ascites, and variceal bleeding, occur more frequently in advanced cirrhosis. Decompensation occurred in only 8/319 (2.5%) of CTP-A patients, but in 42/114 (36.8%) of CTP-B/C patients. Baseline albumin <35 g/dL (HR 3.11, CI 1.23–7.84, $P = 0.005$), baseline MELD score >14 (HR 1.63, CI 1.03–2.61, $P = 0.037$), and HCV genotype 3 (HR 2.05, CI 1.09–3.88, $P = 0.033$) were independently associated with hepatic decompensation during treatment [49].

In the study, 26 patients (25.7%) of CTP B/C had a modest improvement in MELD scores whereas 12 (11.9%) had moderately or markedly increased MELD score, in some cases >20 points. Only 16 (14%) of the CTB B/C patients had MELD 16–21 at baseline [49], once again emphasizing the paucity of data on treatment in high-MELD patients.

The weight of evidence suggests that treating Child B disease patients with lower MELD scores (<20) may give lasting clinical benefit, reduce decompensation, and reduce the need for liver transplantation in at least 30% of all cases. In patients with high MELD scores (≥ 20), low albumin, age >65, sodium <135, and genotype 3, treatment may be harmful, including decompensation and death, and worsened MELD. Response rates are poor (although data are very limited) and even if MELD improves patients may be left in MELD limbo, too sick to be delisted, but not sick enough to compete for a transplant, and not able to receive an HCV-positive organ.

Regardless, patients with decompensated cirrhosis on treatment with DAAs should be very closely monitored and the treatment should be stopped immediately if there is any deterioration clinically or biochemically.

9.2.7 DAA Treatment in Decompensated Cirrhosis with HCC

Patients with hepatocellular cancer have a much lower likelihood of achieving a sustained viral response to DAA therapy. Beste et al. found that the overall SVR was 91.1% in non-HCC, but 74.4% in patients with HCC. Response rates were much better −94.0% in patients where the HCC was treated, with a liver transplant. Among HCC patients, SVR was only 79.1% and 47.0% in genotype 3. After adjustment for confounders, the presence of HCC was associated with lower likelihood of

SVR overall (AOR 0.38 [95% CI 0.29, 0.48], $P < 0.001$). In addition, patients with treated HCC (liver transplant) had higher rates of response to HCV treatment than those where HCC was still present [50]. Further evidence that the presence of HCC inhibits response to HCV treatment with DAAs is shown by Prenner et al. who showed that DAA treatment failed in 21% of patients with HCC compared to 12% of patients without HCC ($P = 0.009$). Of the 29 patients with HCC who failed treatment 27 (93%) occurred when an active tumor was present. DAA therapy in the presence of an inactive tumor or after removal of tumor (resection/transplant) resulted in excellent SVR rates, similar to those without HCC ($P < 0.0001$) [51].

Markov modeling [52] of patients with HCC showed clearly that HCC-HCV patients awaiting transplantation should not be treated for HCV prior to transplant, as they have both survival benefit from receiving HCV-positive donor organs (with resultant reduced wait times) and cost benefit from deferring treatment until after transplant [52]. This is based on

1. That all patients would need a transplant irrespective of whether or not hepatitis C is eliminated prior to transplant.
2. HCV-positive organs would not be offered to HCV-negative candidates.

This model did not even take into account the poorer response in HCC patients, but clearly the lower response rate further strengthens the argument to wait till after transplant to treat HCV if HCC is present.

9.2.8 Cost-Effectiveness Analyses: Insights on When to Treat

A Markov micro-simulation model was done to evaluate the effect on life expectancy of DAA HCV treatment before as compared to DAA treatment after LT [53], for genotype 1 and 4 patients with MELD scores between 10 and 40, excluding HCC patients, using data from the UNOS transplant waiting list. This study showed that life expectancy was increased with pre-liver transplant HCV treatment up to MELD score of 28, but that pre-LT DAA therapy worsened life expectancy if DAA therapy was given pre-LT to patients with MELD >28. The threshold MELD was lower in regions of short waitlist times (threshold MELD 23 in region 3) and highest in regions with long waitlist times (threshold MELD 27 in region 9). This model did not account for shorter awaiting times in HCV-positive patients receiving HCV-positive organs or in the decline of HCV patients needing a transplant, due to successful HCV therapy [53]. Also, treatment response rates in high-MELD patients were extrapolated from responses of low-MELD patients, probably overestimating responsiveness in high MELD. Nevertheless, the study showed that above a threshold MELD, treatment before transplant is unhelpful or harmful.

Other models have shown that for lower but not high MELD scores, quality-adjusted life years were higher with pre-LT HCV treatment compared with post-LT treatment. Pre-LT HCV treatment was cost saving in patients with MELD scores of 15 or less, and cost effective in patients with MELD scores of 16–21. In contrast,

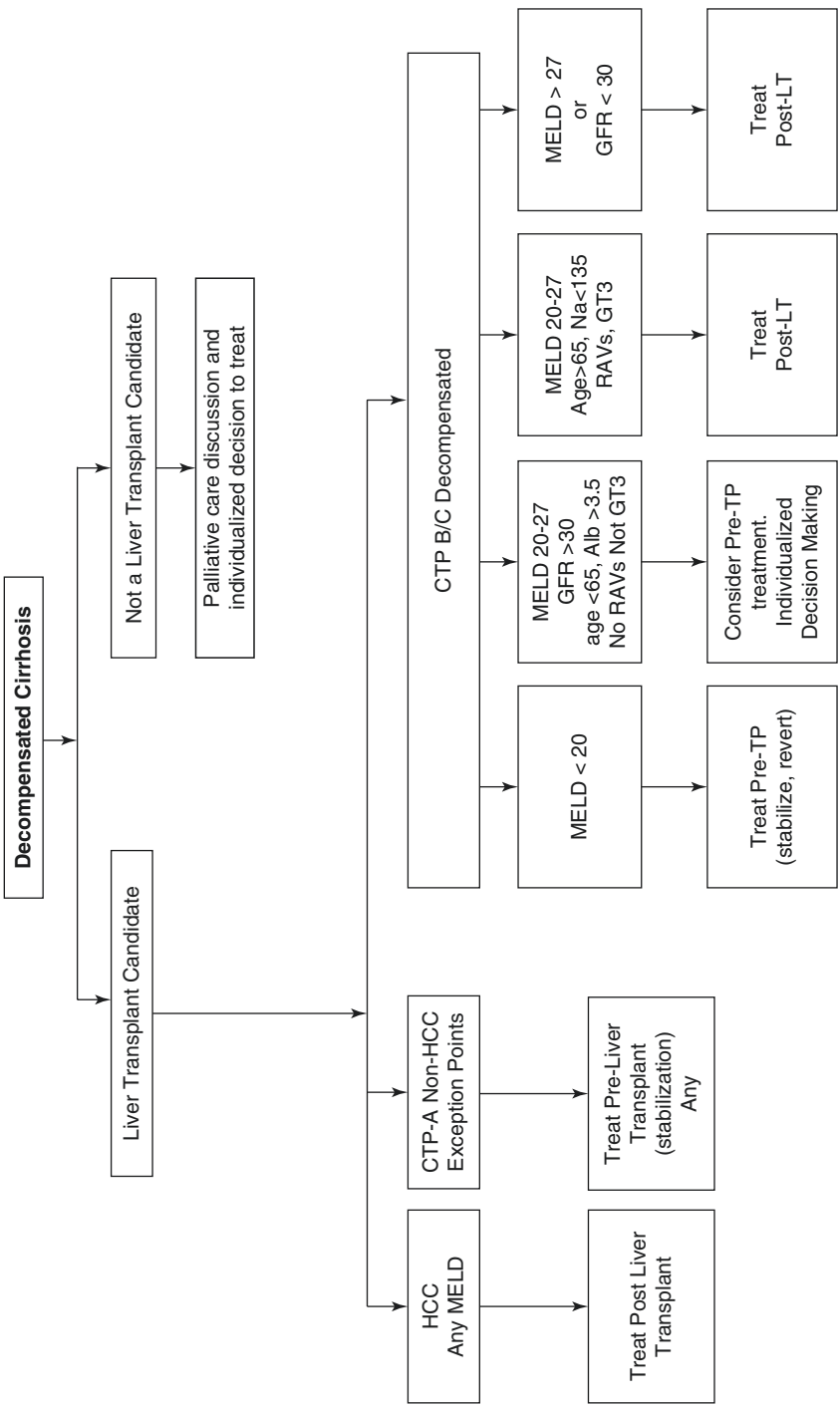
post-LT HCV treatment was cost effective in patients with MELD scores of 22–29 and cost saving if MELD scores were 30 or higher. Results varied by drug prices and by United Network for Organ Sharing regions [54].

Modeling also shows that using HCV-positive donor organs radically changes the best time to do HCV treatment. In the above study, sensitivity analysis shows that using HCV-positive organ to reduce wait time on the list lowered the MELD score at which it became detrimental to treat HCV pretransplant [53].

There have been several cost-effectiveness studies in cirrhotic patients in the DAA era. The majority of these looked at incremental cost-effectiveness ratio and different willingness-to-pay thresholds per quality-adjusted life years gained. All studies have shown that it is cost effective to treat patients before transplant, at a variety of incremental cost-effectiveness ratios and willingness-to-pay thresholds. However, drug charges and willingness-to-pay thresholds differ vastly among countries and change over time, so these analyses are not generalizable [22, 52, 55–58]. In addition, clinical decision-making should be based on the needs of the individual patient, not the needs of society or the needs of the payor. From a societal point of view, fewer transplants for HCV patients means better outcomes for non-HCC patients and suggests that it is cost effective to treat everyone [22].

9.3 Summary

1. All regimens should include the NS 5B inhibitor sofosbuvir plus a NS5A inhibitor ledipasvir, velpatasvir, or daclatasvir. Duration of treatment is generally at least 12 weeks when ribavirin is included or 24 weeks if ribavirin is not included, except for genotype 3 where combination treatment with ribavirin should be extended to 24 weeks.
2. Protease inhibitors as a drug class are contraindicated in people with decompensated cirrhosis, because of increased drug exposure and hepatotoxicity.
3. Treatment is less effective with more advanced disease and poor response can be predicted by high MELD, older age >65, low albumin <35 g/dl, low platelets <75 k/dl, prior treatment failure, genotype 3, and presence of HCC.
4. Patients with a creatinine clearance less than 30 ml/min should not use sofosbuvir because of concerns for accumulation of GS-331007 metabolites. Treatment is better deferred until after transplant in these patients.
5. Patients with high MELD scores (>20–22) should not be treated prior to transplant, as treatment is not cost effective, is frequently not successful, is associated with increased risk of selecting resistant variants, and increases decompensation and death. Even when successful, treatment may leave the patient with poor quality of life but not in a position to get a transplant (MELD limbo). The threshold MELD where treatment may be cost effective is lower if HCV-positive organs are available to the candidate, or they have access to living donor transplant.
6. Patients with HCC should generally not be treated before transplant as they have access to HCV organs, treatment is less effective, and they need a transplant whether or not HCV is cleared.


Decompensated Cirrhosis
Liver Transplant Candidate
Not a Liver Transplant Candidate
Palliative care discussion and individualized decision to treat
HCC Any MELD
CTP-A Non-HCC Exception Points
CTP B/C Decompensated
Treat Post Liver Transplant
Treat Pre-Liver Transplant (stabilization) Any
MELD < 20
MELD 20-27 GFR >30 age <65, Alb >3.5 No RAVs Not GT3
MELD 20-27 Age>65, Na<135 RAVs, GT3
MELD > 27 or GFR < 30
Treat Pre-TP (stabilize, revert)
Consider Pre-TP treatment. Individualized Decision Making
Treat Post-LT
Treat Post-LT

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Extrahepatic Manifestations of Hepatitis C Virus Infection

10

Çetin Karaca

Abbreviations

Anti-CCP	Anti–cyclic citrullinated peptide
DM	Diabetes mellitus
EHM	Extrahepatic manifestation
EMC	Essential mixed cryoglobulinemia
HCV	Hepatitis C virus
HFE	Homeostatic iron regulator
HLA	Human leukocyte antigen
HRQoL	Health-related quality of life
IR	Insulin resistance
KDIGO	Kidney Disease Improving Global Outcomes
LP	Lichen planus
NHL	Non-Hodgkin lymphoma
PCT	Porphyria cutanea tarda
RF	Rheumatoid factor
SVR	Sustained virological response
UROD	Uroporphyrinogen decarboxylase

10.1 Introduction

The hepatitis C virus (HCV) infection is a global health problem. It is estimated that 150–170 million people are chronically infected. It is a hepatotropic virus that causes liver cirrhosis and hepatocellular cancer. Beside its hepatic manifestations, it is considered a systemic disease because of the additional HCV-associated extrahepatic manifestations (EHMs). It is estimated that about 350,000 patients die from

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HCV-related complications. However, the risks of mortality and morbidity are underestimated because studies do not take into account extrahepatic outcomes of chronically infected HCV patients. Extrahepatic complications of HCV infection have been shown to be more prevalent in large cohort studies, where two thirds of patients chronically infected with HCV infection have experienced EHMs [1, 2]. Some of these EHMs are well documented and more common, while others are rare or their association with HCV is unproven. HCV-associated autoimmune or lymphoproliferative disorders, from benign mixed cryoglobulinemia to frank lymphomas, have been reported. More recently, many other extrahepatic HCV-related disorders have been reported, including cardiovascular, renal, metabolic, and central nervous system diseases. Viral eradication of HCV has significantly reduced the rates of hepatic and extrahepatic deaths [1, 3–8]. In this chapter, it is aimed to give a brief objective approach to the epidemiology, pathogenesis, and treatment of HCV-associated EHMs.

10.2 Lymphoproliferative Disorders

10.2.1 Essential Mixed Cryoglobulinemia

Essential mixed cryoglobulinemia (EMC) is also called type II cryoglobulinemia. EMC can lead to the deposition of circulating immune complexes in small-to-medium-sized blood vessels. EMC vasculitis involves mainly the skin, the joints, the peripheral nervous system, and the kidneys [9]. Cryoglobulinemia is described by the presence of circulating immunoglobulins, which precipitate at cold temperatures and dissolve with rewarming. More than 90% of patients with EMC are infected with hepatitis C virus (HCV), and half of all patients with HCV have cryoglobulins. All patients with EMC should be tested for HCV infection [10]. The presentation of EMC is variable, ranging from mild disease (purpura, arthralgia) to fulminant disease (glomerulonephritis, extensive vasculitis). The main symptoms are asthenia, myalgia, purpura, arthralgia, peripheral neuropathy, and glomerulonephritis. EMC typically manifests as recurrent palpable purpura and peripheral neuropathy [9, 11].

Skin manifestations present in EMC include; palpable purpura, chronic cutaneous ulcers, Raynaud's phenomenon, and acrocyanosis, which may evolve into digital ulcerations. Purpura often involves the lower legs and can leave brown spots on the skin after it resolves. Skin biopsy samples generally show cutaneous vasculitis with destruction of blood vessels, with a neutrophilic infiltration in and around the vessel wall. HCV-associated proteins have been observed in vasculitic skin biopsy samples. Vasculitis can lead to ischemic necrosis, skin ulceration, and necrosis of digits. Arthralgia is reported in 40–80% of HCV-infected patients with EMC and is bilateral, symmetrical, and nondeforming. Joint pains involve mainly the knees and hands, and less commonly the elbows and ankles. Rheumatoid factor (RF) is established in 70–80% of patients with EMC. Anti–cyclic citrullinated peptide (anti-CCP) antibodies are usually absent in patients with HCV. Neurological manifestations

vary from sensory axonopathy to mononeuritis multiplex. Vasculitic lesions affecting the vasa nervorum manifest as peripheral neuropathy, which frequently affects lower-extremity peripheral nerves. The most frequent form is a distal sensory or sensory–motor polyneuropathy, presenting with painful, asymmetrical paresthesia. Multiple mononeuropathy may be seen rarely. The most common renal involvement is acute or chronic type I membranoproliferative glomerulonephritis with subendothelial deposits. The most common presentation is proteinuria with microscopic hematuria, a variable degree of renal insufficiency, and hypertension [12–14].

EMC is diagnosed on the basis of the history, clinical manifestations, and laboratory tests. Hypocomplementemia, especially low C4 and cryoglobulin levels, are detected in the laboratory. Elevations in the erythrocyte sedimentation rate and C-reactive protein levels can be present, as can normocytic anemia. A purpuric skin lesion biopsy shows leukocytoclastic vasculitis [15, 16].

Treatment of underlying HCV can suppress the manifestations of vasculitis. Achievement of a sustained virological response (SVR) with pegylated interferon plus ribavirin has been shown to improve HCV-associated EMC manifestations [17], but it has also been reported that sofosbuvir-based direct-acting antiviral regimens are more effective than pegylated interferon plus ribavirin [18, 19]. The main indication for immunosuppressive therapy such as rituximab is progressive systemic disease affecting the kidneys, nervous system, gastrointestinal tract, skin, or digits. A plasma exchange may be required in some patients. The prognosis is variable.

10.2.2 Lymphoma

A causative association between HCV and non-Hodgkin lymphoma (NHL) has been shown in recent studies. HCV monoinfection doubles the risk of developing NHL [20, 21]. The most common HCV-associated lymphoproliferative disorders include diffuse large B cell lymphoma, marginal-zone lymphoma, lymphoplasmacytic lymphoma, splenic lymphoma with villous lymphocytes, and extranodal marginal-zone B cell lymphoma of mucosa-associated lymphoid tissue, as well as primary hepatic lymphoma [20, 22–24].

Marginal-zone lymphoma appears to be the most frequently encountered low-grade B cell lymphoma in HCV patients. The risk of lymphoma may be related to cryoglobulinemia. Between 8% and 10% of patients with type II EMC develop B cell NHL after a long-term infection [25]. Unexplained anemia or development of lymphadenomegaly in patients with HCV and clinically active cryoglobulinemia should increase suspicion in terms of underlying lymphoproliferative disease. There is some evidence that HCV therapy decreases the risk of lymphoma, as shown in a small number of studies in which antiviral therapy resulted in regression of lymphoma [26, 27]. In a case report, follicular lymphoma remission was achieved in a patient whose HCV was successfully treated with direct-acting antiviral therapy [24].

HCV infection may increase the risk of hepatotoxicity associated with treatment for lymphoma. The presence of HCV infection was associated with a high incidence

of severe hepatotoxicity (with a hazard ratio of 15) in patients with diffuse large B cell lymphoma who were treated with rituximab-containing chemotherapy regimens. Thus, hepatic function should be carefully monitored in HCV-positive patients receiving immunochemotherapy [28].

10.3 Dermatological Diseases

10.3.1 Porphyria Cutanea Tarda

Porphyrias are inherited or acquired metabolic disorders caused by reduced activity of enzymes in heme and porphyrin synthesis. Porphyria cutanea tarda (PCT), which is also called symptomatic porphyria, comprises a group of diseases resulting from an inherited (autosomal-dominant) or acquired deficiency of hepatic uroporphyrinogen decarboxylase enzyme (UROD). UROD is the fifth enzyme in the heme synthetic pathway and catalyzes the decarboxylation of uroporphyrinogen to coproporphyrinogen. Reduced activity of UROD causes a subsequent build-up of uroporphyrinogen in the blood and urine [29, 30].

There are two types of PCT. Type 1 is also called the acquired type and accounts for nearly 80% of all PCT cases. It occurs in predisposed individuals with deficient activity of the enzyme in the liver, which is triggered by exposure to liver toxins (hepatotoxic aromatic hydrocarbons, alcohol), drugs (estrogens), cigarette smoking, dialysis, and hepatopathic viruses, with HCV at the forefront [31]. Type 2 is an inherited form, and UROD mutation is inherited in an autosomal-dominant form. Type 2 accounts for nearly 20% of all PCT cases, and there is decreased enzymatic activity in all tissues [32, 33].

Clinical symptoms of PCT are observed when hepatic UROD activity falls below 20% of normal. Accumulation of porphyrinogens causes formation of uroporphyrin and hepatocarboxyl porphyrins, and the conversion continues with the help of different enzymes and modifications by intestinal bacteria. Ultimately, porphyrins are transported from the liver to the skin and lead to phototoxicity. These phototoxic porphyrins damage membranes, lipids, and proteins [34].

A strong association between the acquired form of PCT and HCV infection has been shown in several studies. Although there was marked geographic variability, a mean HCV prevalence of 50% was reported of patients with PCT. All patients with PCT should be screened for HCV infection and should have a comprehensive assessment of liver function, as well as assessment for other potential disease associations, including HIV infection, iron overload, and hemochromatosis (with homeostatic iron regulator (*HFE*) mutation testing). On the other hand, in patients with active HCV-related hepatic disease, routine testing for porphyrin metabolism is not recommended, as there is only a 5% reported prevalence of preclinical or overt PCT in the HCV-infected patient population. The possible mechanisms associating HCV with PCT have not been clearly identified; one possible mechanism may include HCV-induced production of reactive oxygen species, downregulating hepcidin and causing hepatic iron overload, rather than a direct effect on the

enzymatic pathway. Iron overload (hepatic siderosis) is a critical pathogenetic event, disrupting the enzymatic activity of UROD by inducing the formation of an intracellular inhibitor, probably derived from hydroxymethylbilane and/or uroporphyrinogen [35–38].

The skin and liver are the two main sites affected by acquired PCT. Skin disease is characterized by photosensitivity and skin fragility, in which exposure to the sun and/or minor trauma can cause skin erythema and the development of vesicles and bullae that may become hemorrhagic. Hyperpigmentation, hypopigmentation, hirsutism, sclerodermatous changes, hypertrichosis, alopecia, and onycholysis may develop with the passage of time. Sun-exposed areas, such as the backs of the hands, forearms, face, neck, and feet, are more prone to photodamage. Skin lesions may be painful, and scarring of the lesions may progress to contractions and calcifications that resemble systemic scleroderma. Chronic liver disease is common in type 2 PCT. Liver biopsy shows a wide range of changes, including steatosis, mild to severe inflammation, hepatic fibrosis, and cirrhosis. It has also been reported that patients with PCT have an increased risk of developing hepatocellular carcinoma [39–43].

The diagnosis of PCT is typically suspected on clinical grounds and confirmed by the demonstration of markedly elevated urine uroporphyrine and hepatocarboxyl porphyrin levels in symptomatic patients. Another useful tool for diagnosis is the plasma porphyrin fluorescent assay, which has a characteristic peak at 620 nm [44].

The standard of care for PCT includes low-dose antimalarial hydroxychloroquine and phlebotomy—the latter is done to decrease hepatic iron stores. It is also important to avoiding precipitating factors such as sun exposure, alcohol consumption, estrogen use, iron supplementation, smoking, and exposure to polyhalogenated hydrocarbons [45]. In patients with HCV, antiviral therapy seems to heal cutaneous PCT lesions. However, PCT has been independently associated with an insufficient viral response to interferon-alpha treatment [46]. It has been shown that combination of interferon-alpha treatment with iron reduction is more beneficial in patients with HCV infection. New-onset PCT has been observed during treatment with interferon-alpha plus ribavirin [47]. Indeed, ribavirin is known to induce hemolytic anemia, which further aggravates liver iron excess and progression to clinically manifest PCT in predisposed individuals [48]. Finally, despite a lack of data, treatment of PCT with direct-acting antiviral therapy seems to be more effective than interferon-based regimens [49].

10.3.2 Lichen Planus

Lichen planus (LP) is an uncommon disease of the stratified squamous epithelium and is characterized by flat-topped, violaceous, pruritic papules with a generalized distribution. LP may affect the skin, oral cavity, genitalia, scalp, nails, and even the esophagus. It is seen in fewer than 1% of the general population [50]. LP can be seen in patients with particularly advanced liver disease. Although the range of

anti-HCV antibodies in patients with LP is 10–40%, a relationship between HCV and LP has not been clearly shown [51]. However, a meta-analysis of 70 studies revealed that the presence of HCV may be used as a predictive marker of LP, because there was an increased risk of LP development in patients with HCV [52].

The frequency of LP in patients with HCV varies geographically. The prevalence of HCV in patients with LP has been reported to be 4% in Europe and 24% in the Middle East. Seroprevalence differences between geographic regions may depend on human leukocyte antigen (HLA) types and what the most common genotypes are in those regions [53]. Recommendations for HCV testing in patients with LP depend on the geographical area of the patient. LP can occur or be exacerbated during interferon-alpha treatment for chronic HCV infection [43]. Data on the effectiveness of interferon-free direct-acting antiviral treatment in patients with HCV and LP are not available.

10.3.3 Necrolytic Acral Erythema

Necrolytic acral erythema is a rare, pruritic, psoriasis-like skin disorder characterized by well-defined, erythematous to hyperpigmented pruritic plaques with variable scale and erosion on the acral surfaces. Necrolytic acral erythema is strongly associated with HCV, often being seen as an early cutaneous marker of this infection [54]. All patients with necrolytic acral erythema should be tested for HCV infection. The pathogenesis of necrolytic acral erythema is unknown, but it is thought to be related to zinc dysregulation, which can occur as a result of hepatitis C–induced metabolic alterations. Improvement in necrolytic acral erythema has been observed in patients treated with interferon-alpha and oral zinc sulfate [55, 56]. Topical and systemic corticosteroids have variable benefits.

10.3.4 Psoriasis

Psoriasis is a common, chronic, immune-mediated inflammatory disease, which affects the skin and/or the joints. Psoriasis manifests with well-demarcated erythematous plaques with silver scale. Like other immune-mediated disorders, psoriasis results from a complex interplay between genetic factors and environmental triggers. A few hospital-based clinical studies and observational studies have revealed an association between HCV infection and psoriasis. An increased risk of HCV infection among patients with moderate-to-severe psoriasis and psoriatic arthritis has been reported [57–59]. However, according to a population-based database study, psoriasis does not seem to be associated with an increased risk of HCV. A large case–control study has further supported the association between psoriasis and HCV infection. In the same study, there was a significant interaction with smoking—a risk factor common to both psoriasis and progression of HCV-related

liver disease [60]. More prospective studies are needed to support the role of HCV in the pathogenesis of psoriasis and to establish whether psoriasis is a true extrahepatic manifestation (EHM) of HCV infection. However, in patients with psoriasis, HCV testing should be done before commencement of systemic immunosuppressive treatment that can cause HCV reactivation [61].

10.4 Autoimmune Disorders

10.4.1 Production of Autoantibodies

The prevalence of circulating autoantibodies is high in patients with chronic HCV infection, and 53% of HCV-infected patients have at least one immunological abnormality. The most common immunological abnormalities include mixed cryoglobulins (50–60%); RF activity (40%); and antinuclear (20–35%), anticardiolipin (10–15%), antithyroid (10%), and anti–smooth muscle antibodies (7%) [1, 62, 63]. The presence of autoantibodies has not been related to findings of a connective tissue disease, except for EMC. However, the presence of antinuclear antibodies is associated with more advanced liver fibrosis and lower serum HCV RNA levels in chronic HCV infection [64]. Possible reasons underlying the mechanism of autoantibody production include HCV-induced overactivation and proliferation of B lymphocytes.

10.4.2 Sjögren Syndrome/Sicca Symptoms

Sjögren syndrome is a systemic chronic inflammatory disorder characterized by lymphocytic infiltrates in exocrine organs. Most patients with Sjögren syndrome present with sicca symptoms such as xerophthalmia (dry eyes) and xerostomia (dry mouth). Sicca symptoms have been reported in 10–30% of HCV-infected patients. However, the prevalence of HCV-infected patients is lower than 5% [62]. In a recent review, the reported prevalence of Sjögren syndrome was 11.9% in patients with HCV (risk ratio 2.29), versus less than 1% in HCV-negative control subjects [65]. Testing for HCV infection is advised in patients with Sjögren syndrome.

10.4.3 Thyroid Disease

Thyroid disorders are found more commonly in patients with chronic HCV infection—particularly in women—than in the general population. About 13% of HCV-infected patents have hypothyroidism, and up to 25% have thyroid antibodies [66]. Interferon-alpha treatment may induce thyroid disease or unmask pre-existing silent thyroidopathies such as Graves disease or Hashimoto thyroiditis [67]. Thyroid function should be tested when a patient is first diagnosed with HCV and it should be monitored during interferon-based treatment.

10.4.4 Arthralgia/Myalgia

Arthralgia has been reported in 6–20% of HCV-infected patients. Arthralgia generally affects the fingers, knees, and back, and is bilateral and symmetrical [1, 68]. Synovitis is generally absent, and there is no evidence of joint destruction. Arthralgia is often seen in patients with EMC, and its presentation may mimic that of rheumatoid arthritis. High rates of RF positivity in HCV-infected patients may lead to misdiagnosis; however, anti-CCP antibody tests are negative in HCV-infected patients—a feature that is useful to differentiate the two diseases. Arthritis unrelated to EMC is rare, affecting small joints associated with carpal tunnel syndrome and palmar tenosynovitis. Myalgia is less frequent, affecting approximately 2–5% of HCV-infected patients [1, 68]. Interferon-alpha therapy, which is no longer used in HCV treatment, can cause arthralgia and myalgia.

10.5 Diabetes Mellitus

10.5.1 Insulin Resistance and Type II Diabetes Mellitus

Several studies have evaluated the associations between chronic HCV infection, insulin resistance (IR), and diabetes mellitus (DM), which have been linked. A meta-analysis of retrospective and prospective studies confirmed a higher risk of development of type II DM in patients with chronic HCV infection (odds ratio 1.68, 95% confidence interval 1.15–2.20) [69]. Some studies have identified risk factors for the development of DM in HCV-infected patients, such as older age, obesity, severe liver fibrosis, and a family history of DM [70]. HCV also increases the risk of developing DM after liver transplantation [71]. HCV has been linked to IR without overt DM [72, 73]. IR may contribute to hepatic fibrosis progression, particularly with HCV genotypes 1 and 4 and with high serum RNA levels [72, 73]. The pathomechanism of HCV-induced IR is yet not fully understood. Successful treatment of HCV may decrease the risk of DM. Achievement of a sustained virological response (SVR) with interferon-based therapy has been associated with a reduced incidence of DM [74, 75]. IR has been shown to decrease in patients who achieved an SVR but not in patients who failed to respond to treatment or relapsed [76].

10.6 Other Manifestations

10.6.1 Renal Disease

Glomerular disease may occur in patients with chronic HCV infection. The pathogenesis appears to be related to the deposition of immune complexes containing anti-HCV and HCV RNA in the glomeruli. Type I membranoproliferative glomerulonephritis associated with EMC is the most common form of renal disease related to HCV infection [77, 78]. The most common presentation is proteinuria with

microscopic hematuria and variable degrees of renal insufficiency. The Kidney Disease Improving Global Outcomes (KDIGO) Group suggests that all patients with chronic renal disease should be tested for HCV [79].

10.6.2 Fatigue, Depression, Cognitive Impairment, and Impaired Quality of Life

Hepatitis C virus is associated with various neuropsychiatric disorders. The neurological manifestations of HCV include cognitive impairment, which can lead to brain fog and fatigue, markedly impair the quality of life, and increase the risks of cerebrovascular events and stroke. The exact pathophysiology of neuropsychiatric defects in HCV is not fully explained. The detection of HCV genetic sequences in postmortem brain tissue raises the possibility that the presence of HCV infection in the central nervous system may be related to the reported neuropsychiatric symptoms and cognitive impairment [80]. HCV may directly affect the central nervous system through alterations in serotonergic and dopaminergic transmission, with resultant depressive symptoms [81]. This mechanism may explain other central nervous system symptoms seen in HCV infection, such as fatigue and cognitive impairment [82].

Approximately 60% of HCV-infected patients suffer from sleep disorders, fatigue, and mood disorders. Cognitive impairment has also been described. It is a common symptom in persons with end-stage liver disease. HCV eradication leads to improved cognitive function and improved cerebral metabolism [82, 83]. Patients with SVR demonstrate significant improvements in verbal learning, memory, and visuospatial memory.

Fatigue is one of the most frequent and disabling complaints in patients with HCV (occurring in 50–70%) and an independent predictor of poor health-related quality of life (HRQoL) [84]. Fatigue has been independently associated with female sex, age over 50 years, cirrhosis, and depression. Chronic fatigue is associated with poor sleep quality and increased nocturnal activity in patients with HCV [85].

Before commencement of antiviral treatment, patients with HCV have a lower HRQoL than control subjects [86]. HRQoL worsens with more advanced liver disease and therapy, leading to a reduction in adherence [87]. Viral eradication correlates positively with improvements in HRQoL. Achievement of SVR after 12 weeks of follow-up treatment with sofosbuvir and ribavirin has been associated with improvements in HRQoL [88].

10.6.3 Cardiovascular Disease

Chronic HCV infection can trigger cardiovascular disease and has been associated with increased accelerated atherosclerosis [89]. The prevalence rates of carotid artery plaques and carotid intima–media thickening have been shown to be four times higher in HCV-infected patients than in control subjects [90]. Increased

cardiovascular mortality (1.5–25 times higher), as well as higher incidence rates of cerebrovascular disease and acute coronary syndromes, have been noted in HCV-seropositive patients [91]. In addition, an increased rate of peripheral arterial disease in patients with chronic HCV infection has been revealed. The pathogenesis associating HCV and acceleration of atherosclerosis has not been fully elucidated. However, HCV may induce production of proatherogenic cytokines. Rates of cardiovascular events such as acute coronary syndrome and ischemic stroke have been shown to be significantly lower in patients treated with pegylated interferon plus ribavirin than in untreated patients [3]. Although an association between HCV and increased cardiovascular risk has been found in some studies, a correlation between them has not been clearly established [92, 93]. Atherosclerosis in patients with HCV is probably a result of the aforementioned insulin resistance, metabolic disturbance, and proinflammatory cytokine action.

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Acute Hepatitis C

11

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and Dominique Salmon-Ceron

11.1 Epidemiology

11.1.1 Incidence

Hepatitis C virus (HCV) infections remain one of the main causes of chronic liver disease worldwide [1]. According to the last World Health Organization (WHO) Hepatitis Report, in 2015, 71 million people worldwide are living with chronic hepatitis C (Fig. 11.1). Although several studies suggest a global decline in incidence of HCV infections since the second half of the twentieth century, a rise again was noted in the early twenty-first century with still 1.75 million new HCV infections occurring worldwide in 2015 [2]. For example, a decline in acute hepatitis C was described in the United States of America (USA) until the first years of the 2000s [3]. A great contribution to this trend surely came from improvements in injection safety, which has led to a reduction of infections transmitted through unsafe medical procedures [4, 5]. Despite this, during recent years this trend of declining incidence seems to be changing in many countries, related to emerging prevalent routes of transmission (i.e., iv drug use) and improved case detection.

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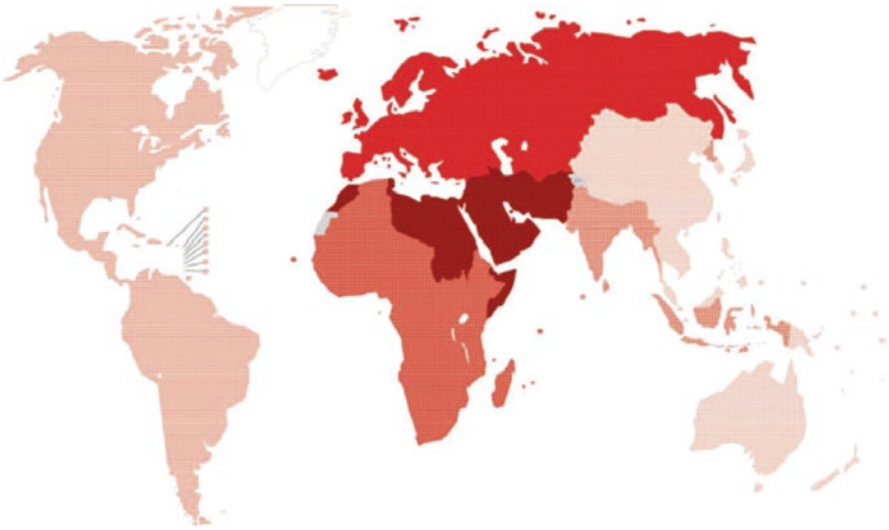

Incidence of HCV infection					
		Incidence rate (per 100 000)		Total number (000)	
WHO region	Map key	Best estimate	Uncertainty interval	Best estimate	Uncertainty interval
African Region		31.0	22.5–54.4	309	222–544
Region of the Americas		6.4	5.9–7.0	63	59–69
Eastern Mediterranean Region		62.5	55.6–65.2	409	363–426
European Region		61.8	50.3–66.0	565	460–603
South-East Asia Region		14.8	12.5–26.9	287	243–524
Western Pacific Region		6.0	5.6–6.6	111	104–124
Global		**23.7**	**21.3–28.7**	**1 751**	**1 572–2 120**

Fig. 11.1 Global incidence and prevalence of hepatitis C. Reproduced with permission of the WHO (Global Hepatitis report 2017)

In the USA 3.5 million people are estimated to be living with hepatitis C. The most common risk factor for transmission, responsible for the majority of infected cases, is injection drug use (IDU). Since the late 1980s, acute hepatitis C incidence has declined because of instituted risk-reduction practices among people who injected drugs (PWIDU) [6]. However, in recent years, from 2010 onwards a 2.9-fold rise in acute HCV infections was noted in the USA which is mainly attributed to an increase in IDU in young people, particular in rural area. For example, a large increase in incidence was observed east of the Mississippi river, especially in Kentucky, Tennessee, Virginia, and West Virginia [7]. A similar situation was reported for Massachusetts, Wisconsin, and New York state. Transmission among men having sex with men (MSM) has also become relevant, especially between those coinfected with HIV [8].

Between 7 and 9 million people live with hepatitis C in *Latin America and the Caribbean* [9]. There is scarce data pertaining to acute hepatitis C infection in South America. A survey conducted in Argentina, Uruguay, and Paraguay found that the most common risk factors for acute hepatitis C were related to nosocomial exposure [10]. In another survey conducted in Brazil, the main risk factors for acute hepatitis C transmission were identified in hospital procedures especially hemodialysis, while it was low IN intravenous drug users [11].

In *Europe* it is estimated that around 19 million people are living with chronic HCV [12]. Incidence rates fluctuate between 2010 and 2014 but are overall steadily increasing. However, the annual epidemiological report of 2015 by the European Centre of Disease Prevention and Control (ECDC) reports 34,651 new cases in Europe, which is a decrease of 4% compared to the previous year. The reason for this is currently not clear but it might be speculated that it is caused by the new direct-acting antiviral agents (DAAs) being used in the treatment of chronic HCV [13]. It is estimated that 1% of all cases are classified as acute infection, mostly due to IDU and health-care-associated transmission. An increase in acute (re)infection is also observed in MSM, coinfected with HIV living in large European cities [14].

Approximately 210,000 people live with chronic HCV infection in *Australia*, with an estimated 80% having acquired their infection through IDU [15]. From 1996 to 2001 a steady increase in new infections was registered with the majority of the cases diagnosed in the age group 20–39 years old related to injection drug use [16]. Again sexual transmission was found to be relevant among HIV positive MSM [17].

The estimated prevalence of chronic HCV in the whole *Asian* continent is 2.8%, accounting over 60% of the estimated cases worldwide. In the Asia-Pacific region prevalence recently has been scaled down, since better seroprevalence studies demonstrate lower rates of active infection in China than previously believed. There are no firm estimates on the incidence of acute HCV around the Asian continent due to the lack of systematic population-based estimates or national surveillance reporting system. Epidemiology is often described by isolated studies or blood bank data [18]. So available data are mostly about chronic HCV infection. China, a large Asian country, has approximately 25–50 million HCVinfected individuals, accounting for 1.8–3.7% of the overall Chinese population [19]. Blood transfusion and IDU are the main routes of transmission. A similar situation was shown for India where transmission is mainly related to unsafe health-care procedures, although it appears to be highly variable according to the geographical site or the population analyzed (0.09–7.89%) [20]. In Thailand there is no national HCV reporting system. Approximately 759,000 individuals are currently anti-HCV-positive and that 357,000 individuals have viremic HCV infection. In Indonesia the prevalence of anti-HCV is estimated to be 0.8% [21] and it is found to be higher in Java then Sumatra, which is probably due to the more dense population in Java [22]. Japan, however, is considered a low prevalence country for HCV with also a low incidence, but also here acute cases among MSM HIV positive patients were recently reported [23]. In Asia, the first study describing a transmission network among HIV-infected MSM was performed in Taiwan, finding an incidence of 9.25 per 1000 PY [24].

In *North Africa*, accurate assessment of the burden of hepatitis C infection is difficult due to the lack of adequate surveillance data and poor resources for proper data collection and management. Despite the geographic proximity of these countries and longstanding interaction between them, the prevalence and complications of HCV greatly differ between them. According to current estimates, the lowest prevalence of HCV is in Libya (0.9–1.6%) whereas the highest is in adjacent Egypt (12.5–26.6%) [25]. In the latter in 2015, it was estimated that 5.3 million individuals were anti-HCV positive. With this high seroprevalence rate, Egypt ranks among the highest in the world [26]. From 2008 to 2015 a significant reduction in prevalence was observed (from 14.7% to 10.0%) because behavioral changes with respect to promotion and expansion of infection prevention and control programs (including safe injections and blood transfusions) led to a decline in HCV incidence in the younger age groups [27].

Sub-Saharan Africa has a substantial HCV disease burden, but detailed epidemiology is limited due to the scarcity of reliable prevalence data and population-based studies. A meta-analysis published in 2015 suggested an overall HCV a seroprevalence of 3% [28] with substantial variation between regions, related to the quality of serological tests used in various studies, the variability of populations screened (e.g., blood donors vs injecting drug users), and the HIV seroprevalence within the countries [29]. Prevalence was found to be the highest in Central Africa region (4.34%).

11.1.2 Definition of Acute HCV

Acute infection classically refers to the first 6 months after exposure to hepatitis C virus [30], though definition varies, mainly because of the absence of specific markers of acute infection and additionally because most patients experience no symptomatology of an acute infection [31]. As is shown in Fig. 11.2, a diagnosis of acute HCV can also be established by seroconversion to anti-HCV, or with the detection of hepatitis C virus nucleic acid (HCV RNA) in serum/plasma in the absence of the specific Ig antibody (anti-HCV Ig) [32].

Identification of acute HCV infections is important from an individual patient's point of view since 70–75% of the patients progress to chronic infection with a possible long-term risk of developing cirrhosis, hepatocellular carcinoma, and decompensated liver disease [33]. From a public health point of view, identification of an acute infection is equally important because of the high risk of transmission these patients have in the acute phase of the infection and therefore spreading of the virus among others. Starting therapy during the acute phase is of particular importance since treatment could reduce transmission and could improve clinical outcome and possibly could also be cost-effective compared to deferring treatment until the chronic phase of infection [34].

Identifying those who are able to spontaneously clear the infection from those who will develop chronic HCV is important. One proposed way of identification of spontaneous clearance was proposed by Vogel et al. [35] who in an intent-to-treat

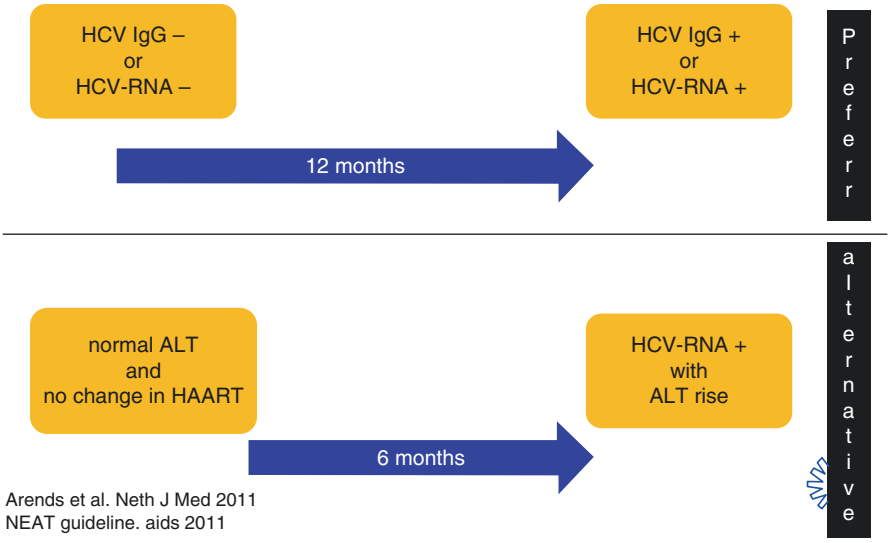

Fig. 11.2 Currently used case definition of acute HCV

(ITT) analysis evaluated spontaneous viral clearance rates in 92 HIV-infected patients with acute HCV. Those patients who did not develop a 2 $\log_{10}$ drop in HCV-RNA at week 4 after the diagnosis had an 85% chance of becoming chronically infected with HCV Since this observation has not been firmly established in prospective randomized trials, this 2 log drop rule has not been adopted in the clinical management of acute HCV [36].

11.1.3 Routes of Transmission and Related Risk Group

Although mode of transmission of acute HCV varies among different regions and within countries, injection drug use (IDU) and unsafe health-care practices remain the leading modes of transmission [37]. Areas with high rates of infection related to unsafe health-care transmission are located in the Eastern Mediterranean Region (62.5 per 100,000, usually related to unsafe health-care transmission) [38, 39] and in the European Region (61.8 per 100,000) where IDU accounts for a substantial proportion of the new cases each year [40]. Worldwide, acute HCV infections are more frequent among male young adults, reflecting the demographic profile of injection drug users [41, 42]. According to a study published in 2013, all forms of drug dependence and related disease were highest in men aged 20–29 years and the majority of new infections are related to illicit drug use [43]. The three countries with the largest populations of IDUs living with HCV are China (1.6 million, range 1.1–2.2), Russia (1.3 million, range 0.7–2.3), and the USA (1.5 million, range 1.0–2.2) [44]. In the early 1990s the incidence of HCV was extremely high in people

who injected drugs. The implementation of HIV sexual transmission prevention programs, methadone substitution, and needle exchange services reduced transmission rates in many countries [12]. But, the rate of new infection remains high or is again rising since iv drug use still remains the primary mode of transmission due to poor health-care services (i.e., Eastern Europe/Russia) or the availability of cheap drugs (USA) [45].

Transmission related to unsafe medical care practice has diminished over time. Before the advent of blood screening assays before transfusion, in the early 1990s most infections were due to transfusions with infected blood and its derivatives or to unsafe medical and surgical procedures. The introduction of large-scale screening assays reduced the risk to less than 1 per 100,000 units of blood [46]. Although the implementation even though the implementation of blood screening strategies in a lot of countries worldwide is successful, the situation still remains alarming in some resources-limited settings (Africa and Americas WHO areas). According to the WHO database on blood safety in 2012, 39 countries did not perform routine screening of HCV in blood products and 47% of all worldwide blood (derivate) donations were tested in settings without any quality assurance [47]. However, a significant decrease of HCV infection was observed in hemodialysis patients in the USA and Europe [48]. Transmission related to dialysis depends on reuse of lines, hygiene and sterilization of equipment, patient rotation of machines, and the undertaking of rigorous universal precaution rules [49]. In addition to transmission via blood transfusions, unsafe injections using contaminated syringes or needles were the most common way to acquire infection in the past and continue to be responsible for a large amount of nosocomial HCV transmissions, both in developed and developing countries [50]. A case report published in 2016 reported acute hepatitis C infection after accidental needle stick injury with a used blood glucose lancet of a diabetic patient with a chronic hepatitis C infection [51]. Egypt's mass campaigns for schistosomiasis treatment may represent the world's largest iatrogenic transmission of HCV [52]. The parenteral anti-schistosomal therapy with tartar emetic injections was administered in a nationwide campaign during the 1950s until the 1980s. Over the 18 years of treatment, 36 million injections were administered to >6 million people, almost all with unsterilized and shared syringes and needles. This intensive transmission established a large reservoir of chronic HCV infection genotype 4, responsible for the high prevalence of HCV infection and current high rates of transmission [53].

Finally, a far less common but incidentally described way of HCV transmission is between hepatitis C and acupuncture. A modest association has been reported in some countries, stressing the importance of exclusively using disposable acupuncture needles [54]. In addition, investigators have reported methods such as tattooing, piercing, coke straw sharing, and cupping as additional agents for HCV transmission [55, 56].

Another possible way of HCV transmission includes sexual contacts with a person infected with HCV. Sexual transmission was long considered an inefficient

mode to spread the infection [57]. Indeed, heterosexual transmission of HCV is estimated to occur at a very low rate of 0–0.6% per year between sero-discordant heterosexual partners [58]. Moreover, a lack of association between specific sexual practices and HCV acquisition was observed. This transmission rate is somewhat higher for heterosexuals with multiple partners or in the context of coexistent STI (0.4–1.8% per year) [59]. For men having sex with men (MSM) however, this is totally different as was learned over the past decade. The first reports of acute infection between MSM mostly associated with sexual and non-IDU behavior date from the beginning of the twenty-first century in London [60, 61] and were soon thereafter followed by additional cases from other European countries, Australia, the USA, and Asia [14, 62, 63]. In the Swiss Cohort Study, HCV incidence increased 18-fold in MSM between 1998 and 2011, while it declined in PWID and remained <1 per 100 in heterosexuals [64]. A similar increase was reported in MSM for the Netherlands (32–53 corresponding to a 65.6% increase) [65]. Similar situation is described in Australia and Asia. Sexual behavior is also responsible for the increase in acute cases in the USA. Several factors have been attributed to this increase such as increased cheap air travel, rising popularity of the internet, increase in extreme sexual techniques, and use of drugs and stimulants for sexual pleasure. However, this does not fully explain the finding in a recent meta-analysis that HIV positive MSM have higher rates of acute HCV infection than HIV negative MSM [66]. It has been hypothesized that the destruction of gut-associated lymphoid tissue (GALT) early in an acute HIV infection might be responsible for a lower immunological barrier in the gut during anal intercourse between MSM leading to increased susceptibility for HCV.

Finally, acute hepatitis has been rarely reported during pregnancy [67]. Vertical transmission from mother to child is the primary route of transmission of HCV infection among children. Infection can occur in utero, intrapartum, and postpartum. It is estimated that the prevalence of Ig antibodies to HCV in pregnant women is 0.1–2.4% and the proportion of women with anti-HCV who have active infection with viremia is approximately 70% [68]. A recent meta-analysis by Benova et al. suggested that vertical risk transmission appears to be limited to infants of viremic mothers, ranging from 5.8% to 10.8% depending on their HIV status and HCV viremia [69]. Spontaneous clearance of the HCV virus has been reported in up to 25–30% of HCV-infected children [70]. Diagnosis could be difficult because specific antibodies (not the ones of the mother) appear 12 months after birth [71] and HCV RNA can be detected only 1 or 2 months after birth and has a low sensitivity [72].

In conclusion, the global incidence of HCV infection seems to decrease and the introduction of DAAs could significantly modify the natural history of the disease due to large-scale treatment implementation programs. At this time IDUs and HIV+ MSM share the largest incidence of acute HCV infections. It would be important to identify if screening strategies in particular populations together with therapy of acute infection, as was recently suggested in a publication for the Netherlands, could indeed contribute to a final stop in the spread of the disease [13].

11.1.4 Spontaneous Clearance and Predictive Factors

Spontaneous viral clearance occurs in about 25% of individuals, generally in the first 3–6 months of infection [73], although cases have been reported after 1 year [74]. A recent study by Ragonnet et al. [75] showed a median spontaneous clearance rate of 184 days after diagnoses.

The outcome of acute HCV is affected by complex interactions between virus and host, which is only partially understood. Diversity of HCV viral quasispecies and HCV genotype might be linked with clearance. Host factors such as female sex, initial cellular immune response, virus-specific neutralizing antibodies, and host genetics such as polymorphism of interleukin-28 gene (IL28B) have been associated with clearance of acute infection [76]. In particular individuals with an IL28B type CC genotype are more likely to clear the infection spontaneously than those with a type CT or TT. There is evidence to support that spontaneous viral clearance is better for building up immunological memory compared to chemically induced clearance. For the latter strong host innate and adaptive immune responses are necessary. For example, Thimme et al. demonstrated that in patients spontaneously clearing their acute HCV infection, a strong, broadly specific, and sustained adaptive cellular immune response is necessary [77]. Long-term follow-up of patients spontaneously clearing HCV infection showed detectable HCV-specific memory CD4 and CD8 T cells up to 20 years after resolution [78]. Similarly, in chimpanzees, memory CD4 and CD8 T cells were detectable in the peripheral blood and liver 7 years after clearing an acute HCV infection [79]. Upon re-challenge with HCV, chimpanzees demonstrated no sterilizing immunity but were characterized by a shorter duration of viremia and lower viral loads. Further evidence to support partial memory after clearance of acute HCV comes from epidemiological studies in high-risk injecting drug users (PWID). Several studies have shown that in those PWID spontaneously clearing one infection it was less likely for them to become reinfected compared to HCV-naïve individuals in the same high-risk circumstances, although this has not been shown for MSM [80, 81]. In HIV-infected patients with acute HCV chances of spontaneous viral clearance were lower (around 10–15%) before C ART, but also highest within the first 12 weeks after the diagnosis [82].

11.1.5 Reinfection

In the presence of maintained risk behaviors, HCV reinfections have been described in PWID and MSM who cleared the infection spontaneously or were successfully treated with either interferon-based therapy or new direct-acting antivirals [76]. In a recent meta-analysis of 61 studies, the 5-year risk of HCV reinfection in HIV-infected MSM was as high as 15% and higher than in studies on PWID [83]. A large cohort study of HIV-infected MSM conducted in Western Europe demonstrated a high reinfection incidence among this population (7.3/100 PY) [84]. It has been suggested in some studies that individuals who spontaneously clear their acute infection may be at lower risk of future HCV reinfection when compared to those

who are treated and achieve SVR due to a stronger immunological response [80, 85]. This indicates that a degree of protective immunity may develop for some patients. An effective immune response against HCV through multiple infections has been shown in animal models [86]. However, studies among PWID have failed to consistently demonstrate a protective effect [87]. This is highlighted by the observation that MSM can be repeatedly infected by acute HCV with either the same genotype or with a different genotype [84].

Other studies demonstrated no difference in incidence of HCV infection in individuals with no previous infection and in those with previous HCV clearance [88]. However, it has been shown that the chance of spontaneous clearance of HCV in case of a reinfection is higher. This is possibly due to a lower HCV RNA concentration, which is generally more transient and shorter in duration than during initial infection [89].

HCV reinfection is a critical health concern among HIV MSM and PWID after successful treatment or spontaneous clearance of acute HCV infection. Prevention strategies—both treatment and behavioral—are needed to target high-risk groups to reduce morbidity and treatment costs.

11.2 Diagnostics

11.2.1 Definition

According to the latest EASL guidelines published in 2016, diagnosis of acute infection is based on seroconversion to anti-HCV, or with the detection of hepatitis C virus nucleic acid (HCV RNA) or hepatitis C virus core antigen (HCV core) in serum/plasma in the absence of the specific antibody (anti-HCV). The incubation period is within 7–21 days after viral transmission and when HCV RNA becomes detectable in serum (Fig. 11.3). Usually, the qualitative detection of HCV RNA

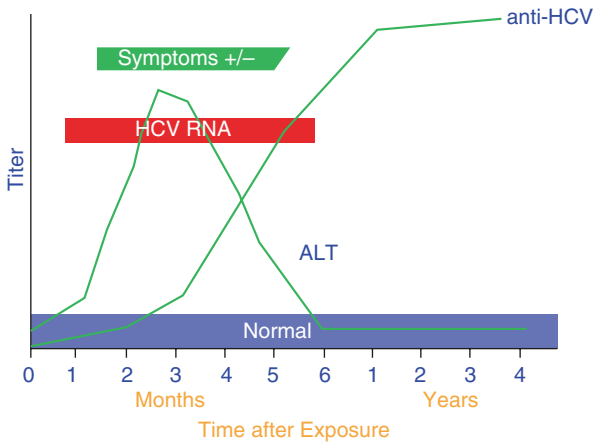

Fig. 11.3 Overview of the serological pattern of an acute HCV infection

confirms the diagnosis [90]. However, the exact time course of virological and immunological markers of HCV infection is not well defined, particularly during the first months of infection, due to differences in the host immune response, specific properties of the infecting virus, and sensitivity of the assays used to determine the appearance of HCV markers.

Following an initial phase (window period) of 1–2 weeks when no virological or serological markers of infection can be detected, the natural course of HCV infection is characterized by the appearance of HCV RNA and subsequently the HCV core p22 Antigen (Ag) in the absence of an antibody response (Ab) by the host. Seroconversion is defined by the development of a specific antibody response in a previously seronegative person occurring within 4–10 weeks after infection.

In Western countries, acute hepatitis C is most often diagnosed in the setting of post-exposure surveillance, or seroconversion in high-risk individuals (e.g., healthcare professionals or injecting drug users) previously known to be seronegative. Seroconversion is most frequently documented in the setting of needle stick injuries, when the exposed individual is followed prospectively, or during surveillance of high-risk individuals [91].

In HIV-infected people, who are usually followed frequently for HIV, an unusual ALAT elevation is a sign of alert in favor of a recent HCV infection. In the other cases diagnosis could be difficult due to different reasons. Firstly, most of the patients do not exhibit symptoms within the first 6 months [92]. The classic clinical picture of an acute hepatitis with jaundice is observed in only 10–15% of the cases. Less commonly, the presentation of acute infection could include constitutional symptoms like nausea, loss of appetite, fatigue, and abdominal pain [31]. A large increase in alanine aminotransferase (ALT), which often can peak around 1000 UI/mL is usually an indicator of an acute hepatic illness. It could however be the presentation of another acute process, such as alcohol-induced hepatitis or a second viral infection superimposed upon a chronic HCV infection [93]. It is therefore likely that these symptomatic patients will be diagnosed as having acute HCV. This is opposite to asymptomatic patients. Since the latter also have a much lower probability to clear the infection spontaneously, they most likely will be diagnosed at some point during their chronic infection [23]. Rates of spontaneous clearance are higher in symptomatic patient and occur usually during the first 3 months after the onset of the symptoms [94].

11.2.2 Assays

Assays detecting HCV infection can be broadly divided into molecular tests, which can directly identify the virus or partial sequences, and include qualitative and quantitative determination of HCV RNA or antigen, and serological tests, which identify antibodies or viral proteins (Table 11.1) [90].

Table 11.1 Virological assays for the diagnosis of acute hepatitis C infection

Assays	Specificity	Sensitivity	Current application	Future application
IGM antibody			Not useful[a]	
IgG antibody	100%	100%	Diagnosis of acute or chronic infection	
Quantitative HCV RNA	95%	95%	Diagnosis of acute and chronic infection	
Qualitative HCV RNA		Some test more sensitive than quantitatives because of low level of detection	Detect the presence of HCV RNA	
NAT	98–99%	99%	– Confirm viremia in patients with reactive serology in short time after exposure (1–2 weeks) – Screening blood donations	
HCV Ag	100%	Less sensitive than NAT	Diagnosis of acute infection in the absence of antibody	– Screening test with antibody – Diagnosis of acute infection in HIV coinfected – Monitor treatment in DAAs era

[a]Present in both acute and chronic infection

11.2.2.1 Serological Assays

Serological assays are based on the immunoassay principle and are available in the form of rapid diagnostic tests (RDTs) or laboratory-based enzyme immunoassays (EIAs), chemiluminescence immunoassays (CLIAs), and electro-chemiluminescence immunoassays (ECLs). Most of these tests have a sensitivity and specificity close to 100% [95]. False negative results may occur in the setting of severe immunosuppression such as infection with HIV, solid organ transplant recipients, hypo- or a-gammaglobulinemia, or in patients on hemodialysis. False positive results are more likely to occur among populations where the prevalence of hepatitis C is low [96]. Current serological markers cannot reliably distinguish acute hepatitis from an exacerbation of chronic infection [97]. The anti-HCV IgM antibody has not proven useful because they are present in similar level in both acute and chronic disease [93], even if someone suggested that IgM levels are undetectable or present with low steady level in reactivation of chronic hepatitis [98]. In recent years much work has been done to develop a test for measuring avidity of the HCV antibody which was proven in other infections to be a more reliable marker for distinction of a recent viral infection. Avidity increases progressively with time after exposure to immunogen due to rapid mutation in the DNA coding for the variable part of the

antibody [99]. It was confirmed that IgG anti-HCV avidity increases with time after primary infection [100] and if detected very early after onset of symptoms it could be useful to distinguish acute process from exacerbation of chronic infection [101]. It has been shown that testing for IgG antibody avidity allows diagnosis in up to 90% of acute hepatitis C [100]. These promising assays still require further evaluation and validation in various clinical settings [102].

11.2.2.2 Molecular Assays

Qualitative and quantitative methods for the detection of HCV RNA—including reverse transcriptase (RT) PCR, branched DNA (bDNA) assays, and transcription-mediated amplification (TMA)—are the most sensitive means to document viremia [91]. Qualitative assays detect the presence of HCV RNA but they cannot measure HCV viral load. The lower limit of detection varies by the method used. The newer real-time PCR detection assays, such as the Cobas TaqMan assay (Roche Diagnostics) and Abbott Real-Time HCV assay (Abbott Laboratories), have very low limits of detection (15 IU/mL and 10 IU/mL, respectively). The Bayer TMA assay (Bayer Laboratories) can detect HCV at limits of 5 IU/mL.

HCV RNA can be quantified by target amplification techniques (competitive PCR or real-time PCR) or signal amplification techniques (branched DNA (bDNA) assay). Five standardized assays are commercially available. Ranges of quantification of the assays refer to the HCV RNA intervals within which quantification is accurate in the corresponding assay [103]. HCV RNA levels falling above the upper limit of quantification of the assay are underestimated and the samples must be retested after 1/10 to 1/100 dilution in order to achieve accurate quantification. It is recommended not to take into account HCV RNA load variations of less than threefold (i.e., $\pm 0.5 \log_{10}$), which may be related to the intrinsic variability of the assays. In contrast, variations of more than threefold (i.e., 0.5 $\log_{10}$) can reliably be considered to reflect significant differences in HCV RNA load. The newer assays are extremely reliable with a very high sensitivity and specificity (both >95%). However, detecting HCV RNA by PCR is not cost-effective in a low-risk population and is not recommended as a screening test for chronic infection [93].

NAT (nucleic acid amplification technology) test is a molecular technique that detects the presence of viral nucleic acid—DNA or RNA—through targeting a specific segment of the virus, which is then amplified. Amplification step enables the detection of low levels of the virus earlier than the other screening methods, thus narrowing the window period to only 4 days. It is used for screening blood donation to reduce the risk of transfusion-transmitted infections in the recipients [104].

Finally, it has been demonstrated that the HCV core antigen level strongly correlates with the HCV RNA level for various genotypes. Currently, core antigen can be easily detected and quantified by means of a chemiluminescent microparticle immunoassay in the fully automated Architect HCV Core antigen test (Abbott Laboratories) [105]. The Architect HCV Ag assay had a specificity of 100%, with a lower limit of detection of 3 fmol/L corresponding to approximately 1000 IU/mL of

HCV RNA [106]. Although a study conducted in the Netherlands suggested that HCV core antigen assay could also be used in the diagnosis of acute HCV infection among coinfected HIV patients [107], as it is a sensitive and specific test, so far it has still not gained a role in the diagnostics of an acute HCV infection.

11.2.3 Assays in Clinical Practice

Since there is no definite test as proof of an acute infection, physicians usually rely on clinical judgments (i.e., the presence of symptoms) in combination with abnormal laboratory results such as elevated aminotransferases, and a positive HCV-RNA or serology in combination with a prior seronegative assay. In specific circumstances, for example in HIV-infected patients with an acute HCV, antibody generation by the host immune response could be initially absent or delayed for months [108]. Also, successful viral clearance may occur in the absence of antibody production or be associated with rapid antibody loss [93]. This suggests that clearance of viremia may be related both to humoral and cellular responses [109]. Among IDUs some studies suggested an average interval from first injection and HCV infection to the development of HCV Ig antibodies of 1 year or even longer. Factors associated with a shorter interval to seroconversion included injecting every day, the shared use of syringes to inject, and the shared use of a cooker or cotton to prepare drugs for injection [110]. In another study conducted on IDUs a delayed and low titers antibody response was observed during acute hepatitis C [111].

Another pitfall in the diagnosis of acute HCV in high-risk HIV+ MSM is the distinction between relapse of infection after DAA therapy or reinfection. When the same genotype again is present, it still might be a reinfection. Only phylogenetic analysis can firmly distinguish between these two entities [84].

11.2.4 Treatment

In a chapter about treatment of acute HCV, a distinction should be made in the era before and after availability of direct-acting antivirals (DAAs). Similar to chronic HCV, DAAs proved to be highly efficacious in the treatment of patients with acute HCV, leading experts in the field to believe there is no distinction anymore between acute and chronic HCV. Therefore, current HCV treatment guidelines recommend a treatment with a combination of two DAAs based on genotype for a total duration of 8 weeks. Patients with acute hepatitis C and HIV coinfection and/or a baseline HCV RNA level >1 million IU/L may need to be treated for 12 weeks with the same combination regimens [32]. However, the question remains if this is totally true. There have been several issues in the pre-DAA era which remain intriguing still today, as we mentioned above. It has been common clinical practice to await spontaneous clearance before considering starting therapy. The publication of the landmark study by Jaeckel et al. [112] clearly demonstrated that treatment of patients with an acute HCV mono-infection with at that time standard

interferon-alfa (trice weekly) for 24 weeks resulted in a sustained virological response (i.e., HCV-RNA negativity 24 weeks after discontinuation of therapy) rate of 98%. Then SVR rates achieved by treating the acute stage of the infection were superior to SVR rates achieved with treatment in the chronic phase. Over time, treatment regimen changed similar to those being administered in chronic HCV. For a long time pegylated interferon-alfa for 24 weeks was the recommended course of therapy for acute HCV mono-infection while ribavirin was added in case of coinfection with HIV [113, 114].

With the availability of DAAs for chronic HCV and its demonstration of high efficacy, it is obvious to use DAAs in cases of acute HCV as well. However, to date none of the currently available DAAs formally registered for the treatment of acute HCV. This is because there is insufficient data about efficacy of particular regimens and treatment durations in acute HCV infection mostly due to the low number of patients per study in the field. An overview of studies regarding treatment of acute hepatitis C is provided in Table 11.2. The largest study to date in patients with an acute HCV treated with DAAs is running in the Netherlands. An interim analysis showed a SVR of 98% after a short course of 8 weeks grazoprevir/elbasvir (an NS3/NS5a combination) (personal communication) [120].

Taken together, the use of DAAs in patients with an acute HCV infection seems promising based on a couple of case reports and small cohort studies but clear recommendations regarding optimal regimen and treatment duration are currently unavailable.

11.2.5 Post-exposure Prophylaxis

Ever since the notion of blood-born transmission of viruses through needle stick injuries, HCV (previously called non-A, non-B hepatitis) has been one of the viruses recognized for causing acute hepatitis syndrome. Early on post-exposure prophylaxis with then available interferon-based therapies was tried but shown to be unsuccessful in the case of a Japanese health-care worker who was treated with a short course of interferon after a needle stick injury [121].

In the current DAA era there are no data on the efficacy or cost-effectiveness of antiviral therapy for pre-exposure or post-exposure prophylaxis of HCV infection.

11.2.6 Prevention of Acute Hepatitis

In the era of highly effective DAAs that promises an individual as well as a collective benefit, the World Health Organization (WHO) launched the first global health strategy on the elimination of viral hepatitis as a public health threat by 2030 [122]. Targets by 2030 are to achieve a 90% reduction of new viral hepatitis infections, a 65% reduction of liver-related deaths, and a 90% diagnosis rate of those being infected. Studies have shown that increased capacity for treatment as well as screening is going to be critical in several countries [123]. However, the former is difficult

Table 11.2 Overview of acute HCV studies performed with DAAs

Study author (year)	Country	Number of patients	Therapy	Duration	Genotype	SVR12	HIV	Comorbidities
Naggie (2017) [115]	USA	17	Sof/RBV	12 ws	1	59%	Positive	
Rockstroh (2017) [116]	Germany, UK	26	Led/sof	6 ws	1, 4	79%	Positive	
Deterding (2017) [117]	Germany	20	Led/sof	6 ws	1	100%	Negative	
Boerekamps (2017) [13]	The Netherlands, Belgium	49	Grazo/ elbasvir	8 ws	1, 4	98%	Positive	
He (2018) [118]	China	33	Sof[a]/Dac	24 ws	2a, 1b	100%	Negative	End-stage renal disease
Brancaccio (published in 2017) [119]	Italy	6	Led/Sof	8–12 ws	1b	66%[b]	Negative	Hematological malignancies

Sof Sofosbuvir, *RBV* Ribavirin, *Led* Ledipasvir, *Grazo* Grazoprevir, *Dac* Daclatasvir, *ws* weeks

[a]Sofosbuvir used in half dose (200 mg)

[b]Two patients died at week 8 after treatment as a result of recrudescence of hematological disease

since the high cost of DAAs in many countries continues to lead to prioritization of therapy [124]. In addition, there are several barriers to scaling-up of HCV treatment in high-risk populations, especially in PWID [125]. To reduce HCV incidence in PWID, combining universal introduction of DAAs with increased diagnosing rates and enhanced prevention measures such as opioid substitution treatment and needle and syringe exchange programs, provided in multidisciplinary settings, was shown to be crucial [126].

Strategies to control the spreading of infection are needed also among MSM. The ECDC published a document focusing on communication strategies for the prevention of hepatitis and other STI, which stressed the importance of counseling information and public awareness of the disease [127]. In Amsterdam a local program (MC Free) organized by the Amsterdam Institute for Global Health and Development (AIGHD) developed online and offline interventions to increase knowledge and awareness of HCV infection among MSM population by increasing regular HCV testing and earlier diagnosis and to stimulate risk reduction behavior. The early treatment of acute infection also seems to reduce the incidence of hepatitis C in this population [13].

An increase in appropriate prevention measures such as safe medical procedures, safe sexual practices, and prevention of mother-to-child transmission needs to be encouraged [128]. Improving public health surveillance could help state-run and local programs to identify and address HCV-related health disparities by documenting and monitoring the impact of testing, care, and treatment services [129].

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