ISTITUTO SUPERIORE DI SANITÀ

RAPPORTI ISTISAN 15|35

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PITER-HCV cohort study as part of the Italian platform for the study of viral hepatitis therapies

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EPIDEMIOLOGIA E SANITÀ PUBBLICA

ISTITUTO SUPERIORE DI SANITÀ

PITER-HCV cohort study as part of the Italian platform for the study of viral hepatitis therapies

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Rapporti ISTISAN 15/35

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2015, vii, 39 p. Rapporti ISTISAN 15/35

Italy has one of the highest prevalence rates of Hepatitis C Virus (HCV) infection in Europe, and HCV infection is the leading cause of cirrhosis, hepatocellular carcinoma, and liver-related death. In light of this, Direct Acting Antiviral Agents (DAAs) would have a huge public health impact in Italy. A longitudinal prospective HCV cohort study known as PITER (*Piattaforma Italiana per lo studio della Terapia delle Epatiti viRali*: Italian Platform for the Study of Viral Hepatitis Therapies) has been developed as a collaboration among the Istituto Superiore di Sanità (the National Institute of Public Health in Italy), the Italian Society for the Study of the Liver, the Italian Society for Infectious Diseases, and their more than 100 affiliated Clinical Centres. The cohort will consist of a representative sample of approximately 10,000 consecutive patients with chronic HCV liver disease with an expected follow-up of at least 10 years. The first round of enrolment began in May 2014; enrolment will be re-opened for three-month periods during subsequent years to catch the introduction of new DAAs.
Key words: Observational cohort study; Hepatitis C; Direct acting antiviral drugs; Equity in health care

Istituto Superiore di Sanità
Studio di coorte osservazionale sull'epatite virale C come parte della Piattaforma Italiana per lo studio della Terapia delle Epatiti Virali (PITER).
Loreta Kondili, Maria Giovanna Quaranta, Loredana Falzano, Alessandra Mallano, Marco Mirra, Liliana Elena Weimer, Luca Fucili, Massimiliano Di Gregorio, Stefano Lucattini, Maurizio Massella, Roberta Terlizzi, Erika Olivieri, Federica Magnani, Alessandra Mattei, Stefano Rosato, Maria Elena Tosti, Stefano Vella e Gruppo collaborativo PITER
2015, vii, 39 p. Rapporti ISTISAN 15/35 (in inglese)

L'Italia è uno dei Paesi in Europa con il più alto tasso di prevalenza di infezione dal virus dell'epatite C (*Hepatitis C Virus*, HCV), causa principale di cirrosi, epatocarcinoma e mortalità correlata a malattie del fegato. Alla luce di questo, i farmaci antivirali "direct acting" (*Direct Acting Antiviral Agents*, DAA) potrebbero avere un enorme impatto sulla salute pubblica in Italia. Dalla collaborazione tra Istituto Superiore di Sanità, Associazione Italiana per lo Studio del Fegato, Società Italiana per le Malattie Infettive e più di 100 tra i Centri Clinici affiliati, è nato lo studio di coorte longitudinale prospettico PITER-HCV (Piattaforma Italiana per lo studio della Terapia delle Epatiti ViRali). La coorte consisterà di un campione rappresentativo di circa 10.000 pazienti consecutivi con infezione cronica da HCV con un follow-up atteso di almeno 10 anni. La prima finestra di arruolamento è iniziata nel maggio 2014; l'arruolamento sarà riaperto per periodi di tre mesi negli anni seguenti per cogliere l'introduzione dei nuovi DAA.
Parole chiave: Studio di coorte osservazionale; Epatite C; Farmaci antivirali ad azione diretta; Equità nella cura

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HCV INFECTION AND NEW ERA OF ANTIVIRAL THERAPY

Hepatitis C Virus (HCV) chronic infection is the leading cause of end-stage liver disease, HepatoCellular Carcinoma (HCC) and liver related deaths. The World Health Organization defines viral hepatitis as a global public health problem and estimates 185 million individuals worldwide to be currently infected with HCV of whom 70% are unaware of infection. Around 500 million people are currently living with viral hepatitis and viral hepatitis is now responsible for 1.4 million deaths every year. Most people with chronic hepatitis B or C are unaware of their infection and are at serious risk of developing cirrhosis or liver cancer, contributing to global increases in both of those chronic diseases (1-3).

It has been recently reported that in 2010 there were approximately 10 times more deaths attributable to viral hepatitis in the European Union than to HIV, with two third of the viral hepatitis deaths associated with HCV infection. Similar data have been reported in the USA, where HCV associated mortality surpasses those due to HIV in 2007 (4) This mortality rate is bound to increase at least until 2030, as complications of end stage liver disease occur decades after infection, the vast majority of which occurred in the 1960s and 1970s (5). This will impose a significant burden on the health care systems worldwide. HCV chronic infection is generally a slowly progressive disease characterized by persistent hepatic inflammation leading to the development of cirrhosis in approximately 10-20% of patients over 20-30 years of HCV infection (6). However, the progression rate of cirrhosis is multifactorial and many co-factors as age at time of infection, male gender, alcohol consumption, obesity, type 2 diabetes, HIV and other viral coinfections, immunosuppressive and genetic factors, etc., have been identified to increase the individual risk of developing progressive fibrosis or cirrhosis. The progression of fibrosis to cirrhosis is reported to be variable from 2-3% to more than 51% over 20 years. It is not uncommon for HCV infected patients to remain undiagnosed until they present the complications of end stage liver disease (7-11). Once cirrhosis has developed, there is a 1-5% annual risk of HCC and a 3-6% annual risk of end stage liver disease (ESLD) (Figure 1). Following an episode of liver decompensation, the risk of death in the following year is between 15-20% (12).

HCV is currently the leading indication for liver transplantation in the Western world. Furthermore, chronic infection with hepatitis C is known to cause several extra hepatic manifestations as steatosis, type 2 diabetes, non-hodgkin lymphoma, crioglobulinemia etc. (13-17). On the other side, chronic hepatitis C infection negatively impact patient's quality of life physically, socially, mentally and emotionally. Hence, it is now well accepted that the effects of hepatitis C, extend far beyond liver related morbidity.

For more than two decades, following its discovery in 1989, interferon has been the basis for HCV treatment. Responses to treatment were improved in 1998 by the addition of ribavirin and then in 2001-2002 by linking the interferon (IFN) molecule to polyethyleneglycol (Peg). However, due to the suboptimal efficacy, low tolerability and protracted treatment duration, the therapeutic regimens, based on Peg-IFN and Ribavirin (RBV), has been considered to have relatively low impact on the decrease of the disease burden (18-20). A breakthrough discovery, which guided the development of HCV research tools, was the cloning of the HCV genome 25 years ago (21). The establishment of the HCV cell culture systems and characterization of HCV particles and replication provided the molecular basis for highly innovative and successful years in HCV drug development.

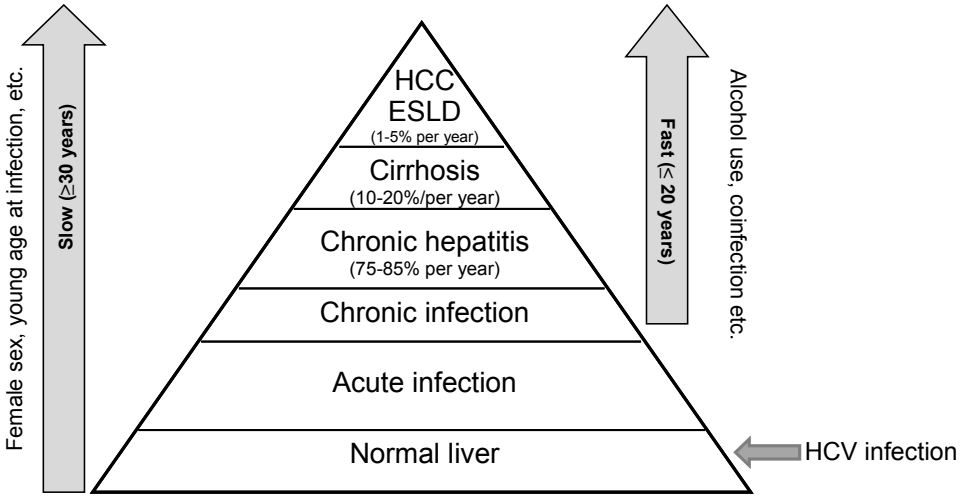

Figure 1. Natural history of HCV infection and rate of progression related to individual risk

With the identification of Direct-acting Antiviral Agents (DAAs), such as NS3/4A protease inhibitors, NS5A replication complex inhibitors, nucleotide and non-nucleoside polymerase inhibitors as well as host cell targeting agents, novel strategies were established and entered clinical testing (22, 23). In fact the past few years have seen a dramatic change in the therapeutic landscape for patients with chronic HCV infection. The era when the only option was a combination of indirect antiviral agents, RBV and peg-IFN, ended in 2011, with the approval of the DAAs telaprevir and boceprevir (24-26).

In late 2013, sofosbuvir (SOF) and simeprevir (SMV), second generation DAAs, were approved. A number of new agents from different drug classes, as ledipasvir, asunaprevir, daclatasvir, ABT-450/r combined with ombitasvir and dasabuvir, MK-5172 etc. and new combinations (even co-formulated in single pills) have been added to the HCV therapeutic armamentarium in the next few months. The introduction of the new drugs and their combined use, will bring simple therapeutic schemes (once-a-day), all-oral, IFN and RBV free, pan-genotypic, safe and well tolerable, with low risk of resistance development, efficacious in difficult to treat patients, with possibility to reach Sustained Virological Response (SVR) in a short time, that bring complete virus eradication and possibly great solution in liver transplantation area (27-38) (Figure 2).

The near future of HCV DAA therapies is already designed. Different very effective combinations have started to be tested in clinical trials. Interferon free DAA combinations include 3 options to date. Specifically:

- protease inhibitor or NS5 inhibitor + Nucleotide Analogue + Non-Nucleoside Inhibitor +/- RBV;
- protease inhibitor + NS5A Inhibitor + Non Nucleoside+/- RBV;
- 2nd generation protease inhibitor + 2nd generation NS5A inhibitor +/- RBV.

Based on these guidelines in DAA combination therapy and in the DAAs already approved, new combinations are expected to be used up to 2017 (39-42).

In this fast-changing field of high possibility for the overall harm reduction by the therapy effectiveness, many challenges and priorities remain beyond the costs.

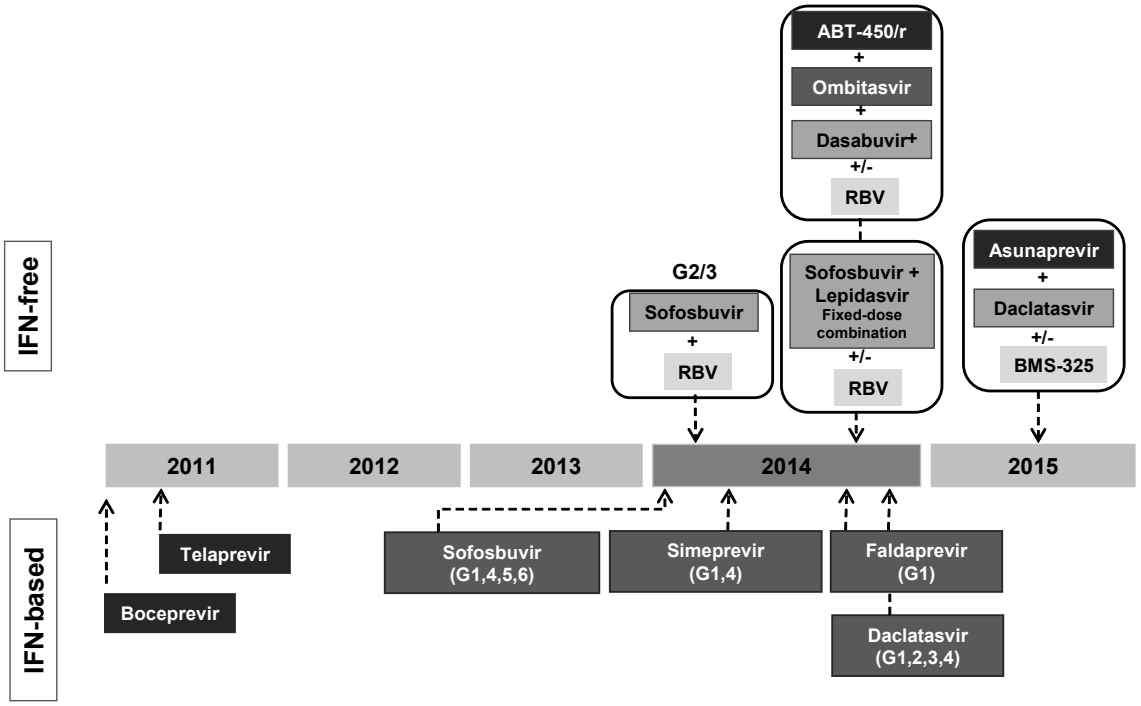

Figure 2. Present of HCV DAA therapies

Considering the exorbitant costs of the drugs, the clinical impact of DAAs in the overall long term morbidity and mortality, according to the clinical profiles of chronic liver disease and also considering co-factors of disease progression (i.e. coinfections and comorbidities) is also a priority challenge that needs to be properly addressed. The real socioeconomic impact of HCV eradication in infected patients, in terms of life expectancy and quality of life at different stages of liver disease need to be better evaluated. The impact of new antiviral therapies in high risk groups, such as patients with *de novo* infection, post liver transplantation, patients who need liver transplantation, those with progressive course of liver fibrosis and cirrhosis, in HIV and/ or HBV coinfected patients and in other socioeconomic fragile (vulnerable) patients, need also to be further investigated.

Thus, the major challenge that needs to be solved out in terms of the overall public health impact of new anti HCV therapies is whom to treat, based on the balance between the benefits and affordability to cure (Figure 3).

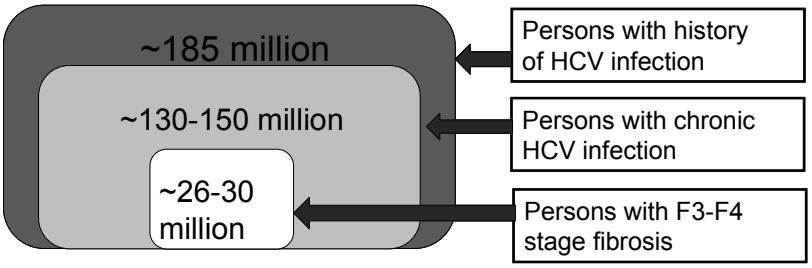

Figure 3. Estimation of persons who need HCV treatment

Clinical and economic impact of DAAs based therapy in Italy

Chronic Liver Disease (CLD) is a leading health problem in Italy. Each year more than 10.000 chronic liver disease complicated deaths are reported and, in more than 65% of them, HCV is the main etiological factor of chronic liver disease. HCC is the 5th cause of death for cancer in Italy. The costs for the CLD management are continuously increasing due to the relative increase of individuals with long lasting HBV and HCV infections, introduction of novel high costs therapies (HCC, antivirals), increase of metabolic and behavioural causes of progressive liver disease (overweight, alcohol use, physical inactivity). Regarding specifically HCV infection, Italy has the highest prevalence of HCV in Europe and the highest death rate for HCC and cirrhosis.

The prevalence, risk factors, and severity of HCV related liver disease in the general population were objects of several studies in different Italian areas conducted during the years 1994-2006. These general population studies, could not be used for valuable estimations of to date real prevalence of HCV because are outdated (1990s, early 2000s), and conducted in small towns or communities, not including immigrants and other fragile populations (43-47).

According to the Dyonisos study (48, 49), which included 6917 subjects from general population that lived in two towns of Northern Italy, HCV infection is widespread and the main etiologic factor of chronic liver disease, but only less than 50% of the anti-HCV positive subjects, particularly those infected with genotype 1b, are associated with a more severe liver disease. Alcohol consumption greater than 30 g a day significantly aggravates the natural course of the chronic liver disease (Table 1).

Table 1. Association between liver disease prevalence and main risk factors (Dyonisos study, 2010)

Risk factors	Condition prevalence	Liver disease prevalence	
		among exposed	general population
HCV infection	(221/6917)	50% (110/221)	1.6% (110/6917)
HBV infection	(83/6917)	25% (21/83)	0.3% (21/6917)
Alcohol*	(1349/6917)	5.5% (74/1349)	1.1% (74/6917)
NAFLD**	(1729/6917)	7.9-11.9% (138-207/1729) Estimated	2-3% (138-207/6917) Estimated

*risk threshold for developing liver disease (>30 g/day/both sexes); ** Non Alcoholic Fatty Liver Disease

The highest HCV prevalence has been reported in Southern Italian areas with a significant increasing trend by age (Figure 4).

In some Italian areas of South very high overall anti-HCV prevalence rates in general population were observed with a likely cohort effect, i.e. decreased risk of infection along generations (>33% in individuals older than 60 years of age compared to 1.3 in those younger than 30 years of age) (Figure 5). These observations may indicate an epidemic or focus of hepatitis C that occurred several years earlier. The majority of anti-HCV-positive subjects in the oldest age group had no clinical evidence suggesting that HCV infection is a very prolonged and indolent disease (43-49).

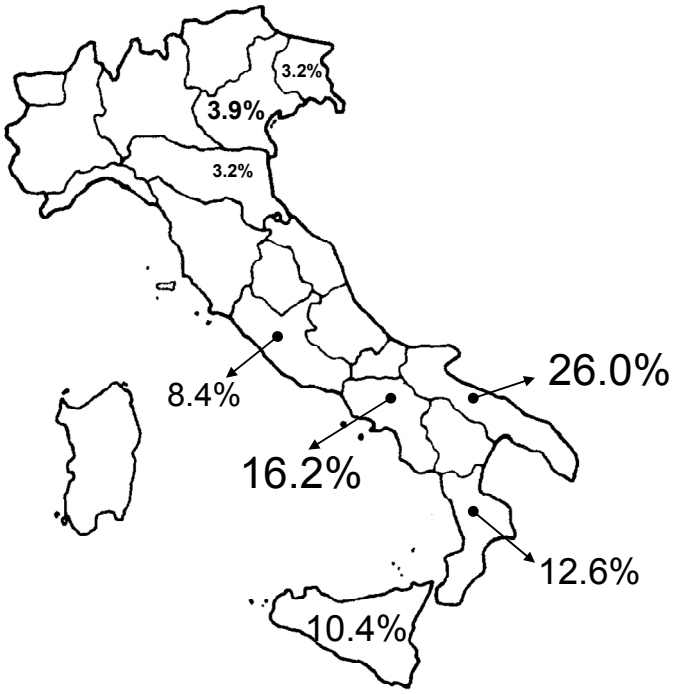

Figure 4. HCV prevalence in Italian general population (Dyonisos study, 2010)

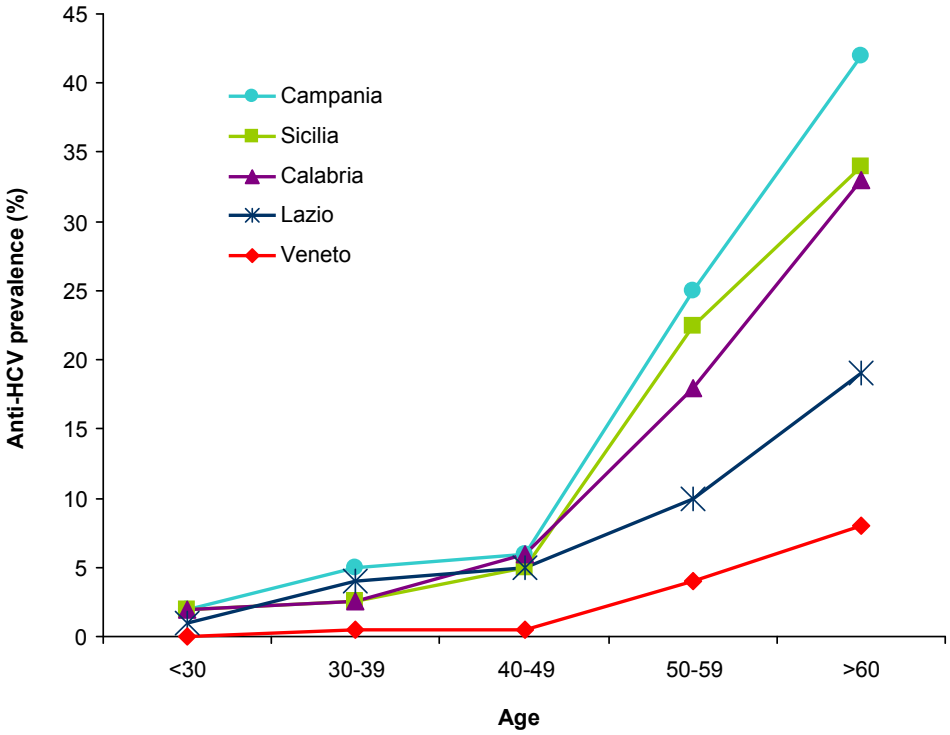

Figure 5. Age adjusted anti-HCV prevalence in the Italian population

Genotype 1 is presented more frequently in Italian patients with chronic HCV infection (in more than 50% of infected people). However, other genotypes – in particular genotype 4, which is prevalent in Africa, and genotype 3, which is more prevalent in drug users – are expected to have higher prevalence compared to what was previously described, considering high frequency of immigration from Africa and drug use, as one of the main factor of acute HCV infection.

According to SEIEVA data (Sistema Epidemiologico Integrato dell'Epatite Virale Acuta), new acute HCV infections have been declined in last decades (Table 2); however, the disease burden of HCV is expected to increase, due to the cohort effect observed for chronic HCV infection in Italy (50).

Table 2. Incidence (per 100,000 inhabitants) of syntomatic acute hepatitis C notified in Italy by age groups (SEIEVA data, 2013)

Year	Age groups (years)			
	0-14	15-24	≥ 25	Total
1985	2.0	16,0	4.0	5.0
1986	1.0	10.0	4.0	4.0
1987	0.5	8.0	3.0	3.0
1988	1.0	9.0	2.0	3.0
1989	0.0	8.0	2.0	3.0
1990	0.0	6.0	2.0	2.0
1991	1.0	5.0	2.0	2.0
1992	0.0	4.0	2.0	2.0
1993	0.0	3.0	1.0	2.0
1994	0.0	3.0	2.0	2.0
1995	0.0	2.0	2.0	2.0
1996	0.0	2.0	1.0	1.0
1997	0.0	1.0	1.0	1.0
1998	0.0	1.0	1.0	1.0
1999	0.2	1.0	1.0	1.0
2000	0.1	0.7	0.7	0.7
2001	0.4	1.0	1.0	0.7
2002	0.1	1.0	1.0	0.7
2003	0.1	0.6	0.9	0.7
2004	0.1	0.4	0.7	0.6
2005	0.0	0.6	0.6	0.5
2006	0.1	0.5	0.6	0.5
2007	0.0	0.4	0.6	0.5
2008	0.0	0.4	0.5	0.4
2009	0.0	0.2	0.2	0.2
2010	0.0	0.4	0.2	0.2
2011	0.0	0.3	0.3	0.3
2012	0.1	0.3	0.3	0.3
2013	0.0	0.3	0.3	0.3

* until 2008 NonA-NonB Hepatitis

Unfortunately, data on HCV induced liver disease profiles are scarce and do not represent the whole country reality. Italy has high HCV prevalence rate, however the ECDC (European Centre for Disease prevention and Control) data are possibly overestimated because they are based on estimates by local regional studies conducted about 15-20 years ago. There are no precise estimates on the burden of HCV infection in terms of number of infected individuals, number of patients according the severity of liver disease and the presence of HCV extrahepatic manifestations. Thus, the real HCV clinical and economic burden in Italy is not known so far.

Considering the still high prevalence of HCV in Italy, the affordability of DAAs remains a challenge for Italian National Health System, as for lots of health systems in the world, thus a rationale resource allocation is an urgent need. The high drug prices impose an access modulation to new therapies, over time which requires an evidenced based policy. Italy represents an interesting context for collecting data on long-term efficacy, safety and tolerability of new anti-HCV treatments.

Comparison among HIV, HBV and HCV infections

HCV infection is similar to HIV in several aspects though it is four times as widespread as HIV/AIDS, and differently from HIV, it can be cured (Table 3).

Table 3. Comparisons among HIV, HBV and HCV infections

Characteristics	HIV	HBV	HCV
Genome	RNA	DNA	RNA
Mutation rates	Very high	high	Very high
Virions produced daily	10^{10}	10^{13}	10^{12}
Viral genetic archiving	YES	YES	NO
Drug targets	Multiple	one	multiple
Cure with current therapy	NO (integrated viral DNA)	NO (cccDNA)	YES
Current therapeutic goal	Lifelong suppression	Lifelong suppression	Cure: clearance from plasma and liver

To tackle the burden of HCV chronic infection, researchers are drawing from the experience of HIV/AIDS, particularly in the area of HCV therapy with second generation DAAs. In about thirty years, thank of antiviral therapy, HIV become a chronic disease, though the combined antiretroviral treatment can have different results depending on the disease stage during which it is administered (Figure 6).

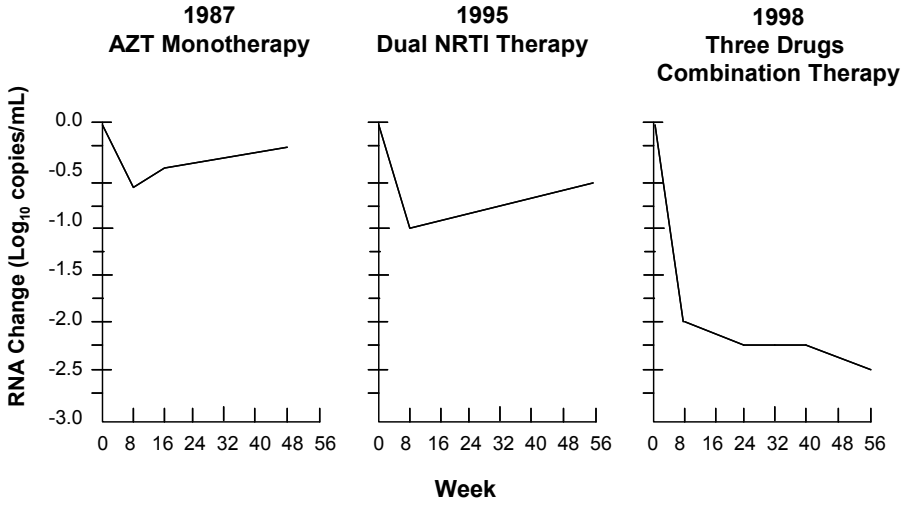

Figure 6. Evolution over the years of the therapeutic strategies aimed to control HIV replication

Moreover, it now appears clear that antiretroviral therapy not only provides clinical benefit to the individual level (in terms of risk-benefit ratio and public health policy) but has also the potential of decreasing the incidence of new infections at a population level (51-55).

The comorbidities during HIV infection play an important role in the natural history of the infection and in the results of antiretroviral therapy. Liver disease is a major cause of morbidity and mortality in HIV-infected patients and liver death count of 15% of HIV associated death. Liver related deaths are largely a consequence of chronic HBV or HCV co-infection, though there was a strong association with immunodeficiency.

Similarly in HCV infection part of comorbidities is part of natural story of infection and others are present due to the advanced age of lots of HCV infected patients. The same HIV is an important factor which increase liver disease progression in patients co-infected, particularly by the toxic effect in the liver of antiretroviral drugs used for HIV infection (56, 58).

The HIV approach is a story of success in that the goals achieved are:

- viral suppression > 90%;
- immune restoration;
- better ARV (AntiRetroviral Therapy) drugs;
- simplified treatment;
- increased survival;
- transmission reduced.

A great impact in HIV successful story is given by cohort studies who addressed several important issues as optimal timing for cART starting, preferred drugs for treatment initiations, management of failure, toxicities and comorbidities, late presentation and clinical management, special focusing on neurologic disease and cancers. In Figure 7 the results obtained from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) study are reported demonstrating that deferred therapy was significantly associated with a 69% increase in the risk of death as compared with the earlier therapy group (59); whereas in Table 4 health indicators are stratified by baseline CD4T cell count (60).

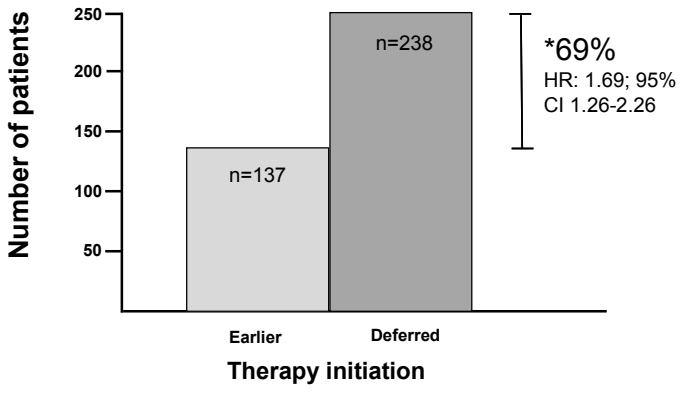

Figure 7. Results from the NA-ACCORD Study (2009)

Table 4. Health indicators stratified by baseline CD4 cell count (NA-ACCORD Study, 2009)

Indicators	<100 cells per µL	100-199 cells per µL	≥200 cells per µL
Mortality rates (per 1000 person-years)			
Overall	21.4	13.4	7.0
Between the ages 20 and 44 years	19.7	10.7	5.0
Potential years of life lost before age 65 years (per 1000 person-years)			
20-64 years	460.9	264.9	138.3
Life expectancy (years; adjusted)			
Exact age 20 years	32.4	42.0	50.4
Exact age 35 years	27.0	30.4	37.2
Percent surviving from 20 to 44 years	59.8%	80.6%	89.9%

Mortality rates are deaths per 1000 person-years (95% CI)

In conclusion the results derived by longitudinal cohort studies have been of great importance in determining clinical and therapeutical challenges during natural course of HIV infection and disease.

The drugs and drug mechanisms against HCV and HIV are very similar and for this reason the Phase II trials necessary for regulatory reasons have been very short for new HCV drugs. There is a good rationale to think even better for HCV infection, because it is completely cured following antiviral treatment, however several challenges needed to be defined to reach this goal for HCV infection. Part of these challenges have been defined in EMA CHMP Scientific Advisory Group in October 2010, in which the revision of the guideline on the clinical evaluation of direct acting antiviral agents intended for the treatment of chronic hepatitis C was presented (61).

The key points indicated to be addressed for the new DAAs for chronic HCV therapy were as follows:

1) virology and drug resistance;
2) pharmacogenetic markers;
3) monotherapy studies;
4) primary study endpoints;
5) clinical trial design in special populations
   - what are appropriate study designs and endpoints in patients with decompensated liver disease/pre transplant patients?
   - what are appropriate study designs and patient populations in exploratory and confirmatory trials in HIV/HCV co-infected patients?
6) clinical trial design with Standard Of Care (SOC) sparing regimens
   - in what populations should proof of concepts studies for novel combinations regiments be performed?
   - what are the key issues underlying study designs, comparator regimens , endpoints and subsequent follow-up?

Thus, researches oriented to answer these challenges in the HCV treatment field should consider these key points. In the case of HCV infection, patients can be successfully cured with DAAs, and in the absence of a specific vaccine, the cure could be part of the disease control, but, considering the exorbitant cost of treatment, providing treatment to all patients, would be prohibitive at least at the near coming years. It is thus imperative that, considering patients'

characteristics and co-morbidities, to determine what the best timing and what the appropriate treatment would be, with cost-effectiveness being a fundamental part of this decision. Reaching this goal would require accurate data on the long-term effects of DAA therapy for individuals in different disease stages. In other words, the impact of DAA use in actual clinical practice must be determined, and, as in HIV cohort studies experience, this would give an important contribution.

PITER: a new approach

In order to address the challenges and unanswered questions in the field of therapy of HCV and other coinfections, the Italian platform for the study of viral hepatitis therapies known as PITER (Piattaforma Italiana per lo studio della Terapia delle Epatiti viRali, www.iss.it/piter) was launched in 2012: a collaboration among the Istituto Superiore di Sanità (ISS, the National Institute of Health in Italy), the Associazione Italiana per lo Studio del Fegato (AISF, the Italian association for the study of the liver) and the Società Italiana di Malattie Infettive e Tropicali (SIMIT, the Italian society of infective and tropical diseases).

Considering the global clinical and economic burden of HCV infection several European countries have promptly built specific registries regarding HCV chronic infection and the clinical impact of DAAs (Figure 8).

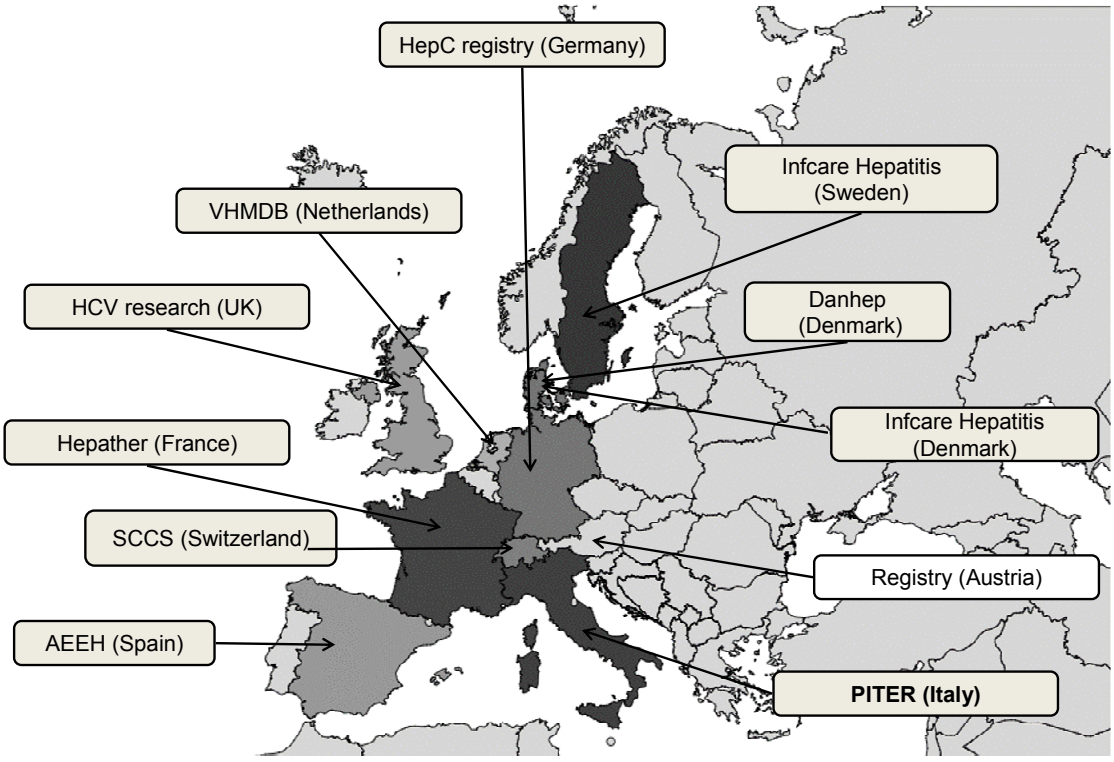

Figure 8. Overwiev of HCV registry engagements in EU

The major goals of PITER research platform are:

- develop formative and research activities either clinical or translational in the field of viral hepatitis;
- monitor the evolution on time of viral hepatitis therapies in terms of quality, appropriateness, and treatment access;
- produce scientific knowledge on efficacy, safety and impact of antiviral therapies on the real life;
- provide vital information about who receives care and what kind of treatment they receive;
- produce evidences useful for health policies and better resources' allocation over time.
- coordinate the Italian researchers in increasing the weight of the research on viral hepatitis in order to achieve higher impact in Europe and over the world.

To reach these goals a longitudinal cohort study has been developed (PITER- HCV cohort study). This longitudinal observational study is built on a unique combination of expertise in chronic liver disease, liver transplantation, infectious disease, internal medicine and antiviral therapy.

PITER-HCV COHORT STUDY IN ITALY

Aims and importance of the study

The first activity of PITER has been the implementation of an observational longitudinal cohort study of patients with chronic HCV infection denominated PITER-HCV cohort study (Figure 9).

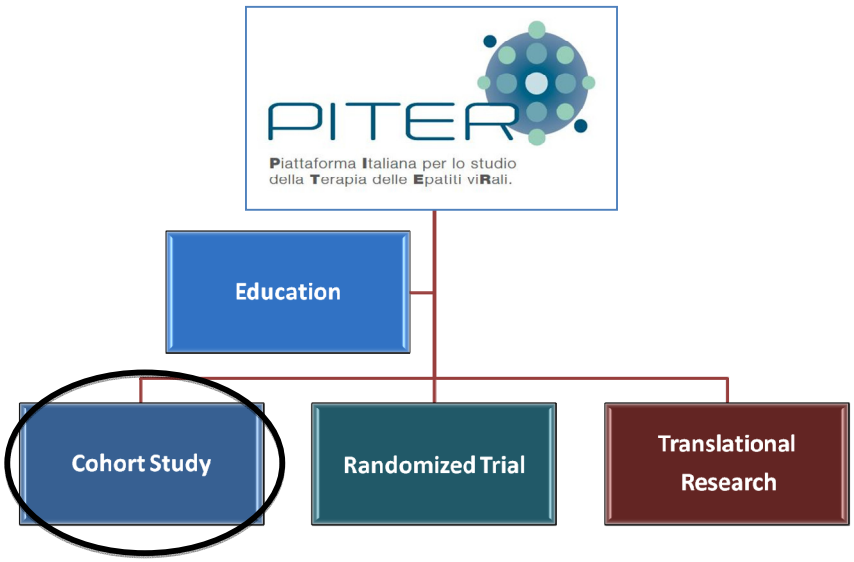

Figure 9. PITER: platform and HCV cohort study

The main protocol of this study has been approved by the central and local ethics committees.

Overall, over 10.000 patients are planned to be enrolled and followed-up for at least 10 years. Over 100 Italian Clinical Centres (both Hepatology and Infectious Disease Units) are actively participating in this study. This huge web-based platform of prospective data, coming from patients in care from different clinical, geographic and social realities will address the lack of reliable information on the HCV-related burden of disease in Italy. The final goal of this longitudinal cohort study is to increase the generation and the use of relevant research evidences in the decision-making processes in order to contribute in the morbidity decrease and to improve the effective life-saving interventions.

The main aims of the PITER longitudinal cohort study are:

- produce of an ongoing and continuously updated picture of the changing epidemiology of HCV infection in the country;
- evaluate medium and long term outcomes of chronic HCV infection;
- evaluate clinical impact of the introduction of new DAAs in different clinical/virologic contexts and in special populations;

- monitor short medium and long term safety of DAAs and of DAAs combinations and their possible pharmacological interactions in the real life;
- design appropriate care and therapeutic algorithms for special, difficult to treat and difficult to reach populations;
- build a continuously updated cost-efficacy framework to give insights on the economic impact of the progressive introduction of the new DAAs;
- personalize treatment in specific populations (elderly people, women, patients not responding to standardized treatment protocols, patients awaiting for liver transplantation or those transplanted);
- evaluate the role of viral variability in the natural history of the disease and in the response to treatment.

Based on these aims, a real-life setting of the expected impact of new DAAs on the natural course of infection and on the long term outcomes in terms of morbidity and mortality in different categories of patients, including those transplanted or awaiting liver transplantation will be evaluated. Specific populations, like the coinfected and patients with comorbidities, will also specifically evaluated. In addition several spin off studies will be planned using as backbone the PITER-HCV cohort data set. Specifically pharmaco-economic models of the direct and indirect costs of the morbidity due to chronic HCV infection versus the huge cost of new treatments are planned to be conducted immediately following the cohort built. This exercise, based on real life data, will produce options for public health decision makers on how to better address the burden of HCV related disease and in how to cope with its negative impact on life expectancy, and on the quality of life of infected individuals.

Governance of PITER-HCV cohort study

The PITER-HCV cohort study is coordinated by the ISS (Dipartimento del Farmaco: Department of Therapeutic Research and Medicines Evaluation). It has gained a considerable experience in clinical trial managements and research activities participating and coordinating various international projects. It has an outstanding experience in conducting large cohorts studies and possess all necessary equipment for the study conduction. It is composed of general and clinical study coordination, scientific secretary, epidemiology, statistic and informatics teams, data entry monitoring, technical and administrative secretaries. The Coordinating Centre of PITER-HCV cohort is responsible for data collection and their evaluation ensuring high quality results.

The Executive Committee of the PITER-HCV cohort is the main scientific and policy adviser of PITER. It is composed of researchers with complementary expertise in different HCV chronic infection disease and treatment fields.

Its specific role is:

- coordinate each project phase;
- oversee the participation of Clinical Centres;
- evaluate study results;
- evaluate the importance of the spin-off studies that will be proposed;
- define the priorities in different research topics within the PITER-HCV cohort data set;
- determine the modalities of results' dissemination and publication;
- coordinate the relationship among health institutions and policy makers as well as public and private financial study sponsors.

The Scientific Committee is the scientific organ of PITER. Its specific role is:

- oversee the research activities derived by the PITER framework;
- design specific spin-off studies within PITER research related areas;
- manage and guarantee the scientific and economic aspects related to the proposed spin-off studies.

Top down and bottom up studies will be conducted based on PITER platform. The respective proposals will be evaluated by the Scientific Committee as schematically represented in Figure 10.

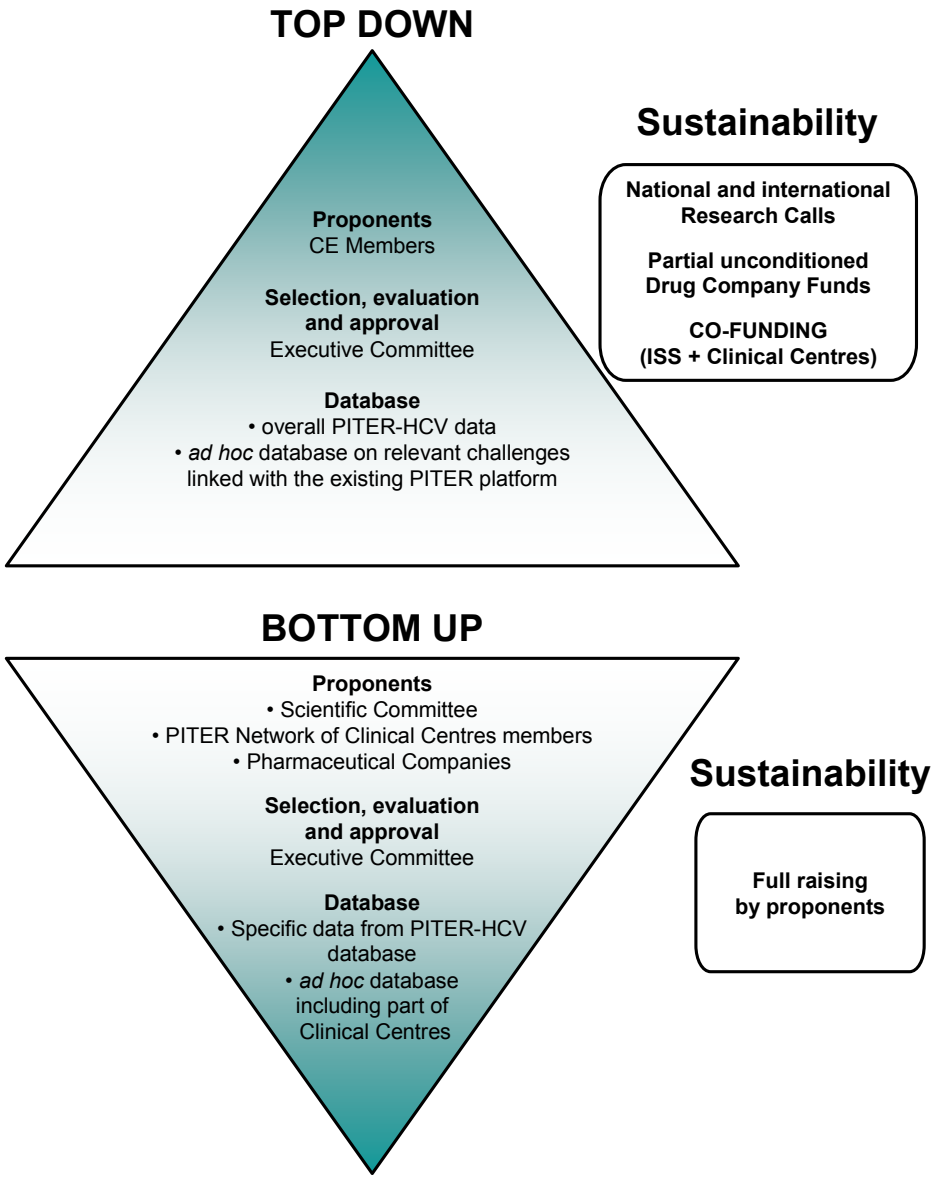

Figure 10. Characteristics of Top down and Bottom up studies

The high level of PITER governance allows an integration of evidences obtain from everyday clinical practice with the specific expertise gained from specialists in the fields of

chronic liver disease management, antiviral therapy and extrahepatic manifestations of HCV infection.

The Executive Committee, after consulting the Scientific Committee, establishes the composition of the following advisory institutions:

- International Scientific Advisory Board;
- Ethical and Legal Committee;
- Patients' Associations Committee.

PITER network of Clinical Centres

All participating Clinical Centres have been selected (in collaboration with AISF and SIMIT) based on their experience in the clinical work conducted according to Good Clinical Practice. All Clinical Centres of the PITER network are provided with the necessary HCV chronic liver disease diagnostic and therapy requirements (both laboratory and imaging). The Clinical Centres distribution, according to the national geographical area, is shown in Figure 11; the platform will include new centres that are interested to participate in this ongoing study, thus the geographical distribution is an up to date process.

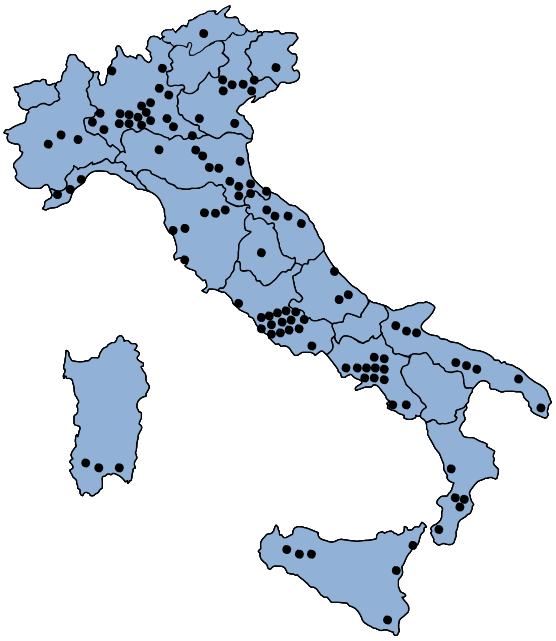

Figure 11. Clinical Centres Distribution in Italy

Study population

The enrolment inclusion criteria are: all HCV infected patients older than 18 years of age that will consecutively reach the out-patients clinics of the participating Clinical Centres in a given time span (approximately 3-6 months) and all HCV infected patients untreated at the time

of enrolment (previously treated patients are eligible independently if SVR was previously reached).

Patients' characteristics are:

- any gender;
- any clinical and histopathologic stage of HCV infection infected by any HCV genotypes;
- with and without HBV, HDV (Hepatitis Delta Virus) and/or HIV coinfections (in any clinical stage of HIV infection, with or without antiretroviral treatment).

Main expected results

The main expected results of the PITER-HCV cohort study will be:

- production of national estimates on the epidemiological and clinical profile of HCV+ patients entering care (specifically national prevalence of HCV infection and disease stratified by stage of chronic liver disease, prevalence of extrahepatic manifestations, rates of HBV and or HIV coinfections, prevalence of major comorbidities), offering important inputs on the current and future HCV burden of disease and therapeutic needs;
- prevalence of real life usage of the different available therapeutic options.
- safety and efficacy (real life) data of DAAs used in different clinical settings;
- identification of factors influencing HCV treatment response in the real life;
- identification of base line clinical and social characteristics which may predict a positive therapeutic response;
- estimate of geographic and gender differences in DAA access;
- rates of SVR for each expected combination of DAAs used;
- prevalence of adverse effects correlated, in real life, to different DDA combinations;
- changing rates of progression or regression of liver fibrosis and extrahepatic HCV manifestations in treated patients;
- change of incidence of liver failure, HCC development, OLT need following the introduction of DAAs;
- overall improvement of HCV clinical care by improved staging and predictability of disease progression and treatment response; assessment of the most appropriate treatment duration for different categories of patients; assessment of patient's quality of life changes with the introduction;
- contribution to a more effective clinical management through the identification of the most cost-effective strategies developing innovative individualized treatment algorithms based on the results of real life patients care and on rational budget allocation.

Impact of the project for the National Health Service

PITER-HCV cohort study will be based on a large prospective cohort of patients, thus representing an innovative approach to actually confirm in real life clinical practice, the findings obtained by "regulatory" short term clinical trials. The specific main goal is to analyze the long term outcomes following the SVR in different categories of patients (the majority of which were not enrolled in the controlled clinical trials).

This research will help to define the more appropriate use of available therapies and resources, in order to produce adaptive models in which treatment provision can be wisely prioritized and tailored according to the patient's characteristics.

PITER-HCV cohort has a target recruitment of 10,000 individuals and will include those commencing a DAA-based therapy as their first therapy, or who have failed a prior IFN/RBV based therapy, but will also follow-up patients not yet receiving DAAs for various reasons, including a non-advanced stage of disease, who could anyway become candidates for future DAA-combination therapy. Thus, it would also represent the starting point and the back-bone data base for future clinical studies and research activities. Specific observational cohorts and spin-off studies, dedicated to target populations derived by the PITER-HCV cohort, will contribute to the optimization of therapeutic protocols and to the formulation of guidelines on the use of new therapies for HCV treatment.

Methods

PITER-HCV cohort study has a Scientific Coordination Secretary situated in the ISS (Dipartimento del Farmaco). This secretary, according to the directives of Executive and Scientific committees, is responsible for the study protocol, ethic aspects, electronic Case Report Files (eCRF) production, data monitoring and elaboration. A permanent operational staff is dedicated to the PITER-HCV cohort, with particular regard to:

- produce the scientific and operative protocols according to the ethical guidance;
- create the web based clinical data gathering;
- actively monitor Clinical Centres;
- perform statistical data analysis.

Ethical aspects and protocol approval

The procedures for the Ethical Approval of PITER-HCV cohort study were as follow:

1. ISS Ethic Committee evaluation and approval of the Study Protocol and of the Patient's Informed Consent.
2. Evaluation and approval of the Study Protocol and of Patient Informed Consent by the local Ethic Committee of each Clinical Centre.
3. Evaluation by the Scientific Coordination Secretary of each specific request raised from the local Ethic Committees. Better clarification of the following points were addressed:
   - *Better explanation of biological samples collection and storage*. It is specified that the sera collection is not mandatory and only Clinical Centres that already have the facilities and are equipped for host and viral test, for the aims of the PITER study, will be proposed to collect and store sera from 5 mL of the enrolled patient peripheral blood during the enrolment and/or follow-up prior to an eventual antiviral therapy. If the patient does not consent the blood drawn, this does not exclude him/her from the study.
   - *Explanation of sample size estimation*. Specifically, the study is not a randomized controlled trial thus no comparison between different treatments will be performed.
     The sample size is based to the expected real life adverse effects of different antiviral drugs estimated about 5% (2% in selected patients participating in the clinical trials) About 10 drug combinations will be evaluated in the real life. Thus in order to make sure that the study could evaluate the possible increase of drug adverse effects (from 2% to 5%) about 400 patients for each treatment combination are necessary to be

evaluated thus about 5000 treated patients overall. Considering that the cohort will include patients who will not undergo antiviral treatment immediately, it is hypothesized that the inclusion of about 10.000 patients will give a great statistical power to the study.

- *Better indication of the timing of data collection during follow-up*. It is specified that the follow-up visits are not predefined in the study design. They will be decided by the specialist doctor according to the Good Clinical Practice. In the respective eCRFs only the available information, presented in the clinical notes of patients followed as outpatients, will be collected.
- *Indication of economic resources for study conduction.* Specifically, no economic resources for blood samples testing or for laboratory analysis are required for the aims of the study, thus no financial support for laboratory analysis is necessary. Public and/or private funds will finance the study coordination and conduction. Each private financial support eventually offered will be evaluated by the Ethical Committees according to strict conflict-of-interest policies in order to ensure study impartiality and integrity.
- *Indication on patient's informed consent.* According to the Italian Legislative Decree 211 of 24/06/2003 the informed consent could be modified by each participating Clinical Centre according to specific centre's policy, in agreement to the study protocol requirements.

All the above points were reported as updated not substantially changes in the protocol and were notified first by the ISS Ethic Committee on 20/10/2014 and subsequently were transmitted to all PITER Clinical Centres. There were no substantial changes in the protocol, thus no amendments of the protocol were necessary.

Start up funds

Clinical Centres are involved in the study on voluntary basis. The study start-up was supported by the following grants: "Research Project PITER 2010" RF-2010-2315839, ISS special funds for the start up of strategic studies and by an unconditioned partial support from Bristol-Meyer Squibb, MSD Italia (Merck & Co.) and Roche. Each private financial support has been/will be evaluated by the Ethic Committee of the ISS, according to strict conflict-of-interest policies, in order to ensure study impartiality and integrity. Future public and/or private funds will be required to support the study coordination and conduction.

Selection of Clinical Centres

The Clinical Centres included in the PITER study, affiliated AISF and/or SIMIT, have accredited reference biochemical and biological laboratories for the host and viral test routinely required for patients monitoring, as well as appropriate clinical instruments to diagnose and treat chronic liver disease. To each of these Clinical Centres a preliminary questionnaire was administered. The following points were addressed:

- interest to participate in the study;
- number of HCV chronically infected patients that were managed in the centre in the last year;
- possibility to collect the clinical data in an eCRF format during a follow-up period of at least 5 years.

On the basis of the data derived from the fulfilled questionnaires, the number of the patients to be enrolled was categorized as:

- from 30 to 50 patients for the "small" local centres;
- from 50 to 150 for centres located in General Hospitals;
- from 150 to 300 patients for University Tertiary Health Care Centres.

Definition of the operative procedures

PITER-HCV research protocol clearly defines the aims of the study, the inclusion and the exclusion criteria, the duration of the follow-up and the sample size. The collected data will include clinical, laboratory and pathological information. All these data will be recorded in the eCRFs, at the enrolment and the follow-up visits. Particular attention will be required to specific patients' populations (HIV, HBV, HDV co-infected, with co-morbidities, with accelerate liver disease progression etc). Patients that will start an antiviral treatment will be followed according to the specific guidelines.

Important issues as the data flow (enrolment, follow-up, therapy, important events due to drug therapies as required by mandatory pharmacovigilance system), the procedures to ensure data confidentiality and anonymity and other ethical aspects, eventual biological sample collection for virological researches are also explained in the protocol and in the procedure's manual that the medical doctor, responsible for data entry, should follow during the conduction of the study.

The main points underlined in the protocol's guide book are:

- the fulfilment of the enrolment's criteria (inclusion and exclusion criteria, ensure the agreement to participate in the study with the respective informed consent, stick the clinical notes with the specific marked label as "PITER study", etc.);
- timing of different eCRF's compilations:
  - real time-fill: enrolment, start of the therapy and important life-threatening events,
  - follow-up: at least once a year reporting in a cumulative way the information reported in the clinical notes during the respective follow-up time;
- definition of *serious for live* adverse effect due to anti-HCV antiviral therapy as required by pharmacovigilance system and the respective eCRF compilation within 24 hours following the notification of the adverse effect.

PITER web-based platform and eCRF

PITER-HCV cohort has built an interactive system for the daily connection with all Clinical Centres that are involved in the study. An *ad hoc* web-based platform, certified to international standards, has been used for the data collection. It is intuitive, simple to be used and could enable interoperability, sharing of information and development of specific studies through complementary competences. The data set included in the platform contains socio-demographic and clinical information, necessary for the main aims of the PITER study; however, it will be implemented with the specific spin off studies regarding patients enrolled within the PITER framework. The possibility to build interconnected databases based in the same informatics platform has been studied and resulted feasible.

The eCRFs were designed in order to present the real data notes of patients that are visited in different out patients' clinics dealing with viral chronic liver disease. The clinical data set to be collected was decided following consultations with experts in the specific areas of HCV virus research, liver disease and therapy. A document that describe all the procedures to be followed

during the data entry in which are specifically reported the necessary steps for the successful compilation of each e CRF has also been created.

Figure 12 and Figure 13 schematically report the data collection in each eCRF ("Enrolment" "Therapy", "Serious adverse events" and "Follow-up") and the workflow of information collected specifying all the timelines. Briefly, the clinical notes of anti-HCV consecutive enrolled patients have to be reviewed by the doctor responsible for data entry. The compilation of the "Enrolment" eCRF is not necessary to be performed during the patient's visit in the out-patient clinic; the information could be tracked by the clinical notes. If the "Enrolment" eCRF is successfully completed, the data regarding the follow-up, therapy and serious adverse events during therapy could be fulfilled in the specific eCRF.

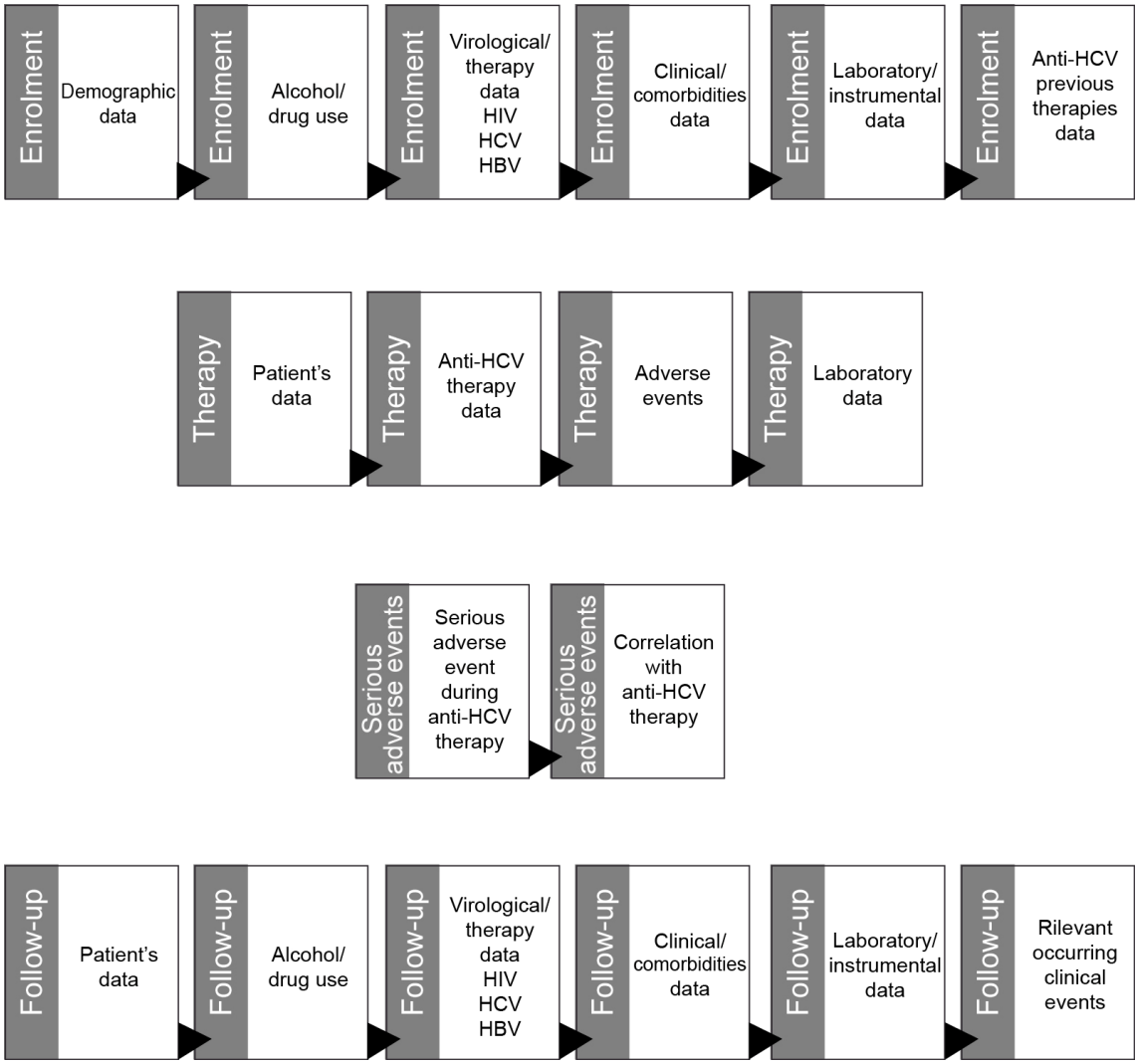

Figure 12. Information collected in the eCRFs: "Enrolment", "Therapy", "Serious adverse events" and "Follow-up"

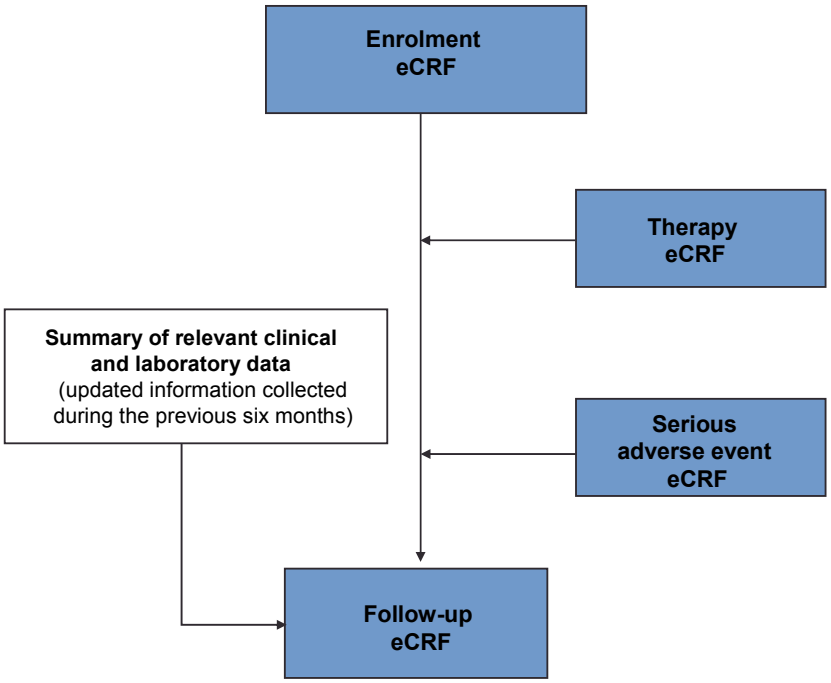

Figure 13. Data collection flowchart

Safety reporting flowchart

Special attention is devoted to the implementation of the procedures for the notification of the very serious for life adverse events occurring during anti-HCV therapy such as (Figure 14):

1. death;
2. life-threatening event;
3. hospitalization (initial or prolonged);
4. disability or permanent damage;
5. congenital anomaly/birth defect;
6. other serious events that require a rapid alert.

The data entry is required to fill the specific eCRF, regarding the Severe Adverse Event, within 24 hours when the adverse effect is notified describing it as required.

It is a clinician's responsibility to communicate the severe adverse event to pharmacovigilance authorities according to the post-marketing spontaneous reporting system. The Clinical Centre is also required to communicate to the coordinating centre the event notification to the competent authority.

In the eCRF that regards the Severe Adverse Event, who is responsible for the data entry has to specify the correlation between the adverse event and the anti-HCV therapy, and, if the adverse reaction is linked to:

1. interactions with other drugs;
2. abuse;
3. off label;
4. professional exposure;
5. therapeutic mistake;
6. overdose.

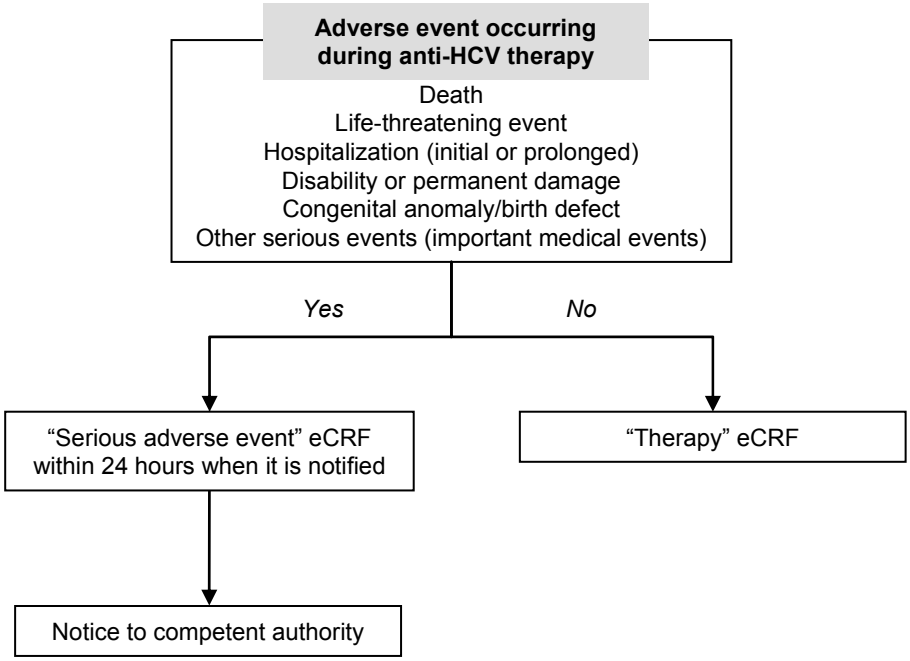

Figure 14. Safety reporting flowchart

All other non serious adverse events occurring during anti-HCV therapy are documented in the eCRF that regards anti-HCV treatment ("Therapy" eCRF) as reported in Appendix. For each adverse event, the degree (form 1 to 4), the actions taken up by the clinician, the outcome of these actions, changes or in the interruption of the anti-HCV therapy are the required information.

Interaction of Coordinating Centre with PITER Clinical Centres and data entry monitor

Educational training through e-learning and interactive meetings among ISS dedicated staff and young investigators of Clinical Centres have ensured the high quality data entry. Furthermore a direct contact of clinical investigators of Clinical Centres with researchers involved in the PITER-HCV cohort study has been provided in order to guarantee a direct assistance in each step of the eCRF's compilation. Annual face-to-face investigator meetings and periodic teleconferences among the Central Coordinating Centre (ISS) and researchers from Clinical Centres of the PITER network are planned to be organized during the time of the study conduction.

The data quality is checked through a remote monitoring using queries specifically designed to check the non appropriate data entry (*see* section "Query elaboration and statistical analysis"). "Discrepancy notes" are sent by the Coordination centre to Clinical Centres with a clear test that identifies the items to be checked and eventually to be corrected. Different issues raised by the young investigators with their answers and problems' solutions are presented as a unique Frequently Asked Questions (FAQ) document, updated continuously, in the dedicated area of the electronic platform.

Query elaboration and statistical analysis

Following the first window of enrolment and the respective eCRF compilation, a descriptive analysis for each item included in the eCRF was performed. The range of acceptable values was previously defined for the "uncontrolled" variables directly during the data input. A list of queries, related specifically with the range of acceptable values was then defined. A second step was the creation of clinical congruencies queries. A series of queries that cross different clinical information related among them were then defined. As the consequences of these two levels of queries, it was decided to insert the first type of queries directly as "out of range value" to be corrected and the second as "to be check and verified value".

A close interaction between the coordinating centre and the participating Clinical Centres will ensure the quality of the follow-up data (Figure 15).

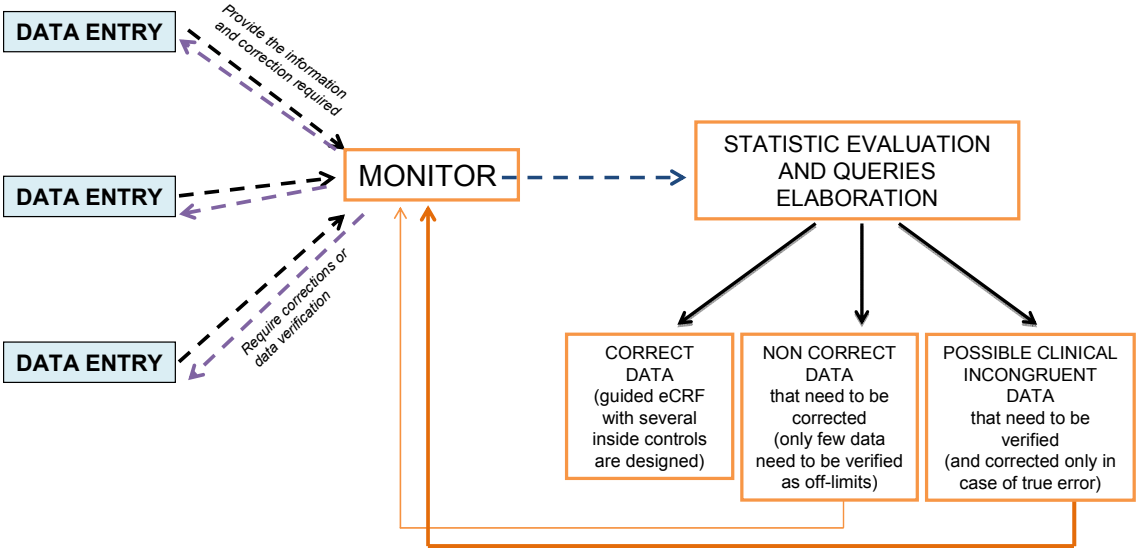

Figure 15. High quality data analysis process

Data analysis

Through its prospective design, the study, which is aimed at following the enrolled patients for at least 10 years (with periodic re-opening windows of new enrolments), will address both the long term outcomes of treated and untreated chronic HCV infection according to the different profiles of disease severity (including transplant patients) and to other prognostic factors (such as coinfections or comorbidities), including a detailed cost-effectiveness analysis based on real-life long term data. Specifically, following the first descriptive evaluation, the statistical analysis is planned to be conducted in two steps: descriptive analysis with a monthly frequency and the analysis of the study primary and secondary endpoints during the follow-up.

The endpoints to be evaluated through cross sectional analyses are:

a) prevalence estimates of the main clinical characteristics of chronic HCV liver disease at different stages of fibrosis with and without complications as portal hypertension, liver cancer and end stage liver failure in need or awaiting liver transplantation;

b) snapshots of extrahepatic HCV related disorders;
c) prevalence of HBV, HDV and HIV coinfections, prevalence of adverse effects during anti-HCV therapy in different subgroups of patients.

The longitudinal prospective analysis will be performed during the follow-up. The progression of liver disease will be estimated through the evaluation of clinical outcomes over time, specifically evaluating changes in the fibrosis stage, development of portal hypertension decompensated liver disease, and or HCC, need for liver and/or other organ transplantation, hospitalizations and overall mortality in patients with different clinical profiles of liver diseases and comorbidities at enrolment. Evaluation of treatment efficacy will be based on the rates and speed of SVR. Safety analysis of different grades of adverse side effects possibly observed due to different concomitant therapies used will be performed. Analysis of morbidity and mortality outcomes will be evaluated in treated and non-treated patients. The long-term effectiveness will be evaluated specifically assessing the residual risk of life-threatening complications such as hepatic failure, portal hypertension, HCC development and the need for liver transplantation after SVR is achieved.

The independent effect of the socio-demographic and of clinical characteristics on liver disease progression and on the achievement of SVR will be evaluated by logistic regression analysis. The Kaplan-Meier method will be used to calculate the probabilities of survival. Log rank test will compare different survival probabilities. Cox proportional hazards regression models will be used to evaluate possible predictors of survival. Incidence rate of HCC and of other outcomes of disease progression will be calculated as the number of new infections per person years observed during the follow-up. For each model, a procedure of cross-validation with a stepwise selection of the explanatory variables will be implemented. In particular, the entire cohort will be randomly split in two samples: the first one will be used to develop the predictive model and the second one for its validation. Characteristics and comorbidities to be included in the models will be defined through a stepwise variable selection. Appropriate statistical tests will be used to evaluate the quality of the models in terms of calibration and discrimination.

Risk analysis and solutions

This is a large multicentric cohort study in which Clinical Centres are distributed throughout Italy, thus, hopefully, the sample will be representative of all HCV patients in care in Italy. In order to limit the selection bias of including in the study only patients with severe disease, the study is clearly designed in the enrolment of the consecutive patients reaching a participating Clinical Centre in a set temporal frame (independent from their clinical status). The enrolments will be re-opened twice yearly, in order to keep the study in line with the introduction of newer DAAs.

The PITER-HCV will include patients on clinical care, and unfortunately could not give clinical information on patients who are unaware of their HCV infection status. However, we assume that the introduction of the new DAAs, will increase the number of asymptomatic individuals willing to eradicate HCV infection, thus the study will hopefully progressively reflect the “real” epidemiology of HCV in the country. The possible initial selection bias can be progressively eliminated.

Results

Enrolment rate and Clinical Centres distribution

Eighty-four of 113 Clinical Centres involved in the study completed the necessary and required ethical procedures and are actively participating in the PITER-HCV network. The first enrolment period was April-November 2014. The second enrolment period for the remaining centres was December 2014-May 2015. The state of the art of the PITER activities as by May 2015 is reported in Table 6.

Table 6. PITER-HCV cohort study phases

Project phases	Period	Status
First enrolment period	April-November 2014	Closed
Second enrolment period	December 2014-May 2015	Closed
Third enrolment period	November 2015	
Subsequent enrolments	Spring /Fall (2-3 months every year)	
Therapy data collection	December 2014	Ongoing
Follow-up data collection	February 2015	Ongoing
Monitor/queries	May 2014	Ongoing

During the first enrolment period, in which participated only 33% of the Clinical Centres involved in the PITER Network, 3520 anti-HCV patients in care were enrolled.

The number of enrolled patients as updated in May 2015 is 6211 (Figure 16).

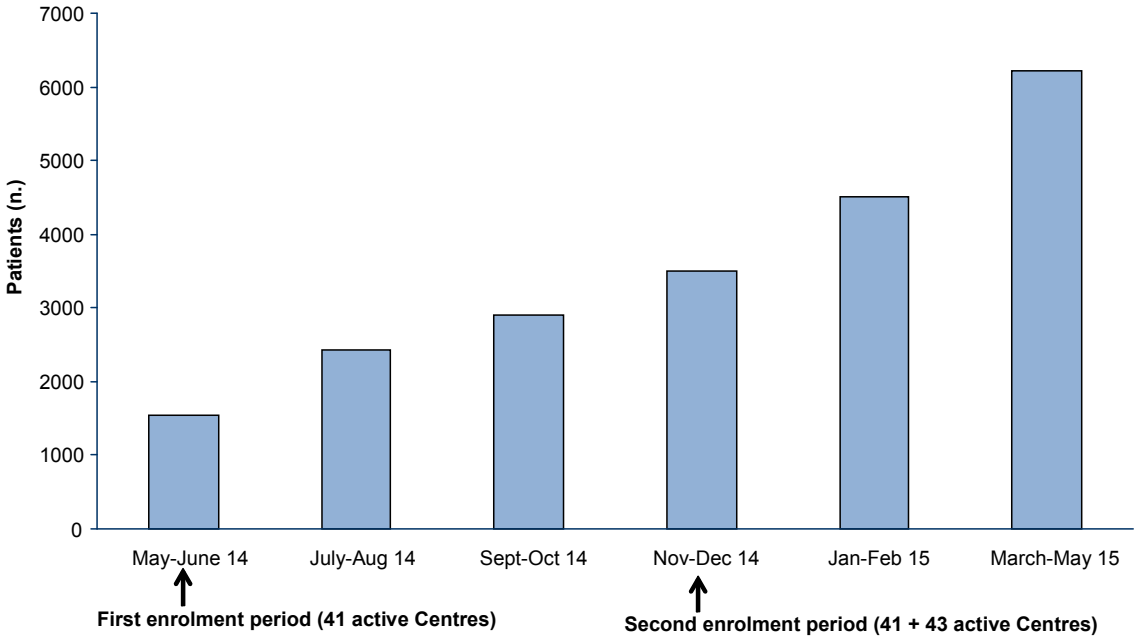

Figure 16. PITER-HCV cohort study: patients enrolled (May 2015)

Characteristics of the enrolled patients

Mean age of the enrolled patients is 59 years (range 20-95 years) and 55 % of them were men. The distribution of patients according to Clinical Centres' specialities and geographical area is reported in Figure 17.

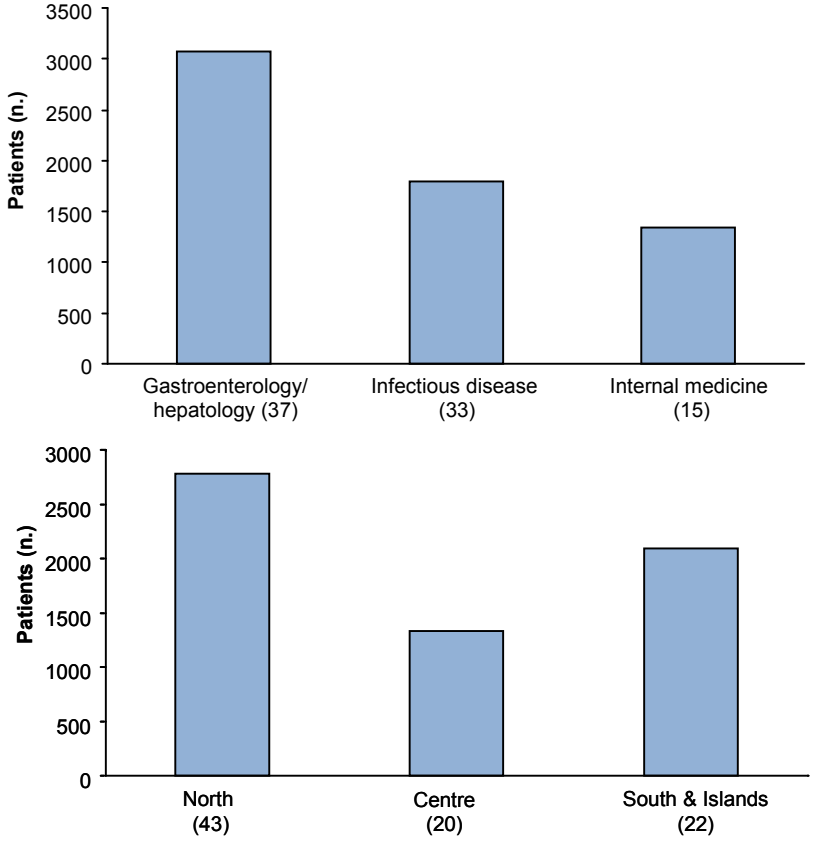

Figure 17. PITER-HCV cohort study: patients' distribution according to the Clinical Centre specialty and geographical area (May 2015)

In Table 7 is reported the distribution of HCV genotypes. Higher prevalence of genotype 1b was observed compared to similar prevalence of genotypes 1a, 2 and 3.

Table 7. PITER-HCV cohort study: prevalence of HCV genotypes (May 2015)

Genotype	Prevalence (%)
1	3
1a	11
1b	44
2	15
3	10
4	7
other	1
not determined	9

In Table 8 the clinical profile of liver disease is reported in terms of fibrosis defined according to the Fibroscan and/or biopsy data (available in 64% of patients) and/or by clinical data that indicate liver cirrhosis as portal hypertension, thrombocytopenia, Child Score.

Table 8. PITER-HCV cohort study: clinical profile of liver disease in terms of fibrosis stage (May 2015)

Fibrosis stage	Fibroscan available (%)	Clinical diagnosis (%)
F0-F1	41	53
F2	15	
F3	12	
F4-Cirrhosis	32	47

In patients diagnosed by Fibroscan the prevalence of severe fibrosis and or cirrhosis was 32% whereas in patients in whom the diagnosis of liver disease severity was performed by the clinical data only, cirrhosis was diagnosed in 47% of patients. Overall within the enrolled patients 40% of them could be classified as having advanced liver disease, whereas about 20% were classified as moderated severity of liver disease. Data on previous IFN based therapies in the enrolled patients according to the fibrosis stage are reported in Tables 9 and 10. The cirrhosis complications more frequently reported are hepatocellular carcinoma and ascites presented in 14% and 11% of patients respectively. More frequently reported co-morbidities are cardiovascular disease and diabetes presented in 40% in 15% of the enrolled patients respectively.

Table 9. PITER-HCV cohort study: previous therapeutic history according to fibrosis stage (Fibroscan and/or clinical diagnosis of cirrhosis) (May 2015)

Previous therapeutic history (5679 analysed)	F0-F3 %	F4-Cirrhosis %
Previously treated	56	43
Naive	66	32
Not known	4	

Table 10. PITER-HCV cohort study: previous therapeutic history according to fibrosis stage as reported only by Fibroscan (May 2015)

Previous therapeutic history (3550 analysed)	F0-F1 %	F2 %	F3 %	F4-Cirrhosis %
Previously treated	32	16	13	38
Naive	50	14	10	26

CONCLUSIONS

The importance of PITER for the Italian National Health System is potentially huge because it will produce data that are urgently needed to support the recently developed National Hepatitis Plan.

To date, about 80% of the participating Clinical Centres to the PITER-HCV cohort study have begun the patients' enrolment (more than 6500 patients have been enrolled until May 2015); the remaining centres are in the process of preparing for enrolment.

The results based in the enrolled patients represent the first "Italian picture" of chronic HCV patients in care. Patients that have an advanced age and a severe stage of liver disease represent 40% of the whole population, whereas 20% of patients have a disease with a moderate severity. The epidemiologic pattern of HCV disease profiles could be changed with the increasing number of the enrolled patients by the actively participated centres and by new centres that will be involved in the next round of enrolment planned to be conducted in November 2015.

PITER will be the backbone for further specific research studies and is expected to provide much needed guidance in evidence-based health policy for better treatment and prudent resource allocation in order to guarantee equity in access to treatment.

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APPENDIX
Non serious adverse events occurring during anti-HCV therapy

List of non serious adverse events separated by anatomical apparatus or system as reported in "Therapy" eCRF

Anatomical apparatus or system	Adverse event
Blood and lymphatic system disorders	Anaemia Leukocytopenia Neutropenia Thrombocytopenias other
Cardiac disorders	Palpitations Tachycardia Arrhythmias Cardiac failure other
Ear and labyrinth disorders	Acuphene other
Endocrine disorders	Hypothyroidism Hyperthyroidism Thyroid autoimmune disease other
Eye disorders	Retinal disease Sight disease Dry eye other
Gastrointestinal disorders	Diarrhea Nausea Vomit Constipation Anal itch Hemorrhoids Proctalgia Abdominal pain Anal-rectal pain Anal Fissure Hemorrhage Stomatitis aphthosa Mouth ulceration Teeth diseases other
Hepatobiliary disorders	Hyperbilirubinemia other
Immune system disorders	Allergic reactions Anaphylaxis Autoimmune diseases other
Infections and infestations	Oral candidiasis other
Metabolism and nutrition disorders	Hyperuricemia Hyperglycemia Hypertrigliciderimia Diabetes other
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia Muscle spasms Muscular weakness Bone pain other

to be continued

continues

Anatomical apparatus or system	**Adverse event**
Nervous system disorders	Headache Syncope Hyperesthesia Syndrome Hypoesthesia Paresthesia Tremor Amnesia Attention deficit Memory deficit Sleepiness Neuropathy Taste loss Encephalopathy Cerebral ischemia other
Psychiatric disorders	Anxiety Depression Insomnia Irritability Instability Agitation Sleep disorders Behavior disorders Libido disorders Panic attack Suicidal ideation other
Renal and urinary disorders	Increase of creatinine levels Pollachiuria Dysuria Nocturia other
Reproductive system and breast disorders	Erectile dysfunction Prostatitis Aspermia Menorrhagia Amenorrhea Dysmenorrheal Vaginal disorders other
Respiratory, thoracic and mediastinal disorders	Cough Dyspnea Nosebleed Nasal congestion Oropharyngeal pain Respiratory tract congestion other
Skin and subcutaneous tissue disorders	Itch Rush Eczema Alopecia Dermatitis Erythema Edema Psoriasis Photosensibility Cutaneous ulcer Hives DRESS other

to be continued

continues

Anatomical apparatus or system	**Adverse event**
Vascular disorders	Hypotension Hypertension Thrombosis other
General disorders or administration site reactions	Administration site reaction Facial edema Peripheral edemas Asthenia SHIVER Sickness sensation Fever Flu-like symptoms Irritated skin other
Appetite disorders	Decrease Increase other
Others	Description report

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