Take-home messages
from Monday 15th January 2018

Marc Bourliere , MD
Hôpital Saint Joseph

11th PHC
Paris
ary 2018

France REcherche Nord & sud Sida-hiv Hépatites
Agence autonome de l'Inserm

Disclosures

- Board member for : MSD, Janssen, Gilead, Boehringer Ingelheim, BMS, Novartis, Roche, AbbVie, GSK, Vertex, Idenix, Intercept
- Speaker for : MSD, Janssen, Gilead, BMS, Abbvie, Intercept

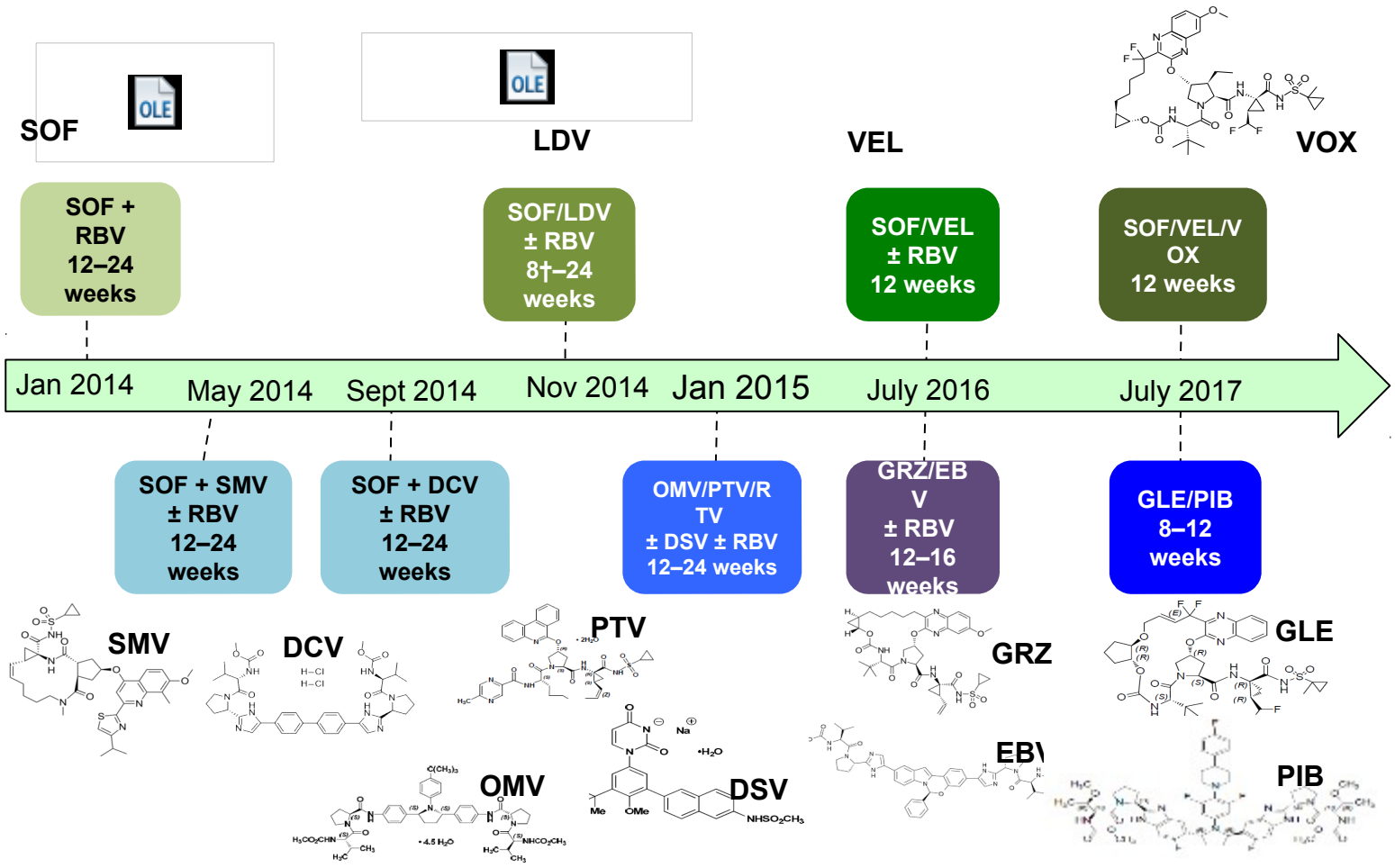
Hepatitis C : first session

Treatment of HCV: 100% cure ?

Difficult to treat patients

Results in real life

Treatment of HCV: 100% cure ?



Asselah, Marcellin & Schinazi. Liver Int 2018, in press.

Treatment of HCV: 100% cure ?

PREVENTION

- Harm reduction
- Infection control
- Blood safety

TEST AND TREAT

- HCV screening (universal)
- Linkage to care : Treat with optimal DAAs

AWARENESS

- Increase awareness
- Fights barriers & stigma
- Advocacy

Tarik Asselah PHC 2018

Difficult to treat patients

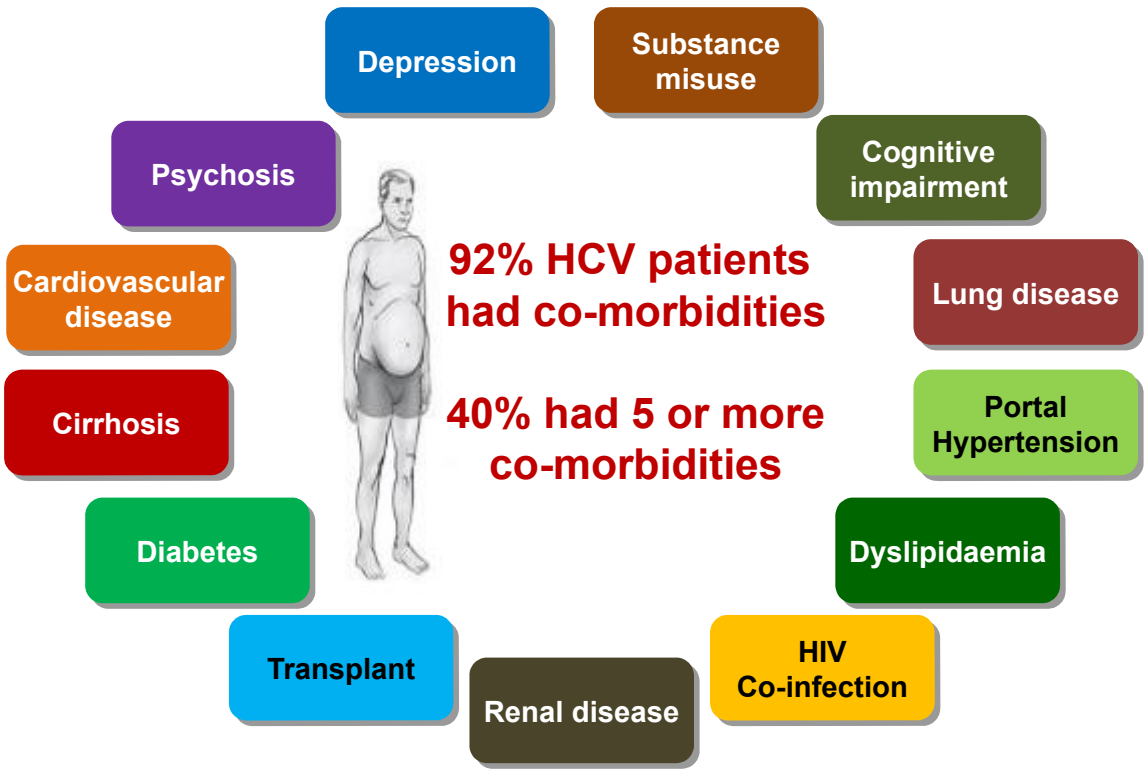
- Broad treatment indications in patients with HCV and (de)compensated cirrhosis, pre- and post-transplant

- Decompensated cirrhosis: Sofosbuvir +NS5A-inhibitor
- Protease and non-nucleosidic polymerase inhibitors are contraindicated in patients with decompensated liver cirrhosis

- Safety of DAAs in these populations not yet fully defined – thorough surveillance during therapy

- Consider drug-drug interactions, in particular immunosuppressants in transplanted patients
- Timing of DAA treatment under discussion in patients with chronic hepatitis C and HCC treated with curative intention
- Patients with HCV-associated liver disease should disappear in the transplant setting

Results in real Life

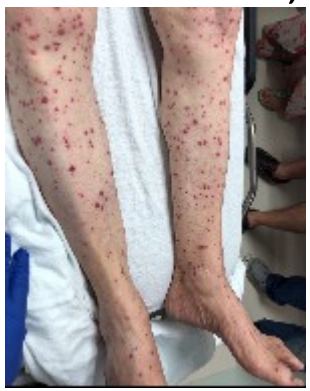


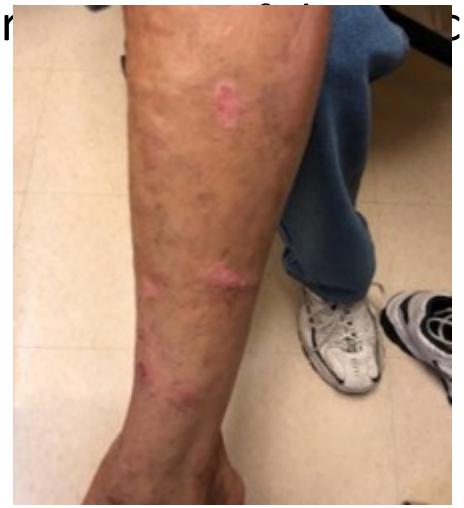
DAAs combinations are highly effective and well tolerated in the real-world setting and globally, data from the real-life cohorts confirm those observed in clinical trials

- **However, in some subgroups of patients it remains difficult to define optimal regimens (treatment duration, use of RBV,…) based on real-life cohorts**
- **In real-life, the majority of HCV patients has co-morbidities and multiple medications leading to potential DDIs**
- **Real-life cohorts are useful to highlight safety concerns (bradycardia with amiodarone or HBV reactivation)**

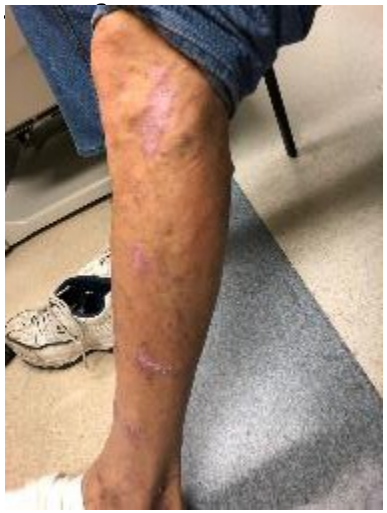
Clinical case: Management of patients with HCV related vasculitis

- Greater than 70% of mixed (II, III) cryoglogbulinemic patients are associated with HCV RNA
- HCV triggers an immune response but most cases are asymptomatic
- Clinical relevant disease include neuropathies, cutaneous ulcers, arthropathies, renal failure, and vasculitis
- DAAs are highly likely to achieve SVR and restoration of immune system
- Advanced stages of the MC-vasculitis require additional pharmacotherapy, e.g. Rituximab, to achieve r culitis in spi





SVR



Hepatitis C : second session

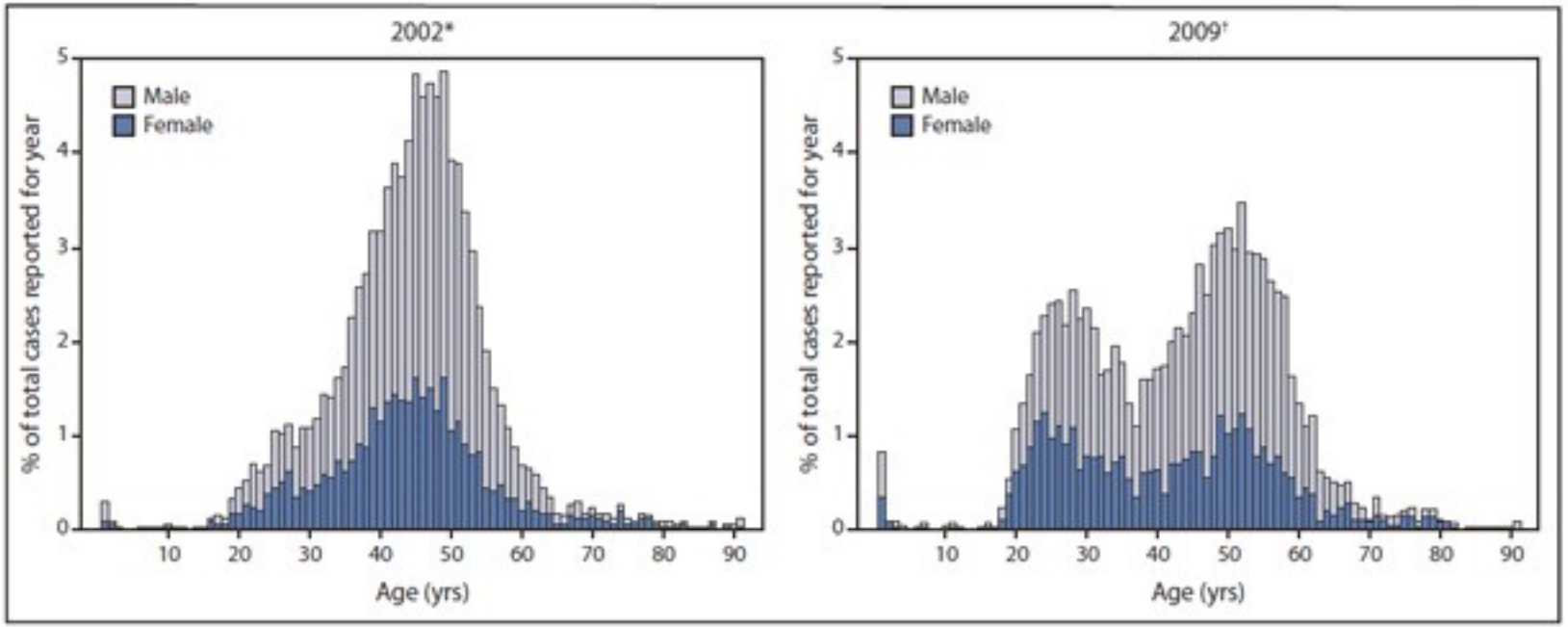
Cost benefit of treatment in F1 patients

Special population

The next waves of HCV : the epidemic of intravenous drug use

Cost-benefit of treatment in F1 patients

What happens if you don't treat early HCV?



Age distribution of newly reported confirmed cases of hepatitis C virus infection --- Massachusetts, 2002 and 2009

Cost-benefit of treatment in F1 patients

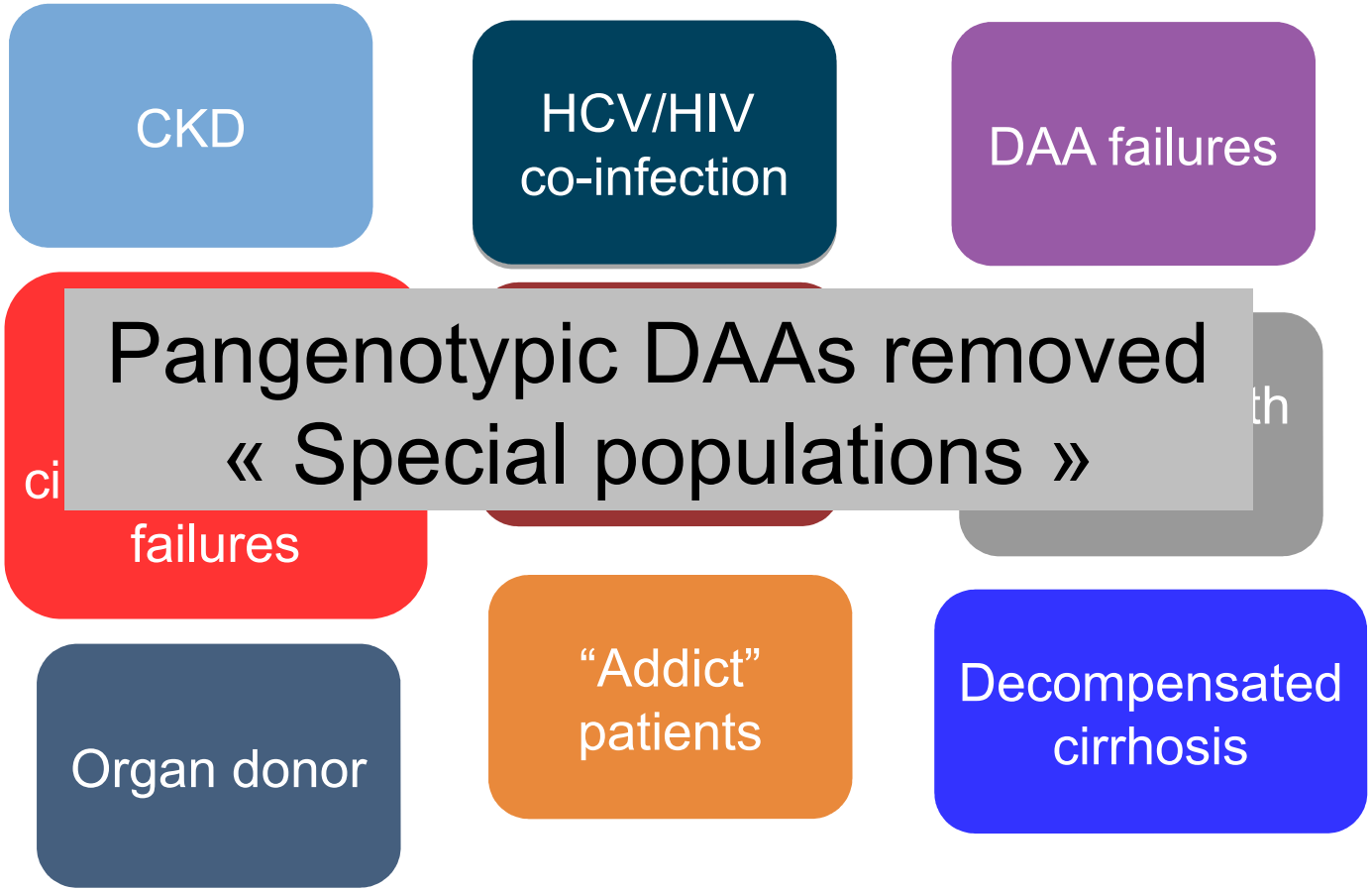
Cost-**benefits** in mild disease

- Avoidance of liver complications **PROVEN** (and avoids long term follow up costs)
- Avoidance of non-liver complications **PROVEN**
- Prevention of transmission **DATA SUPPORTED**

Cost-benefits in mild disease

- Costs of therapy (drugs /admin) **MINUS** costs of follow up
- Costs vary by country but in **ALL** countries drug price should no longer be rate limiting

Treatment of « special populations »

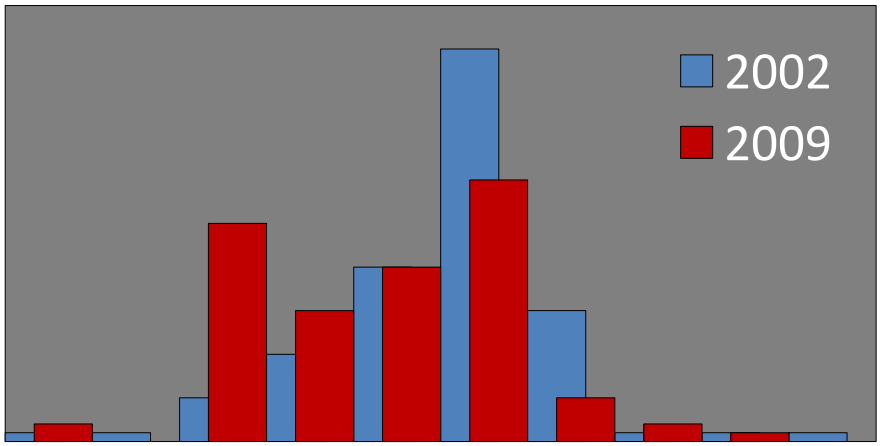


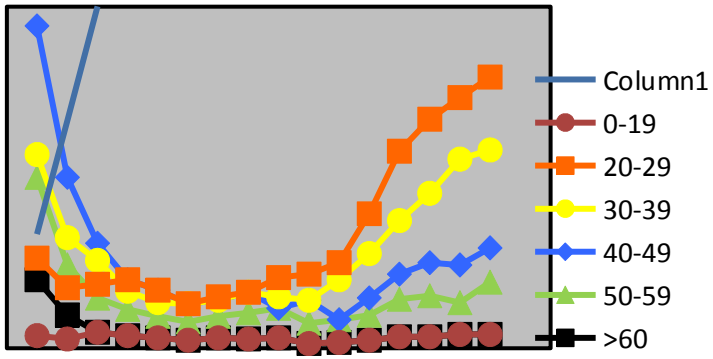
- Safety of DAAs in those populations not yet fully defined –thorough surveillance during therapy

Stanislas Pol PHC 2018

The next wave of HCV : the epidemic of intravenous drug use (USA)

PREVALENCE OF HCV IS CHANGING
TWO WAVES OF PATIENTS





	First Wave	Second Wave
Number of persons	Millions	Thousands
Description	Baby Boomers	Millennials
Age (years)	50-75	20-30s
Mode of infection	Medical care Drug use	Drug use
Alcohol abuse	Moderate	Low
HCV testing	NA for decades	Readily available
Curative treatment	NA for decades	Readily available
At risk for cirrhosis	33-50%	Not significant

Is Global elimination of HCV realistic ?

Disease Eradication vs Elimination vs Control

Many HCV patients unknown to the health care system

DAAs providing

100% SVR

SVR near, but not, 100%

TREAT AND CURE 100% OF INFECTED

No animal reservoir
Large carrier pool as reservoir
Therapy as cure and prevention

PREVENT ALL NEW ACUTE AND CHRONIC NFECTIONS

Reinfection likely in high risk groups

HCV eradication achieved

Without screenings and HCV vaccine HCV can be contained, maybe eliminated > 2030, but not eradicated

Antonio Craxi PHC 2018

Is Global elimination of HCV realistic ?

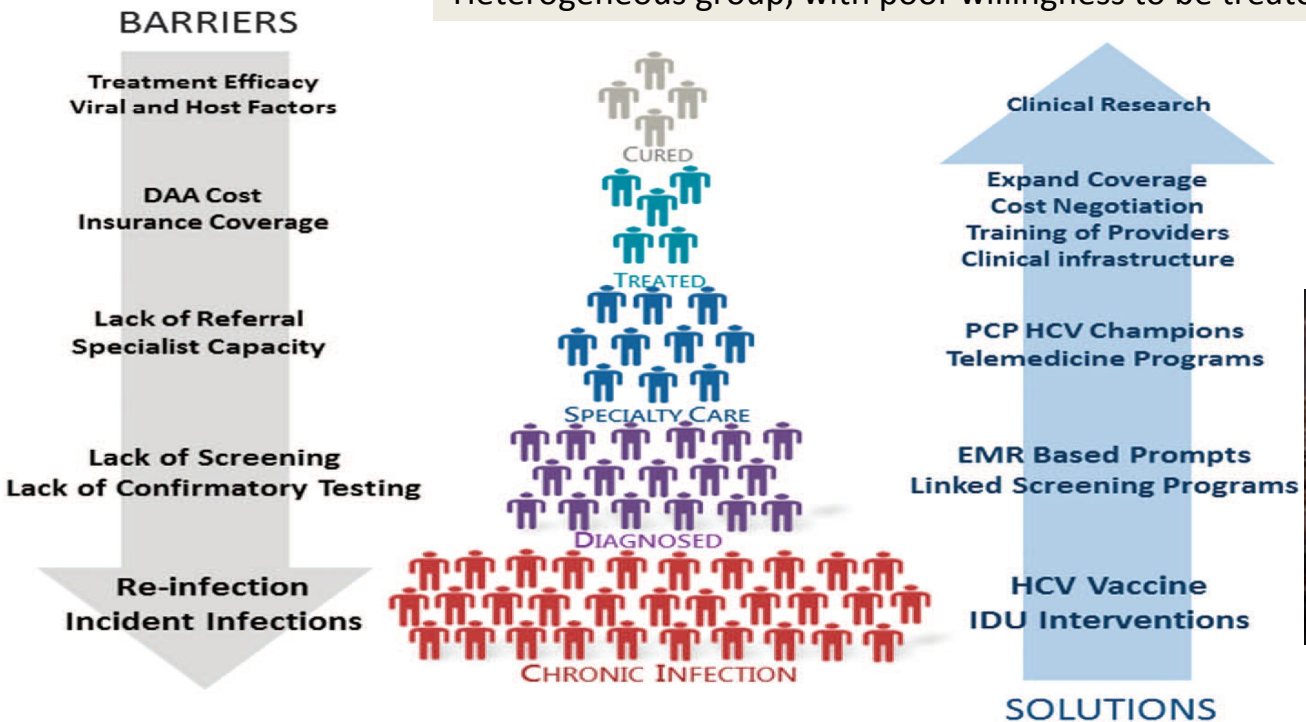
The 'Anna Karenina principle'

"All happy families look alike; each unhappy family is unhappy in its own way"

Patients with chronic HCV present patterns consistent with Anna Karenina effect

<u>Treated or on treatment</u>
They all showed willingness to be treated, link to care, adherence to treatments

<u>Difficult-to-treat</u>
Heterogeneous group, with poor willingness to be treated and difficult link to care



Antonio Craxi PHC 2018

NASH

Worldwide epidemiology of NAFLD

Prognosis of NASH

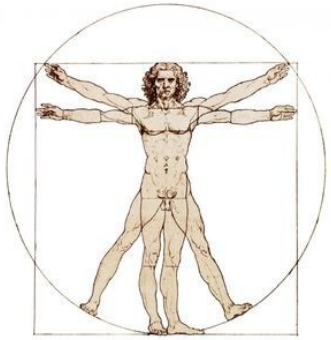
Management of patients with NASH in real life

Future therapies in NASH

Worldwide Epidemiology of NAFLD

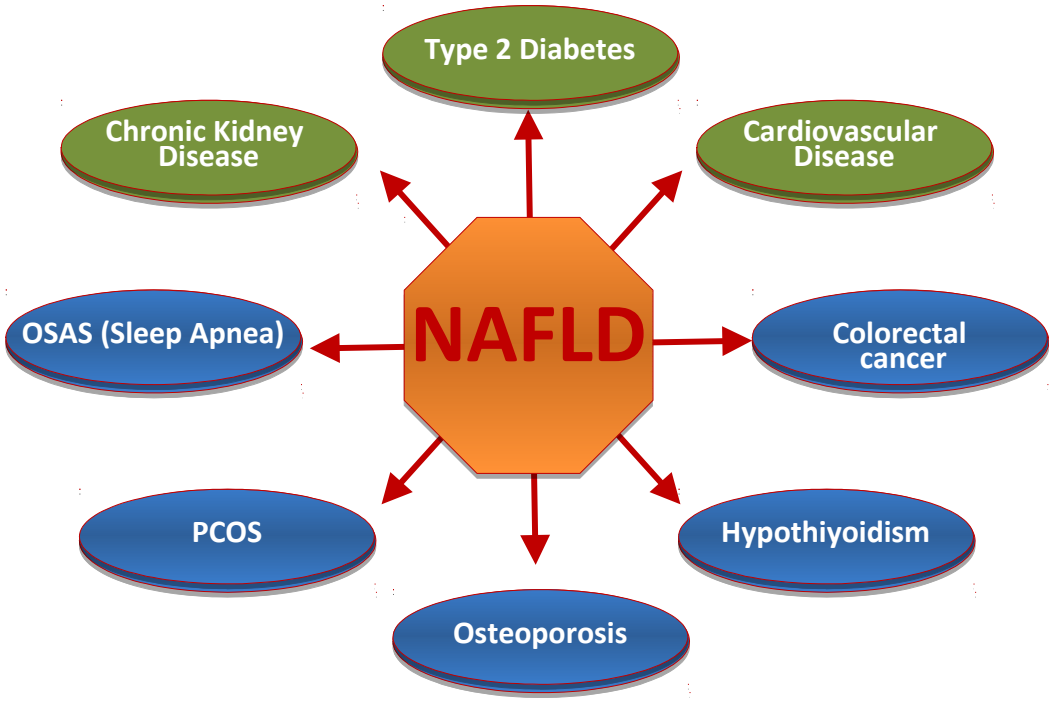
- NAFLD is a chronic liver condition characterized by hepatic fat accumulation in the absence of ethanol abuse (<20g/day) & other identifiable causes
- NAFLD is associated to insulin resistance
- NAFLD is considered the hepatic manifestation of Metabolic Syndrome

Non-alcoholic fatty liver disease NAFLD : a multi-system disease



- **Hepatic**
  cirrhosis,
  HCC
- **Metabolic**
  Central obesity,
  Insulin resistance,
  Type 2 diabetes
- **Cardiovascular**
  Dyslipidemia,
  Hypertension
  Cardiovascular Disease (CVD)

Extrahepatic complications of NAFLD

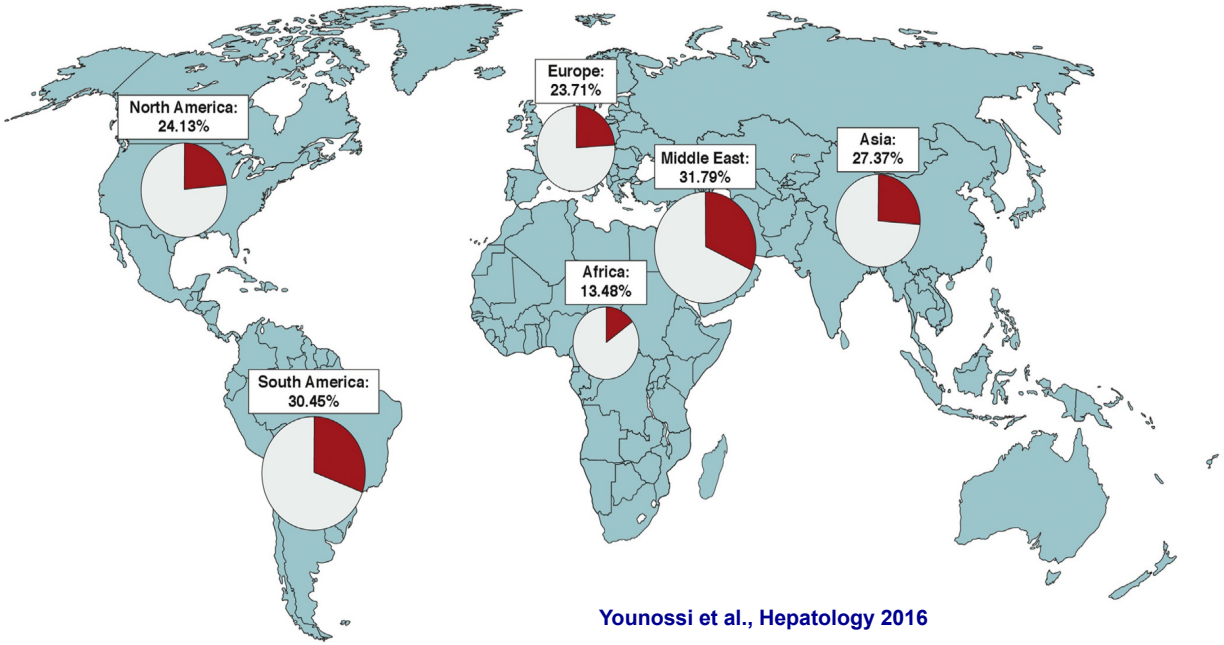


Stefano Bellentani PHC 2018

Worldwide Epidemiology of NAFLD

Global prevalence of NAFLD: 25%

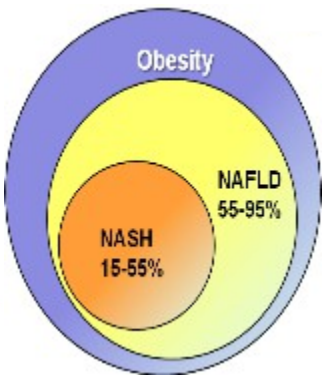
Global prevalence of overweight and obesity: 39%

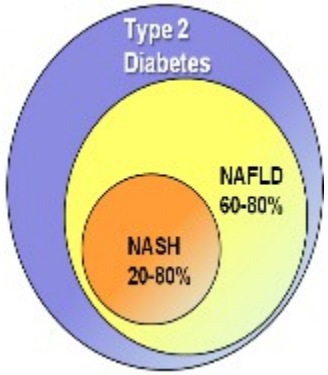


Younossi et al., Hepatology 2016

Obesity: 1 billion subjects overweight or obese around the world

Diabetes: over 380-milion cases, but 550 in 2030





ARE WE READY TO CHANGE FROM A NEGATIVE DEFINITION (=NAFLD/ NASH) TO A POSITIVE ONE ?

Moving to a positive definition of NASH: MAFL (Metabolic Associated Fatty Liver) and MASH (Metabolic Associated SteatoHepatitis) thus revising the old definition and classification

Primary MAFL/MASH	Secondary MAFL/MASH
Metabolically Healthy Obesity (MHO) (visceral obesity)	Associated with endocrine disorders: - Policystic Ovary Sindrome (POS - Hypothyroidism - GH Deficiency
Metabolically Obesity Normal Weight (MONW) (Probably Genetic, too)	Environmental (High fructose diet; high fat diet)
Type 2 Diabetes Mellitus (T2DM)	Drug-related (amiodarone, methotrexate, tamoxifen, corticosteroids..)
Genetic [PNPLA3 and TM6SF2 genes involved]	Jejunoileal bypass
Hypobetalipoprotein syndrome	Total Parenteral Nutrition (TPN), Starvation
Congenital Lipodistrophy	Associated with other hepatic diseases [viral, autoimmune, alcoholic steatohepatitis (ASH), etc.]
Lysosomal Acid Lypase Deficiency (LALD or Non-Obese Fatty Liver)	
Unknown causes (Cryptogenic)	

Prognosis of NASH

- NAFLD patients have increased overall mortality
- compared to matched controls without NAFLD.

- The most common cause of death in NAFLD patients is
- cardiovascular disease followed by cancers.

- Fibrosis is associated with overall and liver-related mortality.
-
- Non-invasive markers of fibrosis predict mortality.

Management of patient with NASH in real life

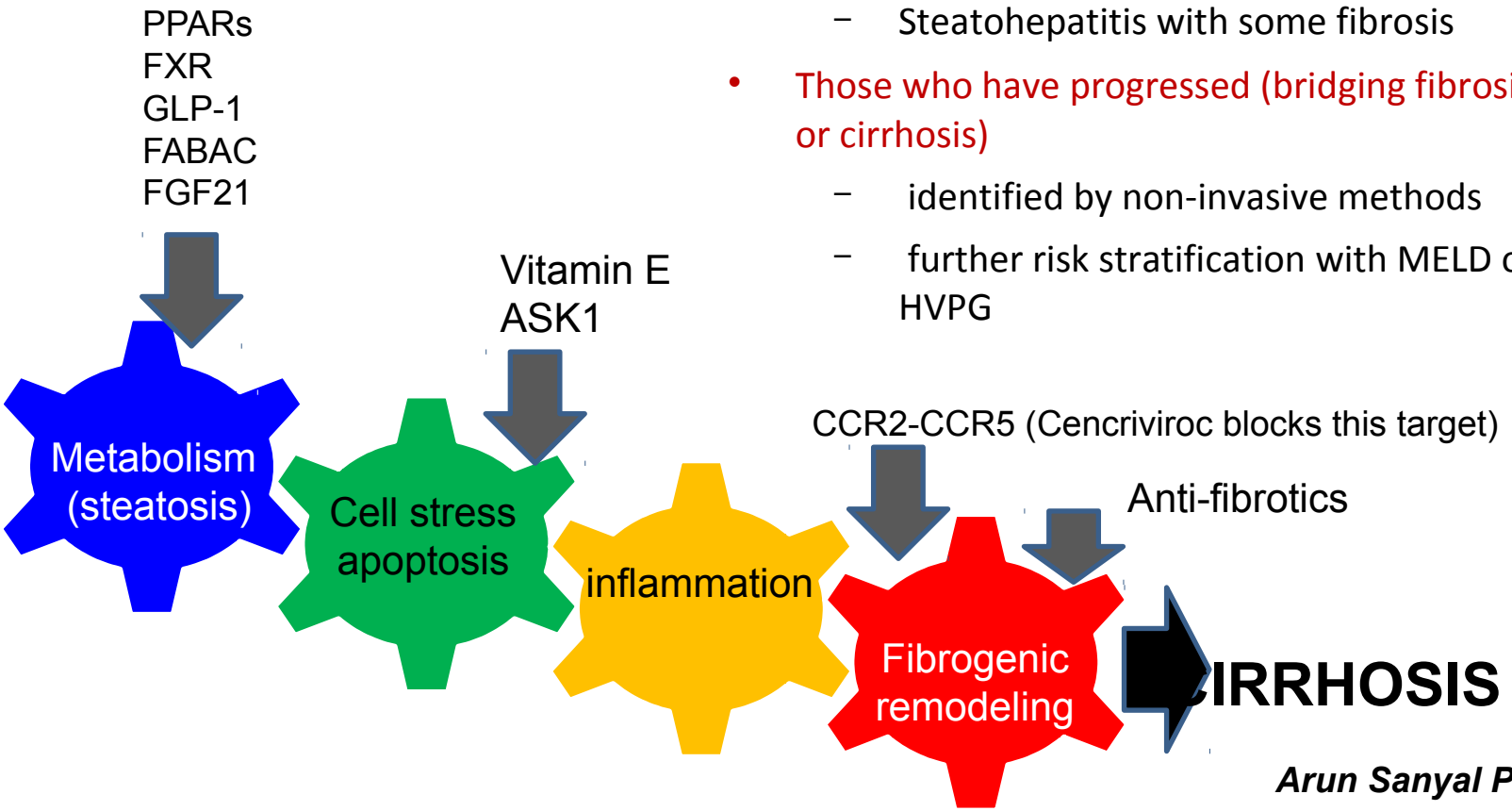
- NAFLD /NASH remains under diagnosed in general and specialist practices
- Pattern of practice for the screening , diagnosis or therapeutic management of NAFLD /NASH are quite heterogeneous according to practitioners profile and country of origin, with poor adherence to guidelines
- This highlight the need for spreading NAFLD/NASH educational in the medical community and to promote the use of simple tools for patients screening .

Future Therapy in NASH

Who needs intervention

- Those at risk for progression:
  - multiple features of MetS (obesity + T2DM or HTN)
  - Elevated ALT
  - Steatohepatitis with some fibrosis
- Those who have progressed (bridging fibrosis or cirrhosis)
  - identified by non-invasive methods
  - further risk stratification with MELD or HVPG

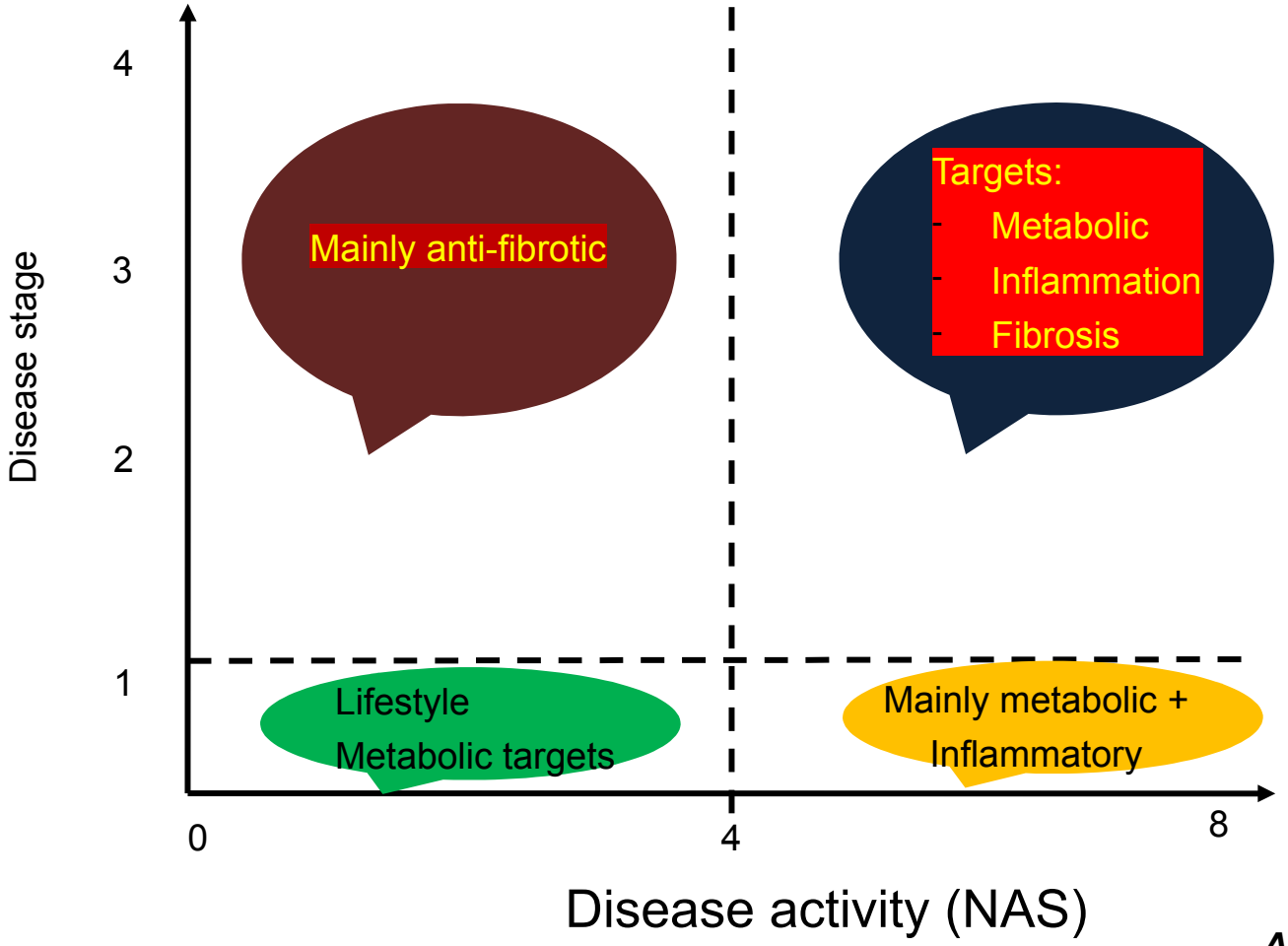
Targets for NASH treatment



Arun Sanyal PHC 2018

THERAPY IN NASH

Rational approach to therapeutics for NASH



Arun Sanyal PHC 2018

Diagnosis of NASH

NIT

Triage
in large
unselected
populations

Liver biopsy

Assessment
in selected
populations or
in clinical
trials

Best used as an integrated system to allow more efficient evaluation of patients with NAFLD

Pierre Bedossa & Laurent Castera PHC 2018

Around the world table : Access to therapy

Western countries

Others countries

Access to HCV therapy in western countries

	Germany	Spain	Italy	France	UK
National Plan	No	Yes	No (soon)	No	No (soon)
Screening program	No	Yes	Soon	No	No
Program to improve access to Trt	No (local)	Yes (Prison , PWID)	No	No	No
Treatment restrictions	No	No (2017)	No	No (2017)	No
Nb HCV Patients	**200,000**	**172-218,000**	**>300,000**	**230,000**	**125,000**
Nb patients treated so far with DAAs	55,000	81,643	109,408	91,764	25,000
Nb patients treated in 2016/17	13,200	29,732	45,201	14960 (2016) 18,800 (2017)	
Untreated Pts		110,000		114,000	

Thomas Berg & Maria Buti & Massimo Colombo & Victor de Ledinghen & Graham Foster PHC 2018

Access to HCV therapy in other countries

	Morocco	Egypt	Russia	Brazil	Poland	Romania
National Plan	Yes (2017)	Yes	No	Yes	No	Yes (2018)
Screening program	No	Yes (2017) 3,300,000	Yes (PWID..)	Yes (2018)	No	Yes
Program to improve access to Trt	No	Yes	No(soon)	Yes (2018)	No	Yes
Treatment restrictions	No (2017)	No	Yes	Yes	No(2015)	Yes
Nb HCV Patients	**450,000**	**6,000,000**	**5,000,000**	**1-1,500,000**	**230,000**	**600,000**
Nb patients treated so far with DAAs	11,000	1,344,496	35,000	112,114 56,997 (DAAs)	25,300	6210
Nb patients treated in 2016/17	5,000	65,000	20,000	36,627 (2016) 12,911 (2017)	12,000	12,000
Untreated Pts						

Mustapha Benazzouz & Gamal Esmat & Vasily Isakov & Raymundo Parana & Robert Flisiak Adriana Popescu PHC 2018

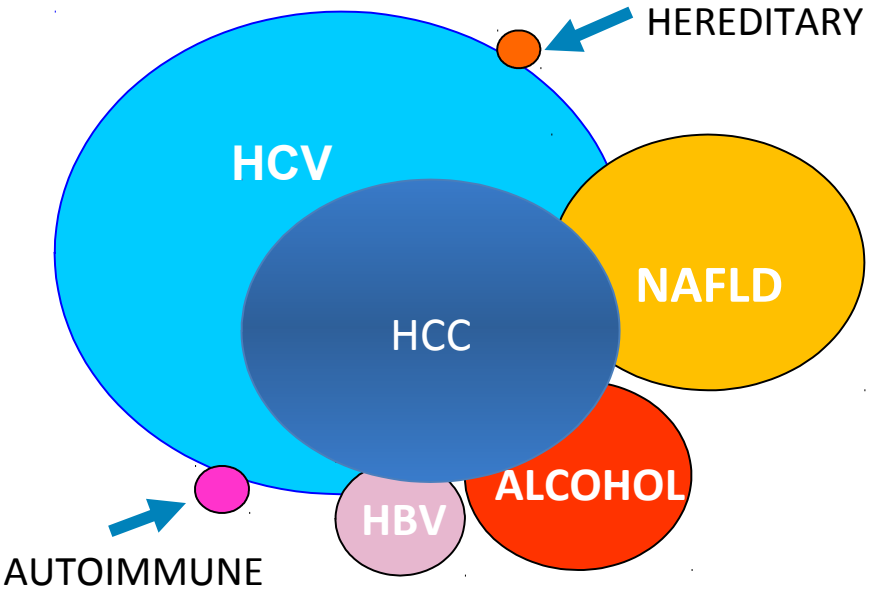
Message from Syria

- Treating chronic viral hepatitis is not an easy task during war
- However Nabil and his college did their best to treat liver patients adequately

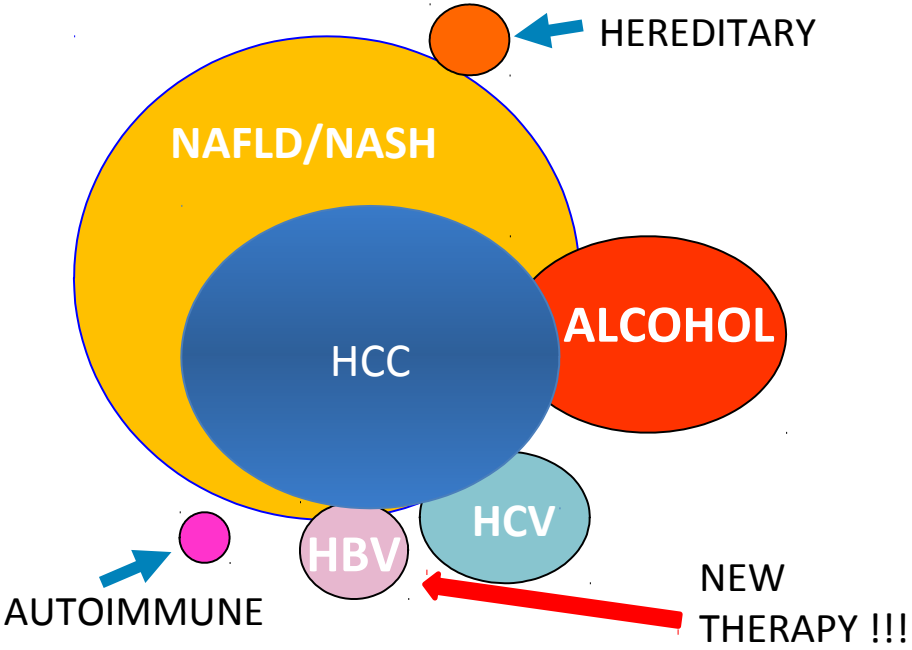
- Sanctions penalize the population dan the patients and has no positive impact on the events or to bring peace back
- Nabil and his colleges ask us to put pressure on the leaders of our countries to lift the sanctions against Syrian population

Conclusions of the day

The Hepatologist Menu - 2017



The Hepatologist Menu - 2030



- HCV Control : feasible
- HCV elimination : a goal
- HCV eradication : a dream that we need to fight hard in order to be achieve

Thank you for your attention

A great thanks to all speakers who provide me their presentation