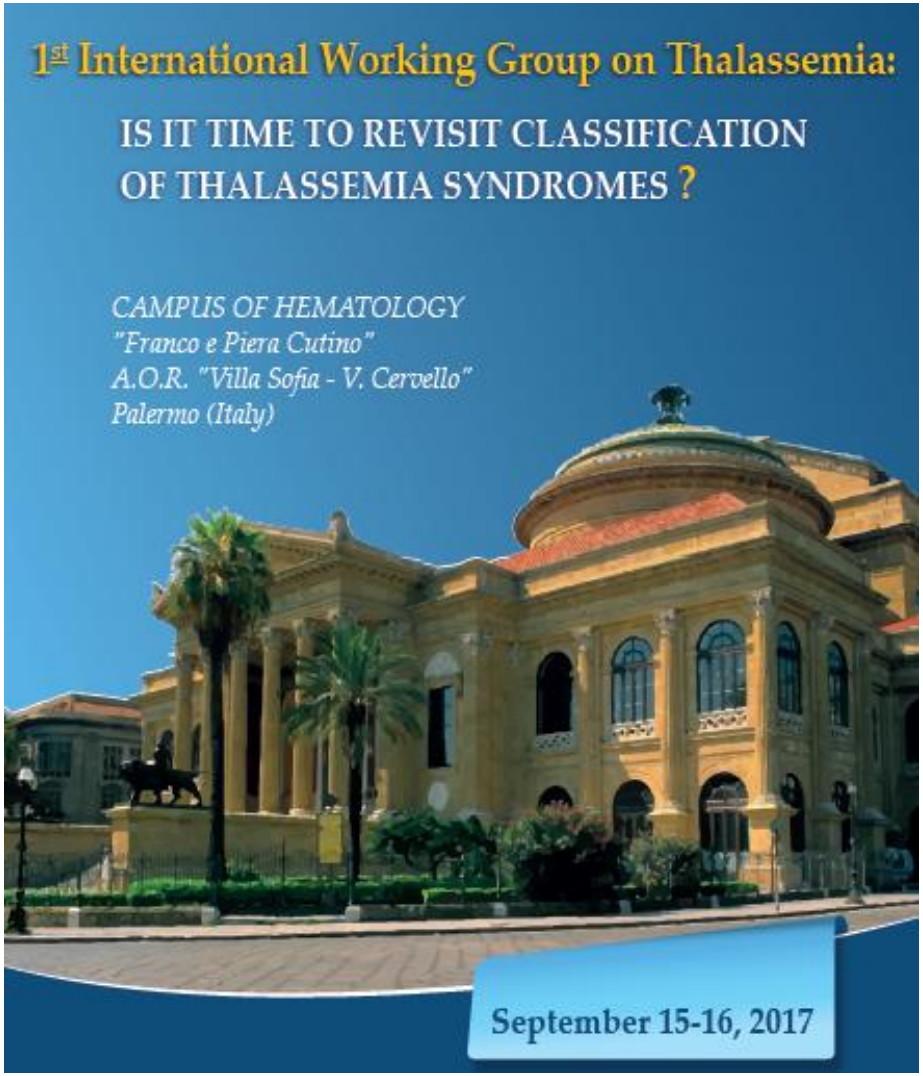

The future of thalassemia patients without HCV infection: a new history

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The past, the present and the future of Thalassemia patients with HCV infection

Key points

- The past : What was the role of HCV in the clinical course of Thalassemia?
  - severity of liver disease
  - complications of liver disease
  - survival
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Liver disease in chelated transfusion-dependent thalassemics: the role of iron overload and chronic hepatitis C.

	HCV-RNA negative (68 patients)	*HCV-RNA positive (58 patients)*	*p*
Age (mean,SD)	13.9±(8.85)	21.2± (8.87)	<0.001
Gender (M/F)	35/33	32/26	0.681
ALT (median, range)	27 (9-200)	82 (17-547)	<0.001
Ferritin (median, range)	1,892 (141-5,952)	1,750 (188- 5,503)	0.590
LIC (median, range)	3.3 (0.3-22)	2.3 (0.4-11.8)	0.064
Histological inflammation (grading)			
Absent	23 (34%)	0	
Mild/moderate	45 (66%)	56 (96%)	<0.001
Severe	0	2 (4%)	
Histological fibrosis			
Absent	23 (34%)	2 (4%)	
Mild/moderate	42 (62%)	37 (64%)	<0.001
Severe/cirrhosis	3 (4%)	19 (32%)	

V. Di Marco et al. Haematologica, 2008

Hepatocellular carcinoma in thalassaemia: an update of the Italian Registry

Popolation: 5,855 thalassaemia patients followed by the centres included in the study between 2002 and 2012.

Overall incidence: 60 patients (1.02%)

- Talassemia Major: 32/4,238 (0.75%)
- Talasssemia Intermedia: 28/1,607 (1.74%)

Virus markers of patients with HCC

- 54 patients (87%) were anti-HCV positive
- 43 patients (69%) were HCV-RNA positive
- 3 patients (5%) were HBsAg positive
- 36 patients (60%) were anti-HBc positive

56 patients (93.3%) had serum markers of exposure to HBV/HCV

C. Borgna-Pignatti, British Journal of Haematology, 2014, 167, 121–126

Chronic HCV infection increases mortality in thalassemia major patients

Project:
Prospective cohort study including all TM patients that were treated at five Sicilian Thalassemia Centers between January 1990 and December 2015 with a mean of follow-up of 16.5 years (range 1–25 years).

Aim:
to evaluate the role of chronic HCV infection on

- heart disease,
- liver disease,
- overall survival

V. Di Marco, A Maggio et al, 2017

Baseline features of 229 patients with Thalassemia Major observed for 25 years

Baseline features	**Group 1 Always negative HCV-RNA patients**	**Group 2 Always positive HCV-RNA patients**	**P value**
Number of patients	113	114	
Age (years, mean, SD)	19 ± 11	25 ± 9	**< 0.001**
Gender (males, %)	56 (49.6%)	64 (56.1%)	0.321
Ferritin (ng/mL, median, range)	1,700 (129 – 8,240)	1,398 (188 – 9,660)	0.163
ALT (IU/mL, mean, SD)	49 ± 66	80 ± 49	**< 0.001**
Liver Histologic staging • F0 • F1 • F2 • F3 • F4	 26 (23%) 41 (36.3%) 24 (21.2%) 6 (5.4%) 16 (14.1%)	 3 (2.6%) 33 (28.7%) 26 (23.5%) 10 (8.7%) 42 (36.5%)	**< 0.001**
Liver Iron Cconcentration (LIC) (mg/g dry weight) • < 7 mg/g • ≥ 7 mg/gr	 96 (85%) 17 (15%)	 81 (71%) 23 (29%)	0.31
Diabetes mellitus	5 (4.4%)	12 (10.4%)	0.081
Cardiomiopathy	12 (10.6%)	17(13.7%)	0.333

Causes of death in 227 Thalassemia Major patients according to HCV status

Cause of death	Group 1 Always negative HCV-RNA patients	Group 2 Always positive HCV-RNA patients	p
Number of patients	113	114	
Overall mortality	15 (13.2%)	39 (34.2%)	**0.003**
Death for Heart Failure	10 (8.8%)	19 (16.6%)	0.1
Death for liver failure/HCC	1	14 (12.2%)	**0.0007**
Other causes • Sepsis • BTM complication • Extra hepatic Cancer • Acute Renal Failure • Pulmonary embolism • Car Accidents	4 (2.7%) 1 1 1 1	6 (2.6.%) 3 1 1 1	0.3

V. Di Marco, A Maggio et al, 2017

Risk factors for **overall survival** by Cox multivariate model

	No Death (173 patients)	Death (54 patients)	P value	Adjusted HR (95%CI)	p value
Age (mean, SD)	21 ± 10.2	24.9± 10.1	0.001	1.03 (1.01 – 1.07)	**0.028**
LIC (mg/g dry weight) • < 7 mg/g • ≥ 7 mg/gr	 152 (88%) 21 (12%)	 35 (65%) 19 (35%)	 < 0.001	 2.64 (1.48 – 4.71)	 **0.001**
HCV- RNA • Always Negative • Always Positive	 98 (52.3%) 75 (47.7%)	 15 (34.5%) 39 (65.5.%)	 0.001	 1.94 (1.05 – 3.60)	 **0.036**
Diabetes	8 (6.6%)	9 (13.8%)	0.006	1.58 (0.75- 3.39)	0.23
Liver disease • Chronic Hepatitis • Cirrhosis	138 (74.1%) 35 (26.4%)	31 (79.3%) 23 (20.7%)	0.002	1.41 (0.74 -2.52)	0.24

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Risk factors for **heart death** by Cox multivariate model

	No death (198 patients)	Death (29 patients)	P value	Adjusted HR (95%CI)	p value
Age (mean, SD)	22 ± 10.5	23.5 ± 9.1	0.019	0-94 (0.90 – 0.99)	**0.011**
LIC (mg/g dry weight) • < 7 • ≥ 7	 172 26	 15 14	 < 0.001	 4.56 (2.19 – 9.50)	 **<0.001**
HCV- RNA • Always Negative • Always Positive	 103 (52.3%) 95 (47.7%)	 10 (34.5%) 19 (65.5.%)	 0.078	 1.79 (0.79 – 4.03)	 0.16
Diabetes	13(6.6%)	4 (13.8%)	0.67		
Liver disease • Chronic Hepatitis • Cirrhosis	 146 (74.1%) 52 (26.4%)	 23 (79.3%) 6 (20.7%)	 0.28		

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Risk factors for **liver death** by Cox multivariate model

	No death (212 patients)	Death (15 patients)	P value	Adjusted HR (95%CI)	p value
Age (mean, SD)	21.5 ± 10.5	29.2 ± 12.1	< 0.001	1-04 (0.99 – 1.09)	**0.08**
LIC (mg/g dry weight) • < 7 • ≥ 7	 174 (82%) 28 (18%)	 13 (87%) 2 (13%)	 0.51		
HCV- RNA • Always Negative • Always Positive	 112 (52.3%) 100 (47.7%)	 1 (34.5%) 14 (65.5.%)	 0.009	 2.4 (1.51 – 11.2)	 0.265
Diabetes	15(6.6%)	2 (13.8%)	0.33		
Liver disease • Chronic Hepatitis • Cirrhosis	 169 (74.1%) 43 (26.4%)	 0 (79.3%) 15 (20.7%)	 < 0.001	 29.9 (3.8-234.6)	 **0.001**

V. Di Marco, A Maggio et al, 2017

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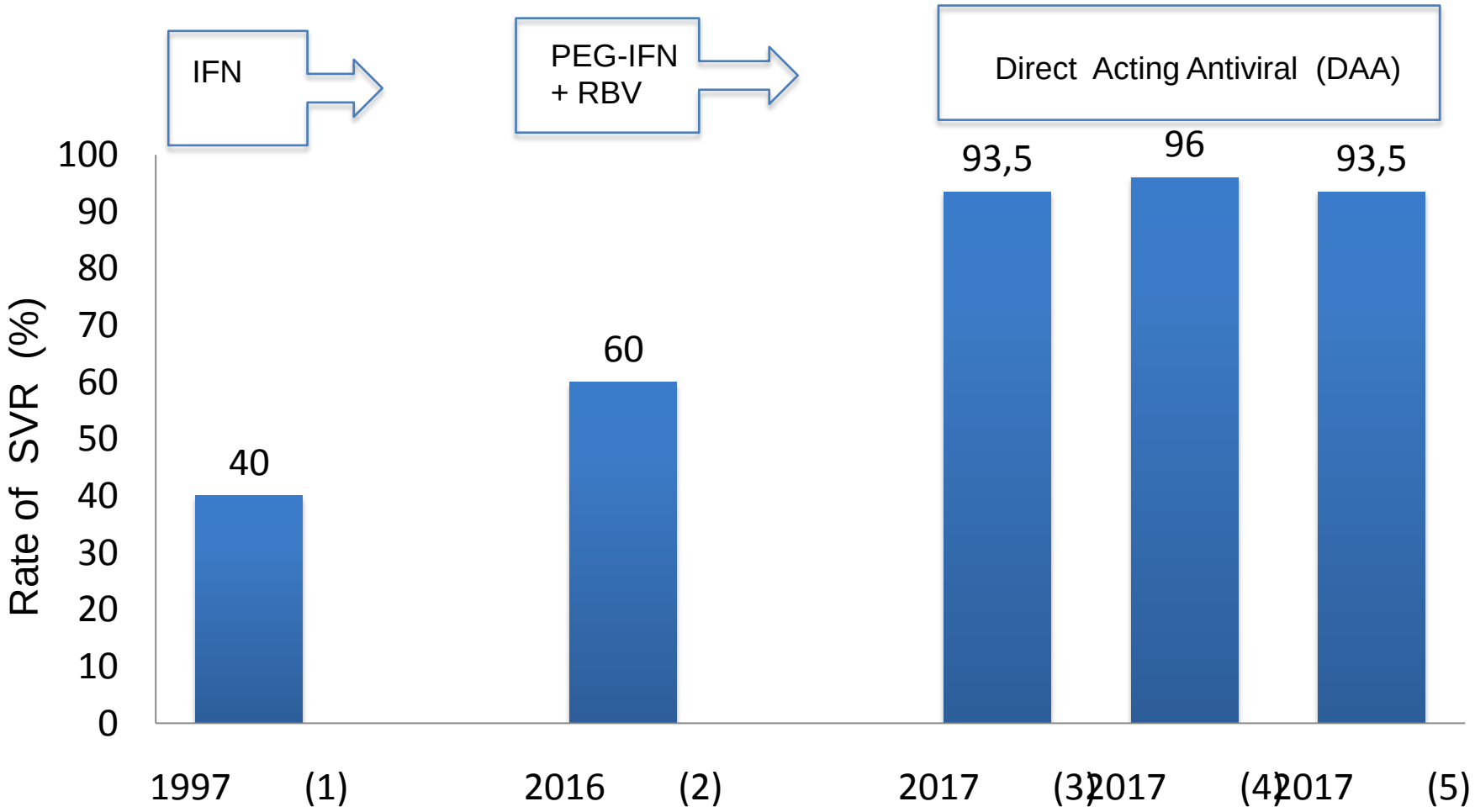
Changes in standard of care for HCV and improvements of SVR



1. Di Marco, Maggio, Craxì et al Blood 1997
2. Di Marco, D'Ambrosio, Forni et, DLD 2014
3. Hezod, Colombo Di Marco Hepatology, 2017
4. Mangia, Forni et al. Liver International, 2017
5. Origa, Piga, Di Marco, Forni et al Submitted

1. 70 pts treated with IFN
2. 230 pts treated with Peg IFN + RBV
3. 159 pts treated with GRZ + ELB
4. 100 pts treated with SOF+LDV
5. 139 pts treated with DAAs

Causes of death in 132 thalassemia patients with HCV chronic liver disease treated with IFN

Cause of death	Patients without SVR after IFN based therapy	Patients with SVR after IFN based IFN	p
Number of patients	67	65	
Overall Death	**19 (28.3%)**	**4 (6.2%)**	**0.001**
Death for heart failure	8 (11.9 %)	1 (1.6%)	**0.03**
Death for liver failure /HCC	9 (3.4%)	1 (1.6%)	**0.01**
Other cause	2 (2.9%)	2 (3.0%)	1.0

V. Di Marco, A Maggio et al, 2017

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Hepatitis and cirrhosis in thalassemia patients : assessment of liver damage in the future

The past: Invasive methods

1. Iron overload (serum ferritin)
2. Liver Iron Concentration **(liver biopsy)**
3. Steatosis (Ultrasound and **liver biopsy)**
4. Liver inflammation **(liver biopsy)**
5. Liver fibrosis **(liver biopsy)**
6. Portal Hypertension (esophageal varices by EGS)
7. Liver function (Child-Pugh score and MELD score)

The future: Non-invasive methods

1. Iron overload (serum ferritin)
2. Liver Iron Concentration **(T2* by MRI)**
3. Steatosis **(Ultrasound and CAP by Fibroscan)**
4. Liver inflammation (AST/ALT)
5. Liver fibrosis **(Liver Stiffness by Fibroscan)**
6. Portal Hypertension (esophageal varices by EGS)
7. Liver function (Child-Pugh score and MELD score)

The clinical features of a cohort of HCV-free thalassemic patients

118 patients followed at Thalassemia Centre of Ospedale Civico-ARNAS of Palermo

Number of Patients	118
Mean age (range)	33 (2-55)
Gender (% Males)	67 (58%)
BMI (mean, range)	23 (14-46)
Hemoglobinopaty - Thalassemia Major - Thalassemia Intermedia - Sickle cell anemia	 106 (90%) 4 (3%) 8 (7%)
Diabetes	6 (5%)
Miocardiopaty	12 (10%)
Serum ferritin (ng/ml, mean, range)	1,157 (98 -8150)
Patients with ALT upper normal limit	22 (20%)
Serum albumin (g/dl, mean)	4.4
Cholesterol (mg/dl, mean, range)	121 (36 -186)

The clinical features of a cohort of thalassemic patients HCV free

Evaluation of liver fibrosis, steatosis and lLIC by no invasive methods in 118 patients of Centro di Thalassemia of Ospedale Civico ARNAS of Palermo

Liver fibrosis: liver Stiffness measurement (LSM) by Fibroscan (Di Marco et al, Br J Haematol, 2010)	**Liver steatosis:** Controlled Attenuation Parameter (CAP) by Fibroscan (Karlas J et al Hepatol. 2017).	**Liver Iron Concentration:** T2* protocol by MRI (ms) (Wood JC et al, Blood, 2005)
< 6 kPa (absent) 57%	< 248 db/m 66%	≥ 18 ms (normal) 28%
6-8 kPa (mild) 23%	≥ 248 db/m (severe) 33%	9.2 – 17.9 ms (bordeline) 28%
8-10 kPa (moderate) 11%		3.9 -9.1 ms (mild) 35%
> 10 kPa (severe) 9%		1.8 – 3.8 ms (moderate) 1%
		< 1.8 ms (severe) 8%

Conclusion (I)

Chronic HCV infection is :

- an independent risk factor of mortality.
- the main risk factor for the development of cirrhosis and HCC.

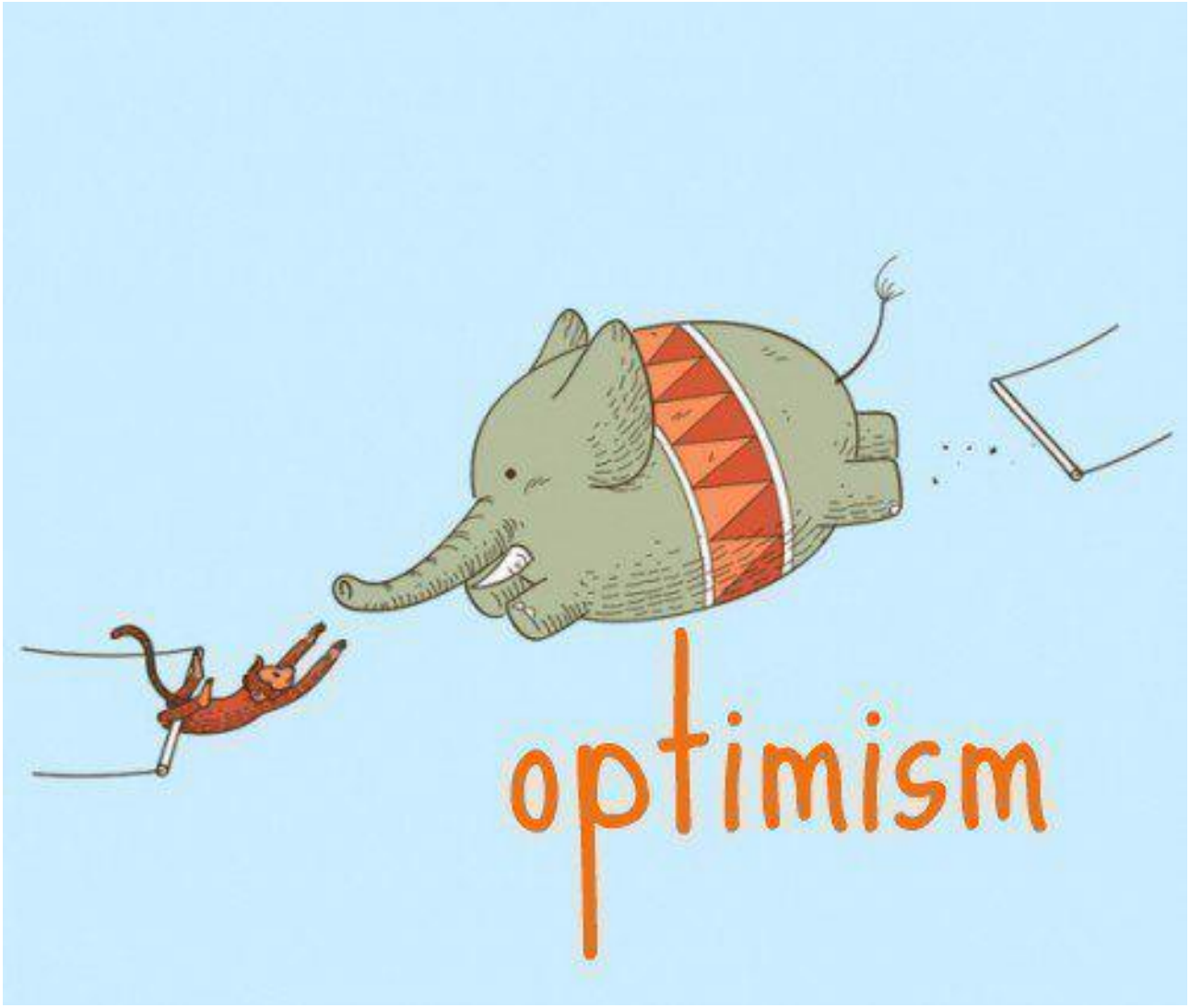
The iron overload is:

- an independent risk factor of mortality.
- the main risk factor for the development of heart failure.

The HCV clearance due antiviral therapy reduces mortality for both heart failure and liver failure / HCC

Conclusion (II)

- ✓ In the future :
  - the liver fibrosis improve in majority of HCV infected patients who achieved a SVR after antiviral therapy.
  - patients with cirrhosis after HCV clearance have a residual risk to develop liver decompensation and HCC.
  - liver steatosis and iron overload will be the main causes of liver fibrosis and advanced liver disease.



2013

2014 - 2015

2015-2017

HCV FREE