



MINISTRY
OF HEALTH, SOCIAL SERVICES
AND EQUALITY

OFFICE OF THE SECRETARY FOR HEALTH AND CONSUMER
AFFAIRS

STRATEGIC PLAN FOR TACKLING HEPATITIS C IN THE SPANISH NATIONAL HEALTH SYSTEM

May 21, 2015

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PROLOGUE

In view of the health problem posed by chronic hepatitis C in our country, the Spanish National Health System's Interterritorial Council unanimously adopted a resolution at its meeting held on January 14, 2015 in favour of preparing a Strategic plan for Tackling Hepatitis C in the Spanish National Health System.

This Plan is structured in 4 strategic directions, setting out some specific objectives and top-priority actions to be carried out over the course of the next three years (2015-2017), which will be carried out in collaboration with different agents: Regional Health Services, the Ministry of Health, Social Services and Equality Management Centres, prison institutions and the Carlos III Health Institute.

This Plan will be provided with an Institutional Committee which will coordinate the implementation thereof within the Spanish National Health System and will be carried out in sequenced stages. Antiviral drugs recently having come out on the market for combatting hepatitis C which are more effective, safer and better-tolerated than the former treatments makes it possible to envision a radical change in the current approach to tackling this disease. The use of direct-acting antivirals simplifies the treatment, considerably reduces the needs for monitoring, increases the cure rates for this infection and delays the onset of the later, severe complications of this disease. At the same time, we are currently lacking sufficient information on actual practice as to the therapeutic efficacy of these drugs and their effect in terms of health outcomes. This Plan shall therefore be putting into practice measures including the assessment of the magnitude of this problem, access to the new drugs under actual conditions of equality and monitoring of their therapeutic efficacy. A systematic follow-up will be conducted, making it possible to assess the degree of implementation thereof and the outcomes achieved.

MINISTER OF HEALTH, SOCIAL SERVICES AND EQUALITY

GLOSSARY		SOURCE
Acute infection	Recent seroconversion (previous HCV negative within the last 12 months) or Detection of HCV RNA or hepatitis C specific core antigen in serum/plasma without detection of HCV antibodies	ECDC
	Presence of HCV within six months of acquiring infection	WHO
Chronic infection	Detection of hepatitis C virus nucleic acid (RNA) or hepatitis C specific core antigen in serum/plasma in 2 samples taken at least 12 months later	ECDC
	Continued presence of HCV six months or more after acquiring the infection.	WHO
Hepatitis C case	Laboratory criteria: <ul style="list-style-type: none"> • Detection of hepatitis C virus nucleic acid (HCV RNA) • Detection of hepatitis C virus specific antigen (HCVcore) • Anti-hepatitis C virus specific antibody (anti-HCV) response confirmed by confirmatory (e.g. immunoblot) antibody test in persons older than 18 months without evidence of resolved infection 	ECDC
Sustained virological response (SVR)	Undetectable HCV RNA three or six months after the end of treatment	WHO
Resolved infection	Detection of hepatitis C virus antibody and no detection of hepatitis C virus nucleic acid (HCV RNA negative result) or hepatitis C virus specific core antigen (HCV-core negative result) in serum/plasma	ECDC
Non- response	Detectable HVC RNA throughout treatment	WHO
Null response	Less than 2 log drop in HCV RNA level by week 12 of treatment	WHO
Partial response	2 log drop in HCV RNA by week 12 of treatment but HCV RNA remains detectable at week 24 or end of treatment	WHO
Relapse	Undetectable HCV RNA at the end of treatment but detectable HCV RNA within 24 weeks of completing treatment	WHO
Rapid virological response (RVR)	Undetectable HCV RNA 4 weeks after the start of treatment	WHO
ACRONYMS		
RBV	Ribavirin	
PEG-INF	Pegylated Interferon	

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1. INTRODUCTION: CURRENT STATUS OF HEPATITIS C IN SPAIN

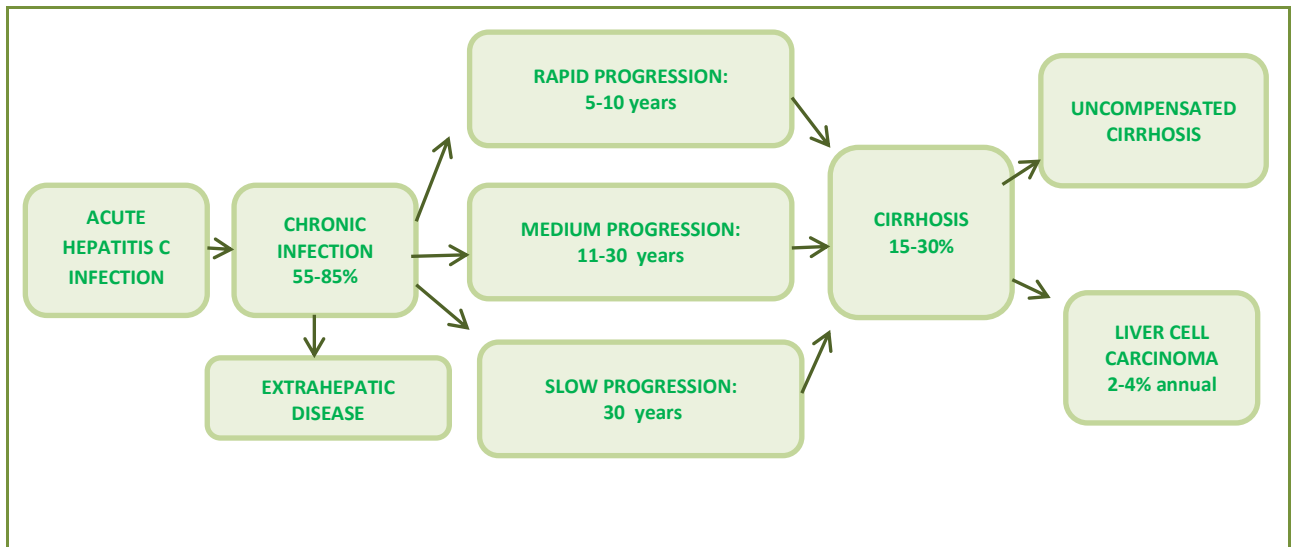
This document is for the purpose of setting out the strategic directions for tackling hepatitis C in Spain in keeping with the prevention, diagnosis and treatment policies implemented at the international level (1, 2, 3, 4) and at the regional level (5, 6, 7, 8, 9, 10, 11, 12) in our country.

Hepatitis C Virus and natural history of the infection

Hepatitis C is a liver disease caused by an RNA virus pertaining to the *Flaviviridae* family, *Hepacivirus* genus, of which there are seven (7) known genotypes, the latest described recently, and at least 67 different subtypes (13). This virus can cause both an acute and chronic infection, the manifestations of which can range from a mild illness to a severe lifelong disease. Generally speaking, the acute infection is asymptomatic. Approximately 15%-45% of those infected experience spontaneous viral clearance within a six-month period without needing any treatment whatsoever, the other 55%-85% developing the chronic infection. A total of 15%-30% of the patients who have chronic infection will evolve into cirrhosis of the liver within twenty years' time (Fig. 1) (14).

The progression of the hepatitis C infection is not random, but rather is influenced by risk factors such as the continued use of intravenous drugs, alcohol abuse, obesity or steatosis, advanced age, genetic factors, coinfection with HIV, which heighten the probability of progression. It is from knowing these factors that the possibility arises of carrying out non-pharmacological interventions for preventing liver complications (15).

FIG. 1: NATURAL HISTORY OF HEPATITIS C



Source: Own work, prepared based on “WHO¹⁴. Guidelines for the screening, care and treatment of persons with hepatitis C infection. April 2014”

Transmission mechanisms

The hepatitis C virus is transmitted mainly parenterally, due to percutaneous or mucous membrane exposure to blood or hemoderivatives infected with the virus.

Thus, transmission has been linked to:

- The use of injected drugs, through the shared use of needles and other injecting materials
- Blood transfusions, use of hemoderivatives and organ transplants from infected donors carried out prior to the systematic detection of the virus
- The reuse or inadequate sterilization of medical equipment, especially syringes and needles, in healthcare settings
- The nosocomial transmission figures would total 15%-25% of the cases, these cases generally being due to failure to comply with the standards of hygiene and often being related to invasive surgical and diagnostic procedures (16).

- Biological accidents, especially due to be stuck by needles used in infected patients
- Tattoos and piercings

HCV can also be transmitted sexually or vertically (there is no transmission via breastfeeding), by intranasal drug use or by inadvertent percutaneous contacts among family members, these being the least frequent forms of transmission.

The population groups most exposed to the risk of HCV are therefore (14):

- Injected drug users (IDUs): this group being one of those at greater risk of infection, especially in some developed countries, with a 67% global HCV prevalence (14). Reinfections are not infrequent in this group.
- Those related to healthcare:
 - Persons receiving infected blood products and the patients having undergone invasive procedures at healthcare centres whose infection control practices are inappropriate
 - Patients having undergone procedures at healthcare centres failing to comply with the standard infection control precautions
 - Patients undergoing haemodialysis
- Children born to mother infected with HCV: The risk of HCV transmission is estimated at 4%-8% among mothers without any HIV infection and at 17%-25% among mothers with HIV infection.
- Persons with HIV infection. HCV and HIV share transmission routes. Coinfection with HIV has been found preferably in IDUs and in haemophiliacs.

- Persons whose sexual partners are infected with HCV: Transmission is infrequent between heterosexual partners. The risk is strongly linked to pre-existing HIV infection, recent outbreaks of hepatitis C having been described among men who have sex with men (MSM) with HIV infection (14, 16, 18).
- Persons who share material when using intranasal drugs (14, 19).
- Persons who have had tattoos, piercings or procedures using sharp-pointed instruments (acupuncture, mesotherapy) without the adequate sanitary controls
- Healthcare workers exposed to procedures entailing a biological risk

Signs and symptoms

The **incubation period** may range from two weeks to six months.

HCV infection may be either **acute or chronic**.

Acute infection is defined as the presence of HCV within the six months after exposure and subsequent infection with HCV.

The acute infections are usually asymptomatic, approximately 80% of the people not having symptoms and, if any at all, they are usually nonspecific and mild. The patients with acute symptoms may have fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, choluria, acholia, joint pain and jaundice.

When left untreated, cases of acute hepatitis evolve into chronic hepatitis in 55%-86% of the cases (Fig. 1) and can lead to cirrhosis, liver failure and liver cancer, chronic hepatitis resulting from HCV being the main cause of cirrhosis and liver transplant.

During chronic hepatitis, the transaminases may be elevated (70%) or at normal levels (30%). Extrahepatic signs are also frequent, such as thyroiditis, arthritis, glomerulonephritis and mixed cryoglobulinemia (20).

Diagnosis

Given that acute infection with HCV is generally asymptomatic or paucisymptomatic, it often goes unnoticed, which hinders its early diagnosis and therefore a true knowledge of its incidence (16).

Those persons who develop chronic HCV infection may go undiagnosed until severe liver damage has occurred.

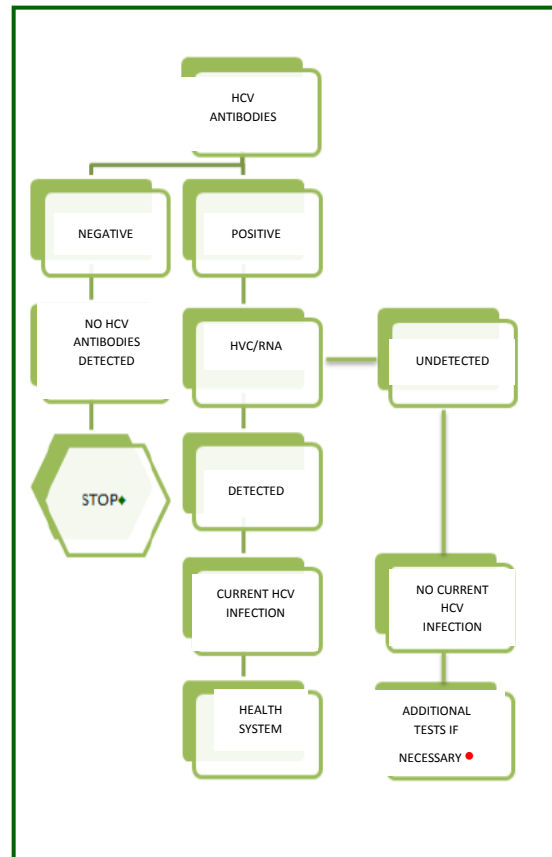
Early diagnosis can prevent health problems resulting from the infection and also the transmission of the virus. Some countries recommend the examination of the persons at high risk of infection.

In view of suspected HCV infection, a full clinical history must be set out and a physical examination of the patient must be conducted. A general analysis must be requested, including parameters such as serum transaminase levels. Serological testing must also be done for identifying other hepatotropic viruses and HIV.

Microbiological diagnosis

The diagnosis of hepatitis C virus infection must be made in sequence.

FIG. 1 Algorithm of the microbiological diagnosis of hepatitis C



Source: Own work based on (21) AASLD. ISDA Recommendation for Testing, Managing and Treating Hepatitis C. 2014

◆ In the case of persons who might have been exposed to HCV within the last six months, the viral RNA assay must be performed and the serology repeated if there were to have been any seroconversion. In immunosuppressed persons, it would be necessary to test the viral RNA.

• For differentiating between resolved infection and false positives, another test should be run for determining anti-HCV antibodies. The RNA assay should also be repeated if it is suspected that the patient has been exposed to HCV during the last six months or shows clinical symptoms of HCV disease and in the case of incidents in the storage or processing of the sample.

The detection of anti-HCV antibodies by means of a serological test is the first step in the process of diagnosing the infection. In the case in which the test results are positive, this may be indicative of both the existence of an active, acute or chronic, HCV infection and a prior, now resolved infection. This may also be a matter of a false positive (20). A first serological test with a positive result for the detection of antibodies must be confirmed by another type of test such as immunoblots with recombinant antigens, which have an excellent specificity.

Next, a viral RNA (PCR) assay must be conducted for detecting whether there is any viremia and classifying the infection as active or inactive, which will condition the patient's subsequent management, including the starting of treatment.

Although used less than the PCR, another direct technique making it possible to detect viremia is the viral antigen (core antigen) assay.

The viral RNA should also be determined in persons with a negative serology who are immunocompromised, which may be the case of persons undergoing haemodialysis and in persons exposed to HCV within the last six months, because they could be within the window period and the antibody assay come back negative (21). Before starting treatment, it is necessary for a quantitative assay of the RNA to be made so as to ascertain the basal viremia, a crucial marker for monitoring the efficacy of the treatment.

In the event that the serology is positive and anti-HCV antibodies are detected and the viral PCR is negative, the patient must be informed as to there being no active infection. In some cases, additional serological tests could be requested for ruling out whether this be a past infection or a false positive. The likelihood of a false positive in a person without any risk factors for HCV is related to the prevalence of HCV in the population. False positives are more frequent in populations with a low prevalence of HCV infection.

The viral RNA assay may be repeated if infection is suspected to a major degree or in patients with known risk factors for this infection.

The techniques used for the specific microbiological diagnosis of the hepatitis C virus infection, both indirect (anti-HCV antibody assay) and direct (showing the viremia through the RNA and viral antigen assay) are summarized in the following techniques (20):

Antibody assay

There are different types of tests for detecting anti-HCV antibodies in serum or plasma. Those employed most often are the Enzyme Immunoassays (EIAs) or the Chemiluminescence Immunoassays (CLIAs).

The third-generation tests detect antibodies against recombinant core antigens, NS3, NS4 and NS5. These tests are high-specificity and very high sensitivity, and their window period is of 6-7 weeks. Some second-generation tests of a lesser degree of sensitivity and specificity with a window period of up to 10 weeks may still be available (20).

There are also fast tests for detecting anti-HCV antibodies on the market. These tests provide good sensitivity and specificity and can be used with different types of samples (blood, serum, plasma and oral swab), providing results in less than 30 minutes.

Immunoblots with recombinant antigens (RIBA and LIA) are also available, these tests detecting antibodies with an excellent specificity. They are used for confirmation and also make it possible to rule out false positives in the screening tests.

HCV antigen assay

Commercial assays are available for detecting the HCV core antigen in serum or plasma by means of a microplate enzyme assay (EIA) or chemiluminescence assay (CLIA). These assays detect the viremia directly and have advantages over

the PCR: They are more economical and faster. These assays are not very widespread due to their lesser degree of sensitivity with low viral loads and because the PCR is the reference technique in many guides.

Their use could have some advantages to offer in the organ donor studies for transplants if a very recent infection is suspected or in event of questionable serologies. They could also be used in monitoring viremic patients.

HCV RNA and viral load assay

HCV RNA being detected in plasma means an active infection and therefore infectivity. A negative or undetectable result does not completely rule out infection, because the virus could be located in the hepatocytes or in the lymphocytes.

Real-time PCR techniques with fluorescent probes are generally used.

This can be used in different situations: diagnosis of acute infection in window period (anti-HCV antibodies not yet detectable), diagnosis of vertical transmission, confirmation of chronic hepatitis C, for confirming the infection in patients with affected humoral immunity (not expressing anti-HCV in plasma) and for monitoring the response to the antiviral treatment (20).

Genotyping

This technique is necessary for evaluating the patient, making the prognosis and deciding as to treatment. Different methods can be used, most of which correctly detect the six main genotypes (1a, 1b, 2, 3, 4, 5, 6) although some do not identify the subtype in 10%-25% of the cases (20).

Polymorphisms

Some markers can currently be used for predicting both the evolution of the infection and the efficacy of the treatment with pegylated interferon and ribavirin. These are what are known as **Interleukin-28B gene polymorphisms**. Patients with certain genotypes considered favourable would respond better to

the treatment, besides having less of a likelihood of chronification and a greater likelihood of spontaneous viral clearance (20).

Liver damage diagnosis

Once chronic hepatitis C has been diagnosed, an assessment must be made as to the degree of severity of the liver damage, a key factor for determining the treatment strategy and the monitoring of the patients. A live biopsy can provide semi-quantitative information on the amount and the scheme of distribution of the collagen in the liver. The amount of liver collagen is usually classified using the METAVIR fibrosis scoring system, which consists of 5 stages from F0 (no fibrosis) to F4 (cirrhosis). A liver biopsy is not devoid of complications and is therefore usually reserved for evaluating patients with concomitant diseases or with discordant values of the non-invasive methods, as a result of which, in clinical practice, non-invasive tests are used instead, such as the serological tests and mainly transient liver elastography. Liver elastography provides instant information on the degree of liver stiffness and makes it possible to precisely differentiate the patients who have a high or low likelihood of advanced fibrosis or cirrhosis. Combining serological fibrosis indexes such as FIB-4 with APRI, the Forns or other combinations with the fibroscan will reduce the probability of overestimating or underestimating the fibrosis to which the fibroscan can sometimes give rise.

Estimating the magnitude of the problem

Hepatitis C virus (HCV) infection is a health problem affecting more than 185 million people in the world according to the most recently updated WHO data (14), although the geographic distribution is not homogeneous. As shown in the following table, the global seroprevalence of HCV is greater in Central and Eastern Asia and in North Africa-Middle East, with figures of 3.8%, 3.7% and 3.6%, respectively. The countries showing the highest prevalences are Egypt (15%), Pakistan (4.8%) and China (3.2%) (22).

Table 1. GLOBAL HCV SEROPREVALENCE		
REGION	PREVALENCE	ESTIMATED NUMBER OF PERSONS INFECTED
Asian Pacific	1.4	>2.4 million
Central Asia	3.8	>2.9 million
Eastern Asia	3.7	> 50 million
South Asia	3.4	> 50 million
Southeast Asia	2.0	> 11 million
Australasia	2.7	> 0.6 million
Caribbean	2.1	> 0.7 million
Central Europe	2.4	> 2.9 million
Eastern Europe	2.9	> 6.2 million
Western Europe	2.4	> 10 million
Andean Region	2.0	> 1.0 million
Central America	1.6	> 3.4 million
South America	1.6	> 0.9 million
Tropical Latin America	1.2	> 2.3 million
North Africa/Middle East	3.6	> 15 million
North America	1.3	> 4.4 million
Oceania	2.6	> 0.2 million
Central Sub-Saharan Africa	2.3	> 1.9 million
Eastern Sub-Saharan Africa	2.0	> 6.1 million
Southern Sub-Saharan Africa	2.1	> 1.4 million
Western Sub-Saharan Africa	2.8	> 8.4 million

Source: ¹⁴ WHO: *Guidelines for the screening, care and treatment of persons with hepatitis C infection*. 2014.

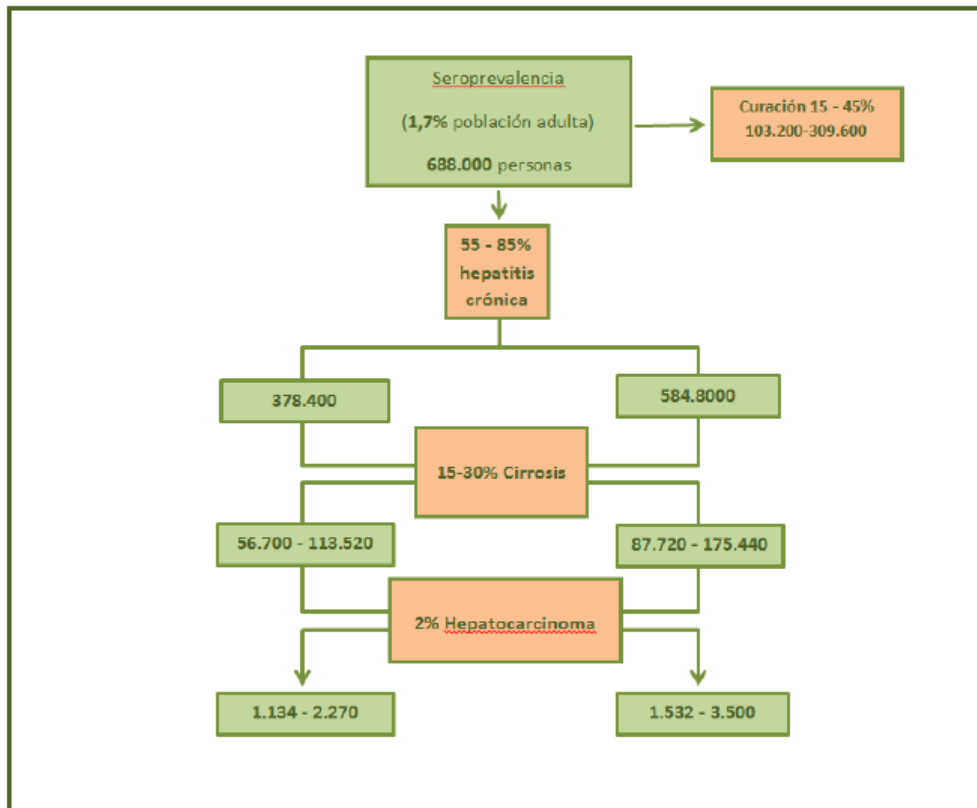
The estimated annual incidence worldwide is of 3-4 million new cases (22), the annual mortality for infection-related liver diseases being estimated at 350,000 persons a year (14).

In 2012, a total of 30,607 cases of hepatitis C were notified in Europe in 27 member countries of the EU / EEZ (not including Spain), meaning a notification rate of 7.8 cases/100,000 inhabitants, a total of 1.7% of which were reported as acute hepatitis, 12.8% as chronic, 77.5% as unknown and 8.1% of the cases having been unclassifiable. Most of the cases classified as unknown are considered as probably being chronic cases (23).

Hepatitis C was notified more often in males than in females (2:1 ratio), and more than half (54%) of all hepatitis C cases were within the 25-44 age range. A total of 9.5% of the cases were under 25 years of age. Drug injection as the transmission route totalled 76.7% of the hepatitis cases. A rise was also found to exist in the increase in the percentage of acute cases in men who have sex with men (MSM), which rose from 0.8% in 2006 to 14.6% in 2012 (23).

In Spain, the data available from recent publications shows antibody prevalence figures for adults of **1.7%** (0.4%-2.6%), a prevalence of viremia in adults of **1.2%** (0.3%-1.8%), which would mean, in absolute figures, a total of 688,000 adults with antibodies (Fig. 3) and 472,000 adults with viremia. The distribution of the cases by most frequent genotypes is as follows: **1b** (43.8%), **1a** (25.5%) and **3** (19.6% (24, 25). (Table 2)

FIG. 3: ESTIMATED EVOLUTOIN OF HCV INFECTION IN SPAIN



Source: Own work, based on:

²⁴ Gower E. et al. *Global epidemiology and genotype distribution of the hepatitis C virus infection. Journal of Hepatology* 2014 vol. 61 j S45-S57.

²⁵ Bruggmann P. et al. *Historical epidemiology of hepatitis C virus (HCV) in selected countries. Journal of Viral Hepatitis*, 2014, 21, (Suppl. 1), 5-33

14 WHO. *Guidelines for the screening, care and treatment of persons with hepatitis C infection. April 2014.*

TABLE 2. ESTIMATED PREVALENCE OF HCV IN ADULT POPULATION IN SPAIN AND MOST FREQUENT GENOTYPES	
Prevalence of anti-HCV Ac	1.7% (0.4% - 2.6%)
Adult population with anti-HCV Ac	688,000 (159,000 – 1,049,000)
Viremia rate	68.6%
Prevalence of viremia in adults	1.2% (0.3% - 1.8%)
Adult population with viremia	472,000 (109,000 – 719,000)
Genotypes Type and frequency	1a: 25.5% 1b: 43.8% 2: 3.1% 3: 19.6% 4: 8%

Estimates based on the following sources:

²⁴ Gower E. et al. *Global epidemiology and genotype distribution of the hepatitis C virus infection. Journal of Hepatology* 2014 vol. 61 j S45-S57.

²⁵ Bruggmann P. et al. *Historical epidemiology of hepatitis C virus (HCV) in selected countries. Journal of Viral Hepatitis*, 2014, 21, (Suppl. 1), 5-33

According to a review from 2006, the territorial variability is great in Spain, the prevalence below 20 years of age is having been found to be low and there being two peaks of prevalence according to age: the first being in patients born within the 1956-1971 period, which might be related to IDUs and a second peak in patients born prior to 1946, in relation to other risk factors, such as the use of glass syringes or blood transfusions prior to the systematic screening of the virus in blood having been put into place in 1990 (26).

The hepatitis C cases notified by the Autonomous Communities through the Compulsory Disease-Reporting System in effect at this time are set out in Table 3.

TABLE 3. NUMBER OF HEPATITIS C CASES BY AUTONOMOUS COMMUNITIES: SPAIN 2010-2014										
Autonomous Communities	2010		2011		2012		2013		2014	
	No. cases	Rate ¹	No. cases	Rate	No. cases	Rate	No. cases	Rate	No. cases	Rate
Andalusia	286	3.42	299	3.55	256	3.03	320	3.79	314	3.74
Aragon	46	3.41	29	2.15	32	2.37	20	1.48	50	3.77
Asturias	*	*	*	*	*	*	*	*	*	*
Balearic Islands	*	*	*	*	*	*	*	*	*	*
Canary Islands	*	*	*	*	*	*	*	*	*	*
Cantabria	7	1.18	12	2.02	5	0.84	18	3.04	18	3.06
Castile-Leon	32	1.23	31	1.21	67	2.63	76	3.02	101	4.05
Castile-La Mancha	25	1.20	31	1.47	20	0.95	29	1.39	17	0.82
Catalonia	24	--	26	--	31	--	48	--	45	--
Ceuta	*	*	*	*	*	*	*	*	*	*
Extremadura	17	--	14	--	15	--	18	--	6	--
Galicia	*	*	*	*	*	*	*	*	*	*
Madrid	50	0.77	63	0.97	73	1.12	100	1.54	68	1.05
Melilla	12	17.86	3	4.00	1	1.28	2	2.40	7	8.28
Murcia	4	0.27	5	0.34	3	0.20	1	0.07	0	0.00
Navarre	5	--	1	--	3	--	7	--	0	--
Rioja	3	0.93	9	2.79	15	4.64	13	4.04	6	1.88
Basque Country	8	0.37	11	0.51	8	0.37	13	0.60	4	0.18
Valencia	215	4.27	332	6.52	263	5.15	271	5.30	154	3.00
Total	660		777		688		788		677	

Source: Cases notified by the Autonomous Communities ¹Rate: per 100,000 inhabitants

*Data not incorporated on having been notified in a way not compatible with the information included in the Table

& There is a degree of variability in the way in which the different Autonomous Communities have notified their cases, although it can be assumed that the majority of those notified have to do with patients with anti-HCV antibodies

Detection of markers in blood donors

All blood donations have been being laboratory tested for the purpose of detecting anti-HCV antibodies since 1990, the Nucleotide Amplification Technology (NAT), also referred to as NAT techniques, being implemented in all Transfusion Centres as of 2002 for detecting this virus. All of the reactive units for any of these tests are ruled out and the donors excluded.

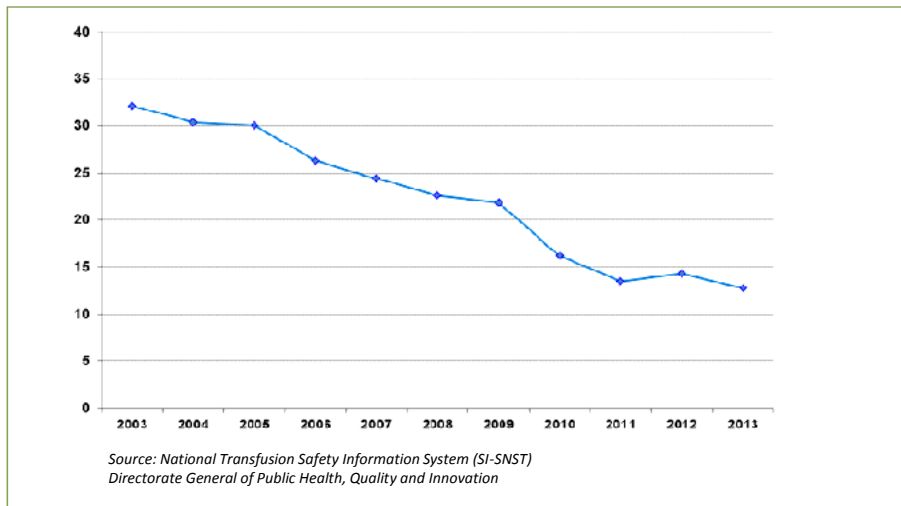
The Haemosurveillance Systems implemented in the 17 Autonomous Communities for the detection and analysis of adverse effects of transfusion have confirmed that the transmission of hepatitis C by transfusion is practically non-existent at this point in time.

Table 4. ANTI-HCV ANTIBODIES IN BLOOD DONATIONS			
	1991	1992	2013
Blood donations	1,174,397	1,217,625	1,698,097
HCV (*) donations	8,419	5,093	217
Prevalence (per 100,000 donations)	716.88	418.27	12.8
Spanish population	38,872,268	39,068,718	46,423,836
Estimated antibody carriers	278,667	163,413	5,933

Source: National Haemotherapy Plan. Spanish Ministry of Health, Social Services and Equality

Within the 2007-2013 period, a total of 13,675,915 blood components (RBC concentrates, therapeutic doses of platelets and plasma) were transfused in Spain, no case of HCV transmission having been notified. The graph below shows the clearly downward trend of the viral markers per 100,000 donations over the last ten years.

FIG. 4: Evolution of positive HCV markers per 100,000 inhabitants



Attributable mortality

In addition to being a major cause of morbidity, chronic HCV infection can lead to a patient's death. In Spain, the number of deaths attributable to HCV was estimated at 4,342 in 2000 out of a total of 360,391 deaths due to all causes (27). By extrapolating this percentage to the Spanish mortality rate for the year 2000, an annual mortality rate for this disease can be calculated as being 10.65 deaths per 100,000 inhabitants.

The mortality figures attributable to the hepatitis C virus are remaining stable, according to estimates from 2006, they would be situated with a range of 3,873 – 4,464 deaths. The mortality rate for liver disease due to hepatitis C virus is equivalent to 1% - 1.2% of the mortality rate in Spain for all causes for that same year (371,478 deaths) (28).

In 2004, a WHO advisory group was set up for the purpose of estimating the burden of Hepatitis C disease by incorporating the consequences of the chronic disease. (29). The study of the burden of disease due to hepatitis C virus within the European Region estimates that more than 90% of the burden of this disease is due to cirrhosis and liver cancer (30).

This data provides a closer idea as to what chronic HCV infection can mean as a public health problem and in terms of burden of disease, but more precise, updated evaluations are needed in order to assess the actual impact of the mortality rate attributable to HCV, taking into account, as is set out in a recent publication (15), that 80%- 85% of all chronic hepatitis C patients may die for non-liver-related causes.

Casuistics for which care is provided in hospitalization for patients diagnosed with hepatitis C. Hospital discharge records – MBDS

Throughout the last three years available, the 2011-2013 period, a total of 113,627 discharges of patients with hepatitis C were recorded. Episodes in which the diagnosis of hepatitis in any of the diagnoses on record were stated. These discharges are for approximately 26,500 patients per year.

The mean age of these patients is over 60 years of age, a total of 892 transplants having been made within those three years. Ten percent (10%) of these patients died in the hospital.

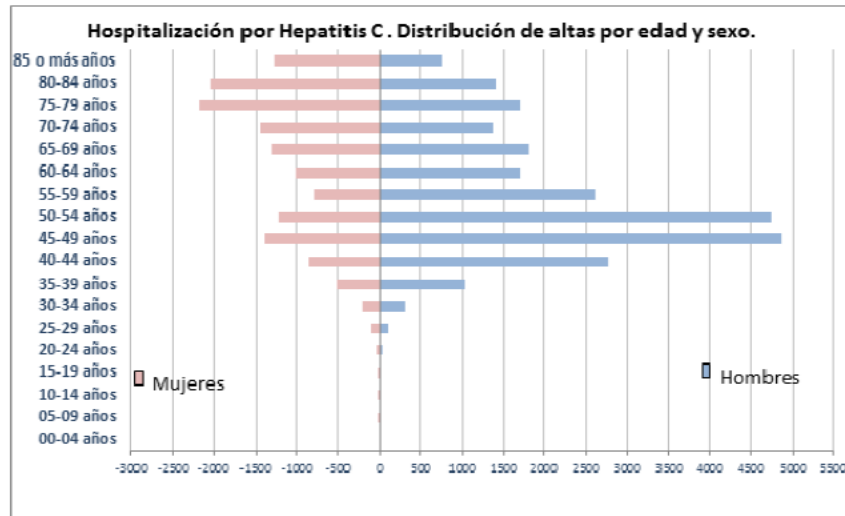
The largest number of patients is found in the association of hepatitis plus cirrhosis: 7,096 patients in 2013, also having an older average than the total number of patients, of 65 years of age, and a 16% mortality rate.

Secondly, hepatitis C with hepatoma totalled 3,200 patients in 2013, with 65 years of age as the average. Their mortality rate was the highest of the three related conditions (20%).

Those who had all three conditions (hepatitis + cirrhosis + hepatoma) totalled 2,257 in number in 2013, with an average age of 68 and an 18% mortality rate.

The distribution of the hospital discharges in 2013 by age and gender shows that nearly 2 out of every 3 discharges were males. The largest number of admissions being in males within the 40-59 age range and in females older than 70 years of age.

FIG. 5



Source: 2013 MBDS. Sub-directorate General of Health Information. Ministry of Health, Social Services and Equality.

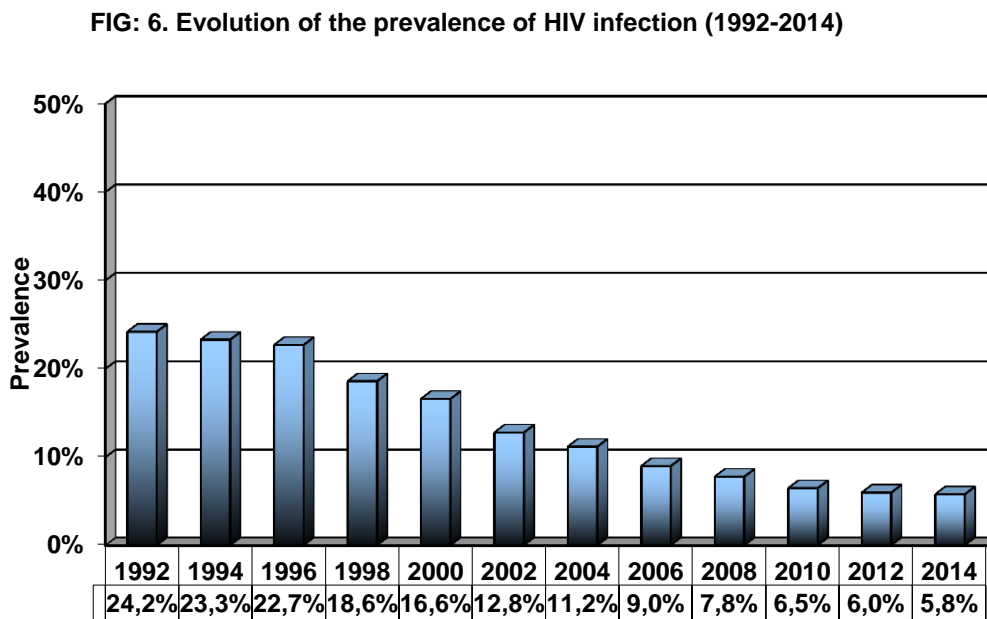
The patients with HIV-HCV coinfection totalled 4% of all of the discharges for the 2011-2013 period, although as the primary or secondary diagnosis, HIV was present in 3,960 of the 27,556 patients with Hepatitis C who were hospitalized in 2013 (14.4%). These coinfecting patients are much younger, averaging 48 years of age, and have a lower mortality rate (8.1%).

Hepatitis C virus infection in prison institutions

In prison institutions, the evolution of the prevalence of both HIC and HCV has clearly undergone a downward trend from the nineties to date, as shown in the following figures (Figs. 6 & 7). A total of 87.5% of the HIV+ inmates are coinfecting with HCV, and a total of 26.8% of the HCV+ inmates are coinfecting with HIV.

The inmates with HIV infection currently total 2,776 in number. Regarding HCV, a total of 9,063 inmates have Ac anti-HCV.

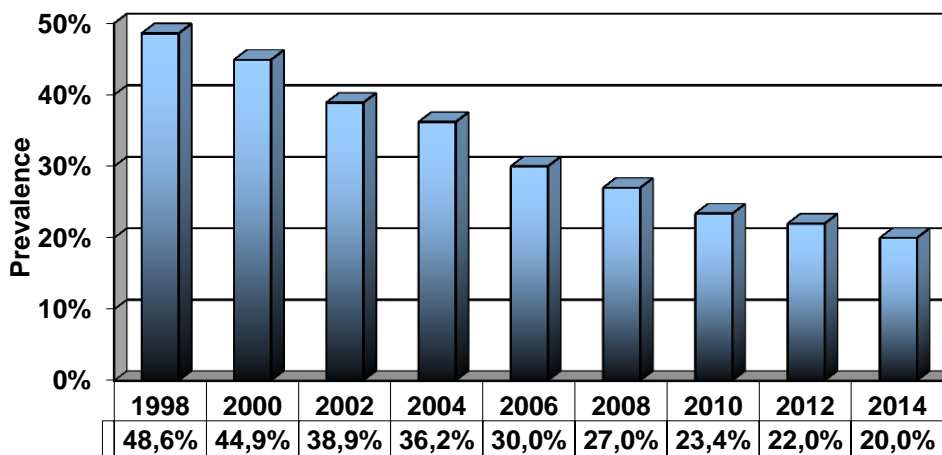
FIG: 6. Evolution of the prevalence of HIV infection (1992-2014)



Source: Ministry of the Interior. Sub-directorate General of Prison Health Coordination 2015

FIG. 7. Evolution of the prevalence of HCV infection (1998-2014)

FIG 7. Evolution of the prevalence of HCV infection (1998-2014)



Source: Ministry of the Interior. Sub-directorate General of Prison Health Coordination 2015

HCV-HIV Coinfection

A total of 4-5 million people worldwide are estimated to be coinfecting with these viruses (14), it being calculated that 20%-25% of the persons infected with HIV globally are also infected with HCV (29).

The prevalence of coinfection varies within each individual population depending on the mechanisms of transmission and depending, above all, on the addiction to injected drugs, the figures ranging widely depending from one geographical area to another (31).

The few studies available on the prevalence of viral hepatitis and HIV coinfection in our country are not nationwide studies, and in those dealing with HIV-hepatitis C coinfection, the data provided generally has to do with seroprevalence, part of these patients therefore possibly having spontaneously resolved their infection and not having chronic hepatitis (31).

HCV and HIV share transmission routes, although they differ in infectivity, HCV being more infective parenterally and HIV more infective sexually.

Coinfection with HIV has been found preferably in IDUs and haemophiliacs, although outbreaks of acute hepatitis by HCV have been described in MSM with HIV infection, probably related to certain risk practices (17, 18, 31).

This coinfection entails an added complication due either to the large number of persons affected or the negative impact of HIV infection on the natural evolution of hepatitis C (rapidly evolving into cirrhosis) or to the complexity of managing these patients, in which treatment changes can come to bear resulting from the interaction of the treatments used for each one of the infections.

It has also been found that, due to the rise in the survival rate of the persons with HIV infection following the start of the HAART, HCV coinfections and also HBV infections are a frequent cause of hospitalization and mortality of the patients with HIV infection in the developed countries (31).

The different guides recommend screening for HCV antibodies in the patients with HIV. Among other data, it has been detected that more than 80% of the patients with HIV infection and positive anti HCV have HCV RNA detectable in serum, and that 20% of the patients with HIV infection and HCV replication can have normal levels of transaminases maintained over the course of time (31).

As discussed in an article by Valdivia et al (33), it was estimated that approximately 50%-60% of patients with HIV infection had HCV coinfection in Spain at the beginning of the 2000-2010 period, which was attributed to the transmission routes of these two viruses being similar. Later, in parallel to the decline in injected drug use, a reduction occurred in HCV coinfection, an incidence of around 20% being found in the new patients infected with HIV. It is a known fact that hepatitis C evolves rapidly in HIV-HCV coinfecting patients, compared to the patients infected solely with HCV, such that the progression to cirrhosis is quite rapid. After onset of cirrhosis, the coinfecting patients also show a more rapid evolution than that of the cirrhosis patients infected only with HCV, with a lower survival rate following the first episode of clinical decompensation

of their liver disease. Some of the reasons considered to be most relevant for these facts are the role of HIV as a booster of the aggressiveness of HCV and the lower sustained response rate to the anti-HCV antiviral treatment in patients coinfecting with HIV. Other factors which might have a bearing are alcohol and cannabis use, which is relatively frequent in patients with HIV infection, and the possible hepatotoxicity of some antiretroviral drugs (33).

HCV-HBV coinfection

This coinfection is detected more often in areas where HBV is endemic, such as in certain countries in Asia, Sub-Saharan Africa and South America. In some areas, more than 25% of the persons infected with HCV are also infected with HBV (14).

The evolution of fibrosis has been found to be more rapid in those patients with HCV-HBV coinfection than in patients infected solely with HCV. The incidence of hepatocarcinoma has also been found to be greater in the coinfecting patients (1).

Tuberculosis-HCV coinfection

The persons at the greatest risk of HCV infection are the same as those at high risk of developing tuberculosis, coinfection being particularly frequent in countries where tuberculosis is endemic and hemoderivatives are not routinely tested (14).

IDUs are at the greatest risk of developing tuberculosis, depending on whether or not they have HIV infection, and it is known that two out of every three of the IDUs affected by tuberculosis have anti-HVC antibodies.

Prison institution inmates have a high risk of acquiring HCV, in addition to having a higher risk of coinfection with tuberculosis.

Properly managing the patients with HCV infection involves ruling out the existence of active tuberculosis and when this coinfection exists, a possibility of interactions and adverse effects resulting from the treatments must be taken particularly into account.
(14).

Epidemiological surveillance in the NHS

Notification of cases: Compulsory Notifiable Diseases (CNDs)

The cases of transmissible diseases are notified by the Autonomous Community Surveillance Services to the National Epidemiology Centre (CNE) in compliance with the protocols of the National Epidemiological Surveillance Network (RENAVE).

The Protocols of the Compulsory Notifiable Diseases are set out in a document approved by Spanish National Health System's Interterritorial Council on July 23, 2013 (34).

These protocols update those of 1997, their later versions. They additionally incorporate diseases which must be placed under surveillance within the framework of the European Union and the European Commission's new case definitions approved for the notification of cases of transmissible diseases within this scope.

The hepatitis C epidemiological surveillance objectives are:

- To identify the cases of infection by way of HCV incidents (cases of recent acute infection) and to describe the risk factors and practices for the purpose of identifying, preventing and keeping a check on the transmission of this disease
- To detect, investigate and control outbreaks both within the scope of the healthcare setting and those related to risk practices
- To identify and monitor the evolution over the course of time of the newly-diagnosed cases of HCV infection and the basic epidemiological characteristic thereof in order to avail of information making it possible to aim the policies for the prevention and control of this disease in the population in the right direction.

As far as how this surveillance is carried out is concerned, the Autonomous Communities have to notify the confirmed cases of recent acute infection on an individual basis to the National Epidemiology Centre (CNE) through the National Epidemiological Surveillance Network (RENAVE). The information included in the epidemiological survey of the case must be sent in on a recommended monthly basis.

The information on the case may be updated after initially having been declared, which must be done with annual consolidation of the information. The cases of resolved infection do not have to be notified.

In the event of an outbreak, the Autonomous Community Surveillance Service shall send the final report of the outbreak to the National Epidemiology Centre (CNE) within the three-month period commencing as of the date on which it has fully completed its investigation. The epidemiological surveys of the cases involved must also be sent to the National Epidemiology Centre (CNE).

If a supra-community outbreak is suspected, or when the magnitude of the outbreak or the scheme of spread require national coordination measures, the Autonomous Community Surveillance Service shall urgently inform the Early Health Warning and Emergencies Coordination Centre (CCAES) and the National Epidemiology Centre of the Ministry of Health, Social Services and Equality. This Early Health Warning and Emergencies Coordination Centre must make an assessment in conjunction with the Autonomous Communities affected as to the measures to be taken and, in the event necessary, the notification thereof to the European Union Early Warning and Fast Response System and to the WHO in compliance with the International Health Regulations.

Table 5 shows the number of hepatitis C outbreaks in Spain for the 1997-2013 period, along with the scope within which these outbreaks occurred.

In addition to the above, the surveillance of new HCV diagnoses will progressively be implemented. Initially, those Autonomous Communities which voluntarily undertake the commitment of taking part in this activity and which conduct the surveillance of these cases in all or in part of their territory for which they can define the reference population will be included. This surveillance system will be evaluated annually as part of the Epidemiology Surveillance Report with the intention of promoting its being extended to all of the Autonomous Communities. The newly-diagnosed cases detected will be notified annually to the National Epidemiological Surveillance Network

(RENAVE) through the National Epidemiology Centre (CNE) in conjunction with basic demographic data along with the reference population of the area under surveillance, by gender and age.

Table 5. HEPATITIS C OUTBREAKS IN SPAIN. 1997-2013				
YEAR	Autonomous Community	CASES	WHERE	REMARKS
1997	Aragon	2	Healthcare Inst.	
1998	Valencia	197	Healthcare Inst.	Anaesthesia
1998	Extremadura	15	Healthcare Inst.	Haemodialysis
1999	Madrid	2	Healthcare Inst.	
2000	Catalonia	11	Healthcare Inst.	Emergency Service
2001	La Mancha	18	Healthcare Inst.	Haemodialysis
2001	La Mancha	18	Healthcare Inst.	Haemodialysis
2001	Madrid	4	Healthcare Inst.	
2002	Andalusia	11	Healthcare Inst.	Oncology
2002	Valencia	3	Healthcare Inst.	Haemodialysis
2003	Madrid	8	Healthcare Inst.	Oncology
2004	Madrid	3	Healthcare Inst.	Illeocavusgraphy
2004	Catalonia	3	Healthcare Inst.	Contrast CAT
2006	Valencia	3	Healthcare Inst.	
2006	Valencia	2	Healthcare Inst.	Transfusion. Partner
2006	Canary Islands	5	Healthcare Inst.	Haemodialysis
2007	Valencia	7	Healthcare Inst.	Haematology
2009	Andalusia	5	Healthcare Inst.	Multidose vial use. Traumatology.
2010	Balearic Islands	3	Healthcare Inst.	Haemodialysis
2011	Madrid	2	Healthcare Inst.	Haemodialysis
2012	Aragon	2	Family	Partner
2013	Andalusia	4	Healthcare Inst.	Operating room
2013	Valencia	2	Family	Partner. Ex-IDU

Source: National Epidemiological Surveillance Network (RENAVE). National Epidemiology Centre (CNE) 2014.

2. GENERAL OBJECTIVE

To reduce the morbi-mortality caused by the hepatitis C virus (HCV) among Spain's population by efficiently tackling the prevention, diagnosis, treatment and follow-up of these patients.

3. STRATEGIC DIRECTIONS, SPECIFIC OBJECTIVES AND PROPOSED ACTIONS

3.1 STRATEGIC DIRECTION 1

Quantify the magnitude of the problem, describe the epidemiological characteristics of the patients with hepatitis C virus infection and determine the measures for prevention.

3.2 STRATEGIC DIRECTION 2

Define the scientific-clinical criteria making it possible to determine the appropriate treatment strategy considering the use of direct-acting antiviral drugs for the treatment of hepatitis C within the scope of the Spanish National Health System.

3.3 STRATEGIC DIRECTION 3

Establish the coordination mechanisms for the appropriate implementation of the Strategy for tackling hepatitis C in the Spanish National Health System.

3.4 STRATEGIC DIRECTION 4

Foster the advancement of the knowledge of the prevention, diagnosis and treatment of hepatitis C in the Spanish National Health System through specific actions in the field of R&D&I.

3.1 STRATEGIC DIRECTION 1

QUANTIFY THE MAGNITUDE OF THE PROBLEM, DESCRIBE THE EPIDEMIOLOGICAL CHARACTERISTICS OF THE PATIENTS WITH HEPATITIS C VIRUS INFECTION AND DETERMINE THE MEASURES FOR PREVENTION.

3.1.1. SPECIFIC OBJECTIVES:

3.1.1.1 *Quantify the magnitude of the problem and describe the epidemiological characteristics of the patients with hepatitis C infection.*

3.1.1.2 *Primary prevention: Reduce the incidence of hepatitis C*

3.1.1.3 *Secondary prevention: Promote early diagnosis in priority populations*

3.1.1.4 *Tertiary prevention: Prevent the morbi-mortality and the complications resulting from chronic HCV infection*

3.1.2 PRIORITY ACTIONS

3.1.2.1 *Quantify the magnitude of the problem and describe the epidemiological characteristics of the patients with hepatitis C infection.*

Once the most relevant articles and reports published in the scientific literature concerning the clinical-epidemiological characteristics of the patients with chronic HCV infection, valid, updated information providing an exact description of the current status of Hepatitis C in Spain was found to be scant, it therefore being necessary to set up, develop and implement some valid, reliable, assessable information systems of broad-ranging territorial coverage which will make it possible to avail of the basic data for evaluating the magnitude of the problem and for decision-making purposes.

The basic epidemiological parameters necessary for monitoring the epidemic would be the prevalence of the infection and the annual incidence.

It will also be necessary to implement a registry of the patients treated with antiviral drugs in the Spanish National Health System for a proper surveillance of the progression of this disease.

SPECIFIC ACTIONS PROPOSED

1. Conducting a hepatitis C seroprevalence survey on the adult population
2. Implementing the newly-diagnosed case information system: National Epidemiological Surveillance Network (RENAVE)
3. Designing and implementing a registry of patients with hepatitis C treated with antiviral drugs in the Spanish National Health System

3.1.2.2 Primary prevention: Reduce the incidence of Hepatitis C

At the current point in time, no vaccines exist for preventing HCV infection, the primary prevention therefore consisting of reducing the risk of exposure to the virus, mainly in the high-risk groups of population: among injected drug users; in healthcare settings; in MSM with risk sexual practices and in patients with HIV infection.

Primary prevention interventions recommended by the WHO:

- Hand hygiene: washing hands and wearing gloves, including hand preparation for surgery
- Safe handling and disposal of sharp objects and contaminated waste
- Safe cleaning of the medical-surgical equipment
- Analysis of donated blood
- Training of the healthcare personnel

PRIORITY ACTIONS PROPOSED

1. Inform the general population in order to prevent further infections: Prepare a WEBPAGE, available at the Spanish Ministry of Health, Social Services and Equality, for providing the public with basic knowledge concerning HCV infection and the mechanisms of the transmission of the hepatitis C virus, including a Frequently Asked Question section. This page would be located on the Ministry of Health, Social Services and Equality website and would have links to each Autonomous Community's Health Department website.
2. Training the professionals: Design and develop a continued education and training program on the infection by hepatitis C virus to be offered for the healthcare personnel working in both Primary Care and Specialized Care, adapted to each individual Autonomous Community's needs and training offer.
3. Maintain and bolster the harm reduction programs for increasing the availability for accessing and using sterile material among injected drug users, especially in prison institutions.
4. Set up screening programs for pregnant women at a higher risk of exposure to the infection.
5. Maintain the test checks of the transfusions of blood and hemoderivatives.
6. Reinforce and update, wherever applicable, the recommendations for preventing biological risks in invasive diagnostic and treatment procedures, as well as the Protocols for Biological Risks at the workplace.
7. Inform and educate patients with HCV as to the risk of transmission to the persons with whom they are living.
8. Review full compliance with the mechanisms for the inspection of establishments where piercing and tattooing is done.

9. Assess placing priority on early HCV infection diagnosis projects in HIV patients for the purpose of detecting coinfection, in the announcements of applications for grants for HIV and AIDS prevention programs of the National AIDS Plan.

3.1.2.3 Secondary prevention: Promote early diagnosis in priority populations

Despite the fact that the incidence of this disease is on the decline, the burden of this disease in terms of cirrhosis and its complications will be increasing over the next few years for reasons including diagnosis being very late (34). Many people infected are unaware of the infection, it being estimated that solely 24% - 35% of the patients with active infection are diagnosed (36).

The diagnosis of the HCV infection entails a benefit both from the individual standpoint (reduction of the patient's morbi-mortality because care is then provided for the patient by the health system) and from the public health standpoint, because the transmission of the virus can be reduced.

Screening programs are necessary for preventing the silent progression of this disease, taking into account that due to their greater risk of infection, the top-priority populations are as follows:

- Injected and sniffed drug users
- Patients treated with blood products prior to 1990
- Patients exposed to nosocomial hepatitis C infection
- Persons living with chronic hepatitis C patients
- Persons with tattoos or piercings and exposed to procedures using sharp-pointed instruments without suitable hygienic-sanitary control (acupuncture and mesotherapy)
- Children of mothers who have HCV infection

- Healthcare professional exposed to procedures involving biological risks
- Patients in haemodialysis (37)
- Men who have risk-involved sexual relations with men
- Patients infected with HIV
- Patients infected with HBV or TB
- Prison Institution inmates

PRIORITY ACTIONS PROPOSED

1. Prepare a *Guide of Recommendations for Early HVC Diagnosis* in top-priority populations within the Primary Care scope.
2. Set up a program for collaborating with prison institutions for improving HCV prevention and diagnosis.
3. Reinforce and update, wherever necessary, the protocols for the prevention of biological risks at the workplace for a better surveillance of the health of the workers infected with HCV.

3.1.2.4 Prevent the morbi-mortality and the complications resulting from chronic HCV infection

The following is recommended to all of the persons infected with the hepatitis C virus:

- Information and counselling regarding care and treatment options
- Immunisation with vaccines against hepatitis A and B for preventing coinfection by these hepatitis viruses and safeguard their livers
- Early, adequate medical care, including, if applicable, antiviral therapy

- Regular follow-up for the early diagnosis of chronic liver disease

It is recommended that the degree of alcohol consumption be evaluated for all of the persons with HCV infection to then offer an intervention aimed at reducing this consumption in those persons whose consumption is moderate to high, due to the risk of rapid progression of the disease. Foster adherence to the treatment and clinical follow-up and prevent the adverse effects related to the treatment.

The likelihood of reinfection must not be overlooked. According to a meta-analysis presented at the AASLD Congress in November 2014, the risk of reinfection is 8.5% at 5 years in IDUs and Prison Institution inmates and up to as high as 23.4% in these same groups when they are coinfecting with HIV (38).

PRIORITY ACTIONS PROPOSED

1. Prepare a Clinical Care Guide for Patients with HCV Infection which will deal with aspects including the following:
 - Advice concerning healthy lifestyles
 - Alcohol consumption assessment
 - Diagnosis of possible coinfections: HIV, HBV, TB
 - Follow-up and evaluation of degree of fibrosis

3.2 STRATEGIC DIRECTION 2:

DEFINE THE SCIENTIFIC-CLINICAL CRITERIA TO DETERMINE THE APPROPRIATE TREATMENT STRATEGY CONSIDERING THE USE OF DIRECT-ACTING ANTIVIRAL DRUGS FOR THE TREATMENT OF HEPATITIS C WITHIN THE SCOPE OF THE NATIONAL HEALTH SYSTEM.

3.2.1. SPECIFIC OBJECTIVES:

- 3.2.1.1 Determine the clinical parameters in the patients with chronic HCV (CHC) which will make the appropriate characterization of the patient subject to treatment, the virological and clinical follow-up**
- 3.2.1.2 Characterize the centres which are going to carry out the control and follow-up on these patients**
- 3.2.1.3 Set out the general criteria for treating CHC in the Spanish National Health System**
- 3.2.1.4 Define the CHC treatment strategy applicable in the Spanish National Health System, considering the medicines available.**

These are presented in following, respecting the structuring of the document presented by the editing group.

3.2.2 PRIORITY ACTIONS

The treatment of the patients with chronic hepatitis C is currently undergoing numerous changes as a result of the official approval of one new oral anti-HCV direct-acting antiviral drug after another within a short period of time. These new prescription drugs plus others currently pending approval for marketing and decision-making concerning pricing and reimbursement are now adding to the combinations available for treating patients in different clinical situations, according to viral genotype and specific stage of the disease.

Given the growing arsenal of prescription drugs already approved plus those currently being researched for the treatment of these patients, the inherent variability of the clinical situations with which the clinics are confronted, the differences in the research conducted and the outcomes achieved with the medicines, as well as the difficulty of immediately dealing with treating all of the patients, makes it necessary to set out a strategy and orderly system for access to these new medicines.

The strategy proper will be updated in light of the new medicines, new knowledge concerning the outcomes achieved and the experience acquired by the Health Services professionals during the use of these treatments. In short, this strategy will continue to be implemented as new medicines are progressively incorporated and will gather together, in practice, those recommendations and general evaluations for the Spanish National Health System (NHS) which are set out in the respective Therapeutic Positioning Reports which propose the ways and routes for accessing treatment specific to likewise specific clinical situations.

For the time being and throughout the upcoming months, in order to maintain an orderly incorporation of the new treatments within the Spanish National Health System, priority will be placed on the use thereof in the patients with significant liver fibrosis and all those in the transplant scenario, whether liver or non-liver (waiting list and those persons already transplanted). This priority-setting strategy, which does not take in efficiency-related criteria, will be reviewed at least once every six months in

accordance with the new evidence available, the changes in the situation regarding the marketing and funding of new drugs and the effectiveness-related results in the patients who are progressively treated within the framework of the Spanish National Health System (NHS).

3.2.2.1 Determine the clinical parameters in the patients with chronic HCV (CHC) which will make the appropriate characterization of the patient subject to treatment, the virological surveillance and the clinical follow-up.

In the patients with chronic hepatitis C virus (CHC), the following clinical evaluation is necessary:

1. Classification of the patients with CHC in terms of whether or not the patient has undergone prior treatment and the response achieved.
 - a. Treatment-naïve patients
 - b. Patients with treatment failure to dual antiviral therapy (pegylated interferon and RBV) and to first-generation protease inhibitors
 - i. Relapsing patients
 - ii. Non-responding patients
2. Virological characterization of the HCV infection: Assay of the genotype, subtype and viral load. It is reasonable, in all patients, to rule out the existence of a coinfection by HBV and/or HIV by means of testing the suitable serological markers.
3. Evaluation of the degree of liver fibrosis. The development of fibrosis is a dynamic, non-linear process which varies from one patient to another, therefore assessments must repeatedly be made over the course of time by means of any of the following procedures:
 - a. Liver biopsy
 - b. Transient elastography or Fibroscan

- c. Combining serological indicators of fibrosis, such as FIB-4, APRI, Forns or others with the Fibroscan will reduce the likelihood of overestimating or underestimating the fibrosis to which the Fibroscan can sometimes lead.
4. IL28B polymorphism and Q80K baseline polymorphism assay solely if the HCV is genotype 1a and the treatment option with Simeprevir with pegylated interferon and RBV is being considered.
5. Virological follow-up:
 - a. All of the patients treated must be monitored by means of conducting the HCV-RNA test during the treatment and at weeks 4 and 12 following the end of the treatment for the purpose of confirming the virological cure of disease (equivalent to sustained virological response). In patients with liver cirrhosis at the point in time of commencing the antiviral treatment, the virological cure of the infection is not exactly the same as the complete cure of the disease. This is the reason why the patients with cirrhosis should be monitored despite the virological cure having been achieved.
 - b. It is recommended that the sustained virological response (SVR) be checked at 6-12 months immediately following the first negative HCV-RNA test.
 - c. Bearing in mind the risk of reinfection, it is advisable to annually monitor the HCV-RNA in patients with risk behaviours.
6. Clinical follow-up:
 - a. In patients with compensated cirrhosis, without esophageal varices at the start of treatment, if there are no other concomitant causes of liver disease, it is not necessary to for endoscopic check-ups to be conducted following the SVR, although these check-ups will be continued in those cases in which they had previously been being conducted.

- b. In patients with compensated cirrhosis, the follow-up schedule must be maintained for the early diagnosis of liver cell carcinoma following the SVR.
7. The SVR is associated with a reduction in the hepatic venous pressure gradient and therefore a lowering of the risk of decompensation and an improvement of the liver disease in patients with decompensated cirrhosis. A marked lowering of the risk of death, hepatocarcinoma and liver transplant at 5 years has been found to exist in those patients in whom the cure of the infection has been achieved.

3.2.2.2 Characterize the centres where the control and follow-up on these patients is going to be carried out.

The incorporation of the new treatments for CHC in clinical practice poses a care-providing, teaching and researching challenge. Although the rate of adverse effects has drastically declined as compared to former therapies, interactions among medications and undesirable effects still continue to exist, making a multidisciplinary approach and constant updating necessary for decision-making purposes. In addition to the foregoing, the logistics of the way in which microbiology laboratories function must enable fast access to the viremia results during the treatment so as to be able to take rational, efficient action. Unduly prolonging the treatment increases the likelihood of resistance mutations arising in the virus, increasing the number of adverse effects of the drugs and unnecessarily raising the cost.

The decision of treatment and the follow-up thereof (at least the visits at week 12 or week 24 of treatment) must be made in units which meet a number of minimum requirements for the correct management and optimum surveillance of patient safety. It is essential that care be provided for the most complex patients within the context of units having practical experience in detecting and dealing with the potential complications. The suitability of the centres is particularly relevant in the F4 patients with advanced disease, patients coinfecting with HIV and transplanted patients. The possibility of consulting with

specialists who can deal with the management of extra-hepatic manifestations is indispensable.

Some of these treatments require some strict rules for suspension which are governed by the HCV-RNA test, which must be conducted often. Any centre or unit which uses these medicines must avail of the results of this test within at least one week's time (maximum 7 days). Similarly, they must be able to avail of the results of the IL28B or Q80K polymorphism regularly.

More specifically, it is recommended that the centres fully meet the following requirements:

- ***Physicians who have wide-ranging experience in managing patients with chronic hepatitis and both compensated and decompensated cirrhosis of the liver and who have used oral antiviral drugs when treating hepatitis C..***
- ***The patients with decompensated cirrhosis who are potential candidates for liver transplant shall be treated at Level 3 or 4 hospitals preferably linked to a transplant program.***
- ***Additional means available:***
 - ***Fibroscan***
 - ***Abdominal echography***
 - ***Additional means accessible:***
 - Rapid (less than a week), serial-numbered HCV-RNA test
 - 28 B interleukin (IL28B) polymorphism assay
 - Q80K polymorphism assay in patients with a genotype 1a infection in which the triple interferon-based therapy is being considered

- Complete records must be kept fully meeting the requirements set out in the Registry of the patients treated with antiviral drugs enabling the Spanish National Health System to verify the proper follow-up on the evolution of the disease.

3.2.2.3 Set out the general criteria for treating CHC in the Spanish

National Health System

- All patients with a CHC, whether monoinfected or coinfecting with HIV, who are treatment-naïve must be considered candidates for antiviral treatment.
- All patients with a CHC, whether monoinfected or coinfecting with HIV, who have not responded to a prior antiviral treatment (independently of the type undergone) must be re-evaluated as candidates for a new antiviral treatment.
- Due to the magnitude of this infection in our country, priority must be given to treating those patients who have significant liver fibrosis and/or clinically relevant extra-hepatic manifestations which compromise the clinical situation of the patient in terms severity and prognosis, especially mixed cryoglobulinemia with extra-hepatic manifestations of vasculitis, B-cell non-Hodgkin lymphoma, late cutaneous porphyria, extensive insulin-resistant lichen planus or type 2 diabetes mellitus.
- The top-priority groups of patients for treatment with oral direct-acting antiviral drugs include:
 - Patients with advanced liver fibrosis (F2-F4), independently of whether or not there are any pre-existing complications of the liver disease
 - Patients on a waiting list for transplant (liver or non-liver)
 - Liver transplant patients with relapse of the infection in the liver graft, independently of whether or not complications exist and of the stage of fibrosis
 - Patients who have not responded to triple therapy with first-generation protease inhibitors
 - Non-liver transplant patients with hepatitis C, independently of the stage of liver fibrosis
 - Patients with hepatitis C with clinically relevant extra-hepatic manifestations of the HCV, independently of the stage of liver fibrosis.
- In these patients, save exceptional cases, the treatment regimen chosen must be interferon-free.

- In the patients with F0-F1 fibrosis, treatment may be deferred and the indication thereof considered individually. These patients must be closely monitored and treated if any relevant changes take place in their evolution or in the progression of their disease.
- In any case, independently of the degree of fibrosis, treatment must be indicated in:
 - Patients at high risk of transmission of the infection
 - Child-bearing aged women expressly wishing to become pregnant
- The treatment-related recommendations included in this document are applicable for both the patients who are monoinfected and patients who are coinfecting with HIV.
- The HCV antiviral therapy must be prescribed by a physician who has a great deal of experience in treating chronic liver disease and who has used oral antiviral drugs in treating hepatitis C.
- The following general rules are set for interferon-free oral antiviral drug therapy:
 - The recommended duration of the treatment in patients undergoing interferon-free regimens with two or more oral antiviral drugs is, as a rule, 12 weeks, depending on the medicine used. Occasionally, the treatment may be either longer or shorter than 12 weeks (39).
 - It is advisable to add RBV to the established treatment regimen, although this must be individualized in terms of the individual patient's characteristics and tolerance, given that, in some cases, this makes it possible to shorten the treatment from 23 weeks to 12 weeks.
 - Patient response-guided therapy must not be used in patients undergoing therapy with interferon-free direct-acting antiviral agents.
- The treatment-related recommendations included in this document are not intended to take place of the clinical guides which the different national and international professional associations have recently published or will be publishing in the near future.

3.2.2.4 Define the CHC treatment strategy applicable in the Spanish National Health System, considering the medicines available.

The treatment strategy is based on the criteria of efficacy of the drugs, safety and therapeutic need. The factors which define the different treatment options are the genotype and stage of fibrosis.

The suggestions made have been based on the analysis of the technical data sheets of the medicines which have been granted approval for marketing, in the different therapeutic positioning reports published by the Spanish Agency of Medicines and Medical Devices and the latest scientific evidence.

Genotype 1, significant fibrosis (F2-F4)

The patients infected with genotype 1 with significant fibrosis (F2-F4) who are treatment-naïve or who have not responded to a prior treatment must be treated with one of the interferon-free oral antiviral drug treatment prescription schemes indicated in following. In the majority of the treatment regimens recommended, no comparisons exist among the different schemes. The treatment regimens currently available are:

- sofosbuvir plus simeprevir with/without RBV
- sofosbuvir plus daclatasvir with / without RBV
- sofosbuvir plus ledipasvir with / without RBV
- paritaprevir/ritonavir, dasabuvir and ombitasvir with without RBV

Patients in whom treatment with protease inhibitors failed

All of the patients in whom the triple therapy based on first-generation protease inhibitors has failed must undergo treatment with PEG-IFN-free DAAs.

- sofosbuvir plus simeprevir with RBV
- sofosbuvir plus ledipasvir with RBV
- sofosbuvir plus daclatasvir with RBV

For the time being, no information exists comparing the outcomes with paritaprevir/tironavir, dasabuvir and ombitasvir.

Genotype 2, significant fibrosis (F2-F4)

The patients infected with genotype 2 with significant fibrosis (F2-F4) who are treatment-naïve or who have not responded to a prior treatment may be treated with one of the drug treatment prescription schemes indicated in following. The treatment regimens currently available and recommended in treatment-naïve patients or patients who have not responded to a prior treatment (with an efficacy higher than 90%) are:

- sofosbuvir and RBV
- sofosbuvir plus RBV, plus PEG-IFN plus if the latter is tolerated or in patients with cirrhosis who have not previously responded

Genotype 3, significant fibrosis (F2-F4)

The patients infected with genotype 3 with significant fibrosis (**F2-F4**) who are treatment-naïve or who have not responded to a prior treatment may be treated with the drug treatment prescription schemes indicated in following. The treatment regimens which are currently available at this point in time are:

- sofosbuvir plus daclatasvir with / without RBV
- sofosbuvir plus ledipasvir with / without RBV
- sofosbuvir plus RBV and PEF-IFN, in patients subject to being treated with PEF-IFN and in patients with cirrhosis who have not previously responded

Solely for patients with fibrosis F2-F3, as they are less than optimum combinations (SVR rates of under 70%) for patients with cirrhosis:

- sofosbuvir plus daclatasvir
- sofosbuvir plus RBV

–

Genotype 4, significant fibrosis (F2-F4)

The patients infected with genotype 4 with significant fibrosis (F2-F4) who are treatment-naïve or who have not responded to a prior treatment may be treated with the drug treatment prescription schemes indicated in following. In the case of genotype 4, all of the regimens stated have an efficacy of over 90%. The treatment regimens currently available are:

- Treatment-naïve and relapses
 - sofosbuvir plus ledipasvir
 - sofosbuvir plus daclatasvir
 - paritaprevir/ritonavir plus ombitasvir plus RBV in non-cirrhotic patients
 - sofosbuvir plus simeprevir. There are no existing outcomes for this combination, however outcomes similar to those reported for Genotype 1 are anticipated.
- Non-responders
 - sofosbuvir plus simeprevir with/without RBV
 - sofosbuvir plus ledipasvir with / without RBV
 - sofosbuvir plus daclatasvir with / without RBV
 - paritaprevir/ritonavir plus ombitasvir plus RBV in non-cirrhotic patient

Patients infected with HCV genotype 5 and 6

Genotypes 5 and 6 have a very low prevalence in Spain, and their treatment will be individualized, case by case. They have been treated similarly to genotype 1, that is to say, with PEG-IFN and RBV for 24 weeks, with SVR slightly higher than genotype 1. At this point in time, the only alternative to dual therapy with PEG-IFN and RBV available would be Sofosbuvir plus PEG-IFN and RBV for 12 weeks, based on the data from 7 patients (one patient with genotype 5 and six patients with genotype 6) where all achieved SVR (NEUTRINO study) (40).

SPECIAL POPULATIONS

Patients with C virus-related liver cirrhosis and with Liver Transplantation (LT) requirements

The antiviral treatment is recommended for all patients on a liver transplantation (LT) list for the purpose of preventing the reinfection of the graft. The optimum duration of the therapy has not been determined, but the risk of reinfection is minimized if it is managed for the patient to be transplanted following a virus-free period of at least 30 days. An improvement in liver function which avoids or delays the need of transplant is also possible (26) (41). The PEG-IFN therapies are contraindicated in patients with advanced cirrhosis, due to the high risk of severe and potentially fatal complications (27) (42). The PEG-IFN-free combinations include:

- sofosbuvir plus simeprevir with/without RBV
- sofosbuvir plus daclatasvir with / without RBV
- sofosbuvir plus ledipasvir with / without RBV
- paritaprevir/ritonavir, dasabuvir and ombitasvir with RBV

Transplanted patients with recurrence of HCV infection

The post-transplant hepatitis C treatment is indicated in all patients. This must be carried out with PEG-IFN-free therapies. It is difficult to determine the priority of one treatment regimen over another due to the paucity of data currently available, although the majority of the combinations with which trials have been conducted have shown themselves to be more than 85% effective in patients with a compensated disease, with excellent tolerance. Similarly, neither the need for RBV nor the duration of the antiviral regimen has been determined in all certainty, although the tendency is to add RBV in patients with an advanced disease.

Patients with decompensated cirrhosis

The patients with decompensated cirrhosis (Child-Pugh 6-12 and/or MELD <20) are candidates for taking antiviral treatment. In these patients, in addition to the SVR, it is extremely important to evaluate the improvement of liver function. In fact, in critical situations (decompensated cirrhosis and fibrosing cholestatic hepatitis), the deleterious consequences of the liver cell insufficiency may take precedence over the control of the viral infection (30) (43). The degree of evidence, both in terms of safety and in terms of efficacy is quite low in Child-Pugh C >12 patients. The treatment regimens available are:

- Genotype 1 patients:
 - o sofosbuvir plus daclatasvir with / without RBV
 - o sofosbuvir plus ledipasvir with / without RBV
- Genotype 2 patients:
 - o sofosbuvir plus RBV
- Genotype 3 patients:
 - o sofosbuvir plus ledipasvir with / without RBV
 - o sofosbuvir plus daclatasvir with / without RBV
- Genotype 4 patients:
 - o sofosbuvir plus ledipasvir plus RBV
 - o sofosbuvir plus daclatasvir with / without RBV

Patients coinfecting with HIV/HCV

In patients coinfecting with HIV and HCV, the liver disease progresses more rapidly, and they have a greater risk of evolving into cirrhosis, decompensation and death for liver-related causes than the patients monoinfected with HCV (36) (44). Besides, the coinfection with HCV can favour the progression of the HIV infection (37) (45). The treatment must be identical to that of the patients monoinfected with HCV. Special attention must be focused on the potential risk of interactions (46).

Final comments

This treatment strategy revolves around the use of the new DAAs, nevertheless, and always when medically indicated, any of the medicines authorized and funded in the Spanish National Health System (NHS) for the treatment of chronic hepatitis C virus may be used (See Table 6).

Table 6. MEDICINES AUTHORIZED AND FUNDED BY THE SPANISH NATIONAL HEALTH SYSTEM FOR TREATING HEPATITIS C			
ACTIVE INGREDIENT	BRAND NAME	APPROVED FOR SALE	LISTED AS FUNDED
Interferon alfa-2a	ROFERON®	01-01-1989	11-01-1991
Ribavirin	REBETOL®	06-01-1999	11-25-1999
Peginterferon alfa-2b	PEGINTRON®	07-06-2000	04-24-2001
Peginterferon alfa-2a	PEGASYS®	07-04-2002	01-09-2003
Ribavirin EFG	RIBAVIRIN EFG	05-07-2009	12-01-2009
Boceprevir	VICTRELIS®	07-27-2011	11-01-2011
Telaprevir	INCIVO®	09-30-2011	01-01-2012
Sofosbuvir	SOVALDI®	03-05-2014	11-01-2014
Simeprevir	OLYSIO®	06-03-2014	08-01-2014
Daclatasvir	DAKLINZA®	09-08-2014	02-01-2015
Sofosbuvir-ledipasvir	HARVONI®	12-15-2014	04-01-2015
Ombitasvir+paritaprevir +ritonavir	VIEKIRAX®	02-03-2015	04-01-2015
Dasabuvir	ECVIERA®	02-03-2015	04-01-2015

As previously mentioned, the prioritization strategy is intended as a tool for orderly access on the part of the Spanish National Health System patients to the new treatments for hepatitis C within the framework of the conditions of public funding of these medicines. Therefore, this tool shall be updated in terms of the scientific evidence set out in the updates of the different therapeutic positioning reports published (39) (47), of the effectiveness-related results in the patients in

terms of the information obtained from the Registry of patients with chronic hepatitis C infection treated with antiviral drugs in the Spanish National Health System (NHS) and the availability of new treatments.

3.3 STRATEGIC DIRECTION 3:

ESTABLISH THE COORDINATION MECHANISMS FOR THE APPROPRIATE IMPLEMENTATION OF THE STRATEGY FOR TACKLING HEPATITIS C IN THE NATIONAL HEALTH SYSTEM.

3.3.1 SPECIFIC OBJECTIVES

- 3.3.1.1 Know all of the therapeutic measures which are currently being carried out in relation to the hepatitis C virus within the framework of the Spanish National Health System.**
- 3.3.1.2 Guarantee access to the new antiviral drugs under conditions of equity to those patients who require them.**
- 3.3.1.3 Monitor the therapeutic effectiveness and the health outcomes in the patients treated.**
- 3.3.1.4 Harmonize insofar as possible the actions of all of the players involved.**

3.3.2 PRIORITY ACTIONS

3.3.2.1 Appointment of the Institutional Committee for the Plan

This Committee is created with the mission of seeing to the proper implementation of the Plan. A Plan representative appointed by each Autonomous Community, a representative from the Carlos III Health Institute, from prison institutions and representatives from the executive management centres of the Spanish Ministry of Health, Social Services and Equality, including the Spanish Agency of Medicines and Medical Devices (see Annex VI) will serve on said Committee.

1. Regular meetings with the Plan representatives from the Autonomous Communities and the other members serving on the Institutional Committee.
2. Place priority on TPR for the new drugs which have recently come on the market.
3. Shorten the length of time necessary for putting the new antivirals on the market.

3.3.2.2 Definition by each Autonomous Community of the Plan implementation strategy most appropriate on the part of the Institutional Committee for the Plan

Through said strategies, tasks including the monitoring of the proper completing and exchange of data of the patient Registry of each Autonomous Community.

3.3.2.3 Guarantee access to the new antiviral drugs under conditions of equity to those patients who require them.

1. Place priority on TPR for the new drugs which have recently come on the market.
2. Shorten the length of time necessary for putting the new antivirals on the market.

3.3.2.4 Monitor the therapeutic effectiveness and the health outcomes of the patients treated

1. Reach a consensus with the Autonomous Communities as to the form for collecting the registry data.
2. Integrate into the online information System supporting the Registry the different forms for collecting information currently in place in the Autonomous Communities.
3. Get the registry of patients with hepatitis C treated with antiviral drugs in the Spanish National Health System under way.
4. Preparation of the six-month report on the analysis of the information furnished.
5. Raise the report with the main results to the Spanish National Health System Interterritorial Council.

3.1.1. Harmonize insofar as possible the actions of all of the players involved

1. Hold meetings with the main Scientific Societies involved in the treatment of hepatitis C.
2. Hold meetings with the main patients' groups and associations.
3. Creation of a Forum for participation, in which Scientific Societies, Official Professional Associations and Councils and patients' associations are represented.
4. Convey to the Institutional Committee the suggestions generated within the framework of the aforesaid Forum.

3.4 STRATEGIC DIRECTION 4:

FOSTER THE ADVANCEMENT OF THE KNOWLEDGE OF THE PREVENTION, DIAGNOSIS AND TREATMENT OF HEPATITIS C IN THE NATIONAL HEALTH SYSTEM THROUGH SPECIFIC ACTIONS IN THE FIELD OF R&D&I.

The Carlos III Institute (ISCIII) is the body responsible for promoting scientific research and innovation within the scope of the Spanish National Health System. Within the framework of this strategy, it is proposed to foster structured activities in the field of hepatitis C virus infection epidemiology and to promote cohort studies aimed at identifying events related to the epidemiological aspects of hepatitis C, nationwide in Spain, using as a tool the Biomedical Research Networking Centre (CIBER).

The specific actions will be designed and implemented within the bounds of the scientific strategy of the Biomedical Research Networking Centre (CIBER) and, more specifically, on the part of the groups conducting research on the topics of epidemiology and liver diseases. The existence of a structured consortium with more than 100 research groups from around the country will make it possible to expedite the process of carrying out these studies and to rapidly extract the data which will be reported to the health authority, who will use this data in the decision-making processes.

These R&D activities will be funded through the Carlos III Health Institute budgeting mechanisms.

3.4.1 PRIORITY ACTIONS

1. Actions which will be carried out based on the use of general population cohorts already determined and validated by epidemiological research teams (ENRICA, PREDIMED, MCC) which would incorporate the study of specific events related to the prevalence and incidence of this infection. Advantages: the entire quite often lengthy screening process does not have to be carried out, and the surveillance monitoring is already in place. The prevalence can be calculated quite rapidly and incidence data could be obtained in within a few years. Limitations: achieving a suitable level of population representativity, particularly in regard to specific age groups.

2. Actions which will promote the study and monitoring of hepatitis C of Spain's population infected with HCV by means of the use of the Spanish cohorts CoRIS, VACS and PISCIS of patients with HIV in order to ascertain the prevalence and incidence of this hepatitis C infection in this population of patients as well as the epidemiological characteristics, the progression of hepatitis C and its determining factors and the response to the treatment and the factors which have a bearing on that response.
3. In this scenario of using new drugs in clinical practice (outside of clinical trials), the patients are often older in age and more severe due to their also having other disorders, more advanced liver disease and numerous criteria for exclusion not being employed. In this scenario, short-term studies (ST < 12 months) and medium-to-long-term (LT 1-5 yr) studies for the purpose of:
 - a. Evaluating the impact of viral clearance on the development of complications of cirrhosis (ascites, encephalopathy, varicose vein –related haemorrhage, hepatocarcinoma) (MT)
 - b. Characterizing the factors predictive of no response to the new direct-acting antiviral drugs and in terms of the risk behaviours (ST)
 - c. Benefit of the treatment on comorbidities associated with HCV infection: metabolic syndromes, arteriosclerosis, changes in renal function, mixed cryoglobulinemia, other extra-hepatic manifestation (ST and MT).
 - d. Risk of reinfection in patients with sustained viral response
4. Creation at the Carlos III Health Institute (ISCIII) of a permanent surveillance platform which will issue annual reports that will be sent to the Plan coordinating group concerning the scientific impacts of all of the measures in the area of R&D within the scope of hepatitis C (research projects, cohorts studied in the Scientific Research Networking Centre – CIBER) which are managed through the aforesaid Institute.

4. EVALUATION

The strategic plan will be evaluated over the course of the entire period throughout which it is carried out and will be published in an annex with the outcomes. For this purpose, a working group will be set up on which members from the Plan Coordinating Group and the Institutional Committee may serve. The main function thereof will be the screening, definition and frequency for estimating the indicators which are deemed pertinent for monitoring the proposed actions dealt with in the Strategic Plan for Tackling Hepatitis C:

- ***Annual Hepatitis C incidence: global and by risk groups***
- ***Injected drug users in syringe exchange programs***
- ***Estimate of the prevalence of infection***
- ***Estimate of the percentage of undiagnosed individuals***
- ***Number of persons in treatment by type of drugs***
- ***Therapeutic effectiveness by prescription schemes***
- ***Evaluation of the useable diagnostic tests, especially those employing the most advanced technologies***
- ***Number of transplanted patients***
- ***Annual mortality attributable to Hepatitis C***
- ***Reports, of a periodicity as yet to be determined, on the results achieved based on the projects funded of the cohorts specifically studied within the framework of this Plan***
- ***Date of approval of the Guide of recommendations for the early diagnosis of HCV in priority populations within the scope of Primary Care***
- ***Date for updating recommendations for the purpose of preventing biological risks in diagnostic and therapeutic procedures***
- ***Date for updating Protocols for Biological Risks of occupational origins***
- ***Date of campaign for the prevention of sexually-transmitted infections, particularly targeting MSM with risk practices***
- ***Number of Autonomous Communities with a neonatal screening program in women at a greater risk of exposure to the infection***
- ***Autonomous Communities with regulation of establishments where piercing and tattooing is done***
- ***Date of Working Agreement with prison institutions for promoting the prevention and diagnosis of HCV***

5. CHRONOGRAM

PROPOSED ACTIONS	2015		2016		2017	
	1 st semester	2 nd semester	1 st semester	2 nd semester	1 st semester	2 nd semester
Survey of hepatitis C seroprevalence in adult population	→					
Implement newly-diagnosed case information system: RENAVE	→					
Design and implement a registry of patients with hepatitis C treated with antiviral drugs in the Spanish National Health System	→					
Prepare WEBPAGE for informing the population	→					
Design continued education and training program on HCV infection for healthcare personnel	→					
Maintain and boost the damage reduction programs, especially in Prison Institutions	→					
Set up neonatal screening programs in women at greater risk of exposure to infection	→					
Maintain checks of transfusions of blood and hemoderivatives	→					
Update the recommendations for preventing biological risks in invasive diagnostic and therapeutic procedures and the Protocols for Biological Risk of an occupational origin	→					
Review compliance with control mechanisms in piercing and tattooing establishments	→					
In grants for HIV and AIDS prevention programs, evaluate the prioritization of early HCV infection detection projects	→					
Prepare a <i>Guide of Recommendations for Early HCV Diagnosis</i> in priority populations within the scope of Primary Care	→					
Set up a program for collaborating with Prison Institutions for the prevention and diagnosis of HCV	→					
Prepare a Clinical Guide for caring for patients with HCV infection	→					
Access to the new drugs under true conditions of equality	→					
Monitor therapeutic effectiveness	→					
Set-up and holding of Meetings of the Institutional Committee comprised of the Plan representatives by Autonomous Communities	→					
Meetings with all players involved	→					
Foster knowledge of the prevention, diagnosis and treatment of Hepatitis C in the Spanish National Health System through R&D&I	→					

6. ANNEXES

ANNEX I. DESCRIPTION OF THE SPANISH NATIONAL HEALTH SYSTEM'S INTERTERRITORIAL COUNCIL RESOLUTION SETTING THE OBJECTIVES AND CONTENTS OF THE CHRONIC HEPATITIS C PATIENT TREATMENT MONITORING INFORMATION SYSTEM (SITHepaC)

The Strategic Plan for Tackling Hepatitis C proposes as a pre-requisite for the appropriate control of therapeutic effectiveness the protocolized collection of treatment follow-up data on patients treated with the new direct-acting antiviral drugs.

This provision will be carried out through what is referred to as the "Chronic Hepatitis C Patient Treatment Monitoring Information System" (SITHepaC).

Given that the use of the aforementioned information system requires the transfer of data of a personal nature legally safeguarded under Article 53 of Spain's Law 16/2003 of May 28th for the cohesion and quality of the Spanish National Health System and under Article 16.3 of Basic Law 41/2002 of November 14th governing patient autonomy and rights and obligations on the subject of clinical documentation and information, it is necessary that the objectives and contents of the information to be furnished be determined by means of a resolution by the Spanish National Health System's Interterritorial Council.

On the basis of the foregoing, the Spanish National Health System Interterritorial Council, adopts, by consensus, the following

RESOLUTION

To establish the objectives and contents of the information which must be furnished to the Chronic Hepatitis C Patient Treatment Monitoring Information System (SITHepac), which shall be as follows.

One. Purpose

The Chronic Hepatitis C Patient Treatment Monitoring Information System (SITHepac) is for the purpose of the Ministry of Health, Social Services and Equality obtaining the information necessary for conducting a monitored follow-up of all of the hepatitis C patients undergoing treatment who are insured under or are beneficiaries of the Spanish National Health System for the proper control of the therapeutic effectiveness of the new direct-acting antiviral drugs by means of collecting the data to which reference is made in the following section.

The Ministry of Health, Social Services and Equality will work with the Autonomous Communities, whether or not they have systems for managing the information to be recorded in SITHepaC, on determining the integration for the incorporation thereof into the system.

Two. Specific data

The data to be incorporated into the SITHepaC which is necessary for fulfilling the purpose stated in the immediately preceding section hereinabove is as follows:

BASELINE REGISTRATION (first visit)	REVISIONS (subsequent visits)
1. General data: Patient's identification code, gender, date of birth, source of data	1. General data: Confirmation of the preceding data
2. Clinical data: Genotype; Degree of fibrosis; Cirrhosis (compensated/decompensated); Situation regarding liver transplantation (transplanted/waiting list); CHC; Extra-hepatic HCV disease; Viral load; Coinfection	2 Clinical data: Viral load; Progression/regressions of the disease; Transplantation-related situation
3. Treatment data: Prior treatments. Treatment indicated with date.	3. Treatment data: Continues in treatment (yes/no); Interruption of treatment (yes/no), and if interrupted, date and reason; Start of new treatment (yes/no)

Three. Duty of confidentiality

Access to the SITHepaC data must be carried out, in all cases, by healthcare professionals bound to professional secrecy or by other persons who are similarly bound by an equivalent obligation of secrecy.

Whenever it is necessary, the persons who access the data must sign a confidentiality document.

Four. Security measures

All of the technical, organizational and security measures for which provision is made under Spain's Personal Data Protection Act 15/1999 of 13th December and the regulations further expanding thereupon shall be guaranteed.

ANNEX II. DESCRIPTION OF THE MAIN OUTCOMES

Outcomes achieved in genotype 1 patients

- Treatment with sofosbuvir and simeprevir. In treatment-naïve patients, the first trial which evaluated the efficacy and safety of sofosbuvir and simeprevir throughout 12/24-week periods was the COSMOS trial (48), having shown a 95% SVR independently of the duration and of the use of RBV. In real-life cohorts (49, 50), a significant number of patients have been included, achieving a SVR of over 80% for both sub-genotypes (the data in the TARGET cohort are SVR4). The addition of RBV does not seem to increase the cure rate of the patients. The results were similar in cirrhotic and non-cirrhotic patients. In previously-treated patients, the first study to have analysed the efficacy and safety, the COSMOS study, showed that in patients with mild or moderate fibrosis (F0-F2) and prior null response to PR, 12 weeks induces the 95% SVR, independently of the use of RBV. The results in patients with advanced fibrosis or cirrhosis (F3 and F4) were similar. However, a small number of patients were included. Both the TRIO and TARGET cohorts provided data for a large number of patients. In the latter of these two cohorts, including failures to triple therapy with telaprevir or boceprevir, the SVR results at week 4 of follow-up totalling overall figures of 85% (90% in G1b and 80% in cirrhotic G1a patients). The results of the TRIO cohort were quite similar.
- Sofosbuvir and daclatasvir (Phase II trials). This combination has also shown a high degree of efficacy in patients infected with treatment-naïve genotype 1 (51). The study compared 12 and 24-week schemes with or without RBV. Despite the limited number of patients included, the SVR rates in the patients treated for 12 weeks were 95% and 100% in those who were given RBV and who were not given RBV, respectively. There were quite a small number of patients with cirrhosis, but all of them achieved cure. The combination of sofosbuvir and daclatasvir has also shown a high degree of efficacy in patients infected with genotype 1 who have failed at a prior treatment with PR and teleprevir or boceprevir (51); were given this combination for 24 weeks with or without RBV (20 patients per branch). The SVR rates were 95% and 100%, respectively. The number of patients with cirrhosis was quite small (n=9); all of them having achieved cure.
- Sofosbuvir and ledipasvir. This therapy administered for 12 or 24 weeks with or without RBV was evaluated in more than 200 patients per branch (52). The SVR ranged from 97% to 100% in all of the branches, with a similar efficacy in patients with genotype 1a, 1b and also in patients with cirrhosis. In a similar study but without including cirrhotic patients, a comparison was made between an 8-week regimen (with or without RBV) and a 12-week regimen without ribavirin (53). The results were similar in the 3 branches of treatment (93% - 95%). In patients previously treated, several studies reveal them to be highly effective. The ION-2 study (54) analysed the efficacy and safety of this combination

administered for 12 or 24 weeks (with or without RBV), including more than 100 patients per branch. The SVR ranged from 94% to 99% in all of the branches. In patients with cirrhosis, the SVR was noticeably lower in the 12-week branches (82% - 86%), whilst in the 24-week regimens, the SVR was 99% - 100%, independently of the administering of RBV. In the SIRIUS study (55), the efficacy of this combination was analysed in cirrhotic patients who had failed at triple therapy with teleprevir or boceprevir: the patients were randomized to be given 12 or 24 weeks of sofosbuvir/ledipasvir with RBV. SVR was achieved in 96% and 97% of the cases, respectively. In patients with failure at prior treatment with sofosbuvir, it was shown that 12 weeks of sofosbuvir and ledipavir with RBV were effective (>95% SVR). (56)

- Paritaprevir/ritonavir, dasabuvir and ombitasvir. Treatment-naïve: The registry studies of this combination have evaluated its efficacy and safety in 12-week and 24-week treatment schemes, and in some patients without RBV administered. In the first study, a total of 473 patients without cirrhosis who were given this combination in conjunction with RBV for 12 weeks were included (57). The SVR rate was 96%, with no differences between genotypes 1a and 1b. In a similar study (58), 12 weeks of the combination with and without RBV were compared; this study having included more than 700 non-cirrhotic patients. The overall SVR was 98% and was 99% in the branches without and with RBV, respectively. Nevertheless, in patients infected with genotype 1a, the SVR was 90% in the branch without RBV as compared to the 97% in the branch with RBV. Lastly, in a study which included solely patients with liver cirrhosis (59), the efficacy and safety of this combination with RBV was evaluated for 12 and 24 weeks. The overall SVR is similar in the two branches (94%). The patients infected with genotype 1b achieved a 100% SRV. The registry studies of this combination have evaluated its efficacy and safety in 12-week and 24-week treatment schemes and in some patients without RBV being administered. In more than 470 patients without cirrhosis previously treated with PR, who were given this combination in conjunction with RBV for 12 weeks, the SVR rate was 96%, without any differences between the prior types of response (60). There is no data on failures at triple therapy with boceprevir or telaprevir.
- Simeprevir + PEG-IFN and RBV. The overall SVR12 rate achieved in treatment-naïve patients was of 80.4% (419/521); 84.9% in the patients with genotype 1a without Q80K polymorphism and 90% with genotype 1b. In patients with cirrhosis, lower SVR12 rates are achieved than in non-cirrhotic patients (60% vs 80.4%). In relapsed patients, the SVR12 is 86% (128/149) in patients with genotype 1b and 70% (78/111) (78% in patients without Q80K polymorphism). (61-63)
- Sofosbuvir + PEG-IFN and RBV. In treatment-naïve patients, this scheme administered for 12 weeks achieved an overall SVR of 89%. In patients with cirrhosis, the SVR12 are lower than in non-cirrhotic patients (80% vs 92%, respectively). There is not clinical trial data on this combination in previously-treated patients.

Outcomes achieved in Genotype 2 patients

- Sofosbuvir and Ribavirin. This combination administered for 12 weeks achieved an SVR of 97% versus 78% with PR for 24 weeks, besides being better tolerated, causing fewer adverse effects and being of a more applicable, shorter duration. In previously-treated patients, Sofosbuvir and RBV for 16 week achieves better results than 12 weeks (SVR 12 94 versus 86%, especially in patients with cirrhosis (SVR 78%) (64).
- Sofosbuvir + PEG-IFN plus RBV. This combination has been evaluated in two studies on patients with failure at PR. In the LONESTAR-2 study, 83% of the patients achieved SVR independently of the presence of cirrhosis (total 22 patients) (65). In another study of retreatments to failures at Sofosbuvir and ribavirin, 22 patients retreated with sofosbuvir + PR achieved SVR in 91% (66).
- Sofosbuvir + Daclatasvir 12 weeks. The use of this combination might be considered in patients who cannot take or are intolerant to RBV. The response rate achieved in treatment-naïve patients with genotype 2 with this combination is of 96% (25/26).
- PEG-IFN + RBV 24 weeks. SVR of 82% in treatment-naïve patients which increases to 90% (370/410) in patients with rapid viral response and to 94% if they additionally have a low viral load (141/150), it being possible to shorten the therapy to 16 weeks. In cirrhotic patients, the SVR rates are lower. This therapy is not recommended in relapsing patients (SVR 50%) or in non-responders (SVR 30%).
- Sofosbuvir + RBV 12 weeks. SVR12 of 97% in treatment-naïve patients and of 90% in non-responders to prior treatment. In cirrhotic patients, the results are lower (83% in treatment-naïve, 60% in prior non-responders). It may be advisable to prolong the duration of treatment to 16 weeks in these patients.
- Sofosbuvir + PEG-IFN+ RBV 12 weeks. In cirrhotic patients who do not have contraindications to treatment with IFN and/or in non-responders, this scheme provides SVR12 rates of 100% in non-cirrhotic patients and of 93% in cirrhotic patients.

Outcomes achieved in Genotype 3 patients

- Sofosbuvir + PEG-IFN+ RBV 12 weeks. The triple therapy PEG + RBV + sofosbuvir for 12 weeks in prior non-responders achieved an 83% (20/24) SVR12 in both cirrhotic and non-cirrhotic patients (65).
- Sofosbuvir plus daclatasvir. The sofosbuvir and daclatasvir combination for 12 weeks has been evaluated in 152 patients infected with genotype 3 and has achieved SVR rates of 97% and 94% in treatment-naïve and previously-treated patients with no cirrhosis, respectively. This combination is less than optimum for patients with cirrhosis with SVR rates of 58% for treatment-naïve patients and of 69% for patients with cirrhosis and failure at prior treatments with IFN and RBV (67). There is no data on the efficacy of this combination in failures at Sofosbuvir.

- Sofosbuvir and RBV. This combination for 24 weeks has been studied in 250 patients infected with genotype 3, a 93% SVR12 having been achieved in treatment-naïve, non-cirrhotic patients, 92% in treatment-naïve patients with cirrhosis and of 86% in previously-treated patients without cirrhosis and of 60% in previously-treated patients with cirrhosis (68). This combination is less than optimum for patients with cirrhosis and prior failure at treatment.
- PEG-IFN + RBV 24 weeks. The overall SVR rate in treatment-naïve patients is 66% and 55% in cirrhotic patients. In patients who achieve rapid viral response (week 4), SVR rates of 83% are achieved in treatment-naïve non-cirrhotic patients and 69% in treatment-naïve cirrhotic patients. This treatment prescription scheme must not be used in patients previously treated with IFN, independently of the type of non-response.
- Sofosbuvir + PEG-IFN + RBV 12 weeks. The triple therapy PEG + RBV + SOF for 12 weeks in prior non-responders achieved an 83% (20/24) SVR12 both in cirrhotic and in non-cirrhotic patients.
- Sofosbuvir + RBV 24 weeks. The SVR12 rate in treatment-naïve, non-cirrhotic patients was of 94% (86/92), 92% (12/13) in treatment-naïve cirrhotic patients, 87% (87/100) in previously-treated, non-cirrhotic patients and 60% (27/45) in previously-treated, cirrhotic patients (68).

Outcomes achieved in Genotype 4 patients

- Sofosbuvir and RBV. This has been evaluated for 24 weeks in Egyptian patients, treatment-naïve patients SVR12 100% (14/14) and previously treated SVR patients 87% (13/15). Seven (7) patients with naïve cirrhosis or failures at treatment all responded (69), results subsequently confirmed.
- There are no results of the Sofosbuvir and simeprevir combination, but results similar to those encountered in Genotype 1 are anticipated.
- Sofosbuvir and Ledipasvir. This combination for 12 weeks has been evaluated in 21 patients (8 failures, 9 Cirrhosis) with SVR-12 of 95% (70).
- Paritaprevir/R plus ombitasvir plus RBV. This scheme has been studied for 12 weeks in 43 treatment-naïve patients and 49 with failure at PR, all without cirrhosis with SVR-12 of 100% (71).
- Simeprevir + PEG-IFN + RBV. The SVR-12 rates were 89% (31/35) in the patients without prior treatment and 86% with prior recurrence (19/22). The naïve and relapsing patients must take 12 weeks of triple therapy followed by a further 12 weeks of PEG-IFN+RBV

(total duration of the treatment being 24 weeks). The results are less than optimum in non-responders to IFN and must not be recommended.

- Sofosbuvir plus PEG-IFN and RBV 12 weeks. In the F2 naïve patients, this PEG-IFN + RBV + SOF combination for 12 months achieves a SVR-12 rate of 96% (27/28). There is no data on previously-treated patients.
- Daclatasvir plus PEG-IFN and RBV. In the naïve patients with a compensated liver disorder, the PEG-IFN + RBV + DCV combination for 24 weeks (plus 24 weeks of PEG-IFN and RBV if undetectable HCV-RNA is not achieved in weeks 4 and 12) achieves a SVR-12 rate of 82% (67/82). In patients who have already undergone a prior treatment, the triple DCV plus PEG-IFN and RBV therapy has not been tested.
- Sofosbuvir plus RBV 24 weeks. The SVR12 response rate in naïve patients was 100% (14/14) and 87% (13/15) in the previously-treated patients. This regimen probably has an extremely high cost-effectiveness at this point in time.
- Sofosbuvir plus PEG-IFN plus RBV. In 28 patients, an SVR of 98% was achieved. There is no data broken down by cirrhosis (65).

Outcomes achieved in patients with liver cirrhosis associated with C virus and with Liver Transplantation (LT) requirements

- Sofosbuvir plus RBV. This combination given to hepatocarcinoma waiting list patients prevented the reinfection of the graft in 70% of the patients. The one sole factor associated with the prevention of relapse was a negative viral load for longer than 30 days prior thereto (72). This treatment must be considered less than optimum at this point in time.
- Sofosbuvir plus simeprevir with or without RBV for 12 weeks in cirrhotic patients on a liver transplantation waiting list from three American hospitals in routine clinical practice, with SVR rates of 83% (73).
- Other combinations (sofosbuvir plus daclatasvir, sofosbuvir plus ledipasvir, Abvvie 3D combo) have undergone trials in cirrhotic patients but not on liver transplantation waiting lists. These outcomes are likely extrapolatable.

Outcomes achieved in transplanted patients with recurrence of HCV infection

- The outcomes in actual clinical practice of the SOF-SMV ± RBV 12 weeks achieved an SVR rate higher than 90% in patients with slight recurrence of hepatitis C and of 76% in patients with advanced disease (74). This same treatment prescription scheme has been evaluated in the TARGET series, with an SVR at week 4 ranging from 77% to 95% (75).
- The combination Paritaprevir/r-ombitasvir + Dasabuvir/12 h + RBV in 34 patients with slight recurrence (<F2) of hepatitis C in the LHT achieved an SVR of 97% (75).

- Sofosbuvir plus ledipasvir with RBV for 12 or 24 weeks shows a high frequency of SVR (above 85%) independently of the severity or duration thereof. The paucity of Child C patients included in the study prevents drawing any conclusions in this group of patients (76).
- The combination of dechlorasvir and sofosbuvir with or without RBV in patients with fibrosing cholestatic hepatitis achieved an SVR of 75% (77). The same combination achieves an SVR of up to in 100% of the patients (78) with a fibrosing disease in the first stage.

ANNEX III: CHRONIC HEPATITIS C PATIENT TREATMENT MONITORING INFORMATION SYSTEM (SITHepaC). DEFINITION OF THE INFORMATION

1. INTRODUCTION

The Chronic Hepatitis C Patient Treatment Monitoring Information System, referred to hereinafter as the SITHepaC, is aimed at being a solution which will organize on a short-term basis a common information point for all of the physicians in the Spanish National Health System who prescribe treatments for chronic Hepatitis C to enter information.

The process of entering information into the system will be adapted to the point in time appropriate for the patient's protocolized follow-up. Hence, this process of entering information will vary depending on whether the physician is going to register the patient for the first time (Baseline Registration) or is going to record a reassessment of the patient's clinical and treatment status (Subsequent Visits).

This document describes the fields comprising the different data entry forms.

2. DESCRIPTION OF THE FORMS FOR ENTERING INFORMATION

This is structured into the following sections for entering information:

- Baseline Registration
 1. General data
 2. Clinical data
 3. Treatment data
- Subsequent Visits
 1. General data
 2. Clinical data
 3. Treatment data

One must bear in mind that the treatment started may be interrupted on any of the visits. In the event of starting a new treatment, this would have to be filled in by way of a visit.

2.1 Baseline Registration

The form for entering data for the baseline registration is comprised of the following fields:

2.1.1 General data

- Patient identification code

The "CIP" Personal Identification Code and the "CITE" Issuing Entity Identification Code will be used; or if the CIP is not available, the Spanish National Identification Card Number will be used.
- Gender (Male/Female)
- Year of Birth (4-digit number)
- Organization/entity in which the registration is entered
- Nationality

The numbers which can be used are included in **Section 3.3**

2.1.2 Clinical data

- Genotype

The possible options will be “1a” “1b” “1c” “1 w/o subtyping” “2” “3” “4” “5” “6”
More than one option may be selected.
The options 1a, 1b and 1c will rule out the possibility of “1 w/o subtyping”.
- Degree of liver fibrosis

The possible options will be “F0” “F1” “F2” “F3” and “F4”, no multiple options allowed.
- Cirrhosis (YES/NO)

If the answer is “YES”, it will be necessary to fill in whether the cirrhosis is:

 - Compensated with imminent risk of decompensation (< 1 year)
 - Compensated without imminent risk of decompensation
 - Decompensated
- Had liver transplant (YES/NO)

If the answer is “YES”, it will be necessary to specify the date of transplant in dd/MM/yyyy format.
- On transplant waiting list (YES/NO)
- Hepatocarcinoma (YES/NO)
- Extra-hepatic HCV disease (YES/NO)

If the answer is “YES”, it will be necessary to specify whether it is clinically relevant.
- HIV coinfection (YES/NO)
- Viral load (in UL/ml) (whole number without decimals)

2.1.3 Treatment data

- Prior treatments (YES/NO)

If the answer is “YES”, it will be necessary to select the list of treatments from the list of available treatments (**see Section 3.1**).
It will be possible to select more than one treatment.
- Prescribed treatment

More than one treatment may be selected from the list of available treatments (**see Section 3.1**).
For each treatment, the starting date can be specified in dd/MM/yyyy format.

2.2 Subsequent Visits

A description is provided in following of the field comprising the form for entering the information on the subsequent visits.

2.2.1 General data

- Patient identification code
The “CIP” Personal Identification Code and the “CITE” Issuing Entity Identification Code will be used; or if the CIP is not available, the Spanish National Identification Card Number will be used.
- Organization/entity in which the registration is entered
- Date of the visit
Date in dd/MM/yyyy format

2.2.2 Clinical data

- Undetectable viral load (<15 UL/ml) (YES/NO)
If the answer is “YES”, it will be necessary to specify the date of the assay in dd/MM/yyyy format.
- Progression of the disease (YES/NO)
If the answer is “YES”, the following fields must be completed:
 - Liver fibrosis
The possible options will be “F0” “F1” “F2” “F3” and “F4”, multiple options not allowed.
 - Liver decompensation (YES/NO)
 - Hepatocarcinoma (YES/NO)If the answer is “NO”, the disease regression section must be completed.
- Regression of the disease (YES/NO)
This section is completed only when it is stated in the immediately preceding section hereinabove that there is no progression of the disease.
In the event that the answer is “YES”, it will be necessary to fill in the degree of liver fibrosis.
The possible options will be “F0” “F1” “F2” “F3” and “F4”, multiple options not allowed.
- Transplant (YES/NO)
If the answer is “YES”, it will be necessary to specify the date of transplant in dd/MM/yyyy format.
- Reinfection (YES/NO)
If the answer is “YES”, it will be necessary to specify the genotype.
The possible options for specifying the genotype will be “1a” “1b” “1c” “1 w/o subtyping” “2” “3” “4” “5” “6”.
More than one option may be selected.
The options 1a, 1b and 1c will rule out the possibility of “1 w/o subtyping”.

2.2.3 Treatment data

- Interruption of the treatment (YES/NO)
If the answer is “YES”, it will be necessary to specify the treatment(s) interrupted, stating in each case the date on which ended and the reason for interruption.

In order to be able to interrupt a treatment, it will be necessary for the treatment to be prescribed by means of a baseline registration or a subsequent visit.

The reason for interruption for each treatment may be selected from the list of reasons for interruption (**See Section 3.2**).

- Start new treatment (YES/NO)

If the answer is “YES” it is necessary to specify the new treatments being started.

More than one treatment may be selected from the list of available treatments (**See Section 3.1**).

For each treatment, the starting date must be specified in dd/MM/yyyy format.

3. THE APPLICATION DICTIONARY

The form uses the following dictionaries for selecting:

- The list of available treatments
- The reasons for treatment interruption
- Nationalities

3.1 List of available treatments

- RIBAVIRIN
- PEG-INTERFERON
- INCIVO
- VICTRELIS
- OLYSIO
- SOVALDI
- DAKLINZA
- HARVOINI
- VIEKIRAX
- EXVIERA

3.2 Reasons for treatment interruption

- End of prescribed treatment prescription scheme
- Inefficacy
- Adverse effects
- Failure to adhere to treatment
- Death

3.3 Nationalities

AFGHANISTAN
ALBANIA
ALGERIA
ANDORRA
ANGOLA
ARGENTINA
ARMENIA
AUSTRIA
AUSTRALIA
BELGIUM
BELARUS
BELIZE
BOLIVIA
BOSNIA
BRAZIL
BULGARIA
CAMEROON
CANADA
CEYLAN

CZECH REPUBLIC
CHILE
CHINA
COLOMBIA
CONGO
COSTA RICA
CROATIA
CUBO
CABO VERDE
CYPRUS
DENMARK
DJIBUTI
DOMINICAN REPUBLIC
ECUADOR
ECUATORIAL GUINEA
EGYPT
ESTONIA
ETHIOPIA

FINLAND
FRANCE
GABON
GEORGIA
GERMANY
GUINEA
GREECE
GUATEMALA
GUINEA-BISSAU
HAITI
HOLLAND
HONDURAS
HUNGARY
INDIA
INDONESIA
IRAN
IRAQ
IRELAND

ICELAND
ISRAEL
ITALY
JAPAN
JORDAN
KAZAKHSTAN
KENYA
KOREA
KYRGYZSTAN
KUWAIT
LATVIA
LEBANON
LIBYA
LIECHTENSTEIN
LITHUANIA
LUXEMBOURG
MACEDONIA
MADAGASCAR
MALI
MALTA
MOROCCO

MAURITANIA
MEXICO
MONGOLIA
MOLDAVIA
MONTENEGRO
MOZAMBIQUE
NEPAL
NICARAGUA
NIGERIA
NORWAY
PAKISTAN
PALESTINE
PANAMA
PARAGUAY
PERU
PHILIPPINES
POLAND
PORTUGAL
PUERTO RICO
RUANDA

RUMANIA
RUSSIA
SALVADOR
SANTO TOME & PRINCIPE
SENEGAL
SERBIA
SLOVAKIA
SLOVENIA
SOUTH AFRICA
SPAIN
SUDAN
SWEDEN
SWITZERLAND
SYRIA
TAIWAN
THAILAND
TRINIDAD & TOBAGO
TUNISIA
TURKEY
UNITED KINGDOM
UNITED STATES
UKRAINE
URUGUAY
UZBEKISTAN

VENEZUELA
VIETNAM
YEMEN

YUGOSLAVIA
ZIMBABWE

UNKNOWN

4. TABLE OF SIThepaC FIELDS

	Field	Possible options	More information
1.	BASELINE REGISTRATION		
1.1.	GENERAL DATA		
1.1.1	Patient identification code		The "CIP" Patient Identification Code and the "CITE" Issuing Entity Identification Code will be used or, if the "CIP" is not available, the Spanish National Identity Card No.
1.1.2	Gender	Male / Female	
1.1.3	Year of birth	4-digit number	
1.1.4	Organization /entity in which the registration is made		
1.1.5	Nationality	<u>See Section 3.3 Nationalities</u>	
1.2	CLINICAL DATA		
1.2.1	Genotype	The possible options will be "1a" "1b" "1c" "1 w/o subtyping" "2" "3" "4" "5" "6"	More than one option may be selected. The options 1a, 1b and 1c will rule out the possibility of "1 w/o subtyping".
1.2.2	Degree of liver fibrosis	The possible options will be "F0" "F1" "F2" "F3" and "F4".	No multiple options allowed.
1.2.3	Cirrhosis	YES / NO	If the answer is "YES", Section 1.2.3.1. must be completed.
1.2.3.1	Characteristics of the cirrhosis	Compensated with imminent risk of decompensation (< 1 year) Compensated without imminent risk of decompensation Decompensated	Complete this section only if the answer to Section 1.2.3 is "YES".
1.2.4	Had liver transplant	YES / NO	If the answer is "YES", Section 1.2.4.1 must be completed.
1.2.4.1	Date of transplant	Dd/MM/yyyy	Complete this section only when the answer to 1.2.4 is "YES".
1.2.5	Extra-hepatic HCV disease	YES /NO	If the answer is "YES", Section 1.2.5.1 must be completed.

1.2.5.1	Clinically relevant	YES / NO	Complete this section only if the answer to 1.2.5 is "YES".
1.2.6	HIV coinfection	YES /NO	
1.2.7	Viral load (in UL/ml)	Whole number, no decimals	
1.3	TREATMENT DATA		
1.3.1	Prior treatments	<u>YES / NO</u>	If "YES", Section 1.3.11 must be completed.
1.3.1.1	List of prior treatments	RIBAVIRIN PEG-INTERFERON INCIVO VICTRELIS OLYSIO SOVALDI DAKLINZA HARVOINI VIEKIRAX EXVIERA	More than one treatment may be selected.
1.3.2	Treatment prescribed	RIBAVIRIN PEG-INTERFERON INCIVO VICTRELIS OLYSIO SOVALDI DAKLINZA HARVOINI VIEKIRAX EXVIERA	More than one treatment may be selected from the list of available treatments*. For each treatment, the starting date must be specified in dd/MM/yyyy format.
2.	SUBSEQUENT VISITS		
2.1	GENERAL DATA		
2.1.1	Patient identification code		The "CIP" Patient Identification Code and the "CITE" Issuing Entity Identification Code will be used or, if the "CIP" is not available, the Spanish National Identity Card No.
2.1.2	Organisation/entity in which the registration is made		
2.1.3	Date of visit	Date in dd/MM/yyyy format	

2.2	CLINICAL DATA		
2.2.	Undetectable viral load (<15 UL/ml)	YES / NO	If the answer is "YES", Section 2.2.1.1 must be specified.
2.2.1.1	Date of assay	Date in dd/MM/yyyy format	Complete this section only if the answer to 2.2.1 is "YES".
2.2.2	Progression of the disease	YES / NO	If the answer is "YES", Sections 2.2.2.1, 2.2.2.2 and 2.2.2.3 must be completed If the answer is "NO", Section 2.2.3 must be completed.
2.2.2.	Liver fibrosis	"F0" "F1" "F2" "F3" "F4"	Complete this section only if the answer to 2.2.2 is "YES". No multiple options allowed.
2.2.2.2	Liver decompensation	YES / NO	Complete this section only if the answer to 2.2.2 is "YES"
2.2.2.3	Hepatocarcinoma	YES / NO	
2.2.3	Regression of the disease	YES / NO	Complete this section only if stated in the immediately preceding section that there is no progression of the disease. If the answer is "YES", Section.2.2.3.1 must be completed.
2.2.3.1	Degree of liver fibrosis	"F0" "F1" "F2" "F3" "F4"	
2.2.4	Transplant	YES / NO	If the answer is "YES", Section 2.2.4.1 must be completed.
2.2.4.1	Date of transplant	Date in dd/MM/yyyy format	Complete this section only if the answer to 2.2.4 is "YES".
2.2.5	Reinfection	YES / NO	If the answer is "YES", Section 2.2.5.1 must be completed.
2.2.5.1	Genotype	"1a" "1b" "1c" "1 w/o subtyping" "2" "3" "4" "5" "6"	More than one option may be selected. The options 1a, 1b and 1c will rule out the possibility of "1 w/o subtyping".
2.3	TREATMENT DATA		
2.3.	Interruption of the treatment	YES / NO	If the answer is "YES", it Sections 2.3.1.1, 2.3.1.2 and 2.3.1.3 must be completed for each treatment which is interrupted.

2.3.1.1	Treatments which are interrupted	RIBAVIRIN PEG-INTERFERON INCIVO VICTRELIS OLYSIO SOVALDI DAKLINZA HARVOINI VIEKIRAX EXVIERA	
2.3.1.2	Date interrupted	Date in dd/MM/yyyy format	
2.3.1.3	Reason for interruption	End of prescribed scheme Inefficacy Adverse effects Failure to adhere Death	
2.3.2	Start of new treatment	YES / NO	If the answer is "YES", Section 2.3.2.1 must be completed
2.3.2.1	Treatment prescribed	RIBAVIRIN PEG-INTERFERON INCIVO VICTRELIS OLYSIO SOVALDI DAKLINZA HARVOINI VIEKIRAX EXVIERA	More than one treatment may be selected from the list of available treatments*, For each treatment, the date on which treatment is started must be specified in dd/MM/yyyy format.



ANNEX IV: REPORT ON THE CONDITIONS FOR FUNDING THE NEW DIRECT-ACTING ANTIVIRAL DRUGS FOR THE TREATMENT OF CHRONIC HEPATITIS C IN THE NATIONAL HEALTH SYSTEM

At the meeting held by the Interministerial Medicine Pricing Commission on February 23, 2015, it was resolved to fund three new oral antiviral medicines: HARVONI, VIEKIRAX and EXVIERA, the latter two generally being used in combination with one another. All three are medicine for hospital diagnosis, for dispensing in hospital pharmacy departments, bearing no price tab seals and being reduced in contribution.

On March 26, 2015, the Spanish National Health System's Interterritorial Council approved the Strategic Plan for Tackling Hepatitis C in the Spanish National Health System (PEAHC), which recommends equitable access, at all times by medical prescription, to these new direct-acting antiviral medicines for the population subject to treatment who have significant liver fibrosis (F2-F4).

Therefore, the incorporation thereof into the Spanish National Health System benefit as of April 1, 2015 has been negotiated in more favourable terms than the medicines previously used for treating chronic hepatitis C.

- **Maximum combined expense ceiling.** 786 million euros for treating 51,900 patients with the three medicines (HARVONI and VIEKIRAX-EXVIERA) for the entire Spanish National Health System, including the Mutual Societies (MUFACE, MUGEJU and ISFAS) and Prison Healthcare, throughout the entire three-year period commencing as of the date of inclusion in the funding.
Either of these two aspects is finalistic, and at the point in time of reaching the ceiling or the treatment of the aforesaid number of patients, negotiations would then be held once again with the laboratories holding the marketing authorizations.
- **Maximum expense per patient (capping).** The costs of treatment are established with a respective maximum limit, independently of the actual duration of the treatment, which is a three-month period.
- **Price-volume agreement** on a nationwide scale per patient; one agreement for the Harvoni medicine and another for Viekirza-Exviera.
A maximum cost per patient is set, variable in steps, which state number of patients starting treatment, and medicines. As the number of patients treated increases and the steps are progressively completed, the cost of the treatment progressively decreases.

HARVONI PRICE-VOLUME AGREEMENT		VIEKIRAX-ZXVIERA PRICE-VOLUME AGREEMENT	
PATIENT STEPS	COST PER PATIENT Harvoni	PATIENT STEPS	COST PER PATIENT Viekirax/Exviera
1 – 8,000		1 – 4,000	
8,001 – 16,000		4,001 – 8,000	
16,001 – 25,000		8,001 – 16,000	
25,001 – 35,000		16,001 – 25,000	
35,001 – 45,000		25,001 – 35,000	
45,001 – 50,000		35,001 – 40,000	

- **Funding support from the Ministry of Finance.** Mechanisms set up for endowing the Autonomous Communities with funding support for facilitating the treatment to the patients with hepatitis C in the Spanish National Health System, with the medicines currently funded (See Table 6) (plan for to 10 years the monetary sums committed in these medicines and a two-year grace period in repaying the principal).

The payment of the invoices which the laboratories holding the authorizations for marketing the medicines supplied to the different Autonomous Communities for the treatment of chronic hepatitis C shall avail of the facilities of the different funding mechanisms set up by the Central Government in terms of each Autonomous Community.

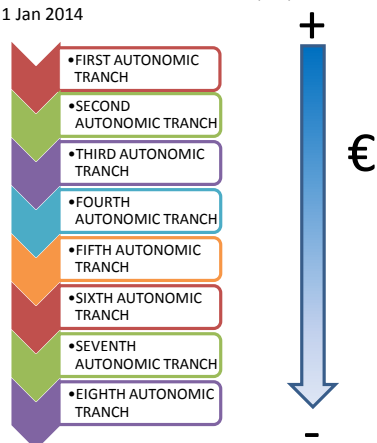
- Autonomous Community Liquidity Fund (FLA)
 - Financial facility compartment
 - Specific mechanisms in the event of not being eligible for the first two
- **Institutional Committee Agreement.** In order to be able to implement these conditions on a nationwide scale at all times respecting the authorities of the Autonomous Communities with regard to the subject of management, the Institutional Committee for the Spanish National Health System Plan for Tackling Hepatitis C has resolved in favour of the following aspects:
 - That the medicines be funded in accordance with the express obligation of their being prescribed and dispensed within the framework of the approved Strategic Plan for Hepatitis C and therefore of the keeping of a patient registry as set forth under said Plan, for the monitoring and follow-up of the treatments under way.
 - Within the first week of each month, Autonomous Communities shall e-mail the Excel files containing the information collected from patients treated the previous month to the Ministry of Health, Social Services and Equality (segter@mssi.es).
 - That it is mandatory for the Autonomous Communities to fully comply, for the funding, with some Autonomous Community steps in terms of the population data as per Spanish National Institute of Statistics (INE) – Official Resident Registry at January 1st, initially provided by the Ministry of Health, Social Services and Equality, for purposes of estimation. These steps are the same as the national steps of the price-volume agreements.

Therefore, although an Autonomous Community were to exceed its Autonomous Community step, the invoicing would not be adjusted until the respective national step were exceeded. Similarly, in the event of the national step having been exceeded, solely those Autonomous Communities which were to have exceeded their respective Autonomous Community steps will benefit from the reduction in the cost per patient.

PRICE/VOLUME AGREEMENTS (PATIENT COST) For each medicine (HARVONI and VIEKIRAX-EXVIERA)

AUTONOMOUS COMMUNITY TRANCHES

AGREED BY THE SPANISH NATIONAL HEALTH SYSTEM PLAN FOR TACKLING HEPATITIS C (PEAHC) INSTITUCIONAL COMMITTEE AS PER SPANISH INSTITUTE OF STATISTICS (INE) OFFICIAL RESIDENT REGISTRY 1 Jan 2014

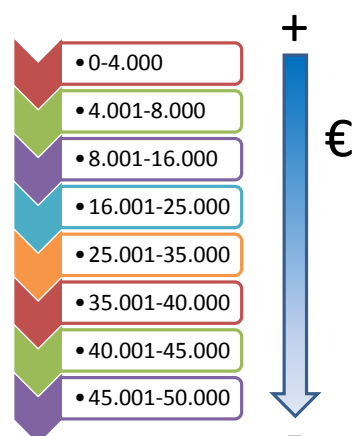


They will be taken into account retrospectively when the equivalent national tranche is exceeded, provided that the Autonomous Community has exceeded its autonomous tranche.

Send in information following end of month prior to the 7th of each month to the Spanish Ministry of Health, Social Services and Equality.

NATIONAL TRANCHES.

AGREED BY RESOLUTION FOR FUNDING WITH THE COMPANY. AS PER ESTIMATE OF PATIENTS Jan 2015.



2015 – 2017/2018

Send in information to the Autonomous Communities when the national tranches are exceeded.

PROCEDURE FOR PROCESSING THE PAYMENT OF THE MEDICINES

At the current point in time, the Spanish Ministry of Health, Social Services and Equality proposes for approval by said Committee the following procedure of sequenced measures for the request, delivery and invoicing of the medicines indicated for the treatment of chronic hepatitis C. In regard to this aspect, the Institutional Committee performs the task of facilitating the communication regarding the patient treatment data necessary for carrying out the process between the companies involved and the Autonomous Communities and this being done homogeneously nationwide.

- Request Orders

The hospitals shall order the medicines, as needed, from the laboratories holding the marketing authorizations. They must simultaneously send a copy of the request order sheet to the Autonomous Communities.

- Delivery and invoicing

Each laboratory holding the authorization to market the medicine in question shall deliver the requested medicines to the hospital, which shall sign a delivery note for each order, and whether or not the invoice is sent to the hospital or to the Autonomous Community shall depend on the management model of the Autonomous Community in question.

– Invoicing Reconciliation

The invoicing shall be done monthly. It shall be with this regularity that the laboratories holding the marketing authorizations and the Autonomous Communities shall reconcile the number of packages with the patients treated in order to proceed to the payment of the invoices.

In the event that any change may arise between two points in time at which reconciliations are made, such as, for example, a lengthening of the duration of treatment (from 12 to 24 weeks) or a change in national step (making it possible to lower the price for the patients already invoiced for an Autonomous Community which has also exceeded its regional step) the respective adjustment shall be made in the immediately following reconciliation, without detriment to the Community setting up other mechanisms in conjunction with the laboratories for putting these matters in proper order.

Whether the payment or adjustment is made in the immediately subsequent invoice at the hospital or Autonomous Community Government Department level will depend on the management model of the Autonomous Community in question and the centre/agency making the payment.

In any case, in order for this process to be carried out harmoniously, a contact person must be appointed at each one of the Autonomous Communities and mutual societies. The payment of the invoices shall be carried out in keeping with the customary mechanisms, without dismissing the possibility of the mechanisms set up by the Central Government Administration depending on each Autonomous Community.

The reconciliation shall be based on the data which the Autonomous Communities and mutual societies have furnished to the Spanish Ministry of Health, Social Services and Equality. The aforesaid Ministry shall inform the Autonomous Communities and mutual societies as to the status of the price-volume agreements on a quarterly basis and shall notify the point in time at which the national step is exceeded.

Successfully managing these medicines requires the commitment of all involved and keeping the information as up-to-date as possible.

ANNEX V. PATIENT ACCESS TO THE TREATMENT IN TERMS OF THEIR NATIONALITY

1. PERSONS INSURED UNDER THE SPANISH NATIONAL HEALTH SYSTEM

These persons shall have access to the Chronic Hepatitis C treatment in the Spanish National Health System:

- The Spanish nationals who are insured under or are beneficiaries of the Spanish National Health System.
- In order to be entitled to be provided with health care on the part of the Spanish National Health System, the nationals of other countries must be insured in Spain or be beneficiaries of persons insured under the same, for which purpose, it is necessary in accordance with the laws and regulations in force (Article 3 of the Law governing the Spanish National Health System Cohesion and Quality and Royal Decree 1192/2012 of August 3rd):
 - To be a worker enrolled in the Spanish Social Security System or have a Social Security pension or other regular Spanish benefit.
 - If the foregoing conditions are not met, they must be registered in the Central Alien Registry or be in possession of a permit to reside in Spanish territory in the case of citizens who are not from the European Space and, in addition thereto, must also not have incomes of over 100,000 euros or compulsory coverage of the healthcare benefit via another means.

2. EUROPEAN CITIZENS. EUROPEAN REGULATIONS AND DIRECTIVE

It is possible to be provided with health care in the health system of another member State by virtue of the application of the European standards: to public health care by the Regulations Governing the Coordination of Social Security Systems in the European Union (Regulations 883/2004 and 987/2009 currently in effect), and it is also feasible, by virtue of the free provision of health care services, to take recourse to another State's public or private health care, to advance the payment of the treatment and to then be refunded in full or in part by way of Directive 2011/24 regarding the enforcement of patients' rights in cross-border health care.

2.1 Social Security System Coordination Regulations (883/2004 and 987/2009)

- Temporary stays in Spain (vacationing, Erasmus scholarships, travel, studies...) would have to use the European Health Insurance Card. This personal, non-transferrable document must be issued by the country of origin prior to any travel. This will entitle the holder to be provided with whatever services are necessary from the medical standpoint during their stay in Spain, taking into account the nature of the services and the anticipated duration of the stay in

keeping with the provisions of Spanish laws and regulation. This is aimed at preventing an insured person from finding himself or herself forced to return to their country of origin prior to the end of their planned stay for the purpose of undergoing the necessary treatment.

- Pensioners on a European pension who move to Spain to reside. The pensioners from a European State who change their place of residence are entitled to be provided with health care in the country where they are going to live, in this case, Spain, as if they were Spanish citizens, but their country pays Spain a lump sum fee (through the Spanish National Social Security Institute) for the care provided in the Spanish National Health System for the citizen in question for the length of time said person resides.

In addition to the above, the care provided for the family members of expatriated workers (lump sum fee) and/or cross-border workers expatriated by their country of origin is also paid for by the country where the person in question is insured.

2.2 European Directive 2011/24/EU and Royal Decree 81/2014. Cross-Border Health Care

New European Directive 2011/24/EU, transposed into our legal system by way of Royal Decree 81/2004 of February 7th, by virtue of which standards are set forth for guaranteeing cross-border health care, allows the provider of health care services, whether public or private, to be chosen. Therefore, a patient could be treated in Spain by paying the cost of the treatment in advance and requesting the refund of the expenses in their country of origin, if the treatment in question is included in his or her country's services portfolio.

Therefore, a patient of another nationality who wishes to opt for:

- Being provided with care in a hospital within the public hospital network of any Autonomous Community in Spain, provided that it be under the same conditions in which a patient from our country would be provided with care (waiting list, etc...). This must be paid for according to the prices stipulated in the Spanish National Health System and will be refunded according to his/her country's own services portfolio.
- Being provided with care by a private Spanish provider. The person must pay whatever price the provider has set.

In Royal Decree 81/2014 of February 7th, there is a "safeguard clause" under Article 6.7 thereof which deals with the possibility of limiting access to certain treatments, in certain situations so as to guarantee sufficient, ongoing access to the health care provided by the Autonomous Community Health Services.

Whatever restrictive measures are adopted must be warranted for reasons of general interest, by the need for planning in order to guarantee a balanced range of high-quality treatments or out of the intent to assure a rational use of the financial, technical and human resources. Additionally, they must be previously assessed by the European Commission and published by the national contact point in order for them to be known beforehand by the patients from other States.

3. FOREIGNERS IN IRREGULAR SITUATIONS

Royal Decree-Law 16/2012 of April 20th has revised Law 16/2003 of May 28th governing the Spanish National Health System cohesion and quality with regard to the protection of the health of foreign nationals who are neither registered nor authorized to reside in our country. It covers, with public funds, the health care for children under 18 years of age, women during pregnancy, delivery and post-partum and the care of all of the persons in emergency situations up to discharge status, as well as all of the public health contingencies, since it has not revised General Public Health Law 33/2011 of October 4th, according to which the public health care services in the Spanish National Health System include actions for preventing, providing care for, monitoring and inspecting situations that are aimed at preserving the population's public health, as well as preventing the risks associated with situations of health alerts and emergencies. In Spain, the health services have long experience in carrying out health prevention and problem-solving programs, as has been being done, for example, in the cases of the persons with HIV/AIDS infection.

The public health-related authorities and measures fall to the Autonomous Communities, who carry them out independently of the health care set-up and are offered for the entire population without distinction of their access to the health care system. By virtue of its authorities, each Autonomous Community may establish specific or supplementary measures, within the scope of its Community, which can be carried out through public health protection programs or measures for health improvement which take in care for the continuation of treatments or reduction of chronicity of diseases or the risk of transmission of diseases.

In this regard, the Document on Health Intervention in Situations of Public Health Risk, approved by the Autonomous Communities within the Spanish National Health System's Interterritorial Council Meeting (December 2013) and published on our Ministry's website.

It was resolved to maintain the public health programs for the purpose of guaranteeing the health benefits of prevention, diagnosis and treatment in the cases necessary, such as infectious diseases, which require a lengthy or chronic medical treatment and which, if left untreated, may involve a public health risk due to their transmissibility and the difficulty of their being brought under control. This includes the entire population and therefore the foreigners in irregular situations, who are not excluded from the prevention and therapeutic treatments, which includes the treatments for chronic hepatitis C virus infection in the necessary cases.

All of the above is summarized in the following table.

Table 7. ACCESS TO HEALTH CARE BY ALIENS DEPENDING ON THEIR NATIONALITY AND THE FRAMEWORK IN WHICH THIS CARE IS PROVIDED		
PERSONS INSURED UNDER THE SPANISH NATIONAL HEALTH SYSTEM	Spanish National Health System Personal Health Card	Worker enrolled in the Spanish Social Security System or on a Social Security pension or collecting some other regular Spanish benefit. Entitled exactly the same as the insured Spanish citizens. If the aforementioned conditions are not met, they must be registered in the Central Alien Registry or be in possession of a permit to reside within the territory of Spain, in the case of citizens who are not from the European Space and must also not have incomes in excess of 100,000 euros or compulsory health benefit coverage via another route. They are entitled exactly the same as the insured Spanish citizens.
EUROPEAN CITIZENS COORDINATION REGULATIONS	European Health Insurance Card	Not entitled to treatment because their stays are temporary and this is not necessary health care.
	Lump Sum Fee	Entitled to treatment because they are residents and care is provided for them the same as for Spanish citizens by way of a lump sum fee paid by their country.
EUROPEAN CITIZENS CROSS-BORDER DIRECTIVE	Directive opting for care in Spanish National Health System	Entitled to treatment under the same conditions as those insured, waiting lists and public hospital care and pricing of the Spanish National Health System, paying directly for the same. Possibility of safeguard clause.
	Directive opting for private care	Entitled to treatment in any private provider, without waiting lists and private hospital care and notified price (free).
FOREIGNERS IN IRREGULAR SITUATIONS		Entitled for emergencies or due to public health-related necessity.

ANNEX VI. THE INSTITUTIONAL COMMITTEE FUNCTIONS AND MEMBERS

1. THE COMMITTEE FUNCTIONS

The mission of the Institutional Committee is to **coordinate the implementation** of the Spanish National Health System's Strategic Plan for Tackling Hepatitis C (PEAHC-SNS).

To this end, it shall carry out the following functions:

1. It shall be fully aware of and conduct a systematic surveillance of all of the measures which are being carried out in relation to the hepatitis C virus within the framework of the Spanish National Health System.
2. It shall see to access being given to the new antiviral drugs under equitable conditions on the part of those patients who need them.
3. It shall conduct an analysis of the information obtained in the follow-up of the monitoring of the therapeutic effectiveness and the health outcomes which are achieved in the patients treated and shall propose measures or actions resulting from this analysis.
4. It shall promote, coordinate and guide the studies of whatever working groups are created for the different strategic directions.
5. It shall harmonize, insofar as possible, the measures of all of the players involved, by promoting the meetings it deems necessary with:
 - The main Scientific-Medical Societies involved in the treatment of hepatitis C
 - The main official professional Councils and Associations involved
 - The main patients' groups and associations
6. It shall raise to the Spanish National Health System's Interterritorial Council the six-month report with the main results achieved in the Spanish National Health System's Plan for Tackling Hepatitis C (PEAHC-SNS).
7. It shall disseminate the main advancements and results of the Spanish National Health System's Plan for Tackling Hepatitis C (PEAHC-SNS).

2. THE COMMITTEE MEMBERS

1. The Committee shall be comprised of the following posts:
 - a. **Chairman:** the Secretary General of Health and Consumer Affairs
 - b. **Deputy Chairman:** the Director General of Basic Spanish National Health System Services Portfolio and Pharmacy
 - c. **Committee Members:**

The Committee Members shall be as follows:

- Heads of:
 - The Directorate General of Public Health
 - The Spanish Agency of Medicines and Medical Devices
 - The Directorate General of Professional Regulation
 - The Carlos III Health Institute
 - The Sub-Directorate General of Medicine and Medical Product Quality
 - The Sub-Directorate General of Basic Services Portfolio and Cohesion Fund
 - The Sub-Directorate General of Health Promotion and Epidemiology
 - The Sub-Directorate General of Prison Health Care Coordination
 - Representatives from:
 - A representative from the PEAHC-SNC for each Autonomous Community
 - A representative from the PEAHC-SNC for INGESA.
 - A representative from the PEAHC-SNC for MUFACE.
 - A representative from the PEAHC-SNC for MUGEJU.
 - A representative from the PEAHC-SNC for ISFAS.
2. Serving as the Committee Secretary, as a non-voting member, will be a civil servant from the Directorate General of Basic Spanish National Health System Services Portfolio and Pharmacy.
 3. Other experts may be invited to attend the Committee meetings and to take part in the different working groups when the subjects to be dealt with at the proposal of the Committee members so makes it advisable.
 4. All those working groups which are necessary to be set up for the purpose of achieving its objectives shall report to the Committee. The aforesaid groups shall serve the purpose of studying, planning and writing the studies of which they are placed in charge, as well as raising the respective documents of findings to the Institutional Committee.

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- Table 2. Estimate of HCV prevalence in adult population in Spain. Most frequent genotypes.
- Table 3. No. of hepatitis C cases by Autonomous Communities: Spain 2010-2014
- Table 4. Anti-HCV antibodies in blood donations
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- Fig. 1 Natural history of hepatitis C
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- Fig. 7. Prison institutions: Evolution of the prevalence of HCV infection: 1998-2014.

7. BIBLIOGRAPHY