VIRAL HEPATITIS C
IN THALASSAEMIA

ENDORSED BY:
THE EUROPEAN ASSOCIATION FOR THE STUDY OF LIVER (EASL)

ADDITIONALLY ENDORSED BY:
THE EUROPEAN LIVER PATIENTS' ASSOCIATION (ELPA) AND
THE EUROPEAN ORGANISATION FOR RARE DISEASES (EURORDIS)

“Unity is our Strength!”

“Knowledge is our power!”

“Patients at the centre of healthcare systems!”

The Thalassaemia International Federation (TIF) will be receiving the “The Dr Lee Jong-wook **Memorial Prize**" in the course of the 68th Wold Health Assembly in May 2015. This award is given to a person, an institution or institutions, a governmental or non-governmental organisation or organisations, who have made an outstanding contribution in **Public Health**.”

ABOUT THALASSAEMIA INTERNATIONAL FEDERATION (TIF) IN OFFICIAL RELATIONS WITH THE WORLD HEALTH ORGANISATION (WHO)

The Thalassaemia International Federation (TIF) is a non-profit, non-governmental organisation founded in 1986 by a small group of patients and parents representing mainly National Thalassaemia Associations in Cyprus, Greece, UK, USA and Italy, i.e. countries, where thalassaemia was first recognised as an important public health issue and where the first national programmes for its control, including prevention and clinical management have started to be promoted and implemented. TIF was officially registered under the Cyprus Company Law in 1987 and since 1996 it works in official relations with the World Health Organisation (WHO). In addition and through the years, TIF has established collaborations and networks with a number of other official health orientated agencies and associations, and patient orientated organizations at the national, regional and international level. Today, TIF (www.thalassaemia.org.cy) has evolved into an umbrella federation with 117 member associations, from 57 countries of the world, safeguarding the rights of patients for quality health and other care.

MISSION

The development and implementation of National Control Programmes including both components of prevention and management in every "affected" country around the world.

VISION

Establishment of equal access to quality health, social and other care for all patients with thalassaemia globally, in truly patient-centred health care systems.

OBJECTIVES

The objectives of the Federation in addressing effectively the needs of the world thalassaemia family have since its establishment remained the same and include:

- The establishment of new and promotion of existing National Thalassaemia Patient/Parents Associations, across the world, aiming to transform patients and parents into knowledgeable, productive and equal partners in the fight to achieve progress;
- Extending the knowledge and experiences gained from countries with successful control programmes to those in need;
- The development and continuous updating and upgrading of an educational programme based on three pillars:
  - Organisation of educational events at the national, regional and international level;
  - Preparation, publication, translation and distribution of educational/awareness-raising/community material, and;
  - Promotion of academic courses/fellowship preceptorships;
- Encouraging and supporting studies and research for further improving prevention and clinical care and for promoting research for achieving the long-awaited final cure, and;
- The establishment and promotion of meaningful and productive Collaborations/Networks/Partnerships with relevant stakeholders, across the world.

Visit us at:
Website: http://**www.thalassaemia.org.cy**
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Executive Summary:

The Thalassaemia International Federation (TIF) representing and safeguarding the rights of patients with Haemoglobin (Hb) disorders across the world for quality health care and services, has taken the decision, in 2014, to act and react on the poor or lack of recognition of the importance of providing anti-viral treatment to patients with thalassaemia infected with Hepatitis C (HCV).
It is recognised beyond any doubt that considerable work is still needed on behalf of a great number of countries in Europe and globally towards increasing access of patients with transfusion-dependent Hb disorders (including thalassaemia and sickle cell disease) to timely, appropriate and effective treatment for Hepatitis C (HCV).

Considering that liver disease in thalassaemia is a multi-factorial consequence with the main *"culprits"*, however, being iron load and viral hepatitis, patients with thalassaemia comprise a particularly vulnerable patient population for developing severe liver disease. In this context, these patients should constitute a priority for Governments and Policy makers to focus attention and resources on the provision of appropriate and effective iron chelation and treatment of viral hepatitis. The rates of infection of patients with thalassaemia with HCV, in the different countries, range between 12% and 85%. In developed countries, the majority of patients infected with HCV are well over the age of thirty (30) years (prior to the introduction of the HCV donor screening test as mandatory), while in the developing world post-transfusion infections are sadly still occurring. Preventing progression to severe liver disease such as cirrhosis and hepatocellular carcinoma (HCC), and the need for liver transplant, is of paramount importance for TIF and constitutes a key objective within the realms of its annual plans and activities for the next five (5) years.

In most European countries, patients with transfusion-dependent thalassaemia and other haemoglobinopathies represent a population of patients that was infected with HCV during the years preceding the development and implementation of sensitive and specific mandatory blood screening for HCV, as mentioned above. In this respect, this population has now aged to adulthood, as compared to the HCV-infected patients in developing countries. In the latter, transfusion-transmitted viral Hepatitis B and/or C is still occurring and thus affects all ages from very young to older ones, and in addition, the majority of patients are sub-optimally treated in terms of iron chelation. In both cases, therefore, the possibilities of developing severe liver disease is very high: in Europe (in most countries), as a result of ageing, and limited accessibility to established anti-viral treatment (Ribavirin contra-indication to haemolytic anaemias and high costs), and in the developing world as a result of on-going viral infections and poor accessibility to both optimal iron chelation and anti-viral therapies.

The present Position Paper has been prepared by TIF, reviewed and adopted by TIF's member associations and other relevant stakeholders and endorsed by the Liver-specific patients' association in Europe, The European Liver Patients' Association (ELPA) and the European Organisation for Rare Diseases (EURORDIS), leading medical experts in the field of thalassaemia and hepatitis (see Annex I), and very importantly

by the relevant scientific body, the European Association for the Study of Liver (EASL). This Paper aims to express TIF's great concerns on and to underscore, on behalf of its member patient associations in 57 countries globally, including 28 in Europe, the vast contribution of viral hepatitis to the development of liver disease in thalassaemia. A medical condition, that today, constitutes, if not the first, one amongst the top causes of morbidity and mortality in these patients, globally.
This Position Paper will constitute our basis for initiating and promoting discussions with official health authorities at the national level in every country, with the new Commission, Parliament and Council of Europe, at the European Level and at the International level with the World Health Organisation (WHO), its regional offices, and other important stakeholders such as European Medicines Agency (EMA) (at the European level), Association of South East Asian Nations (ASEAN) (at the Asian level) and the industry.

We would like to see improvements in the recognition of the need to develop and/or implement policies, for viral hepatitis, prevention and treatment, and evidence integration of such policies in every country's national planning and programmes, in the next five years.

The reduction of the number of new patients with thalassaemia infected with HCV annually, in the developing world is amongst the progress we wish to evidence in the coming years as this is a strong indication of the appropriateness and effectiveness of the measures taken at country level with regard to blood safety and viral hepatitis control. Furthermore, the reduction or prevention of progression to serious viral hepatitis C-related liver disease in thalassaemia patients in the developed countries, will be a strong indication of the increase in availability and accessibility of the patients to effective anti-viral strategies. Increase of access to appropriate iron chelation and good adherence to treatment remain major prerequisites across the thalassaemia patient population, globally.

Today, there are many official declarations, reports, recommendations, resolutions and guidelines, regarding the prevention and treatment of viral hepatitis. These have been developed, through the years, and still continue to be published, updated and upgraded, particularly during the last decade. Their implementation, however, is still pending in many countries of the world, and importantly amongst vulnerable patient groups, such as those with thalassaemia and other transfusion-dependent haemoglobinopathies.

INTRODUCTION:

Liver Disease in Thalassaemia and the contribution of iron overload and viral hepatitis - The scientific perspective

Among the different organs susceptible to damage in thalassaemia patients, the liver represents a major target. Iron overload is the main causative factor (Voskaridou 2012; Lobo 2011; Porter 2009). Hepatitis viruses, hepatitis C virus (HCV) and hepatitis B virus (HBV), remain an important concern (Lai 2013; Triantos 2013; Di Marco 2010; Ragab 2010), although preventive measures importantly, HCV mandatory screening and HBV vaccination programmes, have significantly reduced new cases of infection, particularly in Europe.

The potentially aggravating role of hepatotoxic co-factors, such as dysmetabolism and alcohol, should also be kept in mind. The main risk of chronic liver disease is the development of cirrhosis (Li 2002) with its risk of hepatocellular carcinoma (HCC) (Maakaron 2013; Mancuso 2010), complications which are becoming more frequent due to overall improvements in thalassaemia outcomes.

The diagnosis of both type and severity of hepatic disease in thalassaemia has benefited from the availability of non-invasive techniques. The prognosis of liver disease in thalassaemia should continue to improve thanks to increasingly effective diagnostic, monitoring and therapeutic modalities for treating both iron overload and virus-related chronic hepatitis.

CHAPTER 1:

Hepatic Iron Overload in Thalassaemia

Repeated transfusions represent the major cause of iron overload in thalassaemia major. Each unit of blood represents 200-250 mg of iron. Considering that total body iron stores are approximately 4 grams, and that normal daily iron losses are of the order of 1-2 mg (with a very limited capacity for the body to regulate these losses), one can understand that, when a given individual needs for instance one unit of blood every 2 weeks, body iron overload develops rapidly.

Dyserythropoiesis is another important mechanism accounting for iron excess. It has been shown to result from the decreased production of the iron regulatory hormone hepcidin by the liver. Hepcidin deficiency, through activation of the cellular iron exporter ferroportin (Ganz and Nemeth 2012), leads to an increase in entry of iron into the plasma at two major sites, on one hand, the duodenum, corresponding to an increased intestinal absorption of iron and on the other, and quantitatively 10 to 20 times more important, at the splenic level.

Anaemia and hypoxia also contribute to iron overload by decreasing the impact of erythropoietin on hepcidin synthesis.

These mechanisms are summarised in Figure 1.

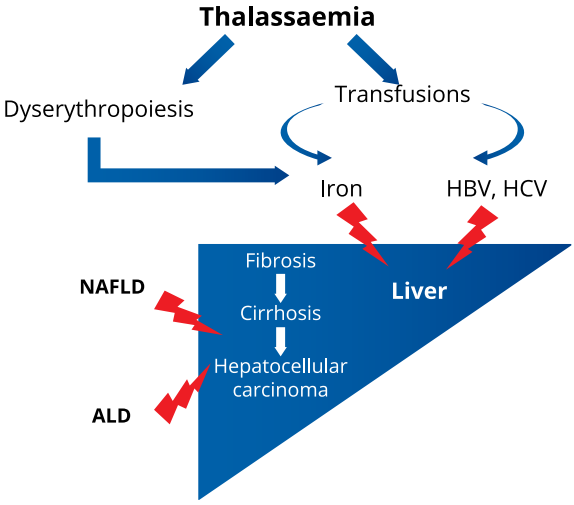
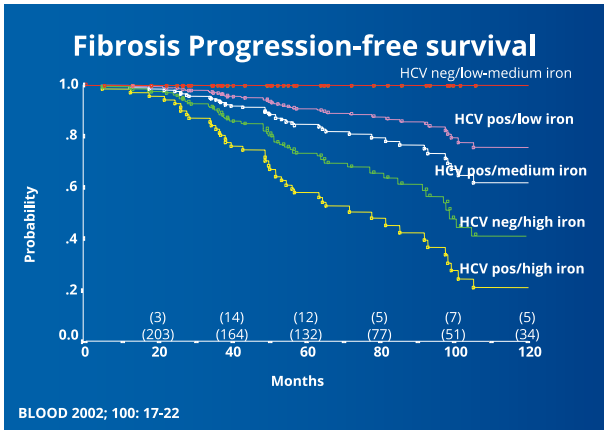


Figure 1: Main causes of hepatic iron damage in thalassaemia. NAFLD, non-alcoholic fatty liver disease; ALD, alcoholic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus.

Natural History of HCV in Thalassaemia

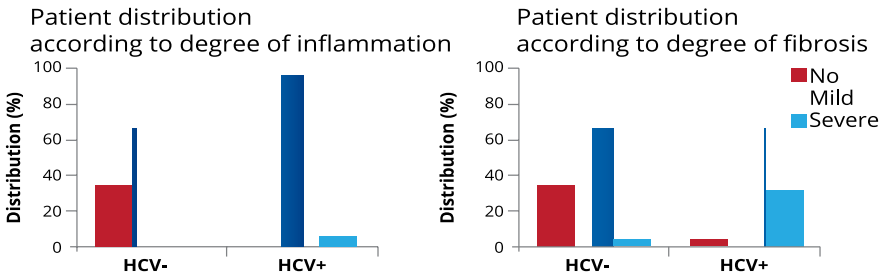
Although the natural history of chronic HCV infection in patients with thalassaemia is unclear, the morbidity and mortality of infected patients may potentially be higher due to the possible co-existence of other factors including iron (see Figure 2) and other hepatotropic viruses. Liver disease is more severe in HCV-infected patients, with active infection (HCV-RNA+ - see Figure 3), and this may be compounded by hepatic siderosis (Alavian SM and Tabatabaei SV, 2010; Zokaee A et al, 2004; Di Marco V et al, 2008). The prevalence of liver cirrhosis in thalassaemia patients with a HCV infection is related to the level of iron and it has been reported to be present from 10% to 20% in several studies (see Figure 2; Angelucci E et al, 2002).

Figure 2:



Iron overload and HCV infection are independent risk factors for liver fibrosis progression (see Figure 2), and their concomitant presence (particularly in HCV-RNA+ patients) results in a striking increase in risk (Angelucci E et al, 2002; 2008, see Figure 3).

Figure 3:



	HCV-RNA- (68 patients)	HCV-RNA+ (58 patients)	p value
Age, years [mean±SD]	13.9±8.85	21.2±8.87	< 0.001
Gender. male/female	35/33	32/26	0.681
ALT. U/L [median (range)]	27 (9-200)	82 (17-547)	< 0.001
Serum ferritin, µg/L [median (range)]	1,892 (141-5,952)	1,750 (188-5,503)	0.590
LIC, mg Fe/g dry wt [median (range)]	3.3 (0.3-22)	2.3 (0.4-11.8)	0.064

Di Marco V, et al. Haematologica. 2008; 93: 143-6.

Male gender, higher alanine aminotransferease (ALT) levels, the existence of an HCV infection, and higher iron concentrations in the liver were significantly associated with severe fibrosis and cirrhosis (Di Marco V et al, 2008; Angelucci E et al, 2002; Prati D, et al, 1998; Cunningham MJ et al., 2004). Adequate chelation therapy usually prevents the development of liver fibrosis in thalassaemia patients who are free of a HCV-infection and it also reduces the risk of developing severe fibrosis in those with chronic hepatitis C.

It has been recognised that the most important risk factor for HCC is cirrhosis (Somi M.H., 2005) and both iron overload and HCV are known risk factors for this condition (see Table 1 & Figure 4, below), where Figure 4 demonstrates the different levels of liver siderosis, very much related to the accessibility or not of optimal iron chelation treatment.

Table 1:

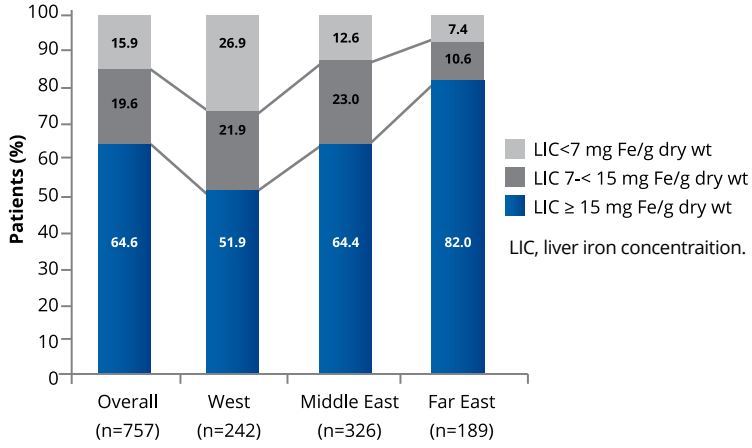
HCC - thalassaemia: An update of the Italian Registry - 2014

YEARS	HCC New Cases	TM	TI
2002-2012	62	52%	45%
HCV+	54	64%	35%
HCV-	8	-	100%
HCV-RNA+	43	60%	38%
No exposure (HBV/HCV)	4	50%	50%
Past HBV Exposure	36	56%	43%
DIED	41	62%	35%
Average Survival for HCC detection to death – 11.5 months (14-107.2 months)			

KEY: TM = Thalassaemia Major
TI = Thalassaemia Inetrmedia

Source: Borgna-Pignati C et al (2014). Br. J. JHaematol. 167(1):121-8
Mancuso A & Perricone G. (2014). Br. J. JHaematol. August 22
Mancuso A (2014). Aliment. Pharmacol. Ther. 40 (11-12):1368-9
Gomatos IP et al (2013). Am. Surg. 79(1):111-3
Maakaron JE et al (2013). Am. Hepatol. 12(1):142-6
Mancuso A et al (2005). Am. J. Hepatol. 78(2):158-9

Figure 4: **Variability of liver siderosis among different regions**



Pennell D, et al. Haematologica. 2012;97 Suppl 1: abstract 0928.

It is thus anticipated that the numbers of thalassaemia patients who develop HCC will increase in the future and it will be one of the leading clinical problems in thalassaemia, if both iron load and HCV infection are not appropriately and timely addressed. It is therefore, reasonable to recommend HCC screening of all thalassaemia patients with one or more risk factors including HCV, as this, would facilitate early treatment, leading to improved outcomes (Mancuso A, 2010).

Preliminary data suggests an incidence of HCC in thalassaemia of about 2%. However, since thalassaemia is endemic in many developing countries where patients are probably not screened for HCC, it is possible that the present knowledge on this issue represents only the tip of the iceberg.

Measuring and monitoring iron load, as well as appropriately chelating patients with both transfusion-dependent (TDT) and non-transfusion dependent thalassaemias (NTDT), are well described in Guidelines[1,2], and Standards of Care[3], published by TIF and International experts. In the case of NTDT, viral hepatitis becomes a major concern, when a subgroup of these patients eventually requires blood transfusion therapy (Cazzola et al., 1987; 1987). Similarly, diagnosis, evaluation of HCV infection and genotyping have reached such high levels of specificity and sensitivity that have allowed, for some time now, the early and accurate detection, assessment of the prognosis, progress, choice of and the level of response to treatment of the HCV infection.

[1] Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT) – 3rd Edition, 2014; Publishers: Thalassaemia International Federation (TIF)
[2] Guidelines for the Management of Non-Transfusion Dependent Thalassaemia (NTDT) – 2013; Publishers: Thalassaemia International Federation (TIF)
[3] Standards of Care – NHS 2012, United Kingdom

Diagnosis of hepatic disease in Thalassaemia

Diagnosis of hepatic disease is based upon both clinical and related parameters. The clinical approach must always be the first step, searching essentially for hepatomegaly (size and consistency of the liver). It should be remembered that hepatic iron overload by itself, even when massive and longstanding, does not produce significant liver dysfunction so that signs of hepatocellular failure or portal hypertension are not usually present (even in case of true iron-related cirrhosis).

Biochemical parameters have value in two main areas. Firstly, to provide a functional evaluation of the liver: in case of substantial hepatic iron excess, a moderate increase in serum transaminase activities (to less than 2-3 times the upper limits of normal) can be observed in the absence of hepatocellular failure (normal prothrombin time) or cholestasis (normal serum alkaline phosphatase, gamma (γ)-glutamytransferase and conjugated bilirubin levels); Secondly, to assess morphology.

There is clear value in imaging. Ultrasound examination is a key method for determining liver morphology and homogeneity (diffuse heterogeneity due to cirrhosis, focal lesion possibly related to HCC) and confirming the absence of signs of portal hypertension. Hepatic transient elastography is increasingly being performed to evaluate, in a non-invasive way, the degree of hepatic fibrosis. It is a measure of hepatic stiffness, based on a mechanical wave generated by vibration. There are two main limitations regarding its interpretation: on one hand it is mostly interesting to differentiate between the extreme situations of cirrhosis versus the absence of (or no significant) fibrosis: it is much more difficult to appreciate the intermediate fibrosis stages; on the other hand, this technique has essentially only been validated in chronic HCV. This said, it may be a reliable tool in both transfusion-dependent (TDT) and non-transfusion dependent thalassaemias (NTDT) (Musallam K et al, 2012).

Liver biopsy remains the key method to studying liver morphology and to establishing and quantifying fibrosis, with the limitations, however, of invasiveness and the possibility that a sample will not be representative (which may make it challenging to diagnose cirrhosis, particularly of the macronodular type).

CHAPTER 2:

GLOBAL EPIDEMIOLOGY OF VIRAL HEPATITIS
General Information:

Viral hepatitis is a group of infectious diseases (see Table 2) that affects hundreds of millions of people worldwide, causing serious illness and death from acute hepatitis infection, liver cirrhosis and liver cancer. Although there are effective tools and strategies for the prevention and treatment of hepatitis, low awareness of hepatitis has limited their impact.

There have been significant advances in the prevention of viral hepatitis. The most important is the wide-scale implementation of universal childhood vaccination for hepatitis B. As of 2011, 180 countries included hepatitis B vaccination in their routine vaccine schedules and the coverage is approaching 80%[4].

In many countries, transmission of hepatitis to patients through unsafe injection practices in health-care settings, sub-optimal blood screening and the continuation of paid blood donation practices are still a problem.

Table 2:

Characteristics of main types of viral hepatitis infections

	Hep A	Hep E		
Mode of transmission	Contaminated food, water		Blood, sex, mother-to-child	
Number chronic infections	0	?	240 million	130-170 million
Annual deaths	34,000	70,000	500,000-700,000	350,000
Health Outcome	Acute hepatic failure	Acute hepatic failure, maternal death	Acute failure, cirrhosis, hepatocellular carcinoma	
Vaccine	√	√	√	
Other modes of prevention	Improved sanitation		Universal precautions, blood screening, behavior change	

Source: S. Wiktor – WHO – 3rd Pan-European Conference on Haemoglobinopathies and Rare Anaemias, Limassol, Cyprus, 2013

Despite the fact that Viral Hepatitis represents the second highest 'killer' of communicable diseases globally, behind HIV, causing death to over 1.3 million people annually, yet the amount of financial resources (budgets) allocated to WHO programmes, an by extent the national governments for the control (prevention and management) of viral Hepatitis, is geometrically disproportionate, when compared with the budgets allocated for tuberculosis and/or malaria for example (see below Figures 5, 6 & 7).

[4] Global policy report on the prevention and control of viral hepatitis – WHO 2013

Figure 5:

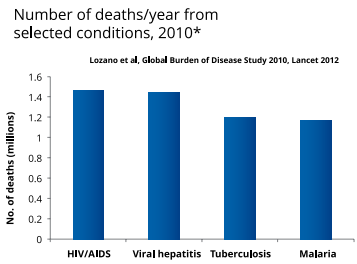


Figure 6:

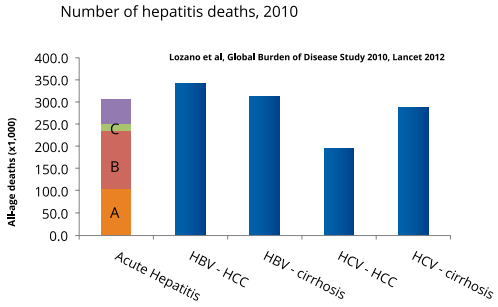
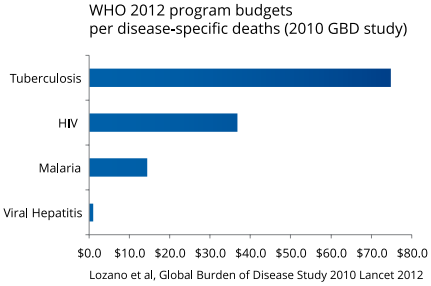


Figure 7:



This worrying state-of-affairs is still unchanged, despite the fact that the WHO adopted, in 2010, a specific Resolution WHA 63.18 (2010) recognising viral hepatitis as a global public health problem, and urging member states to develop comprehensive prevention and control strategies.

Public Health Importance of Hepatitis C:

Today, about 170 million people, representing 3% of the global population, are recorded as being carriers of Hepatitis C (HCV), while about 130-150 millions are diagnosed as chronic carriers, and about 3-4 million as new carriers of HCV every year (see Figures 8 & 9 below).

Figure 8:

Global prevalence of hepatitis C infection, 2005 adults (19-49 years)

Wiktor S. 2013 – 13th International Conference on Haemoglobinopathies

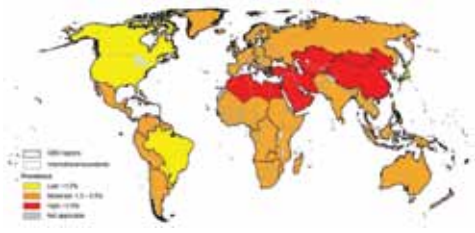
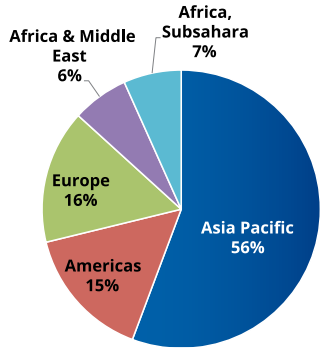


Figure 9:

Regional distribution of estimated number of annual deaths due to hepatitis C

Courtesy of IHME – Global Burden of Disease Study (2011)



Indeed, the number of persons with anti-HCV in the world has increased from an estimated 122 million in 1990 to an estimated 184 million in 2005. The regions with the highest estimated numbers of people with anti-HCV are:

- South Asia (>50 million),
- East Asia (>50 million),
- North Africa / Middle East (>15 million),
- Southeast Asia (>11 million),
- Western Europe (>10 million)

It is also important to underscore that about 350.000 – 500.000 deaths are caused/ related to HCV[5]. In Europe, it is reported that there are about 7.3 – 8.8 million carriers of HCV. Some new and validated studies indicate that there is a progressive increase of this disease across the continent, with 86,000 new deaths (or about 16% of the global population[6]) being recorded annually.

Epidemiology and clinical/public health significance of Hepatitis C in Thalassaemia:

HCV infection which is mainly of transfusional origin remains a major concern in the field of thalassaemia. On average 12%– 85% of thalassaemia patients around the world including Europe are positive for anti-HCV antibodies (Table 3).

[5] WHO: Hepatitis C. Fact sheet No.164 (April 2014)
[6] NIH. NIH Consensus State Sci Statements. 2002;19:1-46. 3. Mühlberger N, et al. BMC Public Health. 2009;9:34

Table 3: Prevalence of anti-HCV-positive thalassaemia patients

Geographic Area	Number of subjects screened	Anti-HCV+ Percentage (%)	HCV-RNA + Percentage (%)
Iran[1]	732	19.3	28.6
Turkey[1]	399	4.4	35.5
Thailand[1]	104	21.2	38
Lebanon[1]	395	14	26
India[1&5]	104	21	52
India[5]	50	60	32
Malaysia[1]	85	22.4	35
Malaysia[1]	72	13	28
Iraq[1]	559	67.3	58
Kuwait[8]	129	33	-
Jordan[9]	143	40	-
Saudi Arabia[10]	142	60	-
Egypt1[1]	63	60	-
Pakistan[1]	35	60	52
Italy[1]	1481	85.2	42
Italy[6]	256	60	30
Bahrain[1]	242	20.5	32
Brazil[1]	32	46.8	39
Hong Kong[1]	99	34	28
United Kingdom[1]	73	23.3	36
Cyprus[2]	61	14.5	33
Greece[3]	211	74.4	42
Greece[4]	57	40.4	36

1- Extracted from Di Marco et al 2010
2- Extracted from abstract of oral Presentation by Lavranos G. 2013
3 - Extracted from Kountouras D et al 2013
4 - Extracted from Fragatou S et al 2010
5 - Extracted from Chakravarti A. 2005
6- Extracted from Angelucci E. 1994
7- Extracted from Hassan M. 2004
8- Extracted from Al-Fuzae et al 1998
9- Extracted from Al-Sheyyab 2001
10- Extracted from Bahakim et al 1991
Extracted from Al-Fawaz et al 1996
Extracted from Al-Hawsawiet et al 2000
11 - Extracted from El-Gohary et al 1995
Extracted from El-Nanawy et al 1995

This concern in most of the European countries is mainly related to the large number of infected patients in a past period, prior to the implementation of specific preventive measures for HCV in the transfusion services (Table 4), while post-transfusion hepatitis is still occurring in many countries of the developing world (Table 5).

Table 4

Regional Prevalence of HBV and HCV in Thalassaemia Patients (TDT) HBsAg
REGION

AGE GROUP	Middle East & North Africa	South East Asia	Western Pacific	Europe
5-10	2.60%	4.20%	6.20%	0.03%
11-12	4.80%	7.60%	7.80%	0.45%
21-30	6.20%	8.90%	12.60%	2.60%
31-40	9.10%	9.60%	16.40%	3.40%
>40	10.20%	10.40%	N/A	5.20%

Anti-HCV
REGION

AGE GROUP	Middle East & North Africa	South East Asia	Western Pacific	Europe
5-10	2.90%	5.20%	1.80%	0.10%
11-12	6.80%	10.60%	10.80%	1.10%
21-30	18.60%	26.80%	14.60%	4.60%
31-40	36.20%	38.60%	N/A	16.50%
>40	60.00%	48.40%	N/A	32.80%

2011 Survey – 3,500 Patients from 42 countries

Table 5

Prevalence of Viral markers in Thalassaemics: India

Study on effectiveness of transfusion program in thalassaemia major patients receiving multiple blood transfusions at a transfusion centre in Western India – April –June 2009

AGE	Units/ Month	Total Transfusions	HCV Positivity
0-5	1	30	5%
6-10	1	100	35%
11-15	2	220	58%
16-20	3	350	70%
21-25	4	455	72%

2011 TIF Survey – 3,500 Patients from 42

CHAPTER 3:

CLINICAL MANAGEMENT OF CHRONIC HEPATITIS C (CHC)

It is important to emphasize that the results, from clinical studies for the management of HCV using newly developed antiviral drugs - which have already been licensed and/or approved and available in the market, or other soon-to-be licensed drugs, after the completion of the last phases of their respective clinical trials are indeed very promising, to the point of hopefully striding for a total cure of the HCV.

These new drugs open new avenues both in terms of their effectiveness and in terms of their administration (oral rather than injectable), and more importantly, manifesting minimal to complete absence of side effects, which has been the main 'disadvantage' of the so far licensed drugs.

Although these have been developed to be given (i) to patients carrying any one of the known Hepatitis C genotypes (GT1-4); (ii) to patients that are non-responders to existing therapies, and (iii) to patients who have developed liver cirrhosis (i.e., the stage of advanced hepatic dysfunction), the most impressive results come from Hepatitis C patients carrying the genotype 1 (GT1); one of the most difficult responders to anti-viral therapy. The greatest challenge however is the high costs of these drugs and the 'avoidance' of national health authorities across the world, including Europe, to include these drugs on their national drugs' lists for providing free-of-charge access to treatment of patients infected with Hepatitis C.

Of even greater concern is the '*avoidance*' of national health authorities across the world, including Europe, to provide access to these drugs to patients with thalassaemia, whose pre-existing condition of haemolytic anaemia has been referred to in previous years as a contra-indication to the use of drugs such as Ribavirin. In the case of the new drugs, the hesitation both from National Health Authorities (NHAs) and the treating haematologists, and Hepatologists derives from the fact that patients with thalassaemia have not been included in any of the clinical trials of these drugs hence no experience is available regarding their potential side effects and effectiveness. One of the most important objectives of our Federation is the establishment of a close collaboration with the Industry in order to compile sufficient data with existing but also with upcoming new drugs, on how to best use and how to report and address possible side effects of these drugs when given to patients with thalassaemia.

In the case of Europe, the experts in this field and other official health–related organisations that under the current, devastating economic crisis that prevails across the continent, are advising the national health authorities to prioritise patients according to their clinical status and the potential severity of possible progression, i.e., to provide the aforementioned drugs to heavily advanced cases of patients with HCV. National health authorities should consider introducing special criteria for the provision of these medicines timely. For example, in the case of the UK, national health authorities came into an agreement with a particular Industry, ('Pay If You Clear' Program Proposed for Olysio in Scotland, October 2014, Hepatitis News) to only cover the costs of treatment of those patients that will have their virus cleared, according

to a pre-designed protocol. Such efforts or initiatives can and should be imitated and extended across the world aiming to increase to the maximum the access of HCV-infected patients to appropriate antiviral drugs.

HISTORICAL PROGRESS IN THE TREATMENT OF CHC

First Treatment Protocols:

The last two decades have been earmarked by rigorous research and the discovery and development of new drugs for the management of Hepatitis C. In the beginning, the percentage of responders to α-interferon, the first and only drug at the doctors' disposal for many years, was relatively low for all the four (4) main and most frequent genotypes of Hepatitis C (GT1, GT2, GT3, GT4), as shown below:

GT1 30%; GT2 and GT3 56.6% and GT4 29.8% (Table 6-demonstrates the Hepatitis C Genotypes in various countries in patients with thalassaemia)

Table 6:

Viral genotypes in thalassaemic patients with Chronic Hepatitis C

Authors	Geographic Area	Number of patients	Genotype 1 (%)	Genotype 2 (%)	Genotype 3 (%)	Genotype 4 (%)	Genotype 6 (%)
Di Marco (2005)	Italy	64	77	9	7	8	
Christofidou (1999)	Greece	28	39	7	35	17	
Ramia (2002)	Lebanon	19	37	5	21	37	
Sharara (2005)	Lebanon	20	75			25	
Sievert (2002)	Australia	27	40	20	40		
Li (2002)	China	18	77				23
Lavranos * (2013)	Cyprus	58	98 (1a & 1b)			2	

Source: Di Marco V. & Angelucci E – Dubai 2006
* = Extracted from the Cyprus Thalassaemia Patients' Registry

The percentage of responders (see Tables 7 & 8) improved significantly by the end of the 1990's with the discovery and use of Ribavirin and the 'upgraded' form of α-interferon, known as pegylated α-interferon (PEG-IFN), which caused the percentage of responders to increase to 45%, 87%, 77% and 56% for GT 1, 2, 3 and 4, respectively. Although very limited, below are some data and results (mainly from Europe) from anti-viral treatment with α-interferon (monotherapy), as in Table 7, α-interferon with Ribavirin (Table 8), pegylated-interferon (monotherapy) and pegylated-interferon with Ribavirin (Table 9), respectively, provided to patients with thalassaemia. In addition, Tables 10, 11 & 12 provide the results of a number of published studies on the treatment of HCV in thalassaemia across the world.

Table 7:

Alfa-interferon in thalassaemic patients with chronic C hepatitis

Authors	Geografic Area	N. of patients	Mean age	Pts with cirrhosis	Doses of IFN	Months of therapy	Rate of SVR(*)
Clemente (1994)	Italy	51	14	0%	3 MU/mq t.i.w.	15	37%
Di Marco (1997)	Italy	70	14	15%	3 MU/mq t.i.w.	12	40%
Wonke** (1997)	UK	33	24	57%	3 MU/mq t.i.w.	12	30%
Spiliopoulou (1999)	Greece	13	14	7.5%	3 MU t.i.w.	18	75%
Sievert (2002)	Australia	28	26	3.5%	3 MU t.i.w.	6	28%

(*) SVR: sustained virological response
** = Extracted from Clinical Aspects and Therapy of Thalassaemia – Maggio A. & Hoffbrand A.V. 2004
Source: V. Di Marco – Consensus Meeting on Chronic Hepatitis in Thalassaemia – Nocosia, Cyprus, 2007

Table 8:

Combination therapy with alpha-interferon and ribavirin in thalassaemic patients with Chronic C Hepatitis.

Authors	Patients	N. of patients	Mean age	Doses of IFN	Dose of Ribavirin	Months of therapy	SVR (*)	Rate of SVR (*)
Telfer (1997)	No responders	8	25	3 MU t.i.w.	1g day	6	2/8	25%
	Relapsers	3	25	3 MU t.i.w.	1g day	6	3/3	100%
Li (2002)	Naive	18	16	3 MU/mq t.i.w.	16 mg/kg day	12	13/18	72%
Sherker (2002)	Naive	3	28	3 MU t.i.w.	1 g day	12	3/3	100%

(*) SVR: sustained virological response
Source: V. Di Marco – Consensus Meeting on Chronic Hepatitis in Thalassaemia – Nocosia, Cyprus, 2007

Table 9:

Peg-Interferon monotherapy and combined with ribavirin in thalassaemic patients with chronic C hepatitis

Drugs	N. of patients	Months of therapy	% of patients cured
Peg-Interferon alone	12	12	4/12 (33%)
Peg-Interferon plus Ribavirin	8	12	5/8 (63%)

Inati A et al, Br J Haematol. 2005

Table 10: Summary of the literature data: Characteristics of treatment and response - Extracted from - From A to Z on Hepatitis C in Thalassaemia: Comprehensive guideline for Medical Practitioners –Dr Seyed Moayed Alavian

Author		Treatment characteristics					Sustained viral response	End of treatment response	Dropout rate
		protocol	IFN doses	RBV doses (mg/day)	Duration w	Interferon total			
1	Clemente, M. G.	IFNα2b	3		60	540	37%	41%	0%
2	Di Marco, V	IFNα2b	5+3		8+18	282	ND	ND	47%
3	Sievert, W.	IFNα2b	3		24	216	28%	28%	7%
4	Spiliopoulou, I.	IFNα2b	3		72	648	76%	100%	15%
5	Artan, R	IFNα2a	5		24-48	720	80%	ND	0%
6	Syriopoulou, V.	IFNα2a	3		48	432	52%	55%	4%
7	Di Marco, V	IFNα2b	5+3		8+40	480	40%	40%	4%
8	Donohue	IFNα2b	3		24	216	ND	ND	0%
9	Pizzarelli, G	IFNα2a	5+3		24+24	576	ND	ND	47%	0%
		IFNα2b	3		48	432				
10	Mirmomen	IFNα2b	3		48	432	31%	52%		7%
11	Mirmomen	PEGα2b	180		48	8640	43%	81%		6%
12	Kountouras, D	PEGα2b	1.5 µg/kg/wk		48	4320*	13%	27%		24%
13	Inati, A.	PEGα2b+RVB	180	6-10 mg/kg	48	8640	62%	75%		0%
		PEGα2b+PLC					33%	41%		
14	Li, C. K.	IFNα2b+RVB	3	16 mg/kg	48	432	72%	72%		0%
15	Telfer, P. T.	IFNα2b+RVB	3	1000	24	216	45%	63%		0%
16	Harmatz, P	PEGα2a+RVB	180	800-1200*	24-48	8640	33%	ND		23%

Table 11: Rate of sustain viral response in genotype 1 infected thalassaemic subjects reported in six trials

Author	Mode of therapy	Responders Genotype 1, % (n/N)	Non-responders Genotype 1, % (n/N)
Sievert, W.	Mono	37.5 (3/8)	47.3 (9/19)
Syriopoulou, V.	Mono	37.5 (6/16)	36.8 (7/19)
Di Marco	Mono	39 (11/28)	71.4 (30/42)
Li, C. K.	Combination	76.9 (10/13)	80 (4/5)
Telfer, P. T.	Combination	50 (2/4)	42.8 (3/7)
Harmatz, P	Combination	75 (6/8)	50 (6/12)

Extracted from - From A to Z on Hepatitis C in Thalassaemia: Comprehensive guideline for Medical Practitioners –Dr Seyed Moayed Alavian

Table 12: Rates of sustained viral response in subgroups of patients stratified according therapeutic agents and genotypes

Subgroup of patients	No. of patients	Rate of sustained viral response (95% CI)	Heterogeneity assessment		
			Q (df)	I2	P value
Genotype 1 (overall)	97	42.2% (26.6-57.8)	10.672 (5)	53.1%	0.058
Genotype 1 who received standard IFN monotherapy	66	29.5% (18.7-40.4)	1.724 (2)	0%	0.422
Genotype 1 who received combination therapy of standard IFN plus ribavirin	31	60.9% (32.4-89.4)	1.533 (1)	53.3%	0.216
Non-genotype 1 (overall)	84	48.6% (38.3-59)	5.702 (5)	12.3%	0.336
Non-genotype 1 who received standard IFN monotherapy	66	51.9% (39.9-63.9)	0.888 (2)	0%	0.642
Non-genotype 1 who received combination therapy of standard IFN plus ribavirin	18	51.5% (23.3- 79.6)	2.107 (1)	52.5%	0.147
PEG-IFN monotherapy	77	28.4% (17.2-52.8)	8.838 (2)	77.3%	0.012
PEG-IFN plus ribavirin combination therapy	33	43.6% (29.4-57.8)	2.80 (2)	28.5%	0.247
Standard IFN monotherapy	277	46.9% (35.1-58.7)	25.027 (6)	76%	<0.0001
Standard IFN plus ribavirin combination therapy	29	63% (46.1-80)	2.163 (1)	53.7%	0.141
Ribavirin combination therapy	62	52.9% (33.7-72.2)	7.71 (3)	74%	0.052

P<0.100 considered significant for heterogeneity assessment; df, degree of freedom calculated by number of trials minus 1
Extracted from - From A to Z on Hepatitis C in Thalassaemia: Comprehensive guideline for Medical Practitioners –Dr Seyed Moayed Alavian

First Revolution in the treatment of CHC:

The first true revolution as far as the clinical management of the first genotype of Hepatitis C (GT1), which is considered to be the most resistant and by extrapolation the most difficult genotype to cure, came in 2011 with the discovery and licensing of two new drugs, namely of the Boceprevir (BOC) and of the Telaprevir (TVR) - First Generation Direct-Acting Antiviral [DAA], see Table 13. Their use increased the percentage of responders of patients with GT1 of HC to 63%-79%, using either of them (BOC or TVR) in combination with Ribavirin and pegylated interferon in a triple combination therapeutic scheme (BOC+RB+PegIFN).

However, many and significant side effects and other medical complications were recorded using the above-mentioned schemes, which, in conjunction with the high costs of these drugs, rendered the inclusion and use of these drugs (BOC and TVR) in therapeutic protocols extremely restricted (see Tables 13 & 14).

Table 13:

Safety of the first generation based DAA triple therapy Telaprevir or Boceprevir +PegIFNa + RBV

"Real life" CUPIC study in patients with liver cirrhosis

Patients, n (% with at least on Adverse Event)	**BOC or TVR + PegIFN + RBV n=485**
Serious Adverse Events (SAE)	**257 (53%)**
Deaths (4 sepsis, 2 pneumonia, 1 oesophageal bleeding, 1 aneurysma bleeding, 1 encephalopathy,1 pulmonary carcinoma)	**10 (2.0%)**
Severe infections (grade 3/4)	**35 (7.2%)**
Decompensation of liver function	**24 (4,9%)**
Serious skin lesions (grade 3/4)	**4 (0,8%)**
Severe anaemia (Hb <8 g/dL)	**38 (12%)**

Fontaine H et al. EASL 2013

Table 14:

Profits and limitations of 1st generation DAA based therapy

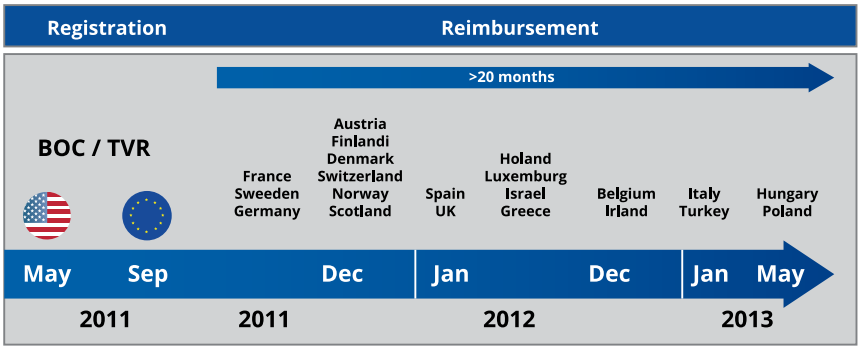
1. High efficacy in naive and relapsers but low in null responders to previous dual therapy.
2. High efficacy in non-cirrhotics but low in cirrhotics.
3. Active against HCV genotype 1 only.
4. Enhanced side effects of interferon and ribavirin olus some additional.
5. Serious safety issues in patients with advanced liver disease.
6. High cost.
7. Complicated protocol of regimen (Boceprevir).
8. Limited access in several EU countries.

Source: 'Economic Crisis and access to public health services: The case of Hepatitis B and C, High Level Meeting Athens, Greece, 2014

Moreover, until today, there is a great number of countries that have not approved the licensing and thus their reimbursement (see Table 15, below).

Table 15:

Registration ≠ Reimbursement



Source: 'Economic Crisis and access to public health services: The case of Hepatitis B and C, High Level Meeting Athens, Greece, 2014

Second Revolution in the treatment of CHC:

To the great relief of the medical, but more so of the patients' communities, the advances in research and clinical trials immediately after 2011, and hence the discovery of the new drugs in 2014, namely those of Sofosbuvir Polymerase Inhibitor (SBV, January 2014) and Simeprevir Protease Inhibitor (SPV, May 2014) and Daclatasvir NS5A Inhibitor (NS5A, September 2014), concomitantly earmarked the second revolution in the therapy or better the cure of HCV (see Table 16, below).

Table 16:

New, approved treatment options in Europe

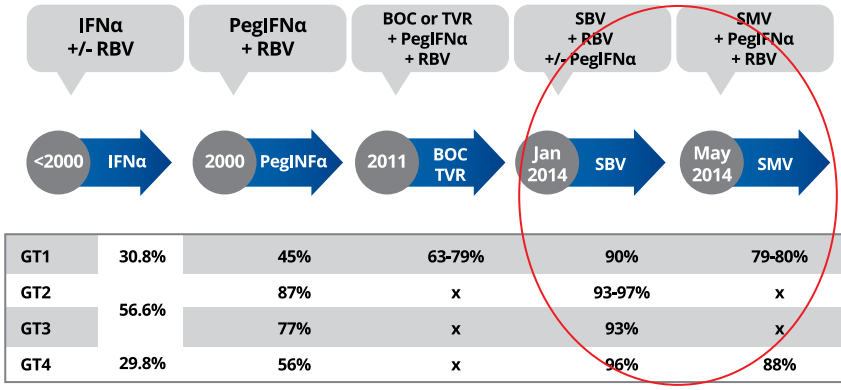
Sofosbuvir	**Simeprevir**	**Daclatasvir**
polymerase inhibitor	protease inhibitor	NS5A inhibitor
400 mg qd	150 mg qd	60 mg qd
All genotypes	Genotypes 1 and 4	All genotypes
Jannuary 2014	May 2014	September 2014

Source: 'Economic Crisis and access to public health services: The case of Hepatitis B and C, High Level Meeting Athens, Greece, 2014

Using *Sofosbuvir* in combination with the already existing Ribavirin (with or without the use of pegylated α-interferon) the percentage of responders with genotypes *GT1,2,3 and 4 reached to 90%, 93% - 97%, 93% and 96%*, respectively. Using Simeprevir (SPV) in combination with Ribavirin (with or without the use of pegylated α-interferon), the percentage of responders for genotype 1 reached 79-80%, while for genotype 4 reached 88%. Figure 10, below provides the history of up to today's approved (authorised) therapies with the response rates of the different combinations described in the literature.

Figure 10

History of registed therapies for chronic HCV infection



GT1	30.8%	45%	63-79%	90%	79-80%
GT2	56.6%	87%	x	93-97%	x
GT3		77%	x	93%	x
GT4	29.8%	56%	x	96%	88%

Fried et. Hepatology. 2013, 58: 1918-29.
Hauser et al. Cochrane Database Syst Rev. 2014 Feb 28;2:CD005441.
Jaroszewicz J, Flisiak R, Dusheiko G. Liver Int. 2014; 34: 6-11
Product Characteristics - Victrelis, Incivo, Sovaldi, Olysio

IFNα - Interferon alpha
RBV - Ribavirin
PegIFNα - Pegylated IFNα

BOC - Boceprevir
TVR - Telaprevir
SBV - Sofosbuvir
SMV - Simeprevir

Moreover, when the two new drugs (SBV and SPV) are used in combination, it was shown that the use of interferon (with all its numerous and well-known undesirable side effects) could be excluded from the therapeutic protocols. This new protocol has tremendously increased the percentage of responders of genotype 1 (1a and 1b) to nearly 100%, showing an extremely improved safety profile, i.e., with exceptionally minimised side effects.

Please note that various criteria (see Table 17, below) have been set regarding their inclusion in therapeutic protocols, based mainly on Fibrosis (F) scoring (F: 0-4-METAVIR Score) of the patients' liver.

Table 17:

Treatment indications

All treatment-naïve and -experienced patients with compensated disease due to HCV should be considered for therapy

Treatment should be prioritized for patients with significant fibrosis (METAVIR score F3 to F4)

Treatment is justified in patients with moderate fibrosis (METAVIR score F2)

In patients with no or mild disease (METAVIR score F0-F1), the indication for and timing of therapy can be individualized

Source: 'Economic Crisis and access to public health services: The case of Hepatitis B and C, High Level Meeting-Athens, Greece, 2014

In addition, the guidelines for their use have been completed both by the USA (AASLD7) and the European (EASL) scientific association, as well as by the W.H.O. Table 18, below, summarises the titles of most official documents, including guidelines, reports, studies and the relevant W.H.O. resolution on Viral Hepatitis (WHA63.18).

Table 18:

OFFICIAL DOCUMENTS / GUIDELINES	
i.	HCV treatment guidelines (WHO)– April 2014
ii.	HBV treatment guidelines (WHO)– end 2014
iii.	Hepatitis surveillance guidelines – 2014
iv.	Guidelines for the Screening, Care and Treatment of persons with HEPATITIS C INFECTION – (WHO) -April 2014
v.	Prevention and control of Viral HEPATITIS / INFECTION: Framework for Global Action (WHO) - 2012
vi.	Global Policy Report on the prevention and Control of Viral hepatitis (WHO) - 2013
vii.	EASL Clinical Practice Guidelines: Management of Chronic hepatitis B viral Infection - 2012
viii.	EASL Recommendations on Treatment Hepatitis C – April 2014
ix.	American Association for the study of Liver Disease (AASLD) Guidelines – 2012
x.	WHA 63.18 Resolution on Viral Hepatitis – WHO – 2010
xi.	Euro Hepatitis Index (ELPA 2012) – Updated version is anticipated within 2015

New authorisations and other in the pipeline:

From a series of other new drugs, namely Beclabuvir, Asunaprevir, ABT450/r + Ombitasvir + Dasabuvir and Ledipasvir (see Figure 11 below). Ledipasvir recently gained approval by the FDA (October 2014) and EMA (November 2014), as a combined one-day tablet (with Sofosbuvir, already existing and approved), under the brand name Harvoni.

The relevant announcement about the approval of Harvoni by the FDA can be found through the following link: (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm418365.htm).

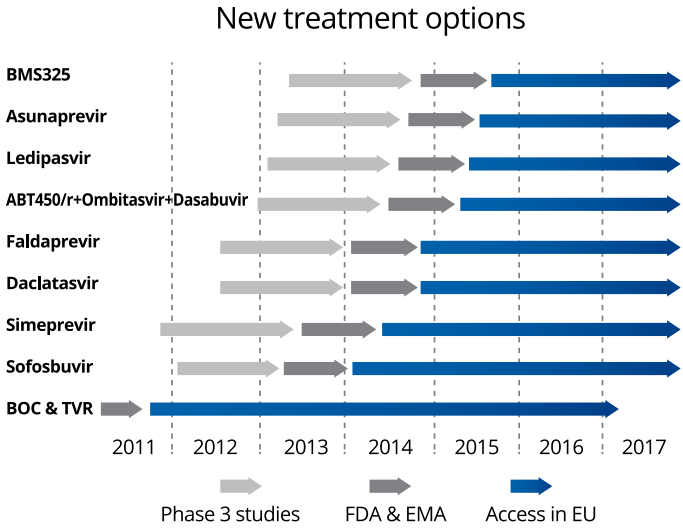
Harvoni is the first combination pill approved, to date by FDA and EMA, to treat chronic HCV genotype 1 infection. It is also the first approved regimen that does not require administration with interferon or ribavirin. A summary of the European Public Assessment report for Harvoni can be found through the following link: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003850/human_med_001813.jsp&mid=WC0b01ac058001d124 .

[7] AASL = American Association for the Study of Liver Disease

Approval and licensing, for the other drugs, as mentioned below, are still pending but are in the pipeline, as these now enter Phase III of their respective Clinical trials.

These new drugs are also promising to have high percentages of response and cure, as well as the mild side effects profile. In light of these facts, it stands to reason that the relevant guidelines will be continuously updated at regular intervals in order to include their use in therapeutic protocols, once their approval and licensing are granted (Figure 11). In addition and very importantly, strict adherence to pharmacovigilance and good reporting of any post-authorisation side effects will allow the verification of their safety and potential adverse drug/drug interactions (www.ntap.org/2015/HCV/032315_01.htm).

Figure 11:



Source: 'Economic Crisis and access to public health services: The case of Hepatitis B and C, High Level Meeting Athens Greece, 2014,

CHAPTER 4

CONCLUSION: OUR POSITION – [A, B, C]

A. POSITION FOR PREVENTION OF VIRAL HEPATITIS TRANSMISION

Governments should promote and implement national control programmes for viral hepatitis that include components such as:

i Spread of awareness and information;
ii Implementation of vaccination programmes, where available (HBV and HAV));
iii Early diagnosis through specific and accurate testing of donor blood;
iv Promotion of national blood transfusion services to ensure quality processing, and donor screening with specific and sensitive tests for HCV and HBV and the implementation of Nucleic Acid Testing (NAT) where local prevalence is high;
v Promotion of voluntary non-remunerated blood donation practices to reach 100%, and;
vi Provision and reimbursement of antiviral treatment, including the new drugs according to patients' needs. The goal should be to CURE or achieve the highest percentage (%) of SVR of the patients to the treatment they are provided with.

B. TIF'S POSITION FOR THALASSAEMIA:

Considering that:

1. Liver disease in patients with thalassaemia (TDT & NTDT) is multi-factorial, with iron overload and HCV being the two main independent factors for liver disease progression;
2. Co-existence of other hepatotropic viruses in these patients is possible and frequent;
3. Patients with Transfusion Dependent Haemoglobin Disorders (TDHbDs) have iron accumulation in the liver to a variable extent (depending on the availability, accessibility and effectiveness of chelation treatment and/or good patient adherence);
4. Many patients did not benefit to the extent they should have had from the early treatment protocols (pegylated interferon and Ribavirin), because of the costs and/or the Ribavirin-related announced contra-indication, included as an exclusion criteria in the official HCV treatment guidelines (for haemolytic anaemia patients);
5. Many patients were not included in any of the clinical trials with the new drugs or those currently in the pipeline, and;
6. Almost none or extremely few patients have been treated with the newly authorised drugs in Europe and globally, mainly due to high costs;

TIF's POSITION is that:

1. Patients with thalassaemia should be tested regularly (at least once a year) for HCV markers, as part of the treatment and monitoring protocol;
2. HCV positive patients should be regularly monitored for viral load with specific and extremely sensitive molecular testing and should also be checked for genotype and when necessary for IL28B polymorphism (according to EASL and AASSLD/WHO guidelines);
3. Appropriate iron chelation according to the individual needs should be available and accessible to patients, in order to prevent iron-related HCV aggravation;
4. A Pan-European Initiative of all 28 EU countries' Ministries of Health to reach a consensus with the Industry on reducing costs of treatment with a single price for each drug across the EU countries (28), in accordance with the Health Equity and Solidarity elements and principles characterizing the establishment of the EU. Such an initiative would open the door to increasing access of patients including those with thalassaemia to new treatment regimens;
5. A Pan-European Initiative/study to collect data, results and/or other information on the current new treatment regimens in order to:

    - Enable Governments to take decisions on reimbursement schemes for these patients;
    - Enable health professionals to acquire knowledge and experience, and demonstrate to the policy-makers (national/European/International) the risk-vs-benefit element of treating timely and effectively these patients considering the high risks of Cirrhosis and/or Hepatocellular Carcinoma (HCC) and the associated need for liver transplantation in a group of thalassaemia patients, which is increasing rapidly, and;
    - Enable the medical community to support policy-makers at National Health Authority-level to define/refine the target patient population who will benefit the most.

C. TIF'S POSITION ON COLLABORATIONS

TIF seeks the productive collaboration between all relevant stakeholders involved with important work, studies and projects in this field: medical specialists in Hepatology, in Haematology, and in Paediatrics, patients/parents' associations for Thalassaemia and Sickle Cell Disease, ELPA and World Hepatitis Alliance (WHA), with common concerns, professional scientific and medical associations such as EASL, the European Haematology association (EHA) and the International Society of Blood Transfusion (ISBT), the World Health Organisation (WHO), the European Commission, Parliament and Council, EMA and the industry, in encouraging and promoting national control policies, including availability and accessibility to appropriate targeted (tailored to each case's needs) anti-viral treatment.

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