World Gastroenterology Organisation Global Guidelines

Diagnosis, management and prevention of hepatitis C

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1 WGO global perspective—resource-sensitive guidelines and "cascades"

This guideline will be of interest to all health professionals in primary and secondary care involved in the management of people with hepatitis C infection in different countries of the world. It covers all stages of the disease management pathway: screening, testing, diagnosis, referral, treatment, care, and follow-up of children and adults with, or exposed to, hepatitis C (HCV) infection.

Numerous guidelines produced annually by prestigious medical bodies outline "gold standard" practices and are aimed at physicians in resource-rich environments. The main international guidelines on the management of hepatitis C are:

- European Association for the Study of the Liver (EASL):
  — Management of hepatitis C virus infection:
  http://www.easl.eu/assets/application/files/4a7bd873f9cccbf_file.pdf
- American Association for the Study of Liver Diseases (AASLD):
  — An update on treatment of genotype 1 chronic hepatitis C virus infection:
  http://www.aasld.org/practiceguidelines/Documents/2011UpdateGenotype1HCVbyAASLD24641.pdf
  — Diagnosis, management, and treatment of hepatitis C: an update:
  http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/Diagnosis_of_HEP_C_Update.Aug%20_09pdf.pdf
- Asian Pacific Association for the Study of the Liver (APASL):
  — APASL consensus statements and management algorithms for hepatitis C virus infection:
  http://link.springer.com/content/pdf/10.1007%2Fs12072-012-9342-y
- National Institute for Health and Clinical Excellence (NICE):
  — Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C:
  http://www.nice.org.uk/nicemedia/live/11589/33503/33503.pdf.
  — Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C—2010 addendum. http://www.nice.org.uk/nicemedia/live/13180/50854/50854.pdf
- Asociación Latinoamericana para el estudio del Hígado (ALEH)
  — Latin American Association for the Study of the Liver Practice Guidelines. Diagnosis, management, and treatment of hepatitis C.:
  http://annalsofhepatology.com/PDF/vol9s1/HP-S101-02.pdf

As such, they are inaccessible and irrelevant for many clinicians in developing countries. Any Western guidelines that fail to acknowledge this may be preventing the dissemination of knowledge and evidence to the full global audience. The WGO has developed the concept of "cascades" in order to make guidelines more applicable to differing resource environments, by providing a collection of related diagnostic and treatment options arranged hierarchically in terms of conditions and available resources [1].

WGO guidelines include alternatives for clinicians with limited funding. These alternatives are usually suggested on the basis of cost, but may also take account of local availability, technology, and infrastructure. Cascades can range from a simple

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list of options to more complex parallel diagnostic and treatment pathways and are transformed from being "resource-blind" to "resource-sensitive." Inevitably, cascades are more heavily based on empirical evidence, rather than gold standard options. Research funding is usually spent on trying to improve "best practice" rather than the practicalities of delivery in developing countries. However, with strong involvement from experienced clinicians in developing countries, a consensus is usually reached. More widespread use of cascades in guidelines may also motivate research into the best options for resource-limited services.

2 Epidemiology—global comparison and resource factors

When the epidemiology of HCV infection globally is being discussed, it is imperative to discuss "north–west" and "east–south" differences as well. These include a low prevalence of HCV infection in the "north" and "west" [2,3] and a moderate to high prevalence [4–6] in the "south" & "east," leading to a high health-resource and financial burden on already resource-constrained countries. The main risk factor for HCV in the "east" is unsafe therapeutic injections, due to poor practical application of universal infection control guidelines, including sterilization of equipment. This affects the treatment strategies in developing countries and emphasizes the need for prevention strategies, public awareness, health education, and sensitizing health-care staff and concerned authorities in governments.

Another factor is the availability and quality of diagnostic tests for HCV infection, which make screening extremely difficult even in high-risk populations, leading to inaccurate data collection and reporting. Similarly, the standardization and methodology of polymerase chain reaction (PCR) testing makes the option of "whom to treat" even more difficult.

The natural history of HCV is also different in the "east" and "west," due to specific risk factors such as alcohol use, addiction, intravenous drug use, coinfections, and superinfections. Other comorbidities and nutritional deficiencies also affect liver histology and progression of the disease.

Data for nonresponders and relapsers will also be different, since conventional interferon (IFN) monotherapy and combination therapy with ribavirin (RBV) are still largely used in developing countries—in comparison with the developed world, where the standard of care is now peginterferon (PEG-IFN) with RBV (PEG-IFN/RBV).

Table **1** Comparison of "resource-constrained" versus "high-resource" countries

	Resource-constrained	High-resource
Risk factors	• Unsafe therapeutic injections • Unscreened blood transfusions • Unsterilized dental procedures • Unsterilized surgical equipment • Unsterilized obstetric instruments • Unsterilized barber practices • Poor implementation of infection-control guidelines in health	• Intravenous drug abuse • High prevalence of HIV/HCV infection • Sexual transmission • Tattooing • Social

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	Resource-constrained facilities	High-resource
Epidemiology	Exact prevalence and incidence in the community is not known, as most studies are hospital-based	Exact prevalence and incidence are well documented
Diagnosis	Methodology of HCV testing is not quality-controlled, uniform, or standardized.	Diagnostic methodology is standardized
Natural history/ contact tracing	Not known, as most patients are diagnosed incidentally. The source and time of infection cannot be traced in most cases. Coexisting nutritional deficiencies often affect the natural history and course of HCV infection	Retrospective and prospective studies are available for reference
Treatment	Treatment protocols are neither uniform nor standardized. Randomized double-blind trials are lacking. Standard IFN and RBV therapy is still in use	All patients are evaluated, treated and followed up in accordance with current international consensus guidelines. PEG-IFN and RBV is the standard of care. DAA therapy for HCV genotype 1 infection is available
Costs of treatment	In lower-resource countries such as Pakistan, the total cost of HCV treatment, including diagnostic tests, physicians' fees, etc., is up to $1500, representing more than half of the country's annual per capita income, which is approximately $2800. The annual per capita income in high-resource countries is approximately $49,000 in the USA, $37,000 in the UK, and $41,000 in Australia	

DAA, direct-acting antiviral; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; IV, intravenous; PEG-IFN, polyethylene glycol–interferon (peginterferon); RBV, ribavirin.

Hepatitis C is a contagious liver disease caused by the hepatitis C virus (HCV). The virus is endemic throughout the world and it currently infects an estimated 175 million people worldwide [7]. The number of persons with anti-HCV antibody in the world has increased from an estimated 122 million in 1990 to an estimated 184 million in 2005 [8]. The WHO estimated that about 3% of the world population has HCV and that there are about 4 million carriers in Europe alone. Anti-HCV antibody is a sign of previous and current infection and does not distinguish between acute and chronic infections.

Intravenous drug use, tattooing, and medical procedures such as dialysis and blood transfusion before the era of HCV screening have all contributed to the wide spread of HCV. It has become a major recognized health problem worldwide [9]. The distribution of HCV infection shows considerable geographic variation, with a higher prevalence in countries in east Asia, Latin America, the Mediterranean, and certain areas in Africa and eastern Europe.

Hepatitis C is a global challenge. According to the World Health Organization (WHO), 3–4 million people are newly infected with HCV every year and 130–170 million people are chronically infected. It is estimated that over 350,000 people die each year from hepatitis C–related liver diseases [10]. The data on the global prevalence are mostly based on HCV seroprevalence studies [11]. However, WHO data are based on published studies and data submitted from different countries and

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regions. Although HCV is a world epidemic, there is great variability in its distribution in different regions of the world [10,11].

The highest prevalence rates are reported from developing poor countries in Africa and Asia, while the developed, industrialized nations in Europe and North America have low prevalence rates. Countries with high rates of chronic infection are Egypt, Pakistan, and China. Unfortunately, there are no good data from African countries, with the exception of Egypt, Morocco, and South Africa. The major transmission route in these countries is thought to be unsafe injections using contaminated equipment—as in the case of Egypt, where the HCV epidemic has been mainly attributed to the prolonged use of parenteral anti-schistosomal treatment (antimony potassium tartrate, tartar emetics) with use of nondisposable glass syringes for more than 30 years.

Chronic hepatitis C is the most common cause of cirrhosis and the most common indication for liver transplantation in Europe, North and South America, Australia, Japan, and Egypt. The risk of developing cirrhosis ranges from 5% to 25% over periods of 25–30 years [12].

Table **2** Prevalence of HCV infection and evidential support in 21 regions

GBD region	Total population in 2005 (millions)	Prevalence (%)	Infected population (millions)	Evidential support
High-income Asia–Pacific	> 180	1.4	> 2.4	Extensive
Central Asia	> 77	3.8	> 2.9	Very limited
East Asia	> 1351	3.7	> 50	Extensive
South Asia	> 1520	3.4	> 50	Moderate
South-east Asia	> 577	2.0	> 11	Moderate
Australasia	> 24	2.7	> 0.6	Moderate
Caribbean	> 42	2.1	> 0.7	Very limited
Central Europe	> 119	2.4	> 2.9	Moderate
Eastern Europe	> 212	2.9	> 6.2	Limited
Western Europe	> 409	2.4	> 10	Extensive
Andean Latin America	> 50	2.0	> 1.0	Very limited
Central Latin America	> 216	1.6	> 3.4	Moderate
Southern Latin America	> 58	1.6	> 0.9	Moderate
Tropical Latin America	> 193	1.2	> 2.3	Extensive
North Africa/Middle East	> 420	3.6	> 15	Moderate
High-income North America	> 337	1.3	> 4.4	Extensive
Oceania	> 8	2.6	> 0.2	Moderate
Central sub-Saharan Africa	> 87	2.3	> 1.9	Very limited
East sub-Saharan Africa	> 317	2.0	> 6.1	Moderate
South sub-Saharan Africa	> 68	2.1	> 1.4	Moderate
West sub-Saharan Africa	> 303	2.8	> 8.4	Moderate

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World	> 6500	2.8	> 184	

Source: Mohd Hanafiah et al. (2012) [8]. GBD, Global Burden of Disease (study).

Table **3** Hepatitis C prevalence rates in developed and developing countries

Country	Prevalence rate (%)
Egypt	18–22%
Italy	2.5–10%
Pakistan	4.9%
China	3.2%
Indonesia	2.1%
USA	1.8%
Japan	1.5–2.3%
India	0.5–1.5%
France	1.1%
Australia	1.1%
Canada	0.8%
Germany	0.4%

HCV is transmitted primarily through percutaneous exposure: injecting drug use, needlestick injuries, and inadequate infection control in health-care settings; nosocomial infections are still occurring throughout the world. Less frequently, HCV transmission occurs among human immunodeficiency virus (HIV)-positive men who have sex with men (MSM) as a result of sexual contact with an HIV-infected partner [13], and among infants born to HCV-infected mothers. Overuse and unsafe injection practices cause an estimated 2–5 million HCV infections globally [12,14–21].

The risk of HCV transmission in a monogamous heterosexual relationship appears to be very low (0.01% or lower).

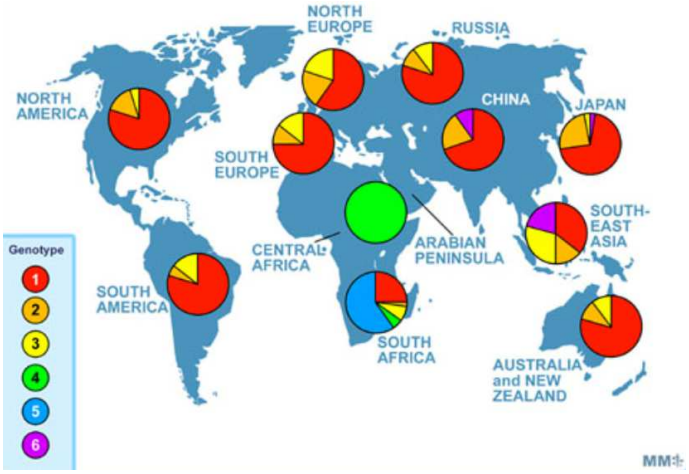

Fig. **1** Global distribution of HCV genotypes. *Source:* WHO Hepatitis C Fact Sheet no. 164 (July 2012): http://www.who.int/mediacentre/factsheets/fs164/en/index.html. Source image: http://www.gregoryledet.com/?p=60.

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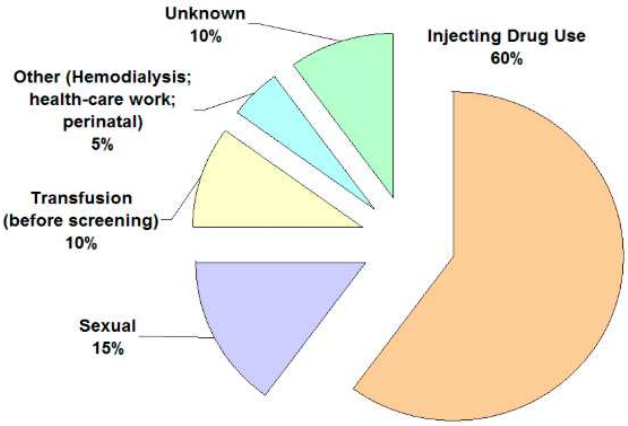

Fig. **2** Sources of HCV infection in the USA. N.B.: "Injecting drug use" is 60% in developed countries. In developing countries, 60% of the sources of HCV infection are unsafe injections. *Source:* Viral Hepatitis Surveillance, USA 2009/2011. Division of Viral Hepatitis and National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. http://www.cdc.gov/hepatitis/Statistics/2009Surveillance/Commentary.htm

3 Natural history and prevention

3.1 Natural history

The infection can range in severity from a mild illness lasting only a few weeks to a serious (acute infection) or lifelong illness (chronic infection). Approximately 80% of patients infected with HCV will become chronically infected, and most of these patients will show evidence of chronic hepatitis. The incubation period is 14–180 days (average 45 days), and no vaccine against hepatitis C is currently available.

Risk factors for chronic hepatitis C [22]:

- Male sex
- Age > 25 years at moment of infection
- Acute infection is asymptomatic
- African-American ethnicity
- HIV infection
- Immunosuppression

Hepatitis C infection is usually slowly progressive over a period of many years, and between 5% and 15% of patients with chronic hepatitis may progress to developing liver cirrhosis over a period of 20 years [23]. However, several studies have suggested a more benign course of the disease [24] and indicate that fibrosis is a highly unpredictable process [25]. A recent publication [26] has reported that spontaneous virus elimination occurs in about 50% of newly infected HCV patients [27].

Approximately 4–9% of patients with cirrhosis will develop progressive liver failure, with a 1–4% annual risk of developing primary hepatocellular carcinoma (HCC) [28]. The mortality rate due to progressive liver failure or HCC will continue to increase during the next few decades. In some countries, HCV infection is the main cause of death from liver disease and is the leading indication for liver transplantation [29].

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Approximately 70–80% of patients with hepatitis C are asymptomatic; in acute or acute-on-chronic hepatitis, the symptoms of all types viral hepatitis are similar and can include one or more of the following: fatigue, abdominal pain, poor appetite, jaundice.

3.2 Prevention

Counseling of infected persons on avoiding transmission of HCV:

- The infected person should cover any bleeding wound or cuts and apply disinfectants immediately in order to keep the blood away from others.
- An infected person should not donate blood or organs.
- Those who use injected drugs should be counseled regarding the risk of transmission of HCV and to inject safely if they intend to continue.
- Vomit and other bodily secretions from an HCV-infected patient should be disposed of with disinfectant—e.g., bleaching powder and glutaraldehyde solution.
- The risk of sexual transmission of HCV is low. Spouses are not recommended to take barrier precautions as a risk reduction strategy.
- Transmission of HCV is low through breast milk, so breast-feeding should not be stopped.
- Household contacts and physical contact are not recognized risk factors for HCV transmission, so an HCV-infected person should not barred from any activities of normal life.

Prevention in the community and health-care settings:

- All blood donors must be screened for hepatitis C antibodies and/or HCV RNA.
- In health-care settings, adherence to universal precautions for infection control is essential. This should include the use of disposable or adequately sterilized materials for invasive procedures, and adequate cleansing and sterilization of instruments.
- It is important to educate tattooists, barbers, foot/hand care workers, and practitioners of traditional or alternative therapies, about ways of minimizing blood contamination. This involves sterilization techniques for procedures that involve skin penetration or breaks to mucosal surfaces.
- As transmission of HCV via injecting drug use is an increasing trend, it is important to implement an education campaign about the harm of drug use, especially among school-age children. Harm reduction programs such as needle/syringe programs should also be implemented.
- Anyone who has received surgical or dental treatment has a higher risk of HCV infection and should be offered testing.
- Individuals with history of blood transfusion have a higher risk of HCV infection and should be offered testing.
- Chronic hepatitis C patients should be vaccinated against hepatitis B after screening.
- Use of injections by health-care professionals and quacks should be discouraged; if necessary, only single-use syringes should be used.
- An appropriate protocol for needlestick injury should be drawn up and followed in all hospitals (public and private), as recommended by the Centers for Disease Control and Prevention (CDC).

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- All skin lesions on the hands of health-care workers should be covered with waterproof dressing, and if possible double gloving with a blood indicator in the glove.
- Health-care workers should be vaccinated for HBV.

4 Diagnosis and screening

Infection with HCV is diagnosed by testing for specific antibodies using enzyme-linked immunoassay (ELISA). The presence of HCV antibody shows that a person has been infected with HCV virus, but it does not indicate whether the infection is acute, chronic, or has resolved. Antibodies may not be detectable during the first few weeks after initial infection, due to the "window period," or if patient is immunocompromised.

In contrast to hepatitis A and hepatitis B virus, in which the diagnosis of acute infection is based on immunoglobulin M (IgM) antibodies, there is no serologic marker for acute HCV infection. Screening tests for chronic HCV infection are enzyme immunoassay (EIA) or chemiluminescence immunoassay (CIA) for anti-HCV and verification by an additional, more specific assay—e.g., nucleic acid testing for HCV RNA.

The diagnosis of acute hepatitis C is based on:

- Marked elevation of alanine aminotransferase (ALT; more than × 10)
- With or without jaundice
- Detectable serum HCV RNA
- Followed by anti-HCV seroconversion weeks later

If both anti-HCV and HCV RNA are detectable from the start, differential diagnosis between acute and chronic HCV infection with a flare of ALT may be difficult.

Table **4** Interpretation of HCV assays

Anti-HCV	HCV RNA	Status
+	+	• Depending on clinical status: acute or chronic HCV infection
+	–	• Resolution of HCV—acute HCV infection during a period of low-level viremia
–	+	• Early acute HCV infection • Chronic HCV in a setting of immunosuppressed status • False-positive HCV RNA test
–	–	• No HCV infection

Screening is recommended for at-risk or specific age groups—risk factors vary from country to country, as does the HCV infection risk in various groups. If screening according to this list is not practicable (for example, are patients aware that they have been injected with used syringes?), patients should be screened on the basis of elevated aminotransferase levels at their initial presentation. The Centers for Disease

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Control in the USA recommend testing all baby boomers; in Europe, this is not recommended.

Table **5** HCV infection risk groups

• Those who have received a transfusion of blood or blood products at any time	• Family members of HCV-infected patients
• Those who have undergone surgical procedures/operations	• Sex workers
• Women during antenatal check-ups	• Thalassemic or hemophilic patients with multiple transfusions
• Women with interventional deliveries	• Dialysis patients
• Anyone who has had injections with used or glass syringes	• Children born to HCV-infected mothers
• Those with commercial/barber shaving	• Intravenous drug users
• Those who have undergone dental treatment	• Those with abnormal and unexplained aminotransferase levels
• Those with a history of nose/ear piercing or tattoos	• Prisoners
• Health-care workers	• Organ transplant patients
• Those with household contact with HCV-infected patients	• Those with HIV infection
	• Healthy liver donors

5 Management of HCV infection

5.1 Treatment goals

The goal in treating HCV infection is to reduce virus-related complications. This goal is achieved by eradicating the virus to achieve a sustained viral response (SVR). Patients who achieve SVR have clearance of the virus, and the chances of virus reactivation are negligible. Improvements in liver necroinflammation, fibrosis, and in the risk of hepatocellular carcinoma risk have been demonstrated in patients who have achieved SVR.

Patients in whom an acute HCV infection has resolved without therapy do not require antiviral treatment. Depending on the sources, between 15% and 50% of patients are reported to recover spontaneously.

Table **6** Definition of treatment responses

Abbreviation	Description	Defining HCV RNA level	Timing
LVL	Low viral load	< 400,000 IU/mL	
HVL	High viral load	> 400,000 IU/mL	
RVR	Rapid viral response	Undetectable	After 4 weeks of therapy
eRVR	Extended rapid viral response	Undetectable; used for triple therapy with telaprevir	At week 4 and at week 12

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Abbreviation	Description	Defining HCV RNA level	Timing
EVR	Early viral response	Undetectable (< 50 IU/mL)	After 12 weeks of therapy
NR	Null response	Less than 2 $\log_{10}$ decrease (IU/mL) from baseline level	After 12 weeks of therapy
LVR	Late viral response	More than 2 $\log_{10}$ decrease	Detectable after 12 weeks of therapy
DVR	Delayed viral response	More than 2 $\log_{10}$ decrease	Undetectable after 24 weeks of therapy
EOTR, ETR, or ETVR	End-of-treatment (viral) response	Undetectable	At the end of therapy
SVR	Sustained viral response	Undetectable	24 weeks after the end of therapy
Relapse	Relapse	Undetectable	At the end of therapy
		Reappearance	After the end of therapy
PR	Partial response or partial nonresponse	More than 2 $\log_{10}$ decrease from baseline	At 12 weeks of therapy; detectable at week 24
BT	Breakthrough	Reappearance	At any point during treatment after viral response

Source: Adapted from the APASL Guidelines (http://link.springer.com/content/pdf/10.1007%2Fs12072-012-9342-y).

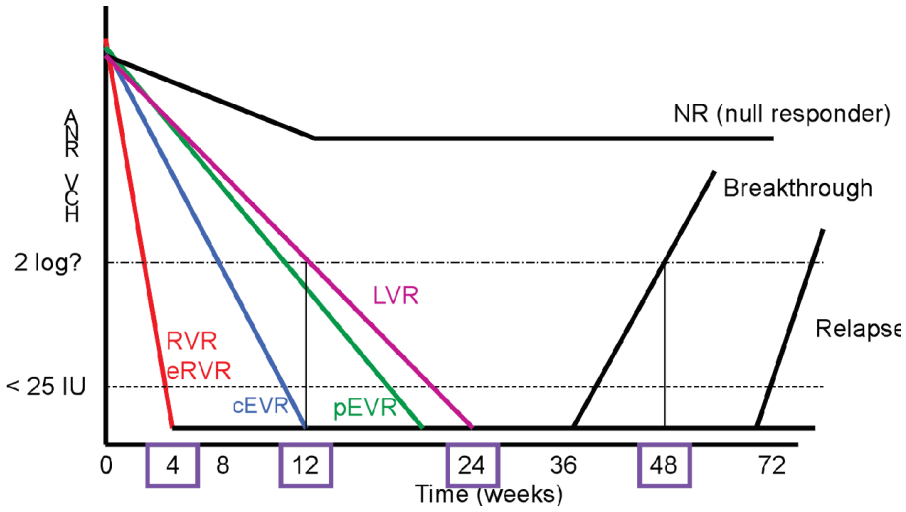

Fig. **3** Pattern of viral responses with peginterferon/ribavirin (PEG-IFN/RBV) therapy.

5.2 Treatment principles

Patients with acute hepatitis C should be considered for antiviral therapy (PEG-IFN alfa-2a 180 µg/week or PEG-IFN alfa-2b 1.5 µg/kg/wæk, for 24 weeks) in order to prevent progression to chronic hepatitis C. High SVR rates (nearly 90%) have been reported with PEG-IFN alfa monotherapy, regardless of the HCV genotype. Some

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experts recommend only follow-up in these patients, with HCV RNA quantification every 4 weeks and treatment only being carried out in patients who are still positive at 12 weeks after the initial presentation.

Treatment and cure of hepatitis C has been shown to prevent the long-term risk of complications and is the primary form of management for chronic HCV infection. Not everyone with HCV infection will develop cirrhosis and its complications, and an approach involving monitoring for disease progression will be used in many situations.

Non-1 HCV genotypes are the most common in densely populated countries of South Asia, the Far East, Africa, and the Middle East. It is also important to note that in developing countries, before the era of PEG-IFN, more than 50% of patients with chronic hepatitis C (CHC) were treated with conventional IFN monotherapy or conventional IFN/RBV combination therapy. After 2002, PEG-IFN/RBV (the standard of care) became available, but its high cost means that it is available only to a small, affluent proportion of the vast population of resource-constrained countries. The lack of a health-insurance system in these countries further complicates the matter.

Before PEG-IFN/RBV became available, the guidelines in the developed countries also recommended the use of conventional IFN/RBV. Thereafter, dual therapy with PEG-IFN/RBV was recommended. The SVR rate is 40% in genotype 1 (GT1) with PEG-IFN/RBV [30–32]. Currently, triple therapy with PEG-IFN, RBV and a direct-acting antiviral (DAA) is recommended (2012). European guidelines do not support general use of triple therapy.

Some older studies [33–36] reported a 40–50% response to standard IFN/RBV combination therapy in genotype 1 CHC patients and a viral response of up to 70–80% in genotype 2/3 CHC patients; in acute HCV, the rate is close to 100%.

The data regarding the SVR rate using conventional IFN/RBV are conflicting, even for genotypes 2a and 3a [30]. Using PEG-IFN/RBV increases the convenience, but not the efficacy, of therapy. In pivotal clinical trials, patients infected with HCV genotypes 2 and 3 achieved an SVR rate of 80% with PEG-IFN/RBV. However, an SVR rate of 30–50% has been reported in different regional studies [37].

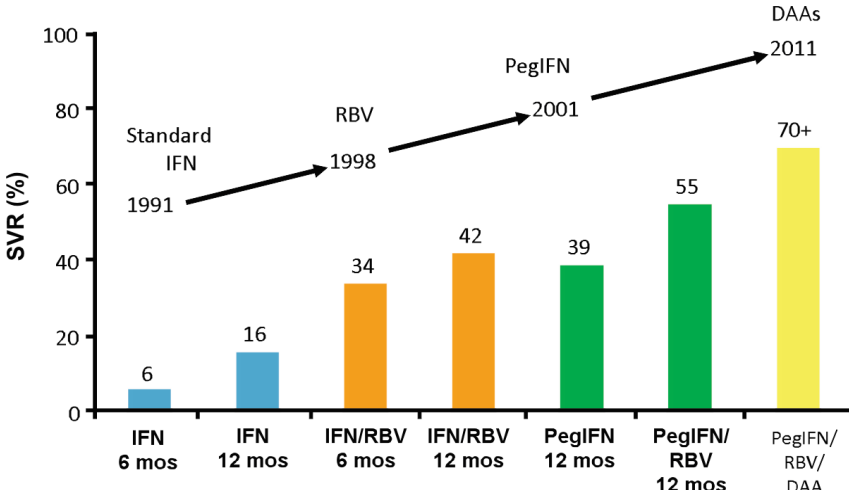

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Fig. **4** Sequential development of treatment of CHC and SVR rates. *Source:* adapted from the U.S. Food and Drug Administration Antiviral Drugs Advisory Committee Meeting, April 27–28, 2011, Silver Spring, MD.

PEG-IFN-a2a should be used at a dosage of 180 µg once per week, whereas PEG-IFN alfa-2b should be used at a weight-based dosage of 1.5 µg/kg per week. The ribavirin dosage depends on the HCV genotype. Patients with HCV genotypes 1 and 4–6 should receive a weight-based dose of ribavirin: 15 mg/kg body weight per day. Patients infected with genotypes 2 and 3 can be treated with a flat dosage of 800 mg of ribavirin daily, unless there are baseline factors suggesting low responsiveness—i.e., body mass index (BMI) > 25, insulin resistance, metabolic syndrome, severe fibrosis or cirrhosis, older age—in which case they should receive a weight-based dosage of ribavirin, similar to genotypes 1 and 4.

The treatment options discussed in this guideline depend on the health care and financial resources available and are based on some empirical evidence from regional experts and societies, without deviating much from evidence-based medical practices. This is an effort to make hepatitis C treatment globally applicable, practically feasible, updating the knowledge of practicing physicians at all levels thus allowing maximum benefit to all hepatitis C patients all over the world. It is the role of governments to make treatment affordable to patients in need, as is the case with HIV. A good example is Egypt, where the cost of treatment is about $2000. This has evidently improved access to treatment for more than 250,000 patients during the last few years, with the majority of them being treated at government expense.

Finally, the guidelines are not fixed rules, but represent a dynamic and ever-changing process, guiding physicians to treat patients accordingly and taking into account individualized approaches wherever needed. The guidelines always need improvement and updating as newer studies and evidence become available.

5.3 Treatment monitoring

5.3.1 Treatment response predictors

Patients with the favorable CC genotype at rs12979860 have a more than twofold likelihood of spontaneous HCV clearance in comparison with heterozygotes (CT) and TT homozygotes. There is marked ethnic variation in the prevalence of IL28B genotypes. Caucasian patients with HCV genotype 1 and CC IL28B have an approximately 80% chance of SVR, in comparison with just 40% among those with non-CC genotypes [38]. The CC genotype is highly prevalent among Asians, has intermediate prevalence in Caucasians and Hispanics, and is relatively uncommon in Africans. Similar associations have been reported for the rs8099917 single nucleotide polymorphism (SNP), in which the favorable allele is coded with a T and the unfavorable allele with a G [39].

Predictors of poor response:

- Obesity
- Metabolic syndrome/insulin resistance
- Black race
- Advanced liver fibrosis
- Coinfection with HBV or HIV

Favorable factors:

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- IL28B genotype
- HCV RNA: low viral load (< 400,000 IU/mL)
- HCV genotype: non-1
- Adherence to therapy dose and duration
- Rapid viral response (RVR)

5.3.2 Pretreatment assessments

Before IFN/RBV therapy is started, the following tests and assessments should be done. Since individualized treatment helps to save money without losing efficacy, pretreatment quantitative assessment of HCV RNA and HCV genotype is mandatory.

Table **7** Pre-IFN/RBV therapy assessments

Assessment	Notes
Full medical history and clinical examination	
Baseline laboratory tests	Including liver biochemistry, prothrombin time, renal function, complete blood count, TSH and blood sugar
HCV RNA quantitative	Mandatory for response-guided therapy
HCV genotype	A must in today's world of continuous migration. Treatment recommendations are based on the genotype. Possibly optional in "monogenotype" populations, such as Pakistan (type 3) and Egypt (type 4)
Liver biopsy	If appropriate—e.g., in patients with comorbid conditions such as diabetes mellitus, obesity, coinfection. Adequate fibrosis staging is necessary to manage resources, especially in countries in which treatment is restricted by regulatory recommendations (fibrosis grade 2 or over should be treated) and sometimes for deciding the length of therapy (possibly with DAA). Whilst liver biopsy is practical for stage CLD in underdeveloped areas, simple scores such as the APRI score are cheap, noninvasive and often as accurate
Noninvasive evaluation of liver fibrosis [40]	Should be considered in patients who decline liver biopsy, to decide on the duration of treatment: APRI, AST/ALT ratio, Forns index, FibroTest, Fib-4 and transient elastography
Cardiac and pulmonary evaluation	If indicated—stress ECG in patients at risk for coronary heart disease; chest radiograph
Psychiatric evaluation	If indicated
Pregnancy test	Indicated when ribavirin is used. Clear information should be given to the patient and partner about the risk of becoming pregnant during and 6 months after the end of therapy
HIV testing in high-risk groups	E.g. addicts, sex workers, those with a history of multiple blood transfusions
HBsAg, serum ferritin, and ANA	To exclude other coexistent liver diseases
Abdominal ultrasound	Useful to evaluate and stage patients with liver disease
IL28B	Optional
Upper endoscopy in cirrhotic patients	To exclude varices

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ALT, alanine aminotransferase; ANA, antinuclear antibody; APRI, aspartate aminotransferase/ platelet ratio index; AST, aspartate aminotransferase; CLD, chronic liver disease; DAA, direct-acting antiviral; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; TSH, thyroid-stimulating hormone.

Counseling—before antiviral therapy is started, all patients should receive explanations about:

- The natural history of the disease and liver-related complications
- Chances and success of all categories of treatments available
- Adverse effects of the available treatments
- Cost of the available treatments (especially PEG-IFN) and cost of supportive treatment when required

5.3.3 In-treatment monitoring

The following tests should be carried out during treatment:

- Assessment of side effects and clinical examination at every visit
- Laboratory test controls at weeks 4 and 12
- Complete blood count every 4 weeks

Thereafter:

- Serum HCV RNA (qualitative) for response-guided therapy quantification at weeks 4 and 12
- Thyroid-stimulating hormone (TSH) testing at 6 months (if clinically indicated)
- Psychiatric evaluation (if indicated—e.g., depression)
- Chest radiograph, ophthalmic or audiogram examination (if indicated)
- Cardiac assessment (if indicated)
- Repeated advice regarding the need for contraception during and at least 6 months after treatment

5.3.4 Post-treatment monitoring

- If an end-of-treatment response (ETR) is achieved, the patient should be followed up and serum HCV RNA (qualitative) should be reassessed 24 weeks after the end of therapy to document SVR (for details, see the algorithm section below).
- Effective birth control should be continued for at least 6 months for patients who have taken ribavirin.

5.4 Treatment with PEG-IFN/RBV—standard of care therapy

5.4.1 Who should be treated?

- All chronic hepatitis C patients with compensated liver disease with no contraindication to PEG-IFN/RBV should be considered for treatment.
- Treatment with PEG-IFN/RBV is strongly recommended for patients with moderate to advanced fibrosis (grades F2–F4).
- Patients with mild disease (F0–F1) should be considered for treatment on an individual basis, taking into account their age, gender, metabolic syndrome, symptoms, and motivation.
- Symptomatic cryoglobulinemia is an indication for antiviral therapy regardless of the stage of liver disease.

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Table **8** Characteristics of patients for whom therapy should be individualized

• Those in whom prior treatment has failed (nonresponders and relapsers), either IFN with or without ribavirin or PEG-IFN monotherapy
• Current users of illicit drugs or alcohol who are willing to participate in a substance abuse program (such as a methadone program) or alcohol support program. Candidates should be abstinent for a minimum of 6 months
• Liver biopsy evidence of either no fibrosis or mild fibrosis
• Acute hepatitis C
• Coinfection with HIV
• Under 18 years of age
• Chronic renal disease (with or without hemodialysis)
• Decompensated cirrhosis
• Liver transplant recipients

5.4.2 Reduced benefit or chance of treatment response

- Morbidly obese males, BMI > 35
- Genotypes 1/4/6 and untypable
- Dual active infection with HCV/HBV
- Relapsers or nonresponders to conventional IFN and ribavirin

5.4.3 Contraindications for IFN and RBV

- Uncontrolled seizures
- Hepatic decompensation
- Pregnancy (RBV) or couples unwilling to use adequate contraception
- Severe heart disease (RBV)

5.4.4 Special caution for IFN therapy

Special caution is required if IFN is administered in the following circumstances (adapted from APASL/AASLD/EASL guidelines):

- Present or past psychosis or severe depression
- Uncontrolled diabetes mellitus
- Uncontrolled hypertension
- Retinopathy
- Psoriasis
- Autoimmune thyroiditis or other active autoimmune disorders, including autoimmune hepatitis
- Symptomatic heart disease or severe vascular disease
- Anemia/ischemic vascular disease
- Renal failure (RBV)
- Neutropenia (neutrophil count < 1500 cells/µL)
- Thrombocytopenia (platelet count < 85,000/ µL)
- Organ transplantation (e.g., kidney and heart transplants)
- History of autoimmune disease
- Presence of thyroid auto-antibodies

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- Comorbidity and the risk of progression in older patients
- History of depression
- Age < 5 years

5.4.5 Adverse effects

Almost all patients treated with PEG-IFN and RBV experience one or more adverse side effects during the course of treatment, including: influenza-like symptoms, neuropsychiatric side effects, hematologic abnormalities (anemia, neutropenia, and thrombocytopenia) and induction of autoimmune disorders. The use of ribavirin is associated with hemolytic anemia. Since it is cleared by the kidneys, ribavirin should therefore be used with extreme caution in patients with renal failure. It is also teratogenic, and pregnancy should be avoided during treatment and 6 months thereafter in female patients and female partners of male patients.

5.5 Treatment with directly acting antiviral (DAA) agents

5.5.1 Treatment of CHC genotype 1: protease inhibitors

- The standard of care treatment for patients with PEG-IFN and RBV has been in use since June 2002.
- The sustained viral response (SVR) rates at 48 weeks are reported to be 80% in genotypes 2 and 3 and 40–50% in those with genotype 1.
- The development of DAA and availability of telaprevir and boceprevir have changed the optimal treatment of HCV genotype 1 infection.
- AASLD [41] and APASL [42] have updated their treatment guidelines with the introduction of DAA for genotype 1 HCV infection.
- Boceprevir (BOC) and telaprevir (TVR) are potent inhibitors of HCV genotype 1 and are commercially available for treatment of patients with chronic hepatitis C.
- To date, the use of protease inhibitors is limited to genotype 1. Treatment with protease inhibitors is not recommended for the large numbers of patients with genotypes 2–6.
- Second-generation DAAs are being developed in order to achieve combination antiviral agents with additive potency that lack cross-resistance and have a good safety profile [43].
- Different classes of drugs are in the pipeline for treatment of chronic hepatitis C patients. These drugs act on different steps in the HCV life-cycle, including HCV NS3–4A protease, NS5B polymerase, and NS5A inhibitors. To date, the Food and Drugs Administration (FDA) has only approved unstructured protein 3/4A (NS3/4A) serine protease inhibitors.

5.5.2 DAA for treatment of untreated (naïve) genotype 1 HCV patients

- It is recommended that naïve CHC HCV genotype 1 patients with non-CC + IL28B and fibrosis F3–F4 should be treated with triple therapy (DAA + PEG-IFN/RBV) for 48 weeks. Naïve patients with CC genotype IL28B and F1–F2 receive standard of care treatment (PEG-IFN/RBV) for 48 weeks, with almost the same SVR rate.

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- Special caution is needed in the treatment of patients with clinically apparent cirrhosis (although they have the greatest need for treatment). The treatment is poorly tolerated and is associated with a 2% mortality rate [44].

5.5.3 DAA for patients with previous treatment failure

- It is recommended that all patients in whom PEG-IFN/RBV treatment has failed, relapsers, partial responders, and null responders should be treated with triple therapy.
- Special caution is needed when treating patients with clinically apparent cirrhosis.

5.5.4 Stopping rules in treatment-naïve patients and treatment failure

Observing stopping rules and ensuring adherence to treatment are necessary to prevent viral resistance. Table **9** lists futility rules [45] for BOC-based or TVR-based triple therapy in treatment-naïve patients and those in whom treatment has previously failed.

Table **9** Futility rules in treatment-naïve patients and those in whom treatment has previously failed

Stop all therapy if…	… the HCV RNA result* is…	…at week
Boceprevir	≥100 IU/mL	12
	Detectable	24
Telaprevir	>1000 IU/mL	4
	>1000 IU/mL	12
	Detectable	24

* Quantitative HCV RNA assays with a lower limit of quantification of near to 25 IU/mL and a lower limit of detection of approximately 9.3–15.0 IU/mL should be used repeatedly when managing patients who are receiving telaprevir-based or boceprevir-based triple therapy.

5.5.5 Adverse effects and drug interactions

- Numerous medications have a potential drug–drug interaction with BOC or TVR, including antiarrhythmics, anticoagulants, anticonvulsants, antihistamines, antibacterials, antiretrovirals, statins, herbal products, immunosuppressants, phosphodiesterase inhibitors, and some sedatives/hypnotics.
- Interaction with oral contraceptives can reduce their efficacy, and a second method of contraception should be used during treatment with these agents.
- Fatal and nonfatal serious skin reactions, including Stevens–Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), have been reported in patients receiving telaprevir combination treatment.
- Anemia has been reported with PEG-IFN alfa and ribavirin therapy. The addition of telaprevir to PEG-IFN alfa and ribavirin is associated with an additional decrease in hemoglobin concentrations.

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- Patients should be informed that TVR combination treatment may cause a skin rash that can be serious, may be accompanied by fever and skin breakdown, may require urgent treatment in a hospital, and may result in death. Patients should promptly report any skin changes or itching to their health-care provider. Patients should not stop TVR due to a rash unless so instructed by their health-care provider.

Source: FDA Highlights of prescribing information for telaprevir (Incivek) (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/201917s003lbl.pdf).

6 Treatment categories and cascades

In this section, patients with chronic hepatitis C who are eligible for treatment in accordance with the diagnostic criteria are stratified following internationally accepted criteria into six categories on the basis of genotype, whether or not treatment-naïve, failure of treatment, treatment response, and stopping rules. These parameters are evidence-based and are an integral part of the AASLD, EASL, APASL, and other regional society treatment guidelines.

The categories include recommendations for high-resource countries, as well as "constrained-resource" alternatives for clinicians with limited resources in terms of cost, local availability of drugs, diagnostic facilities, expertise, and health-care infrastructure.

All patients should be treated with PEG-IFN/RBV in accordance with the standard-of-care therapy. Decision-making on DAA treatment should take account of the factors mentioned above affecting resource-constrained countries. The alternatives are standard IFN/RBV, and in some cases, "wait and watch" policies for minimal and mild disease—based on histology (liver biopsy) or noninvasive markers (FibroScan, FibroTest, FibroSURE, etc.), depending on availability.

Two special categories (sections 6.4. and 6.7) apply to resource-limited countries in which the implementation of gold-standard care is not economically feasible but a decision "not to treat" could cause harm to the patient in terms of disease progression and resulting complications, adding significantly to the morbidity and mortality and further increasing the economic burden on already exhausted and depleted health resources in these countries.

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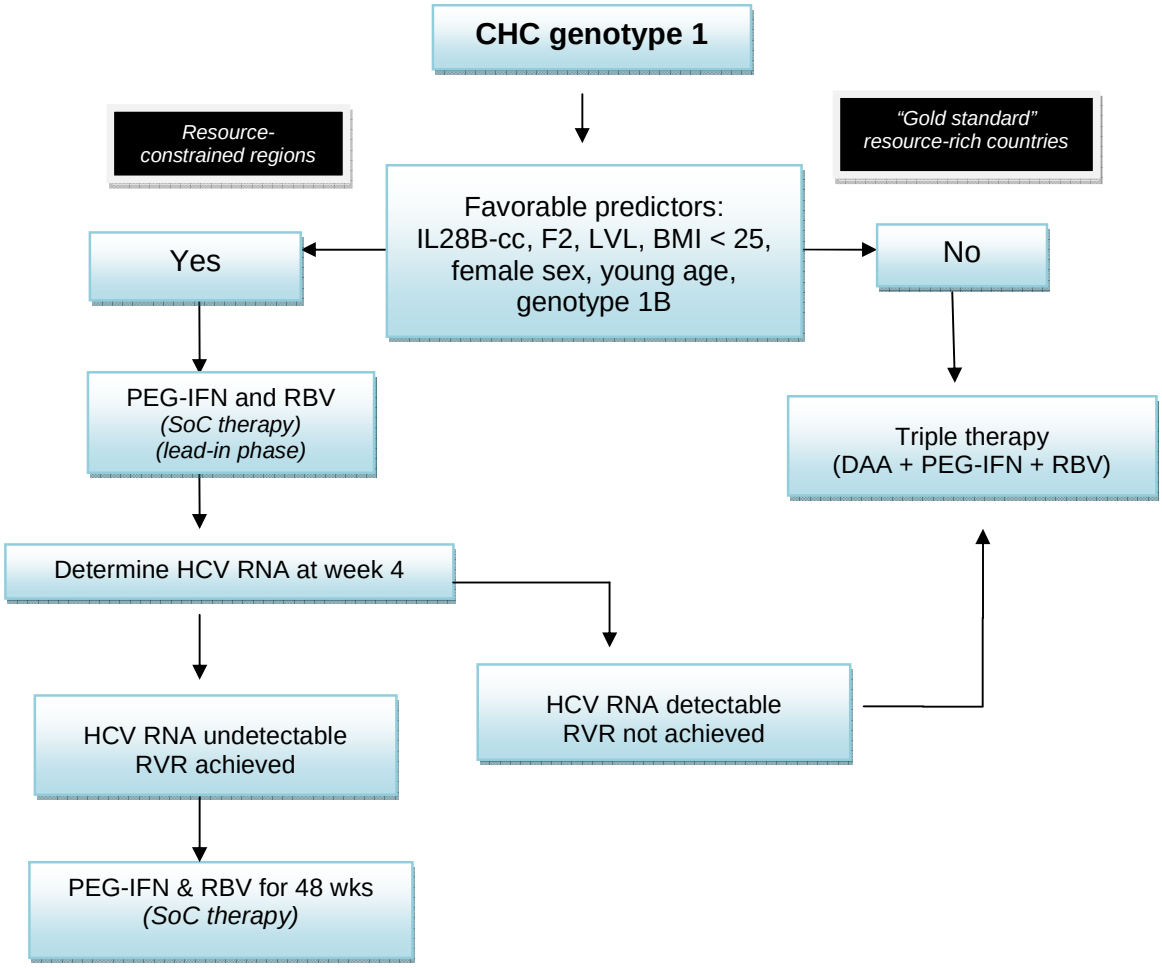
6.1 CHC genotype 1—high-resource and constrained-resource regions

Sequential steps in response-based therapy for chronic hepatitis C virus genotype 1 infection, with triple therapy.



BMI, body mass index; CHC, chronic hepatitis C; DAA, direct-acting antiviral (agent); HCV, hepatitis C virus; LVL, low viral load; PEG-IFN, polyethylene glycol interferon; RBV, ribavirin; RVR, rapid viral response.

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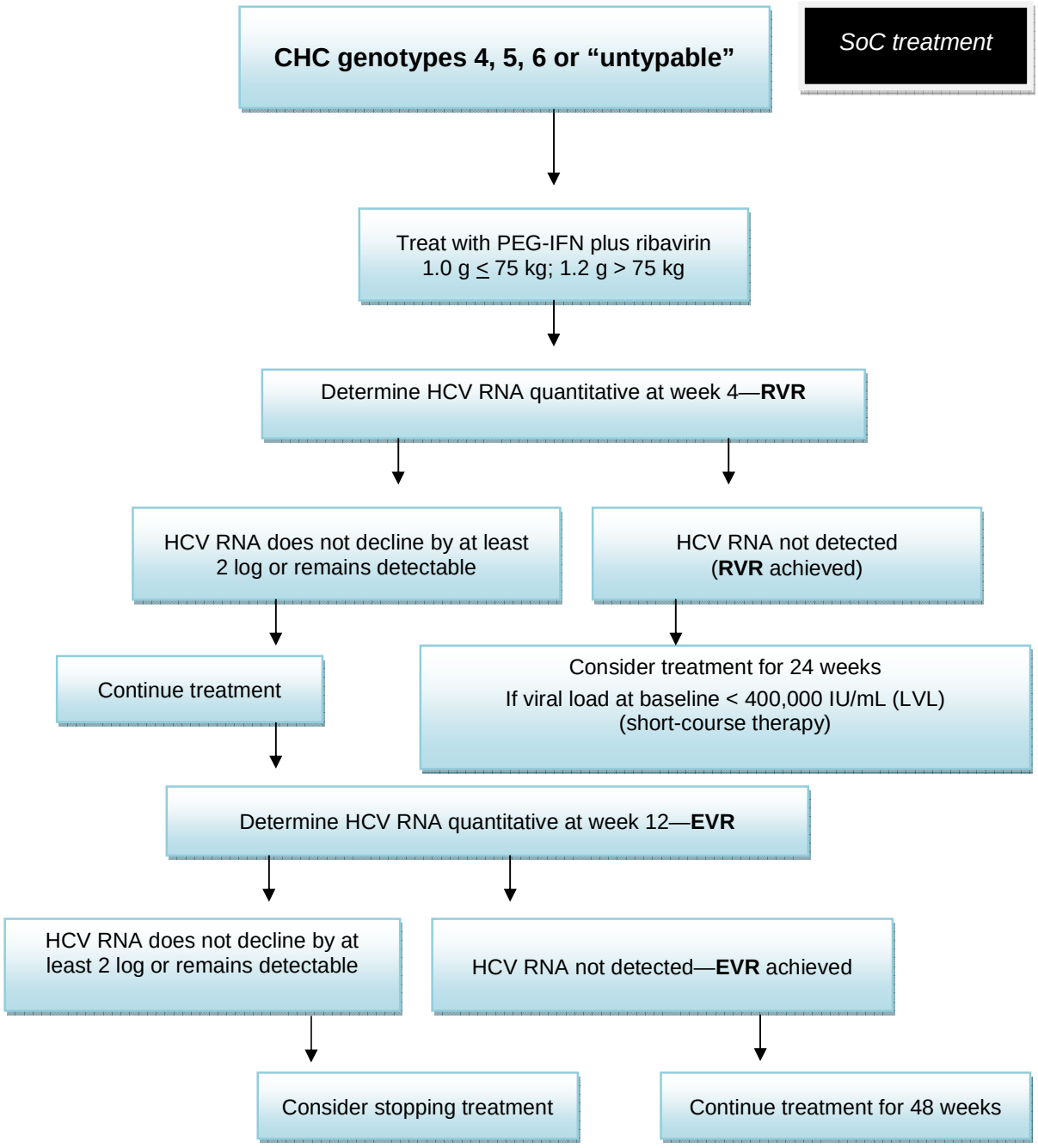
6.2 CHC genotypes 4–6 or "untypable"

Sequential steps for treating patients with chronic HCV infection, genotypes 4–6, or "untypable."



Note: Patients with partial EVR (HCV RNA decreased by 2 log at 12 weeks) and delayed viral response (HCV RNA-negative at week 24) should be treated for 72 weeks.

CHC, chronic hepatitis C; EVR, early viral response; HCV, hepatitis C virus; LVL, low viral load; PEG-IFN, polyethylene glycol interferon; RVR, rapid viral response; SoC, standard of care.

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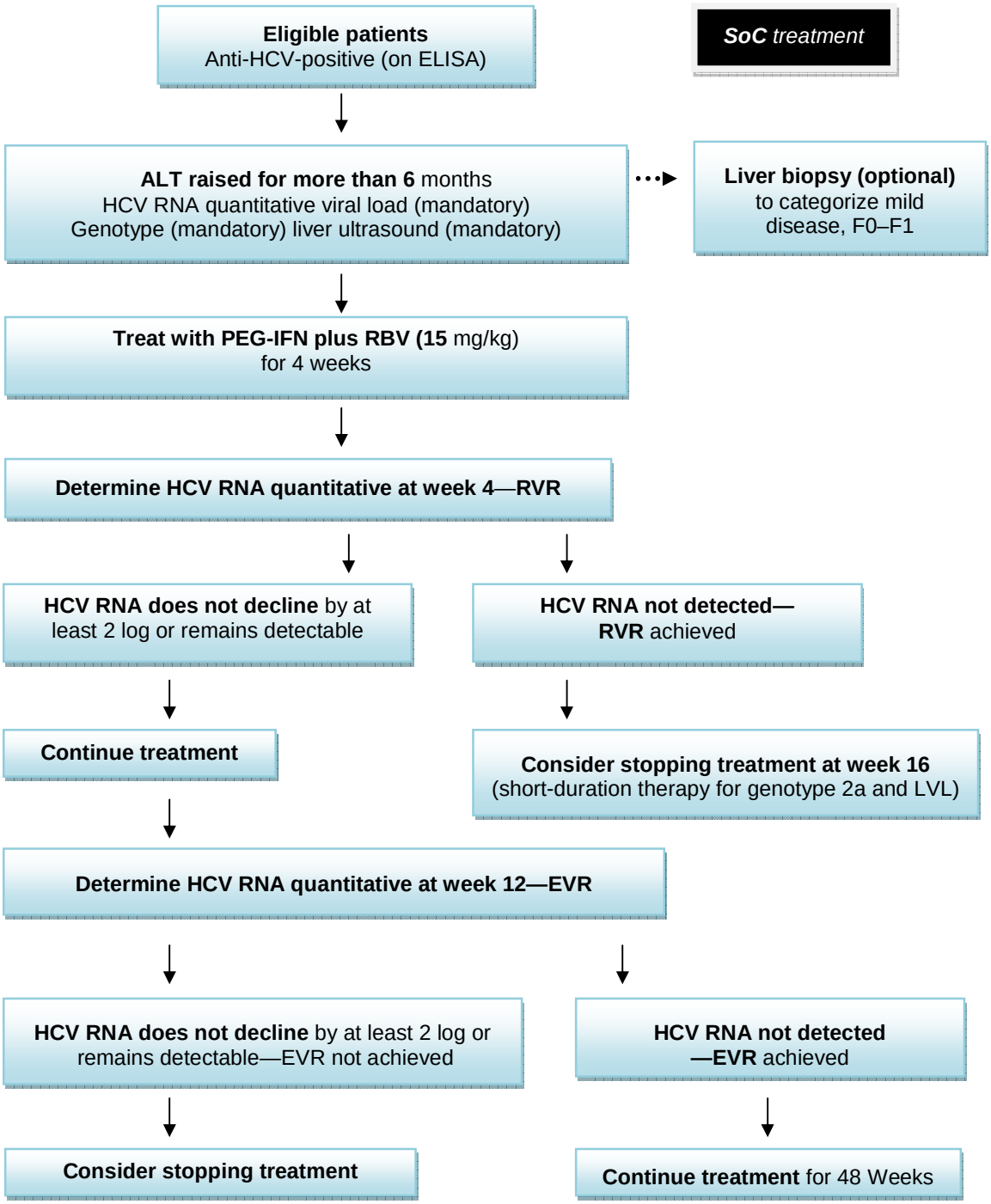
6.3 Naïve CHC genotypes 2/3

Sequential steps for treating patients with chronic HCV infection, genotypes 2 or 3, with PEG-IFN and RBV therapy.



Note: Patients with partial EVR (HCV RNA decreased by 2 log at 12 weeks) and delayed viral response (HCV RNA-negative at week 24) should be treated for 72 weeks.

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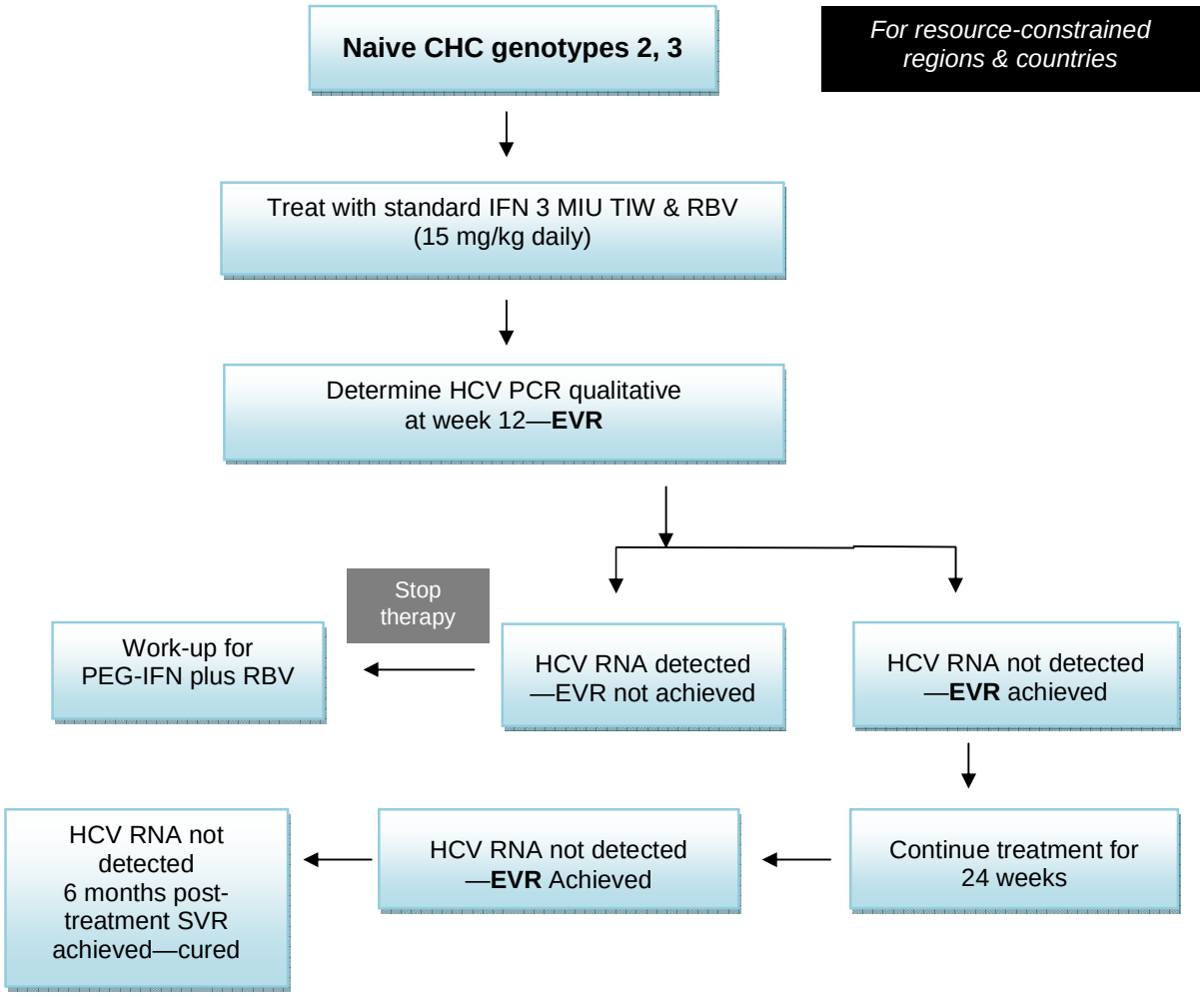
ALT, alanine aminotransferase; ELISA, enzyme-linked immunoassay; EVR, early viral response; HCV, hepatitis C virus; PEG-IFN, polyethylene glycol interferon; RBV, ribavirin; RVR, rapid viral response; SoC, standard of care.

6.4 Naïve CHC genotypes 2/3—constrained-resource regions

Sequential steps in response-based therapy for chronic HCV infection, genotypes 2 or 3, with conventional IFN plus RBV[4,33–37,42,46,47].



CHC, chronic hepatitis C; EVR, early viral response; HCV, hepatitis C virus; IFN, interferon; MIU, million international units; PCR, polymerase chain reaction; PEG-IFN, polyethylene glycol interferon; RBV, ribavirin; SVR, sustained viral response; TIW, three times a week.

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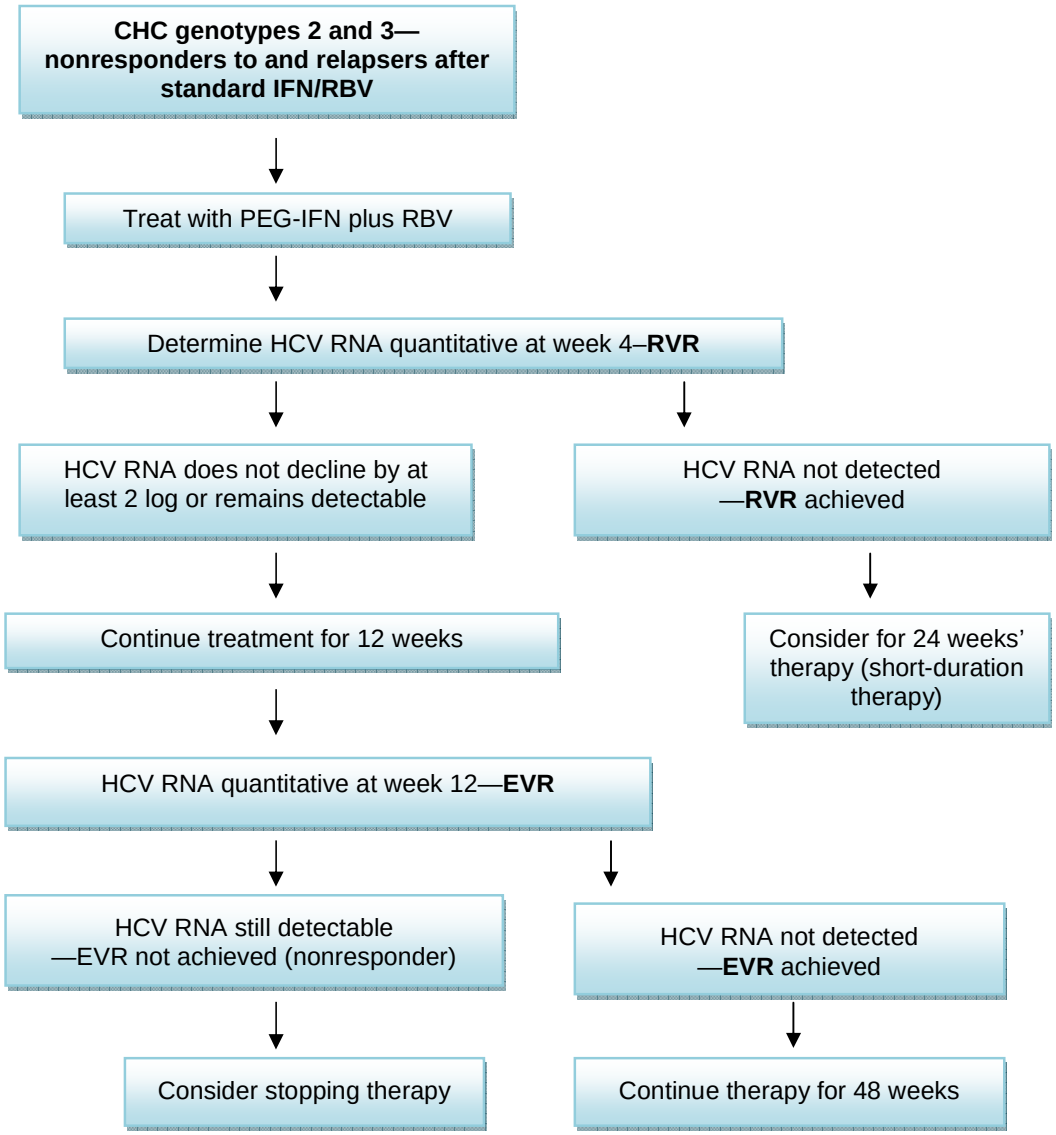
6.5 CHC nonresponders to/relapsers after standard IFN/RBV

Sequential steps for treating patients with chronic HCV infection, genotypes 2 or 3. Nonresponders to or relapsers after standard IFN and ribavirin therapy.



CHC, chronic hepatitis C; EVR, early viral response; IFN, interferon; PEG-IFN, polyethylene glycol interferon; RBV, ribavirin; RVR, rapid viral response.

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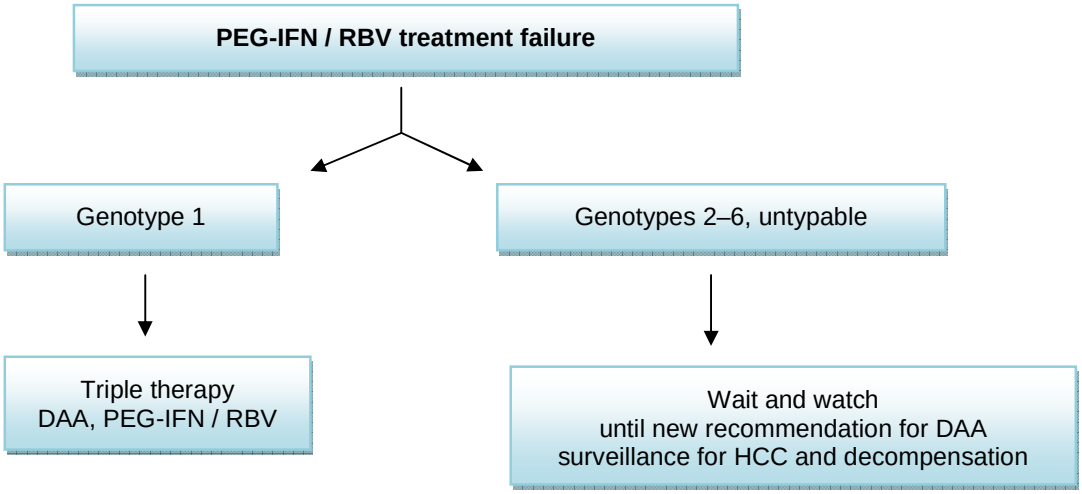
6.6 CHC nonresponders to/relapsers after PEG-IFN/RBV therapy



DAA, direct-acting antiviral (agent); HCC, hepatocellular carcinoma; PEG-IFN, polyethylene glycol interferon; RBV, ribavirin.

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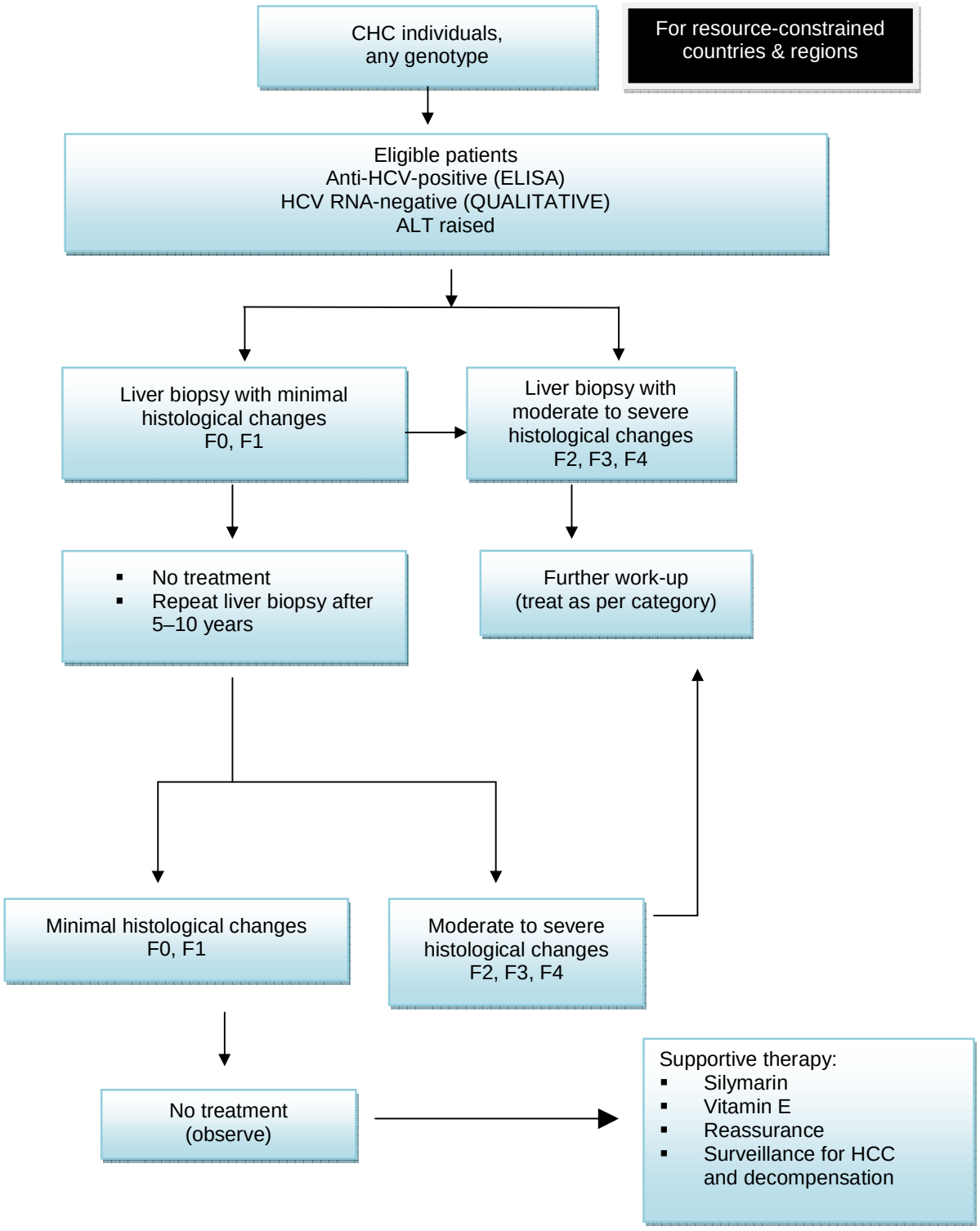
6.7 CHC minimal / mild disease F0/ F1, any genotype—constrained resource regions

Sequential steps in the evaluation and treatment of chronic hepatitis C patients with mild disease (F0 and F1), based on liver histopathology (liver biopsy).



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6.8 Summary—recommendations and evidence levels

Recommendations for the treatment of HCV infection—with resource and evidence levels:

1. Chronic hepatitis C (CHC) genotype 1 patients
   a. Treat with PEG-IFN/RBV for 48 weeks and standard of care—*resource-sensitive* (level B)
   b. Treat with triple-therapy DAA (12 weeks) PEG-IFN/RBV (48 weeks)—*resource-rich (*level A)
   c. Nonresponders to/relapsers after PEG-IFN: treat with triple therapy (level A)
2. Naïve CHC genotype 2 or 3 infection
   a. Treat with PEG-IFN/RBV for 24 weeks or 48 weeks, depending on RVR—*resource-rich* (level A)
   b. Treat with conventional IFN/RBV for 24 weeks, depending on EVR—*resource-sensitive* (level C)
3. CHC genotypes 4, 5, 6 and untypable
   a. Treat with PEG-IFN/RBV for 48 weeks (level A)
   b. Genotype 4 can be treated for 24 weeks, depending on RVR in individual patients (level B)
4. CHC genotypes 2 or 3 nonresponders to/relapsers after PEG-IFN/RBV
   a. Treat with PEG-IFN/RBV for 48 weeks
   b. Can be treated with PEG-IFN for long-duration 72 weeks—*resource-sensitive* (level C)
   c. Newer IFN—e.g., consensus IFN or albinterferon (Albuferon). The response to therapy is usually poor—*resource-rich* (level C)
   d. "Wait and watch" surveillance for cirrhosis and HCC with liver ultrasonography, computed tomography (CT), alpha-fetoprotein (AFP) and platelets as per protocol—*resource-sensitive* (level C)

Treatment of HCV infection in special groups:

1. Acute HCV infection
   a. Start treatment at the time of diagnosis with PEG-IFN monotherapy or combination therapy for 12 weeks for genotypes 2/3 and 24 weeks for genotype 1—*resource-rich* (level A)
   b. Start treatment at diagnosis with high-dose standard IFN for 24 weeks—*resource-sensitive* (level C)
   c. Treatment for acute hepatitis C can be delayed for 8–16 weeks for spontaneous clearance of HCV infection, especially in symptomatic patients—*resource-sensitive* (level B)
2. Treatment of HCV infection in children

   The perinatal transmission rate of HCV infections is about 3–7%. Diagnosis of perinatally acquired HCV infection is by a positive test for anti-HCV antibody after 18 months of age. HCV RNA becomes positive at the age of 1 or 2 months and this should be used as a criterion for early diagnosis. The usual age of treatment is 2–17 years.
   a. Treat with PEG-IFN/RBV for 24–48 weeks, depending on the genotype
   b. The dose of PEG-IFN should be modified according to body surface area and RBV at a dosage of 15 mg/kg/day

Notes:

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- Other special groups of CHC patients—e.g., patients with renal failure, those with coinfection with HCV/HIV and HBV, organ transplant recipients, and others, are treated in specialized liver units; practice recommendations can be found in other international guidelines (see section 1).
- See the Appendix below (section 7.2) for the evidence grading system used—from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

7 Appendix

7.1 Regional treatment notes

7.1.1 Malaysia (K.L. Goh)

- Although the most prevalent genotype is type 1, the majority of strains in Malaysia belong to Type 3 [48]. This has important implications in planning and budgeting for treatment, as the treatment duration across the board would be shorter.
- Treatment of hepatitis C has so far been largely confined to specialists. However, there have been programs in the country to train primary-care physicians in outpatient practices to treat hepatitis C patients, with a "preceptorship" program in collaboration with hepatologists/gastroenterologists who are familiar with the treatment of hepatitis C.
- In general, it is believed that Asian patients respond better to combination IFN and ribavirin therapy [49].
- In some Asian countries like Malaysia, genotype 3 predominates. However, the reason for the better response rate regardless of genotype may be the higher prevalence of favorable ILB28 polymorphisms among Asians [50].

7.1.2 Pakistan (M. Umar)

- The national practice guideline published by the Pakistan Society of Gastroenterology (PSG) and Pakistan Society of Hepatology (PSH) recommends screening of high-risk patients using ELISA.
- Resource-based data have approved qualitative PCR testing followed by conventional IFN plus ribavirin treatment for 6 months for genotypes 3a and 2a.
- Patients who are either nonresponders to or have relapsed after conventional IFN plus ribavirin are treated with PEG-IFN plus ribavirin for 1 year.
- Patients who are nonresponders to or have relapsed after PEG-IFN plus ribavirin require monitoring and surveillance for detection of HCC and end-stage liver disease.
- In 2005, the Pakistan government initiated a national hepatitis prevention and control program. The key points included:
  — Public awareness and health-care personnel awareness regarding prevention, reducing the risk factors for transmission and decreasing the disease burden.
  —Provision of standardized diagnostic and treatment facilities to patients who cannot afford them free of charge or at subsidized cost. (This also addresses the issue of quality control and data collection for future strategies).

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- Another project involved a private–public partnership and corporate induction with pharmaceutical industries for the establishment of local industries for manufacturing IFN/RBV, which paved the way for the provision of hepatitis C treatment at an affordable cost, rather than importing the same drugs at high cost from foreign sources.
- Finally, the government is currently being forced by public representatives and professional societies to pass legislation for effective screening programs for HCV/HBV in high-risk individuals and blood products, along with prevention of other modifiable risk factors, strict quality control practices, and implementation of infection control guidelines by individuals as well as in public and private health-care institutions.

7.1.3 Argentina (F. Villamil)

- The scenario in Argentina is quite close to that in North America and western Europe. This means, for example, that triple therapy for uninsured people will be available soon (2014)—but available at last.

7.1.4 Chile (R. Zapata)

- In Chile, still an underdeveloped country, there can be confidence that there will be approval of DAAs even in the public health-care system within a couple of years (as in Argentina, as noted above).
- The country's public system currently ensures dual treatment for anyone needing treatment. In underdeveloped countries, we therefore need to set priorities for treatment and see which patients can wait.

7.2 Level of evidence grading used

Table **10** Evidence grading system used

Evidence	Code	Notes
High quality	A	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	B	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality	C	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain
Recommendations		**Notes**
Strong	1	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient important outcomes and cost.
Weak	2	Variability in preferences and values or more uncertainly. Recommendation is made with less certainly, higher cost or resource consumption.

Adapted from the GRADE system [51].

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References

1. Mandeville KL, Krabshuis J, Ladep NB, et al. Gastroenterology in developing countries: issues and advances. World J Gastroenterol 2009;15:2839–54.
2. Zou S, Tepper M, EI Saadany S. Prediction of hepatitis C burden in Canada. Can J Gastroenterol 2000;14:575–80.
3. Palitzsch KD, Hottentrager B, Schlottmann K, et al. Prevalence of antibodies against hepatitis C virus in the adult German population. Eur J Gastroenterol Hepatol 1999;11:1215–20.
4. Umar M, Khaar HB, Khan AA, et al. Diagnosis, management and prevention of hepatitis C in Pakistan 2009. Pak J Gastroenterol 2009;23:7–67.
5. Qureshi H. Prevalence of hepatitis B & C in Pakistan. Islamabad, Pakistan: Pakistan Medical Research Council, 2008.
6. Frank C, Mohamed MK, Strickland GT, et al. The role of parenteral antischistosomal therapy in the spread of HCV in Egypt. Lancet 2000;355:887–91.
7. Sarbah SA, Younossi ZM. Hepatitis C: an update on the silent epidemic. J Clin Gastroenterol 2000;30:125–43.
8. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology 2013;57:1333–42.
9. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001;345:41–52.
10. World Health Organization. Secretariat. Viral hepatitis. Sixty-Third World Health Assembly A63/15. Provisional agenda item 11.12. 25 March 2010. Geneva: World Health Organization, 2010.
11. Shepard CU, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005;5:558–67.
12. Seeff LB. Natural history of chronic hepatitis C. Hepatology 2002;36(5 Suppl 1):S35–46 .
13. Tohme RA, Holmberg SD. Is sexual contact a major mode of hepatitis C transmission? Hepatol 2010;52:1497–505.
14. Vandelli C, Renzo F, Romanò L, et al. Lack of evidence of sexual transmission of hepatitis C among monogamous couples: results of a 10-year prospective follow-up study. Am J Gastroenterol 2004;99:855–9 .
15. Puoti C, Guarisco R, Spilabotti L, et al. Should we treat HCV carriers with normal ALT levels ? The “5Ws” dilemma. J Viral Hepat 2012;19:229–35.
16. Kane A, Lloyd J, Zaffran M, Simonsen L, Kane M. Transmission of hepatitis B, hepatitis C and human immunodeficiency viruses through unsafe injections in the developing world: model-based regional estimates. Bull World Health Organ 1999;77:801–7.
17. Khan AJ, Luby SP, Fikree F, et al. Unsafe injections and the transmission of hepatitis B and C in a periurban community in Pakistan. Bull World Health Organ 2000;78:956–63.
18. Kaldor JM, Dore GJ, Correll PK. Public health challenges in hepatitis C virus infection. J Gastroenterol Hepatol 2000;15 Suppl:E83–90.
19. World Health Organization. Global surveillance and control of hepatitis C. Report of a WHO Consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. J Viral Hepat 1999;6:35–47.
20. Janjua NZ, Nizamy MA. Knowledge and practices of barbers about hepatitis B and C transmission in Rawalpindi and Islamabad. J Pak Med Assoc 2004;54:116–9.
21. World Health Organization. Global alert and response (GAR). Hepatitis C. Geneva: World Health Organization, 2002. Available at: http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index4.html.

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22. Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci 2006;3(2):47–52.

23. Freeman AJ, Dore GJ, Law MG, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatology 2001;34:809–16.

24. Levine RA, Sanderson SO, Ploutz-Snyder R, et al. Assessment of fibrosis progression in untreated Irish women with chronic hepatitis C contracted from immunoglobulin anti-D. Clin Gastroenterol Hepatol 2006;4:1271–7.

25. Jacobson IM, Davis GL, El-Serag H, Negro F, Trépo C. Prevalence and challenges of liver diseases in patients with chronic hepatitis C virus infection. Clin Gastroenterol Hepatol 2010;8:924–33.

26. Beinhardt S, Aberle JH, Strasser M, et al. Serum level of IP-10 improves predictive value of IL28B polymorphisms for spontaneous clearance of acute HCV infection. Gastroenterology 2012;142:78–85.

27. Vogt M, Lang T, Frösner G, et al. Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening. N Engl J Med 1999;341:866–70.

28. Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. Hepatology 1997;26(3 Suppl 1):S34–8.

29. Kim WR. The burden of hepatitis C in the United States. Hepatology 2002;36(5 Suppl 1):S30–4.

30. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975–82.

31. Hadziyannis SJ, Sette H Jr, Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004;140:346–55.

32. Manns MP, Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. Gut 2006;55:1350–9.

33. Poynard T, Marcellin P, Lee SS, et al. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). Lancet 1998;352:1426–32.

34. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358:958–65.

35. McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 2009;361:580–93.

36. McHutchison JG, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. N Engl J Med 1998;339:1485–92.

37. Hamid S, Umar M, Alam A, et al. PSG consensus statement on management of hepatitis C virus infection—2003. J Pak Med Assoc 2004;54:146–50. Available at: http://www.psg.org.pk/new/PSGHCV.pdf.

38. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009;461:399–401.

39. Tanaka Y, Nishida N, Sugiyama M, et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet 2009;41:1105–9.

40. Martínez SM, Crespo G, Navasa M, Forns X. Noninvasive assessment of liver fibrosis. Hepatology 2011;53:325–35.

41. Ghany MG. Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for

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the Study of Liver Diseases. Hepatology 2011;54:1433–44. Available at: http://www.aasld.org/practiceguidelines/Documents/2011UpdateGenotype1HCVbyAASLD24641.pdf.

42. Omata M, Kanda T, Yu ML. APASL consensus statements and management algorithms for hepatitis C virus infection. Hepatol Int 2012;6:409–36. Available at: http://www.chinesefms.com/doc/zhw/zxdt/201203/P020120321562034553835.pdf.

43. Asselah T, Marcellin P. Direct acting antivirals for the treatment of chronic hepatitis C: one pill a day for tomorrow. Liver Int 2012;32 Suppl 1:88–102.

44. Beinhardt S, Staettermayer AF, Rutter K, et al. Treatment of chronic hepatitis C genotype 1 patients at an academic center in Europe involved in prospective, controlled trials: is there a selection bias? Hepatology 2012;55:30–8.

45. Myers RP, Ramji A, Bilodeau M, Wong S, Feld JJ. An update on the management of hepatitis C: consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol 2012;26:359–75.

46. Hussain AB, Hussain T, Anwar M, et al. Treatment response in HCV related chronic hepatitis. J Coll Physicians Surg Pak 2004;14:466–9.

47. Qureshi S, Batool U, Iqbal M, et al. Response rates to standard interferon treatment in HCV genotype 3a. J Ayub Med Coll Abbottabad 2009;21:10–4.

48. Ho SH, Ng KP, Ngeow YF, Kamarudin R. Genotypic manifestation of hepatitis C virus in a multi-ethnic society of Malaysia [abstract]. J Gastroenterol Hepatol 2012;27(Suppl 5):P02-20.

49. Yu ML, Huang CF, Huang JF, et al. Role of interleukin-28B polymorphisms in the treatment of hepatitis C virus genotype 2 infection in Asian patients. Hepatology 2011;53:7–13.

50. Yu ML, Chuang WL. Treatment of chronic hepatitis C in Asia: when East meets West. J Gastroenterol Hepatol 2009;24:336–45.

51. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol 2011;55:245–64.

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