Take-home messages from Monday 30th January 2017

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Disclosures

- Board member for : Schering-Plough, Merck, Janssen, Gilead, Boehringer Ingelheim, BMS, Novartis, Roche, AbbVie, GSK, Vertex, Idenix
- Speaker for : Roche, Schering-Plough, Merck, Janssen, Gilead, BMS, Abbvie

Hepatitis C : first session

Universal HCV treatment : strategies for simplication

Policies for HCV elimination

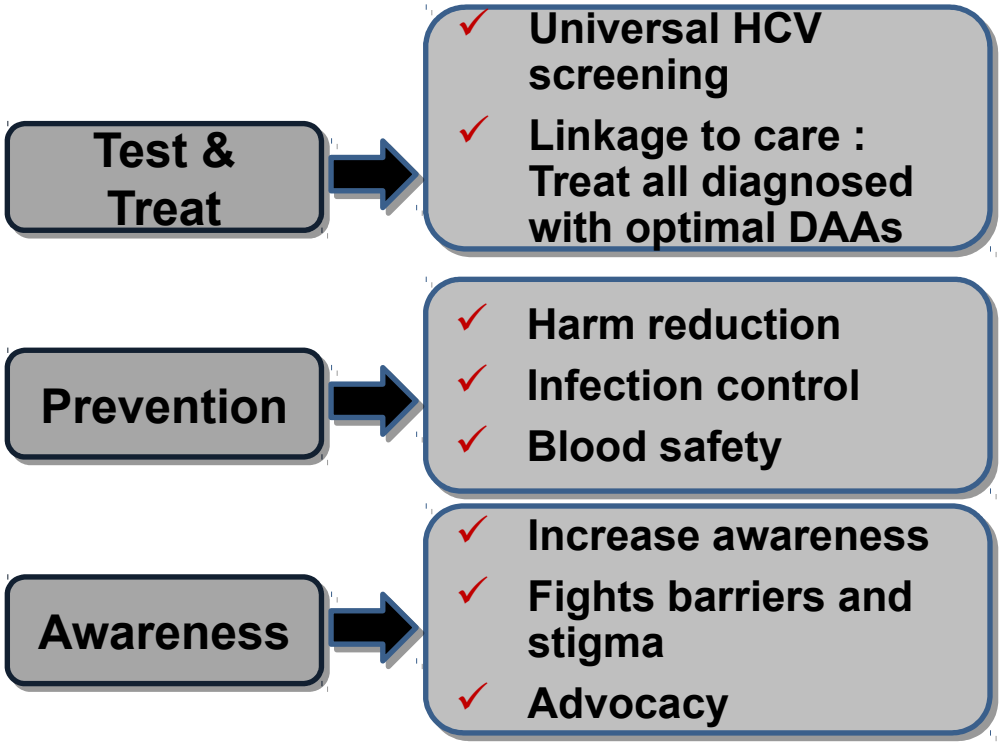
Impact of therapy on the QOL

Strategies for simplification

Top Priorities for Direct-Acting Antiviral Agents

- Potency (SVR)
- Genotype Coverage
- Resistance Barrier
- Safety/Tolerability
- Treatment Duration
- Half life & Pills burden
- Drug-drug Interaction
- Access/Cost

Strategies for HCV elimination



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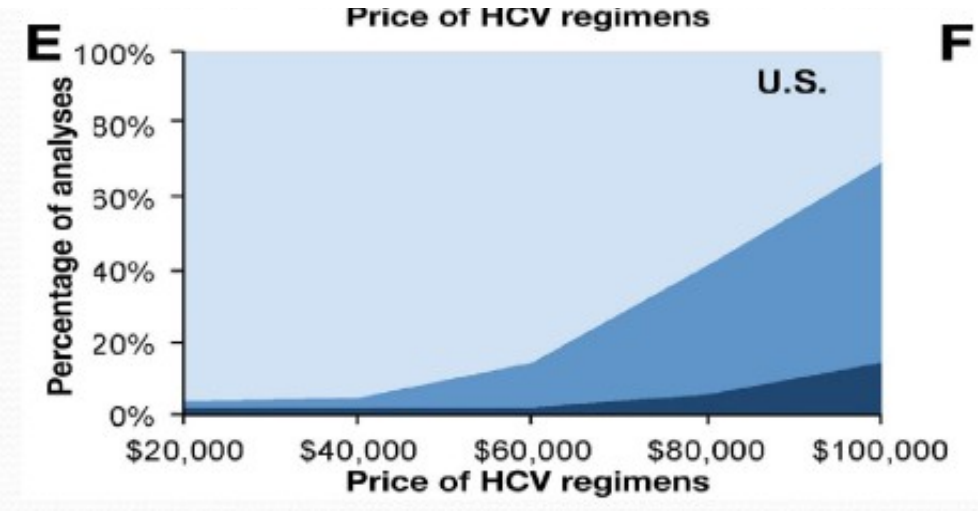
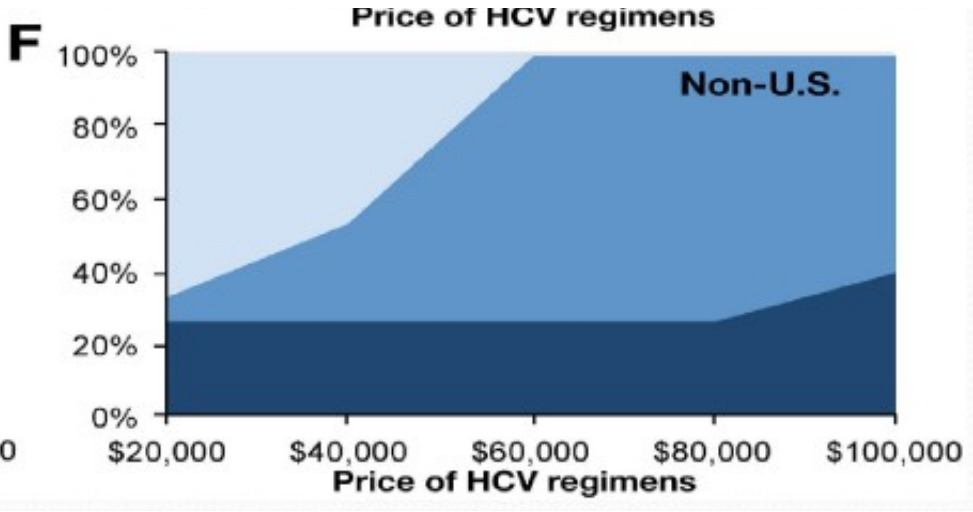
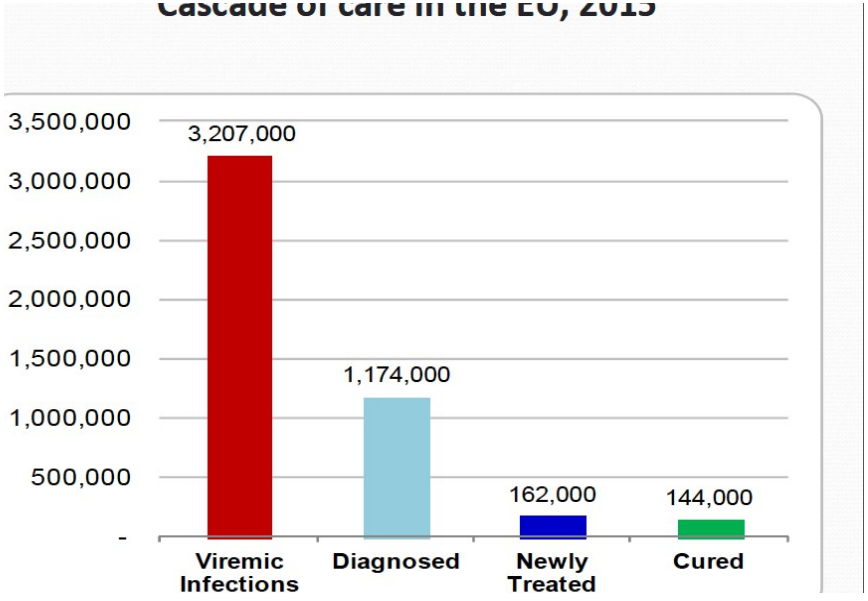
Policies for HCV elimination

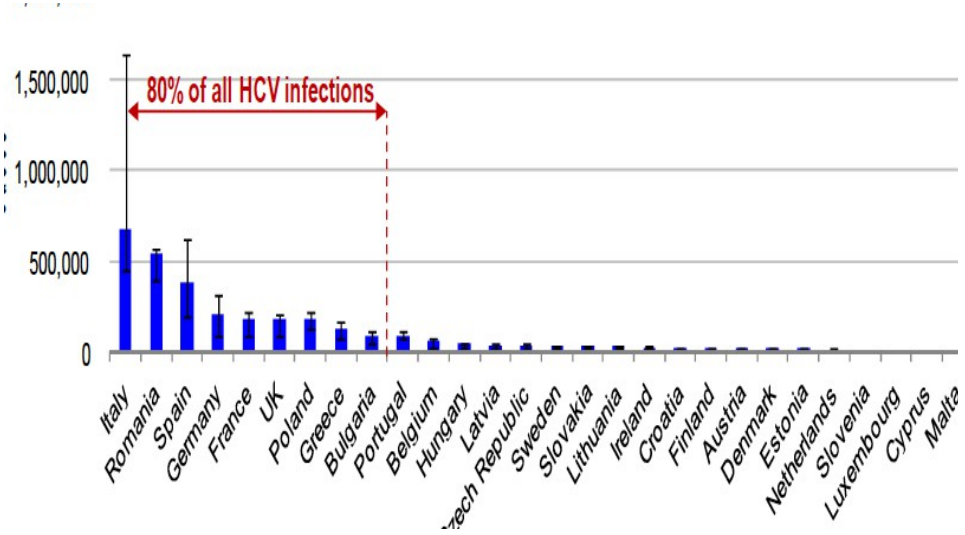
- WHO strategies and policies to eliminate Viral Hepatitis
- Prospects for HCV elimination in EU
- Challenges for HCV elimination within EU

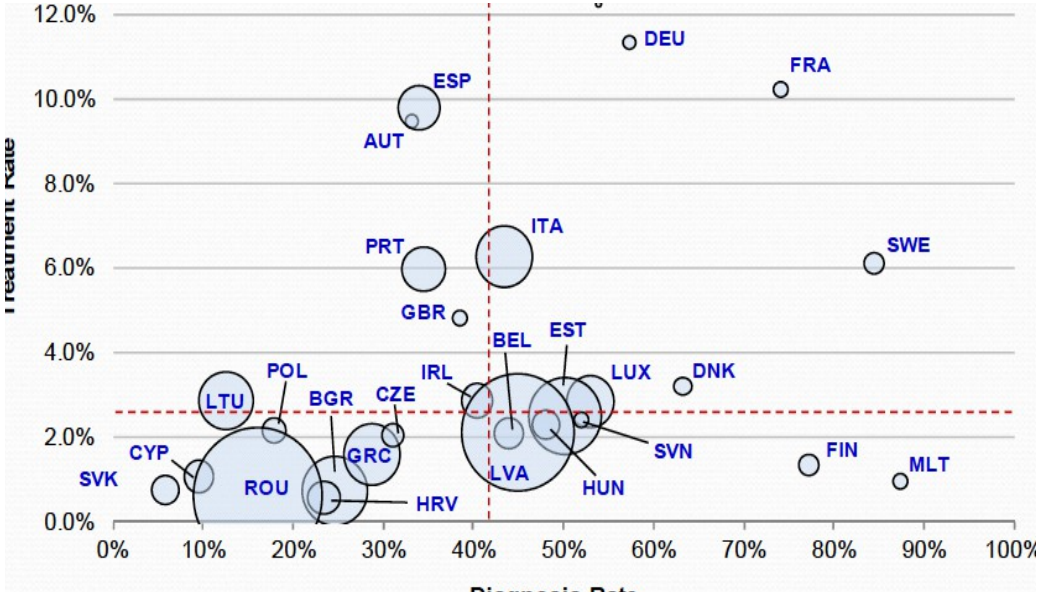




Policies for HCV elimination







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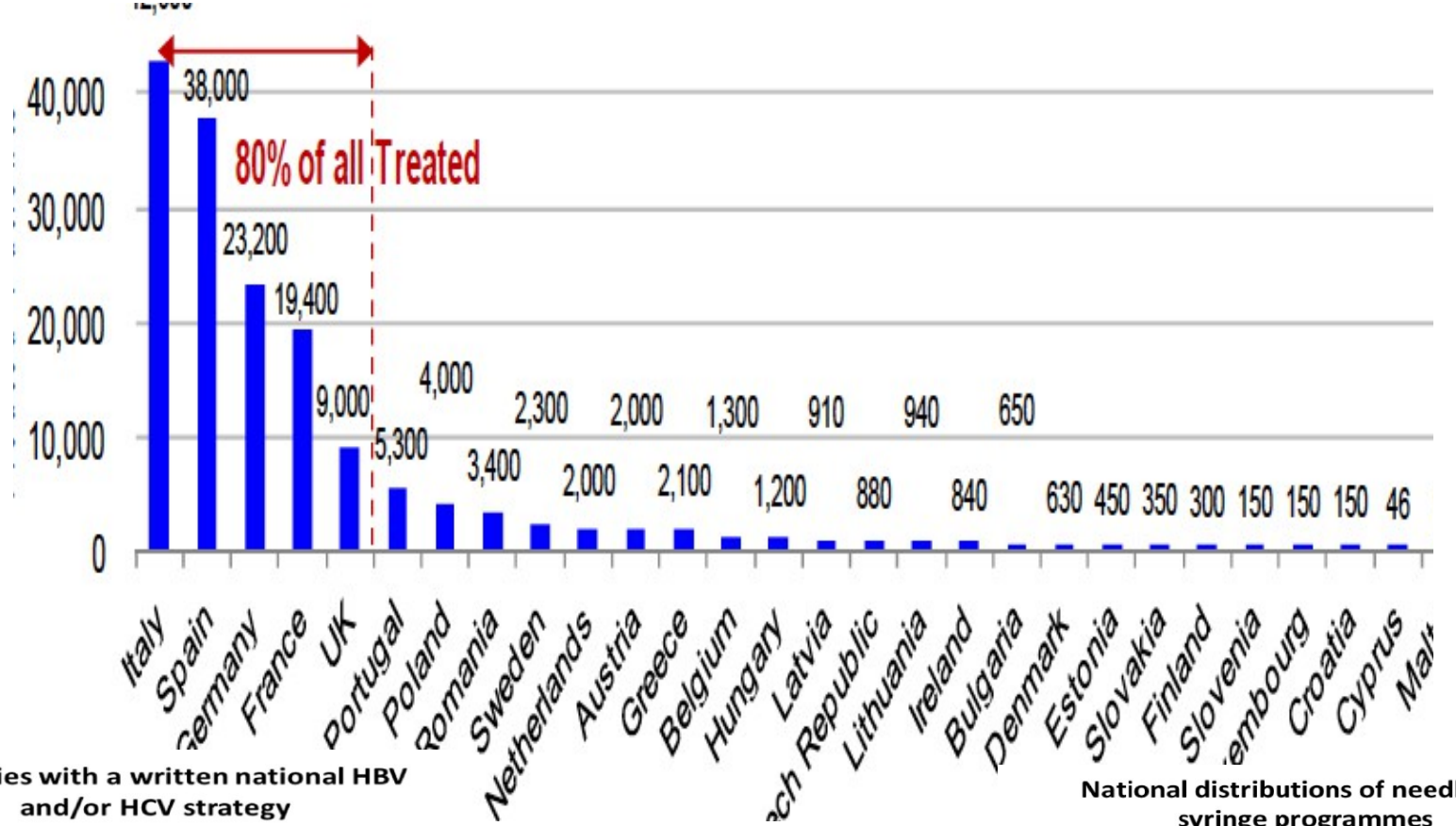
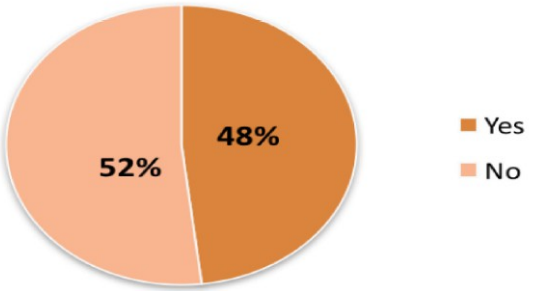
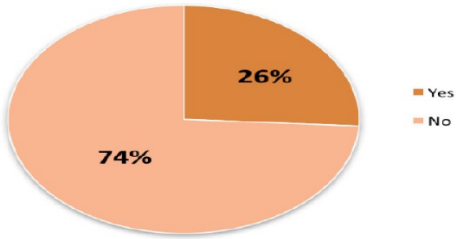
Policies for HCV elimination



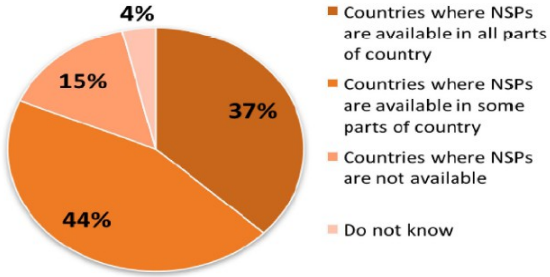
Countries with a written national HBV and/or HCV strategy



Percentage of countries that have conducted viral hepatitis awareness campaigns since January 2015, other than World Hepatitis Day



National distributions of needle and syringe programmes



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Impact of therapy on QOL

- Several systematic reviews of PROs
  - comprehensive analysis suggesting improved patient reported outcomes with direct acting anti-viral treatment.
- DAAs overcome the disadvantage of interferon (and ribavirin) containing regimens
  - Significant improvement in quality of life parameters have been noted with DAA therapy.
- Improvements in HRQOL indices are an encouraging aspect of an SVR.
- Instruments to assess current impact HCV on on health, and PRO's less frequently used to determine priority for treatment than is stage of disease.
- It is unclear whether these measurable HRQOL improvements can be translated into a net benefit improvement in work productivity and a social dimension significant enough to convince payers.

Hepatitis C : second session

Impact of therapy on metabolism and public health

Special population

Results in real life

Impact of therapy on metabolism and public health

- 1. Chronic HCV can lead to insulin resistance (IR) and type 2 diabetes mellitus (T2DM).
- 2. T2DM is associated with an increased risk for cardiovascular and cerebral disease, and end-stage renal disease (ESRD).
- 3. Chronic HCV increases the risk of acute coronary syndrome, stroke and ESRD in patients with T2DM.
- 4. Achieving a SVR is associated reduces the risk of developing IR, T2DM, acute coronary syndrome, stoke and ESRD.
- 5. Eradicating HCV will reduce mortality from liver failure and T2DM and there significantly impac the public health.

Treatment of « special populations »

- Few « special populations » left in HCV
- ESRD/hemodialysis
  - Paritaprevir/r + Ombitasvir ± Dasabuvir (HCV-1, 4)
  - Grazoprevir + Elbasvir (HCV 1, 4)
  - Glecaprevir+ Pibrentasvir (Pangenotypic)
- Decompensated cirrhosis: Sofosbuvir + NS5A inhibitors
- Safety of DAAs in those populations not yet fully defined –thorough surveillance during therapy
- No data in patients with ESRD and decompensated cirrhosis

Results in real life

1. Effectiveness and safety of „new era” HCV regimens in RWE is similar to achieved in clinical trials.
   - for GT1 SOF/LDV, OPrD and SOF+DCV is superior to SOF+SMV
2. Shortening of treatment to 8 weeks is reasonable in patients with fibrosis <F3.
3. Risk of on-treatment hepatic decompensation is related first of all to decompensation history and baseline liver function.
4. For GT3 infected patients PegIFN+SOF+RBV regimen for 12 weeks still seems to be the most effective.
5. Risk of HCC recurrence after IFN-free regimens is similar to IFN-based and related mostly to the disease advancement.
6. To avoid problems - test for HBV before HCV treatment (particularly in HBV high prevalence regions) and do not delay HBV treatment.

Clinical case: impact of therapy in a F1 patients

- All HCV F1 patients should be treated including asymptomatic ones
- Benefits of therapy
  - Quality of life improves
  - Extra hepatic manifestations can resolve
  - High rates of cure, cessation of fibrosis
- Limiting factor is not safety or efficacy, but access and cost

rom HCV to HBV cure

- ✓ Hepatitis C solution is one of the greatest success story in human medical History.
  - Products are getting better and better
  - Nanoparticles and **shorter treatments** will offer efficient , convenient way to reduce cost and increase adherence
  - Treatment as prevention: powerful tool for global elimination and eventual eradication
- ✓ Elimination of HBV is possible.
  - We have the tools, we need to have the will power to make this a priority

The best is yet to come, the game is not over

Raymond Schinazi PHC 2017

NASH

Epidemiology of NASH

Pathology of NASH

Lifestyle intervention in NASH

Therapies in NASH

Epidemiology of NASH

The global average prevalence in general population:

ADULTS NAFLD=25%, NASH=2-3%,

CHILDREN NAFLD=12-20%, NASH=1.2-2%

- **Increases with age;**
- **Higher in males vs female;**
- **Higher in Caucasian and Hispanic;**
- **Increase trends in time (Big epidemic public health burden in the next future !)**

Epidemiology of NASH

About one fourth of world's population have NAFLD

The subgroup of NASH (2-3%) is progressive in 20-30% of the cases to cirrhosis/HCC

In the US, NASH is the second leading indication for LT and HCC

NAFLD is higher in patients with hyperthension, diabetes or alteration of lipid metabolism

The economic and public health burden of NAFLD is enormous and increasing

Epidemiology of NASH

Prevalence of NAFLD/NASH is higher in:

- **Obese subjects (36-78%)**
- **Pts. with hyperglicemia or diabetes (43-62%)**
- **Pts. with hyperlipemia (45-65%)**
- **Pts. with hypertension (35-45%)**
- **Pts. with metabolic syndrome**
- **Pts. with HCV infection (55%)**
- **Pts. consuming artificial fructose in the diet (soft drinks and junk food) and NOT consuming coffee**
- **Pts. consuming late-night meals and skipping breakfast and lunch**

Epidemiology of NASH

- A pioneering Italian study (Bruno S et al BMJ, 2005) performed on a cohort of hysterectomized women reported an incidence rate of NAFLD of approximately 2 per 1,000 women/year

- The pooled regional NAFLD incidence estimates for Asia and Israel were reported to be approximately 52 per 1,000 and 28 per 1,000 person-years, respectively (Younossi ZM et al, Hepatology 2016).

NATURAL HISTORY AND PROGNOSIS OF NASH

- NAFLD/NASH warrants screening for cardiovascular diseases (proved increased mortality !!), colorectal cancer and progressive liver disease
- Progression to cirrhosis/HCC is slow.

- HCC-NASH is associated with lifestyle risk factors and with metabolic diseases (obesity, diabetes, etc.),
-
- HCC-NASH could develop in the absence of cirrhosis (45%)
- Survival of treated HCC-NAFLD is similar to treated HCC-HCV

- Prevention and surveillance strategies for HCC-NAFLD are lacking

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

An International Consensus event is needed with these priorities :

1- Change the name from NASH to MESH
(Metabolic Associated Steato Hepatitis) ?
or simply Dis-metabolic Chronic Hepatitis (DCH).

2- Develop new protocols for the diagnosis, treatment of patients with NASH and new policies for the surveillance of patients with NASH at risk to progress to cirrhosis and HCC

Pathology of NASH

- NAFLD is the combination of several histological features of variable intensity and different prognostic values including steatosis, fibrosis and activity.
- The dichotomous classification distinguishing NAFL (steatosis) from NASH is an oversimplification which is no more relevant in clinical practice. New proposals have been formulated.
- NASH is defined by histological criteria. Therefore, biopsy is needed if diagnosis and evaluation of severity are required.
- Non invasive markers are urgently needed but, so far, only liver biopsy can accurately assess and quantitate all NAFLD features at once.

Lifestyle intervention in NASH

- A 7%-10% weight loss should be the goal in all overweight/

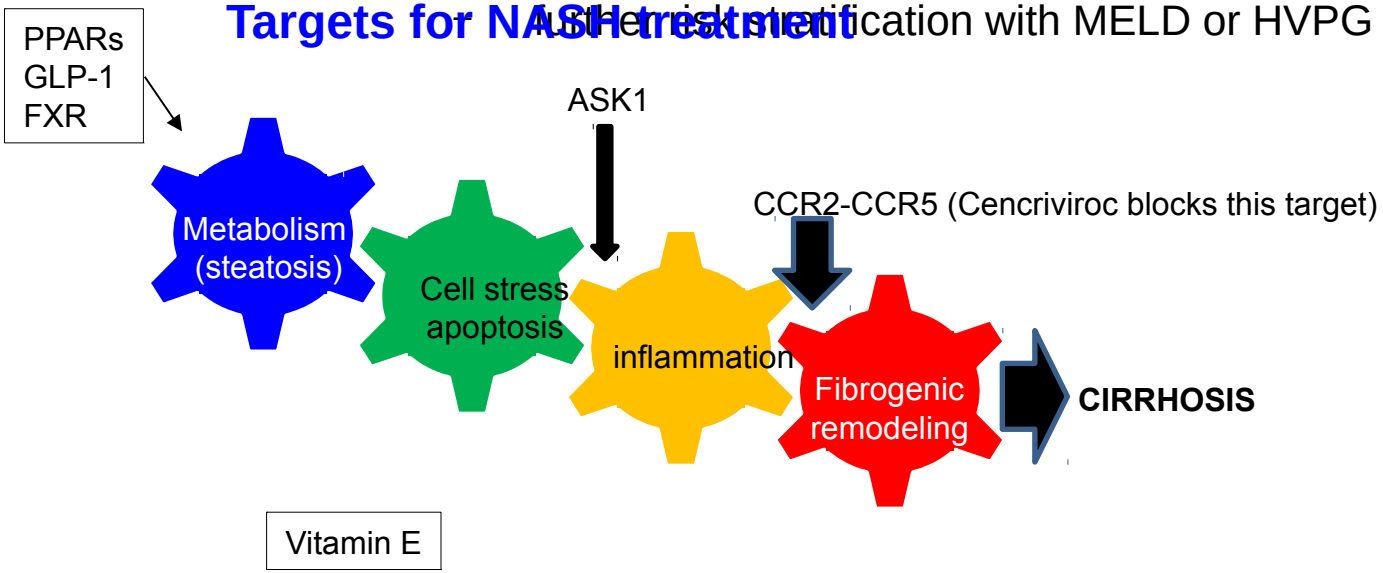
  obese NAFLD or NASH patients. No particular diet seems to be clearly beneficial beyond weight loss.
- Weight loss improves liver histology including hepatic fibrosis if ≥10%. However, improvement of histologically advanced NASH by weight loss interventions is significantly decreased.
- Physical activity should be implemented because it improves metabolism, has protective effects on cardiovascular disease and the risk of cancer. Vigorous rather than moderate activity and resistance training should be encouraged.
- A sedentary lifestyle should be strongly discouraged.
- Implementation and long-term adherence are the

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
  - Histologic stratification with MELD or HVPG

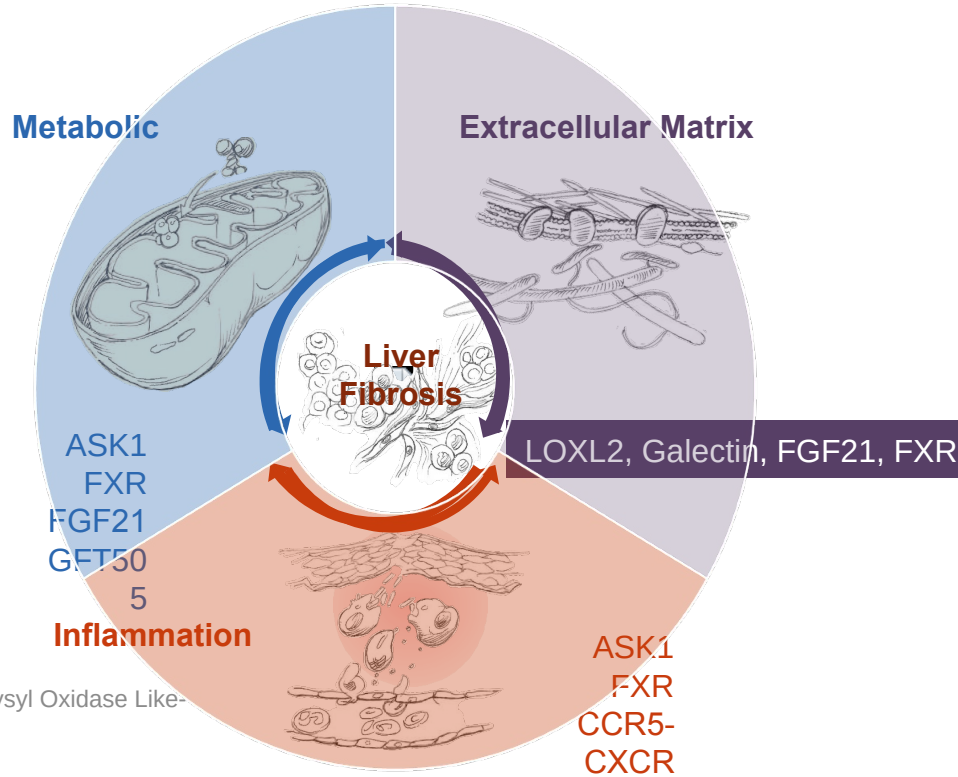
Targets for NASH treatment



Vitamine E
Obeticholic acid
FXR agonist
Aramchol
Elafibranor
Liraglutide
Cencriviroc
ASK1 inhibitors
(GS-4997)

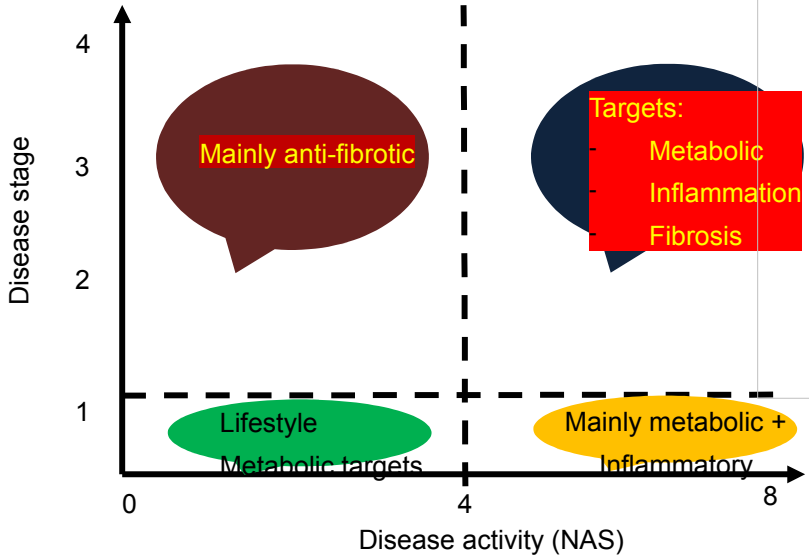
THERAPY IN NASH

NASH: Prospects for Combination Therapy



LOXL2, Lysyl Oxidase Like-2.

Rational approach to therapeutics for NASH



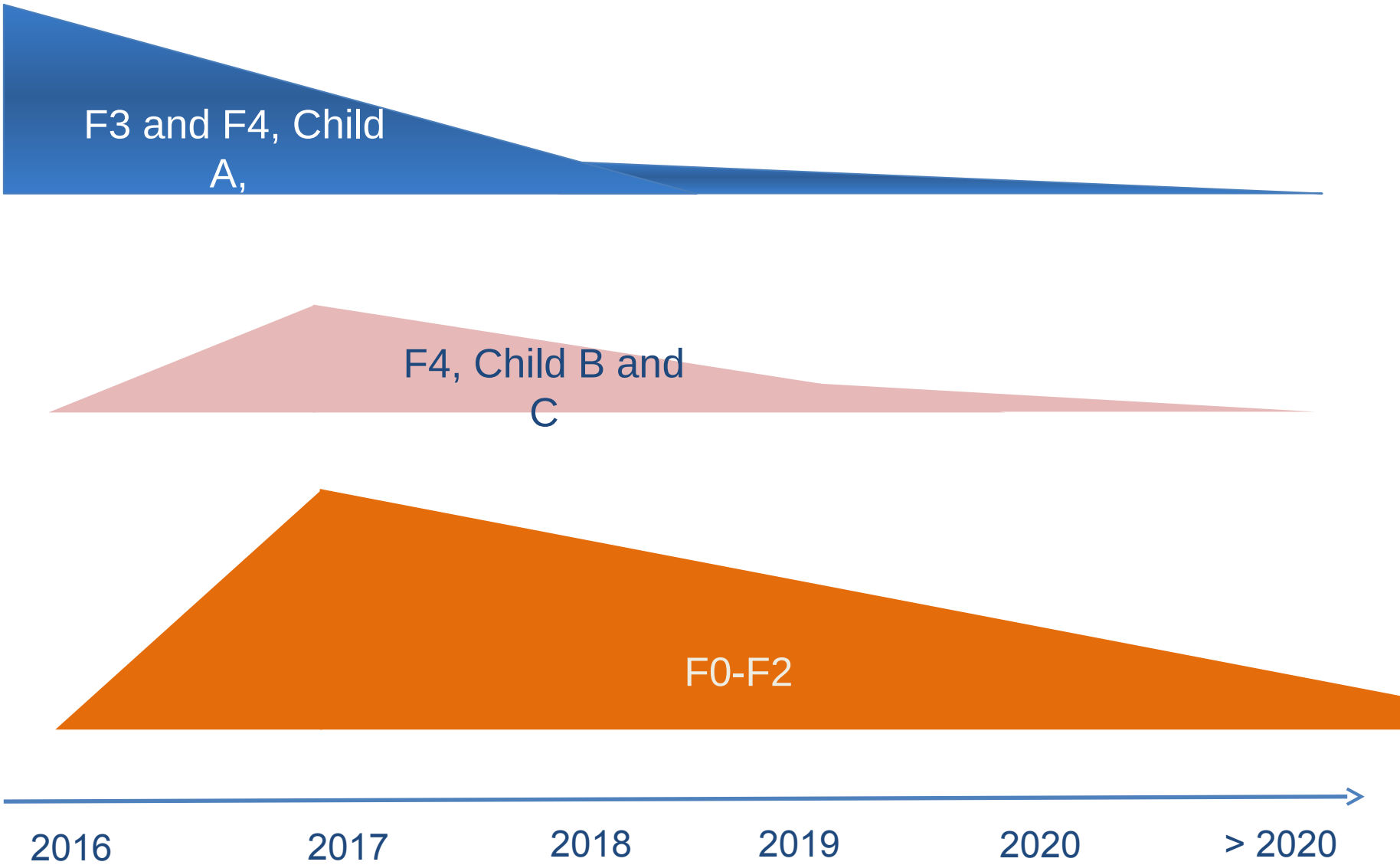
Arun Sanyal PHC 2017

Around the world table : Access to therapy

Western countries

Others countries

The HCV treatment scenario in Italy



Antonio Craxi PHC 2017

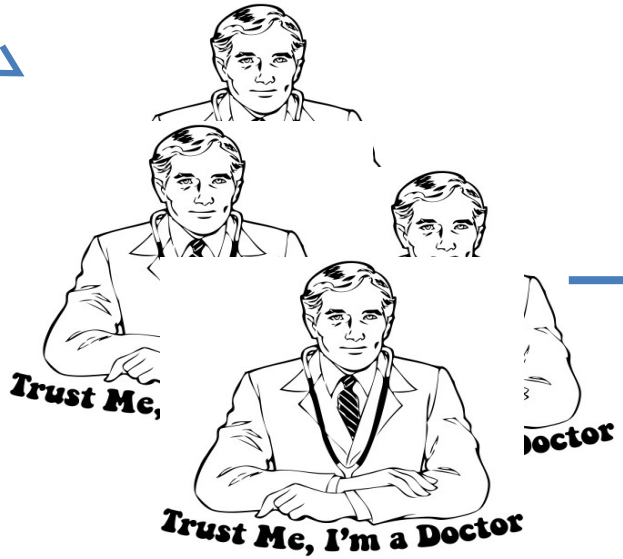
Specialist Commissioning
The HCV Model - Networks

ANY doctor

ANY drug worker

ANY pharmacist

ANY nurse

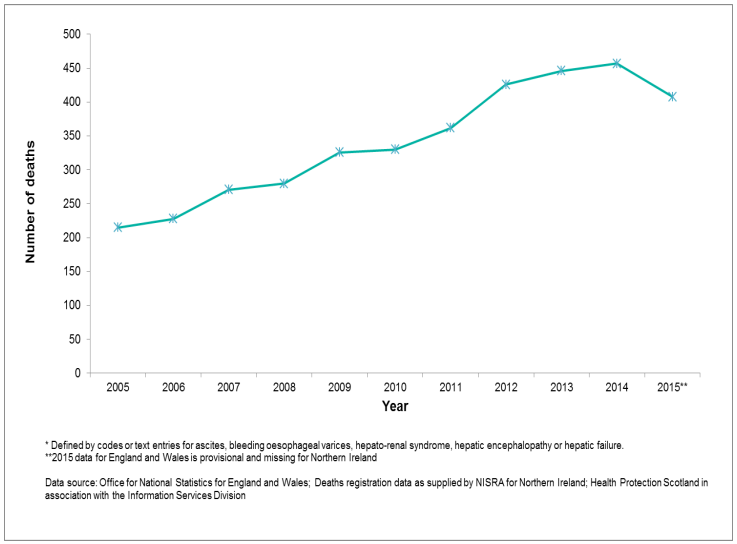


Treatment approved
Delivered locally

22 Regional networks –
Fixed number of treatments
Least acquisition cost drug MUST be used

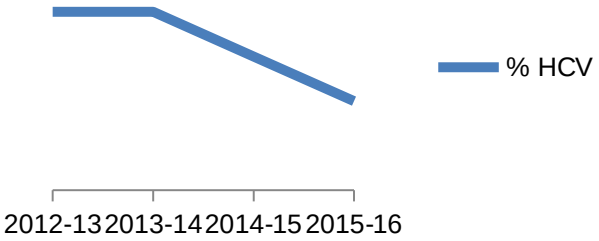
The English Approach - Outcome

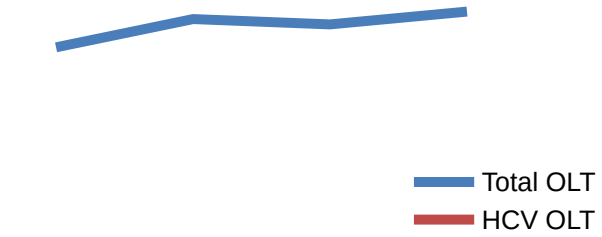
~ 10% of patients treated (12,000)
90% + SVR
Within budget

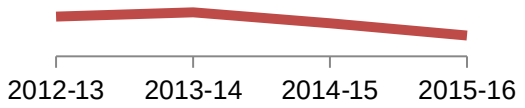


Deaths from HCV or HCC
in patients with HCV
(PHE report on HCV 2016)

% HCV



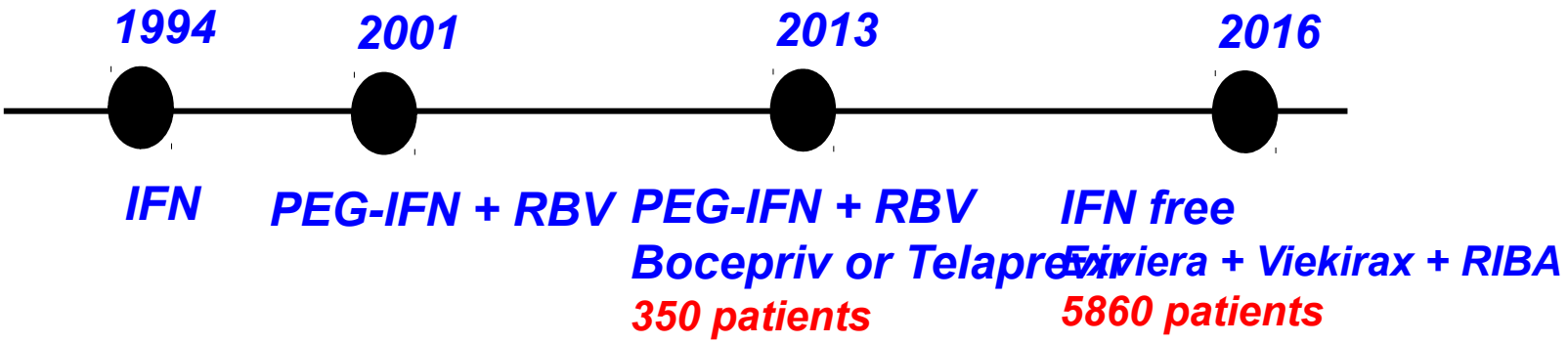




Transplants for HCV

The English Approach
Next steps

- Most centres are now running out of patients
- ‘Trace & Treat’ strategies are being evaluated in immigrants, drug users and prisons
- The next phase of the programme will be driven by the networks



1994 ⟶ starts INF therapy: 4.000 patients

2001 ⟶ starts PEG INF + RIBA: 26.000 patients / 10 years

2013 – 350 patients treated on compassioned bases with I generation PI

2016 – Start the IFN free therapy with Exviera and Viekirax on a cost-volume-efficacy based contract of The National Health Insurance House with Abvie Company for initially 5000 patients/year, with advanced fibrosis –F4 – compensated cirrhosis. Preliminary data assess that 99% of these patients have SVR.

2017 We expect very soon the new contract cost-volume-efficacy for to extend the indication to F3 and F2 with co-morbidities.

The Future of research on viral hepatitis

- A long way to go for global implementation of even current advances
- More work to be done on known viruses: HAV, HBV/HDV, HCV, HEV
- There will be surprises and new challenges
- Getting rid of the viruses isn't necessarily the end game
- Many unanswered questions in pathogenesis mechanisms
- Fundamental research and knowledge provide readiness for future challenges
- Clinicians—please support basic and clinical research!

Thank you for your attention