

Hepatitis C virus: a success story for modern medicine

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Chair, National Strategy Group for Viral Hepatitis

Hepatitis C **virus**: a success story for modern medicine: Some definitions

- Virus: an infectious agent, on the borders of life – only “comes alive” when inside a cell

Hepatitis C virus: a success story for modern medicine: Some definitions

- “Hepar” = Liver
- “itis” = Inflammation

- Inflammation of the liver: Top causes in the UK:
 - 1) Alcohol-mediated
 - 2) Fatty liver disease Obesity-related
 - 3) Viruses

Liver disease is important!

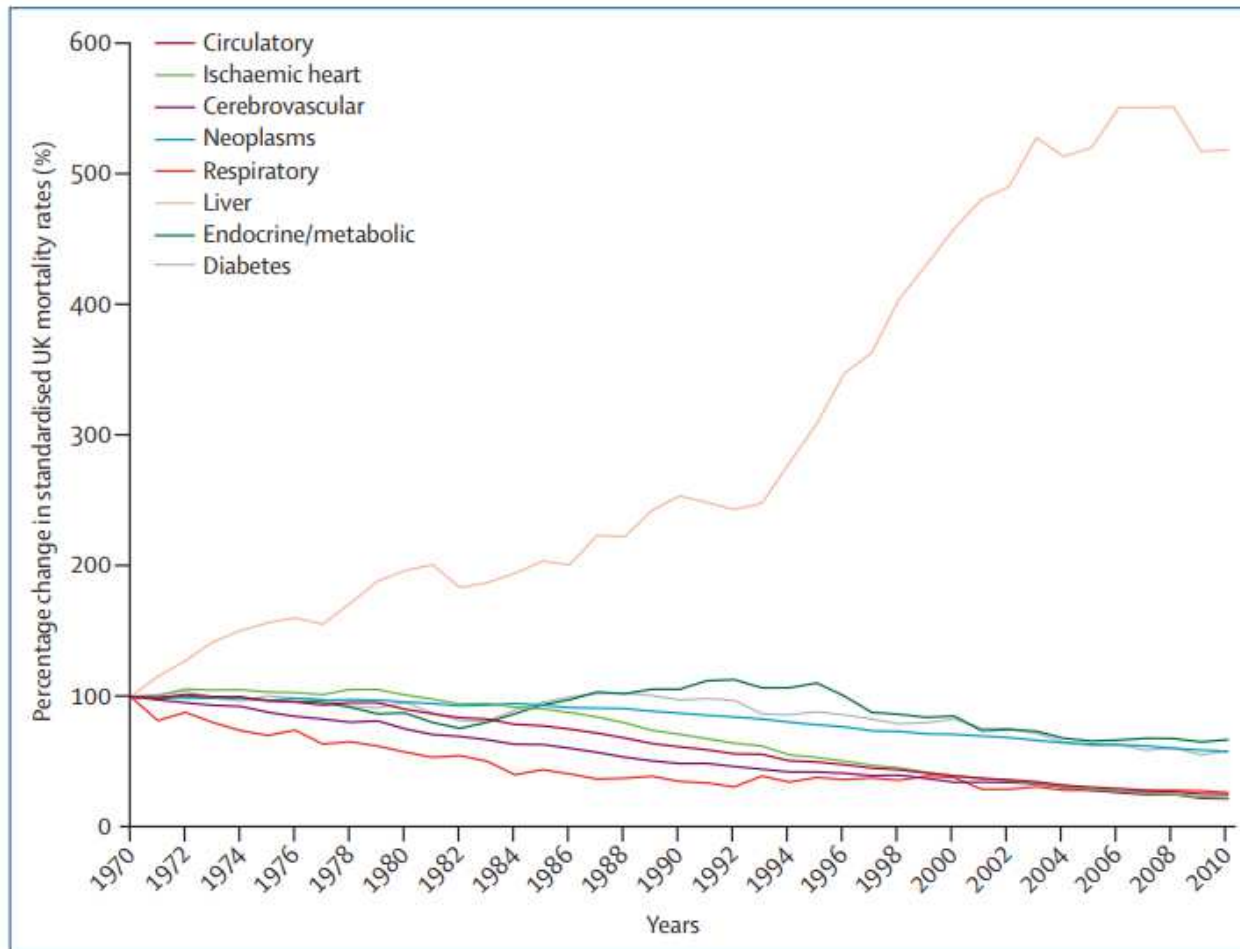
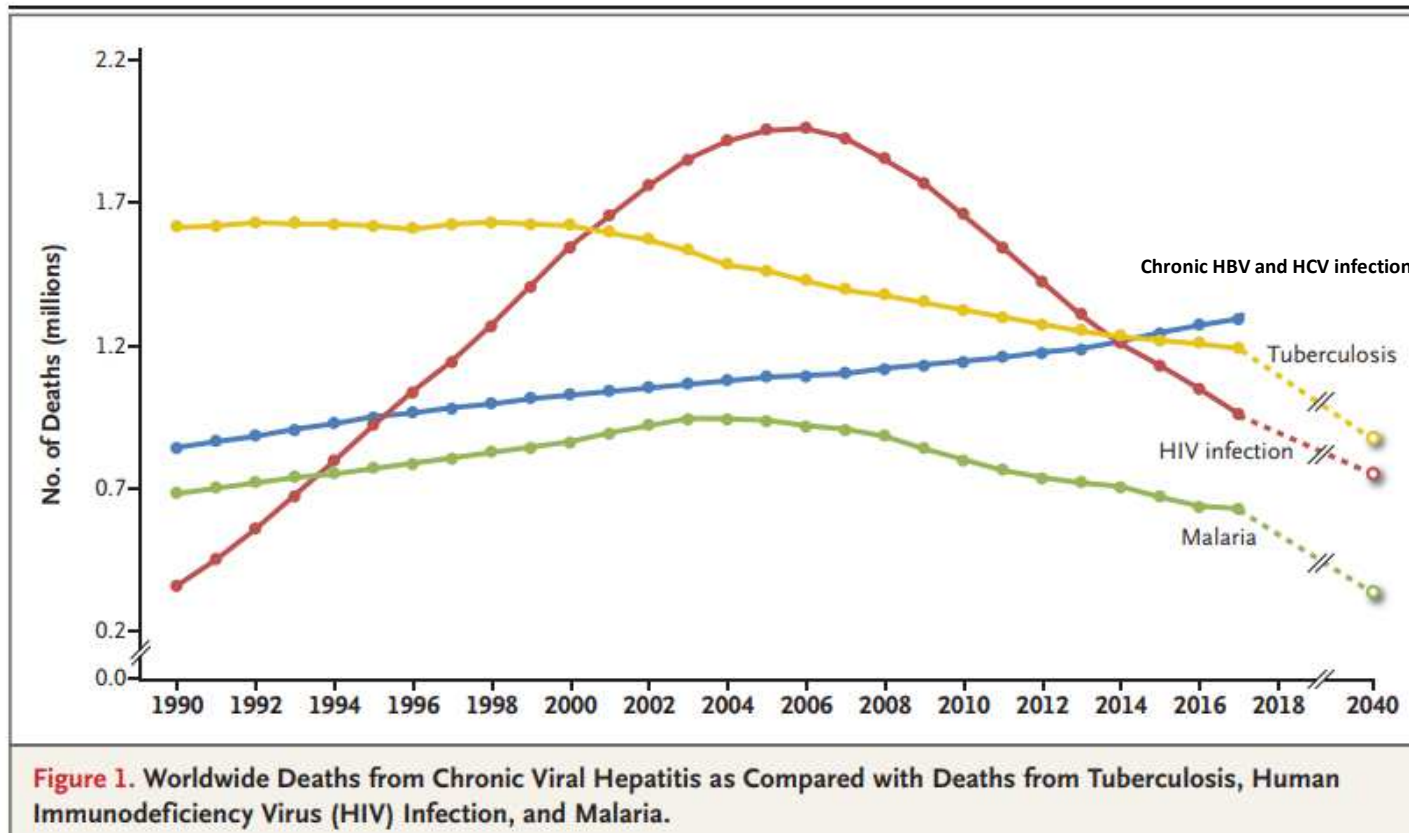


Figure: Percentage change in standardised UK mortality rates (age 0-64 years) normalised to 100% in 1970

Viral hepatitis is important!



Thomas DL. New England Journal of Medicine 2019; 380: 2041-50

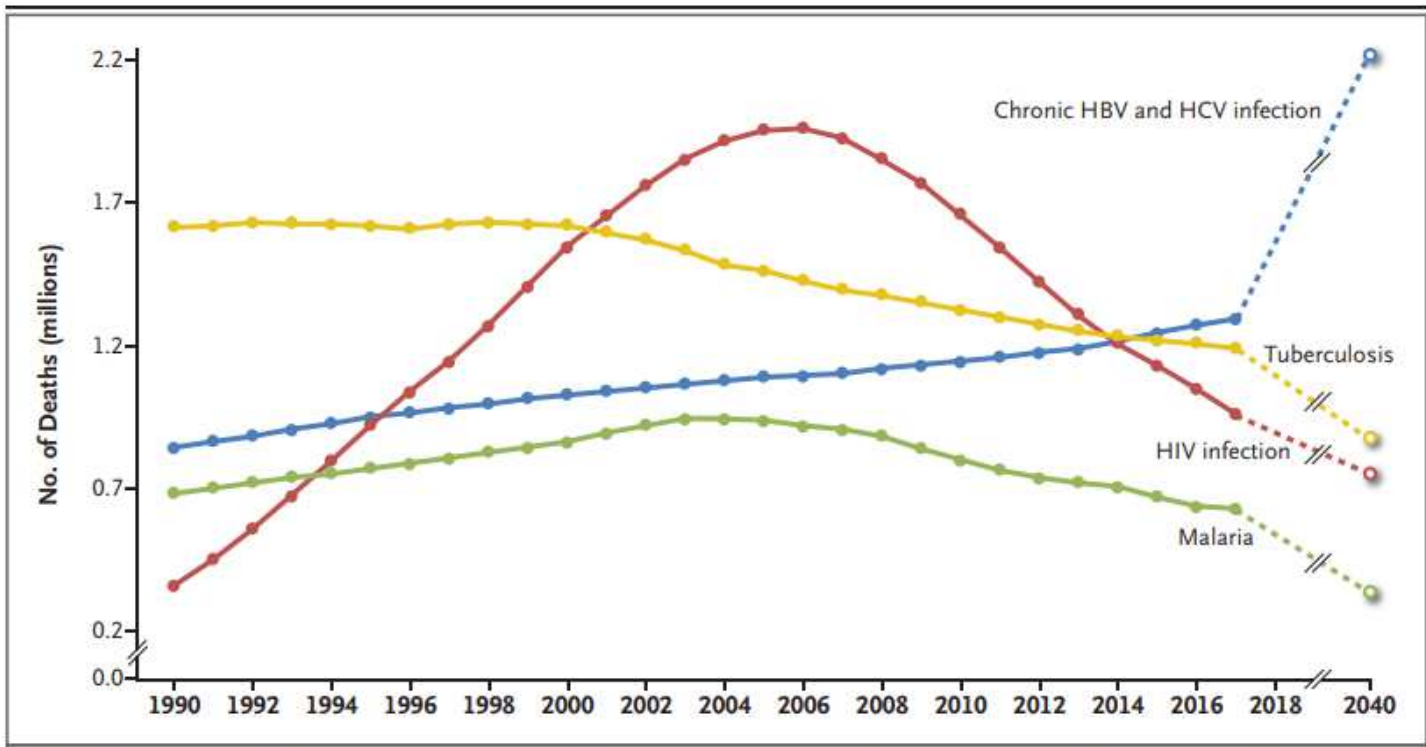


Figure 1. Worldwide Deaths from Chronic Viral Hepatitis as Compared with Deaths from Tuberculosis, Human Immunodeficiency Virus (HIV) Infection, and Malaria.

Thomas DL. New England Journal of Medicine 2019; 380: 2041-50

Hepatitis C virus: a success story for modern medicine: Some definitions

Causes of viral hepatitis

Hepatitis A virus

Hepatitis B virus

Hepatitis C virus

Hepatitis D virus

Hepatitis E virus

~~Hepatitis F virus~~

Doesn't exist

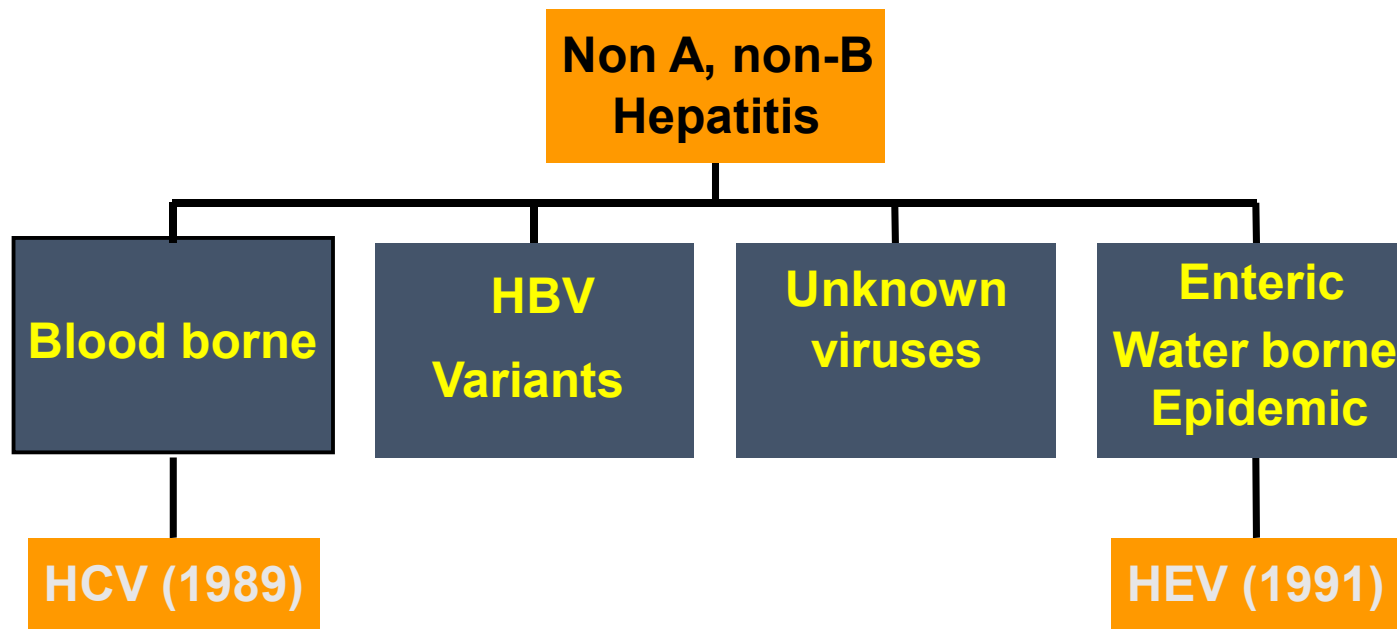
~~Hepatitis G virus~~

Doesn't cause hepatitis

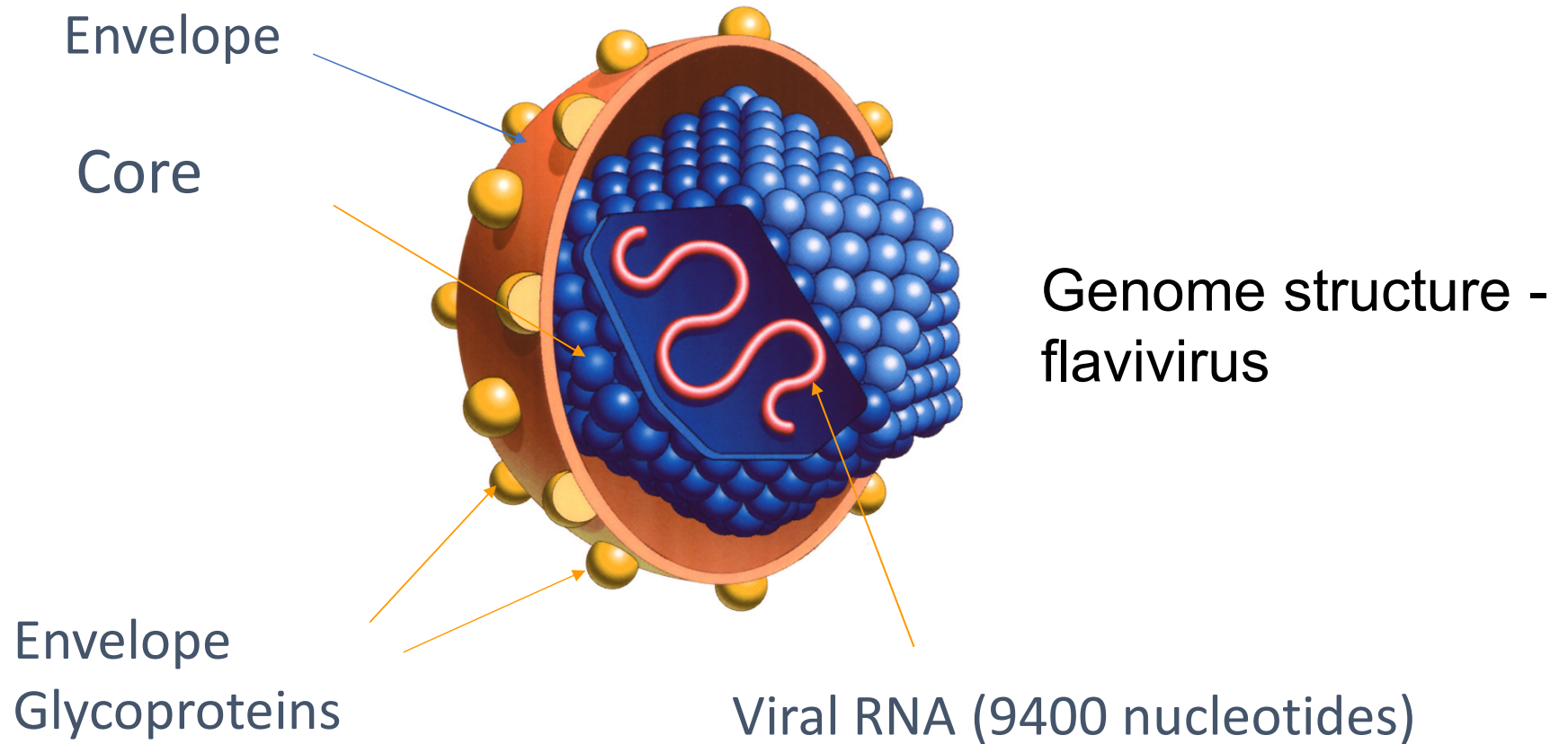
1970s Hepatitis A (water-borne) and Hepatitis B (blood-borne) viruses characterised
Non-A, non-B hepatitis recognised; hunt for NANB viruses was on

**Non A, non-B
Hepatitis**

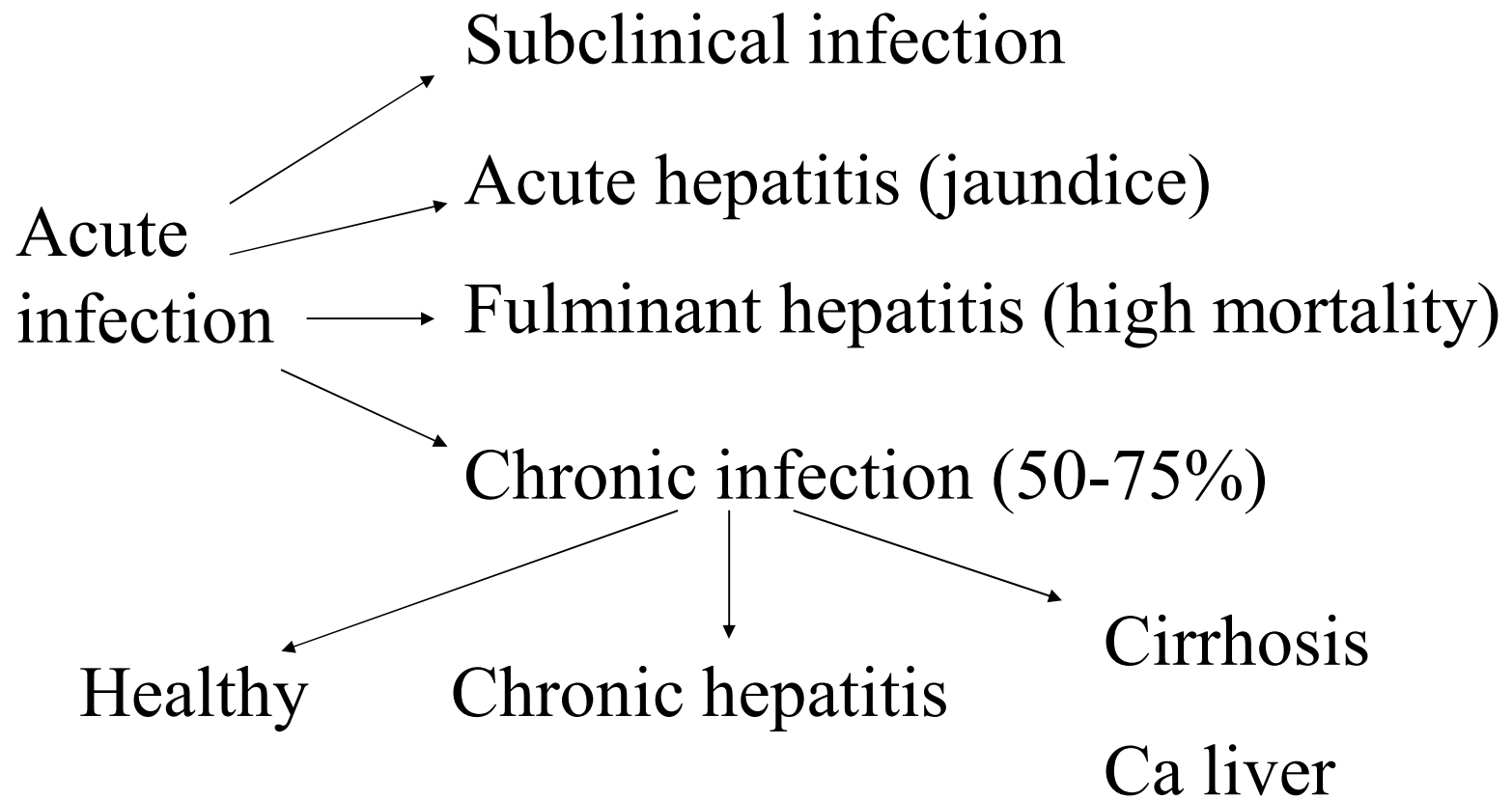
1970s Hepatitis A (water-borne) and Hepatitis B (blood-borne) viruses characterised
Non-A, non-B hepatitis recognised; hunt for NANB viruses was on



Hepatitis C Virus (HCV)



Natural History of HCV Infection



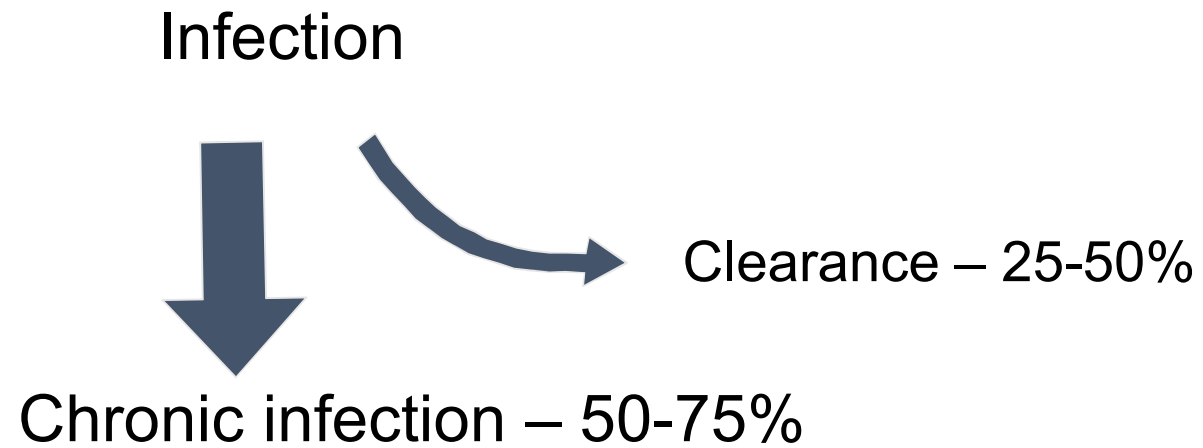
Cirrhosis of the liver



Cirrhotic liver with a hepatocellular carcinoma

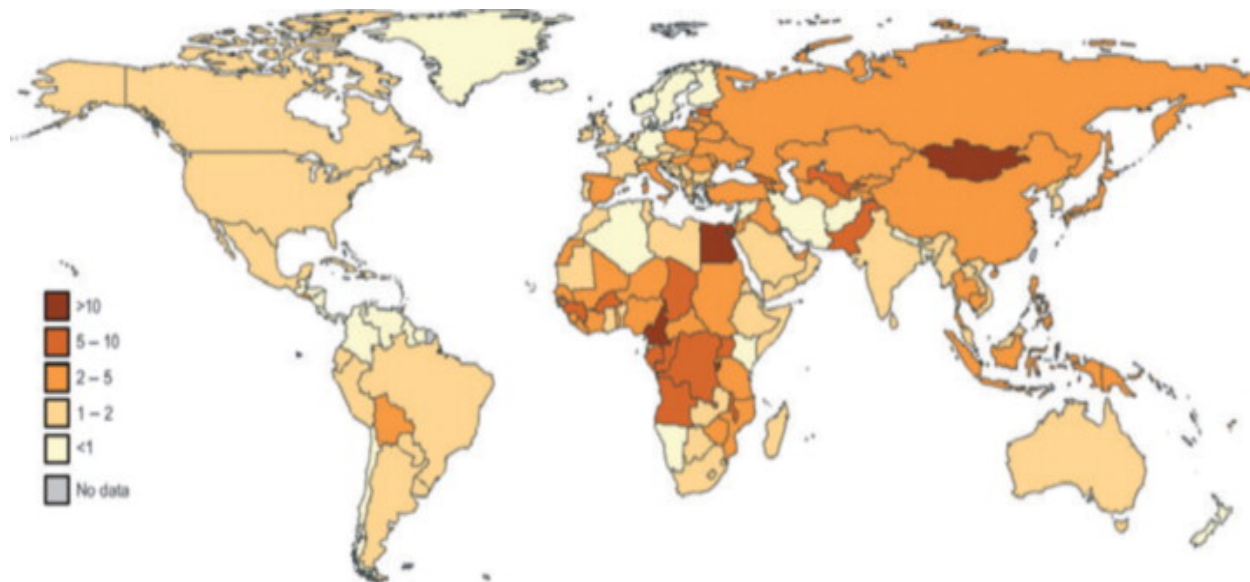


HCV: Natural History



Hepatitis C virus: routes of transmission

- HCV is a blood-borne virus (BBV)
 - Injecting drug use
 - Blood/blood products (hence the Infected Blood Inquiry)
 - Other needles e.g. acupuncture, tattoo, needles for medical use
- Mother-to-baby (1-5%)
- Sexual (?real)



The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt

Christina Frank, Mostafa K Mohamed, G Thomas Strickland, Daniel Lavanchy, Ray R Arthur, Laurence S Magder, Taha El Khoby, Yehia Abdel-Wahab, El Said Aly Ohn, Wagida Anwar, Ismail Sallam

The origin of the epidemic has been attributed to mass campaigns of intravenous schistosomiasis treatment in rural areas in the 1960s to 70s [Frank et al., 2000]. Treatment consisted of several (up to 12) intravenous injections of tartar emetic administered in weekly doses to anyone living in schistosomiasis-endemic areas, and particularly children and young boys treated while at school. Evidence suggests that HCV transmission occurred due to insufficient sterilization of injection equipment between patients. This mode of HCV trans-

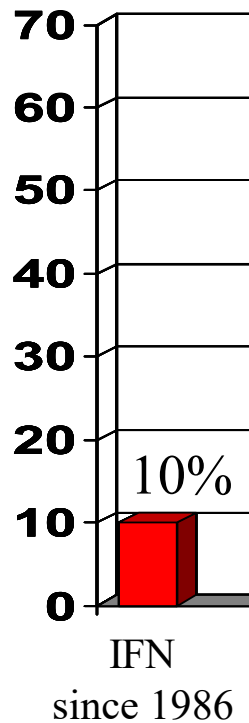


Treatment of hepatitis C

Treatment of Hepatitis C

Sustained Virologic Response (SVR): undetectable HCV infection 3 months after the end of treatment = cure

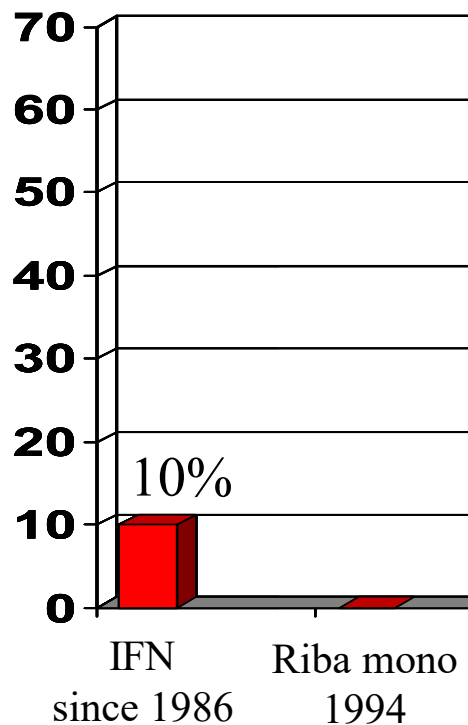
% of patients achieving SVR (cure)



IFN = Interferon

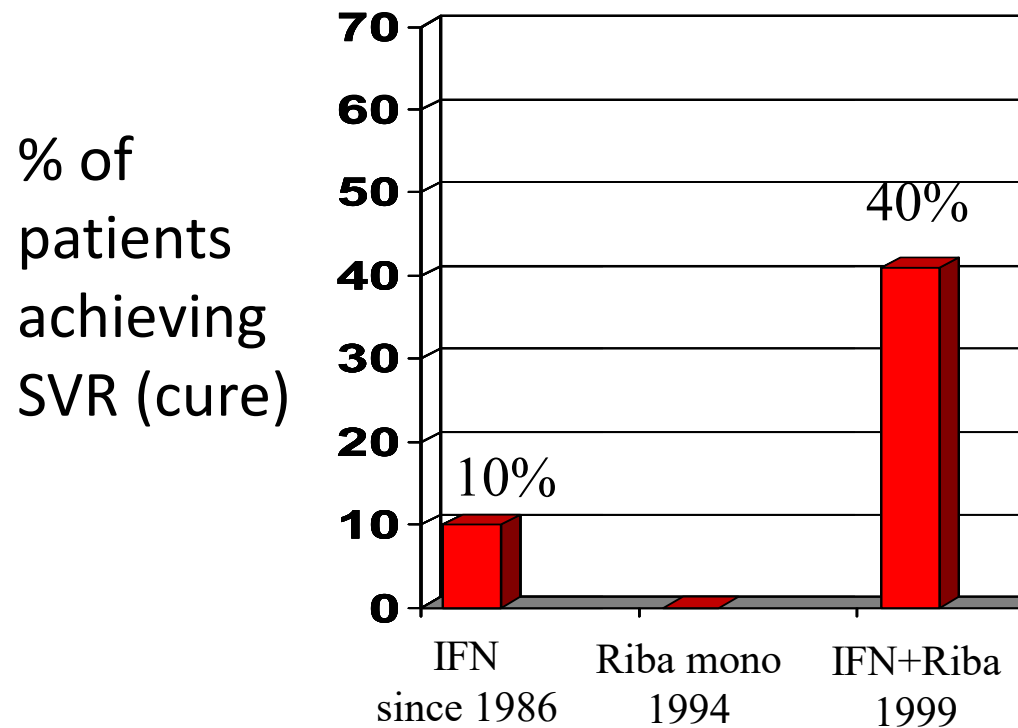
Treatment of Hepatitis C

% of patients achieving SVR (cure)



Riba = Ribavirin, an antiviral drug, mechanism of action unclear

Treatment of Hepatitis C



[IFN]

Concentration
of IFN in
blood stream

Monday

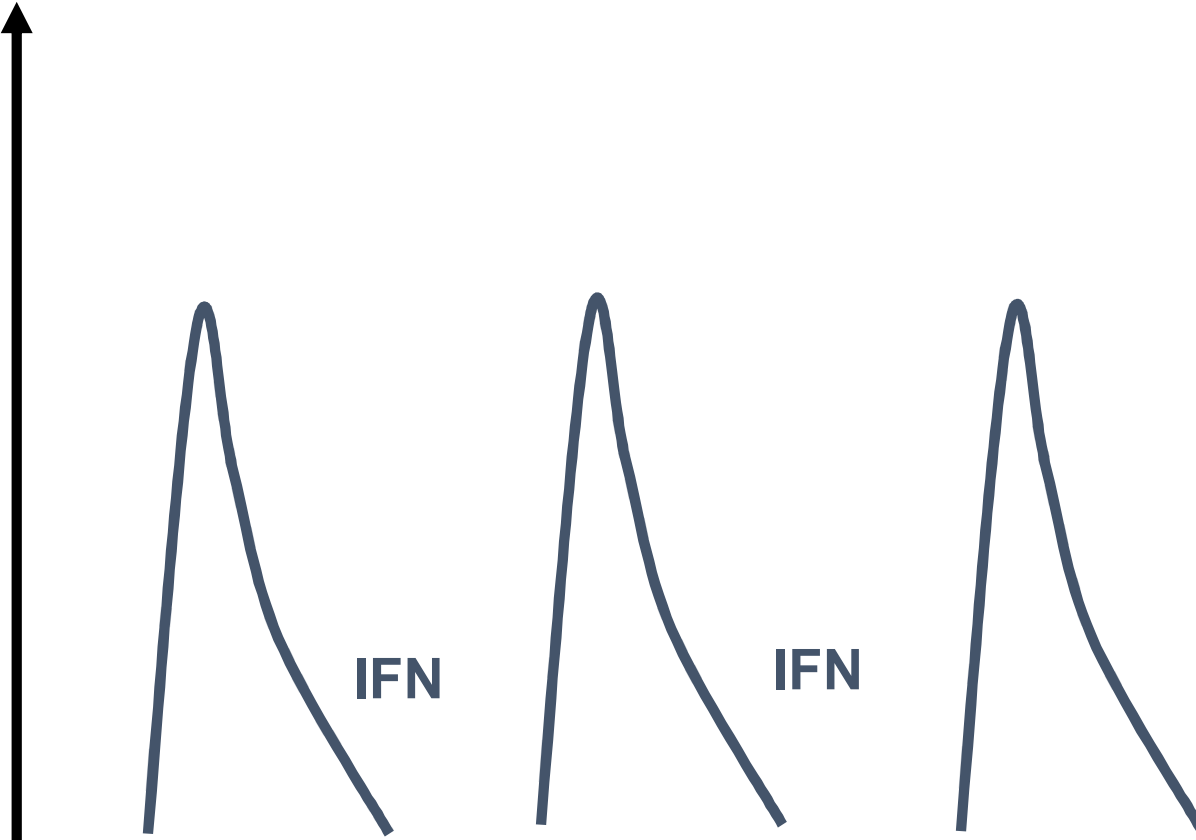
Wednesday

Friday

IFN

IFN

IFN

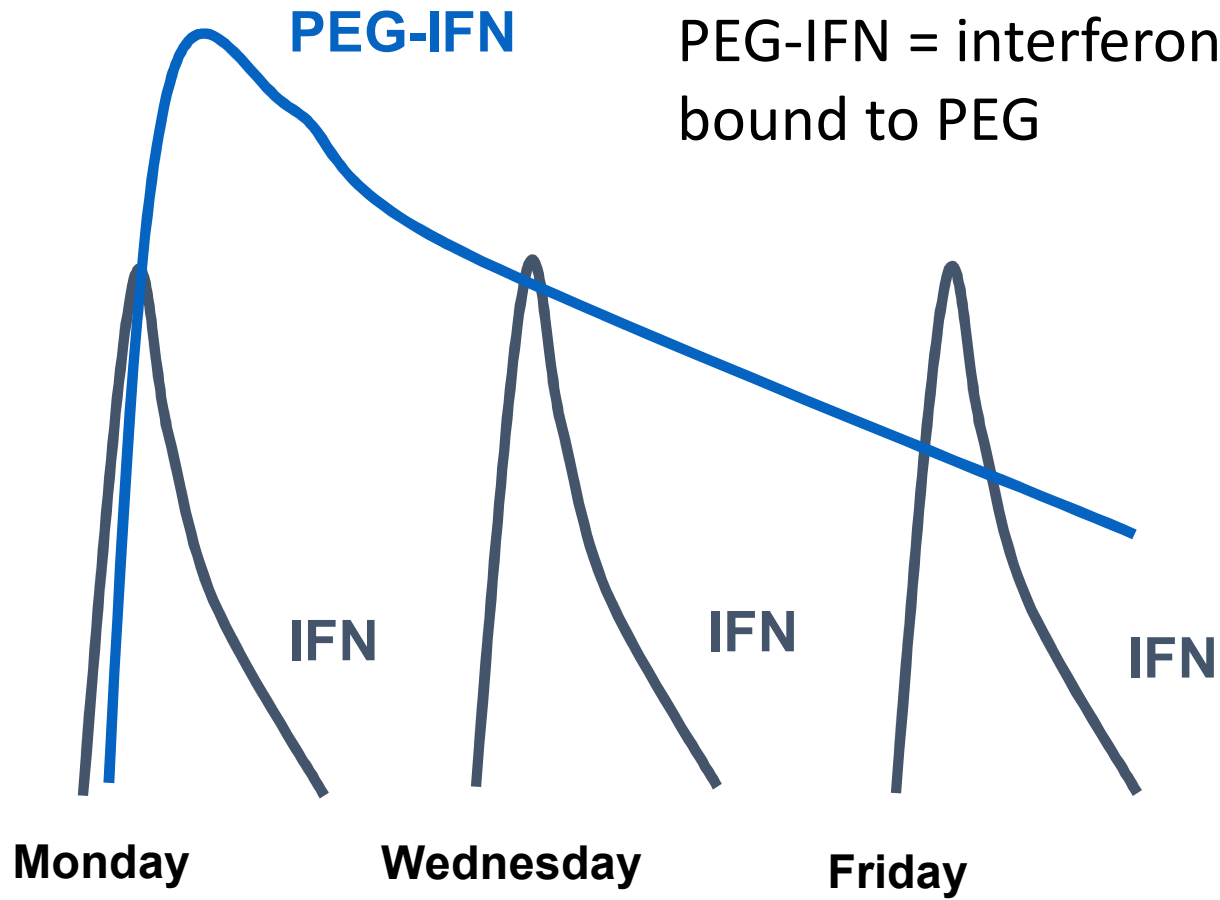


[IFN]

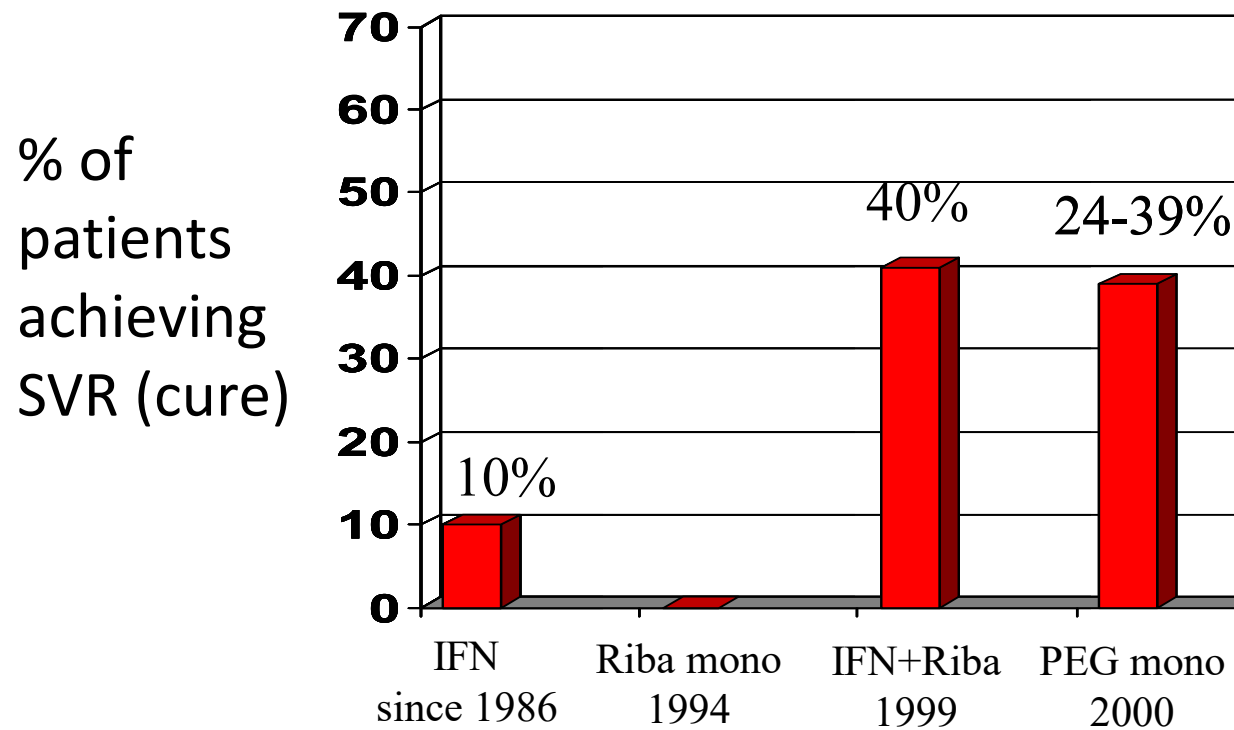
PEG = Polyethylene glycol

PEG-IFN = interferon chemically bound to PEG

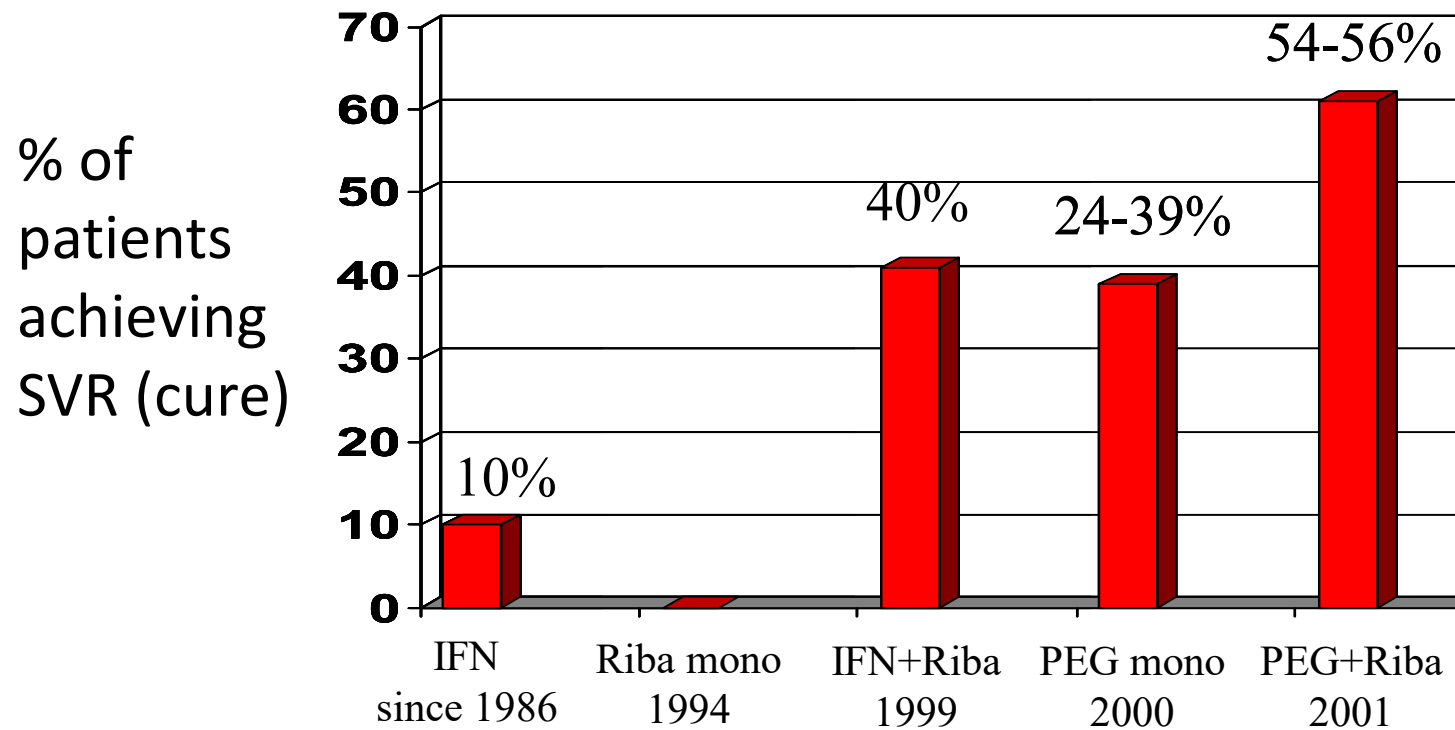
Concentration of IFN in blood stream



Treatment of Hepatitis C



Treatment of Hepatitis C



HCV

NS = Non-structural

NS5 encodes 2 proteins
NS5a and NS5b

NS3 is a
protease
enzyme

NS5a helps
viral
assembly

NS5b is the
RNA
polymerase
enzyme



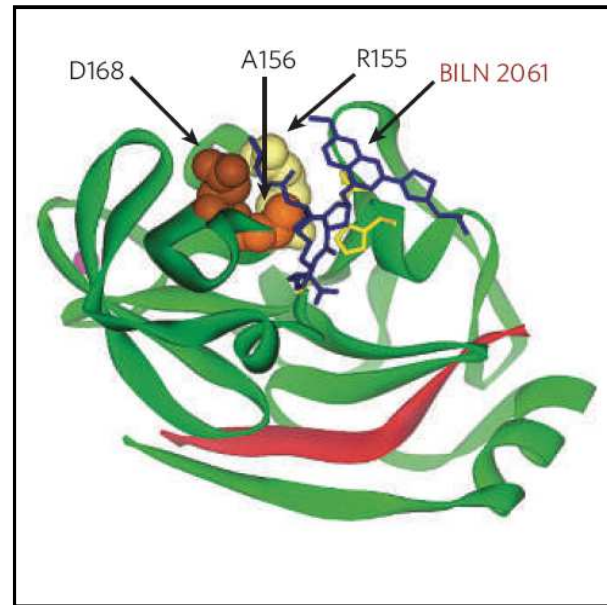
**STRUCTURAL
GENES**

**NON-STRUCTURAL
GENES**

Directly-Acting Antiviral Agents (DAAs): Designer Drugs

Viral proteins
crystallised and their
3-dimensional
structure worked out

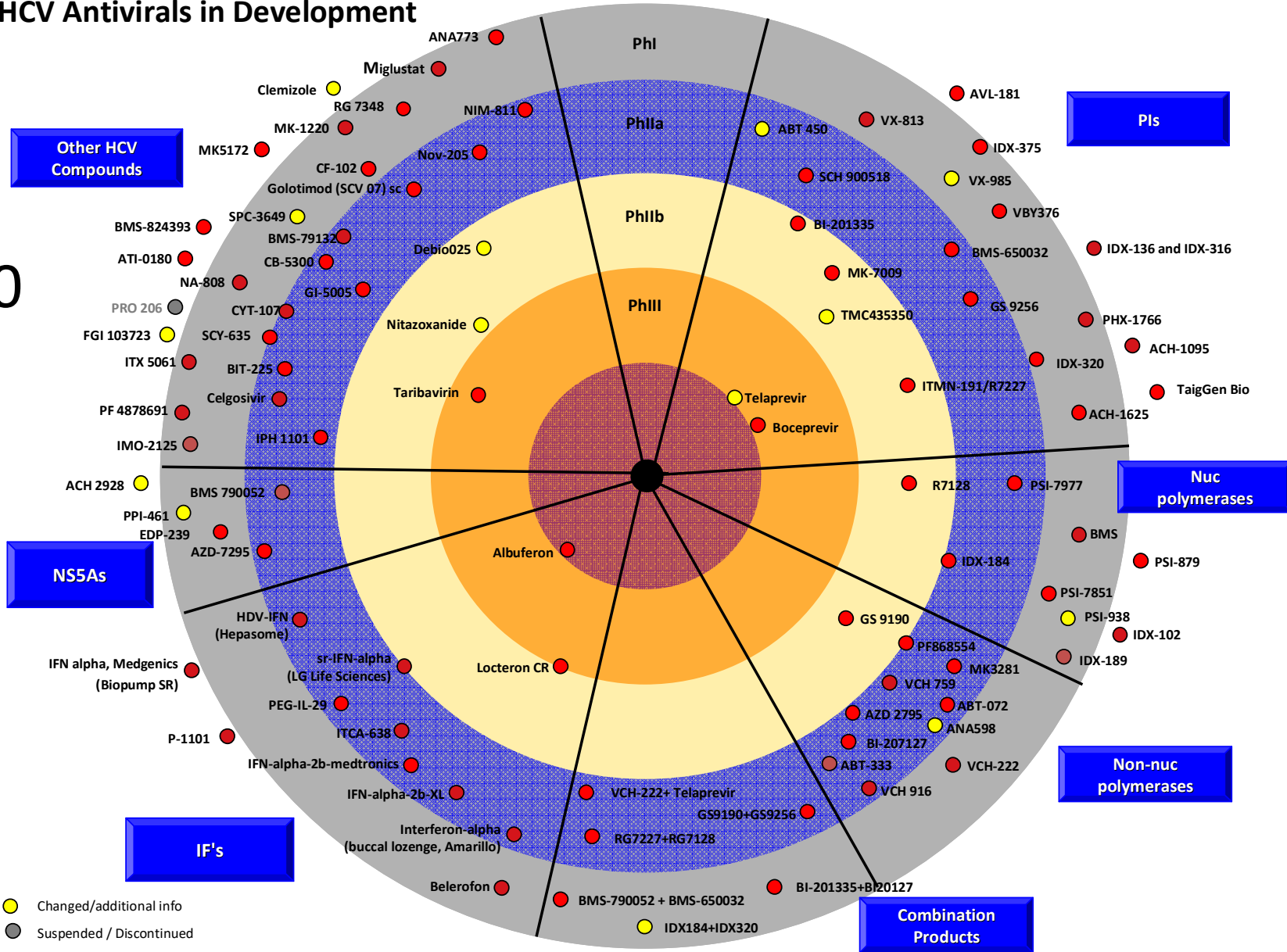
Drugs then designed
to bind to the
structure and inhibit
function



Protease inhibitor BILN-2061 targets the enzyme active site

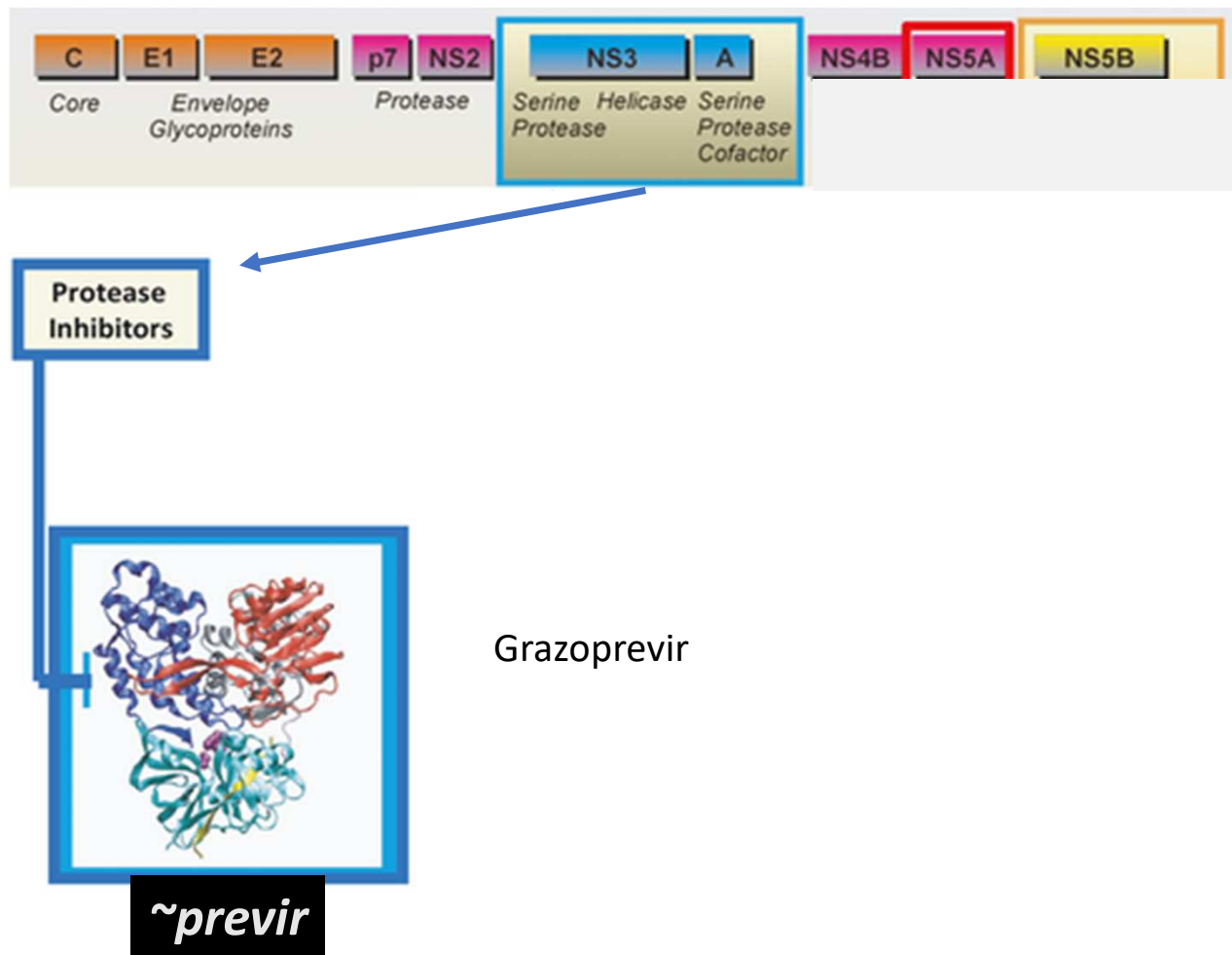
HCV Antivirals in Development

In 2010

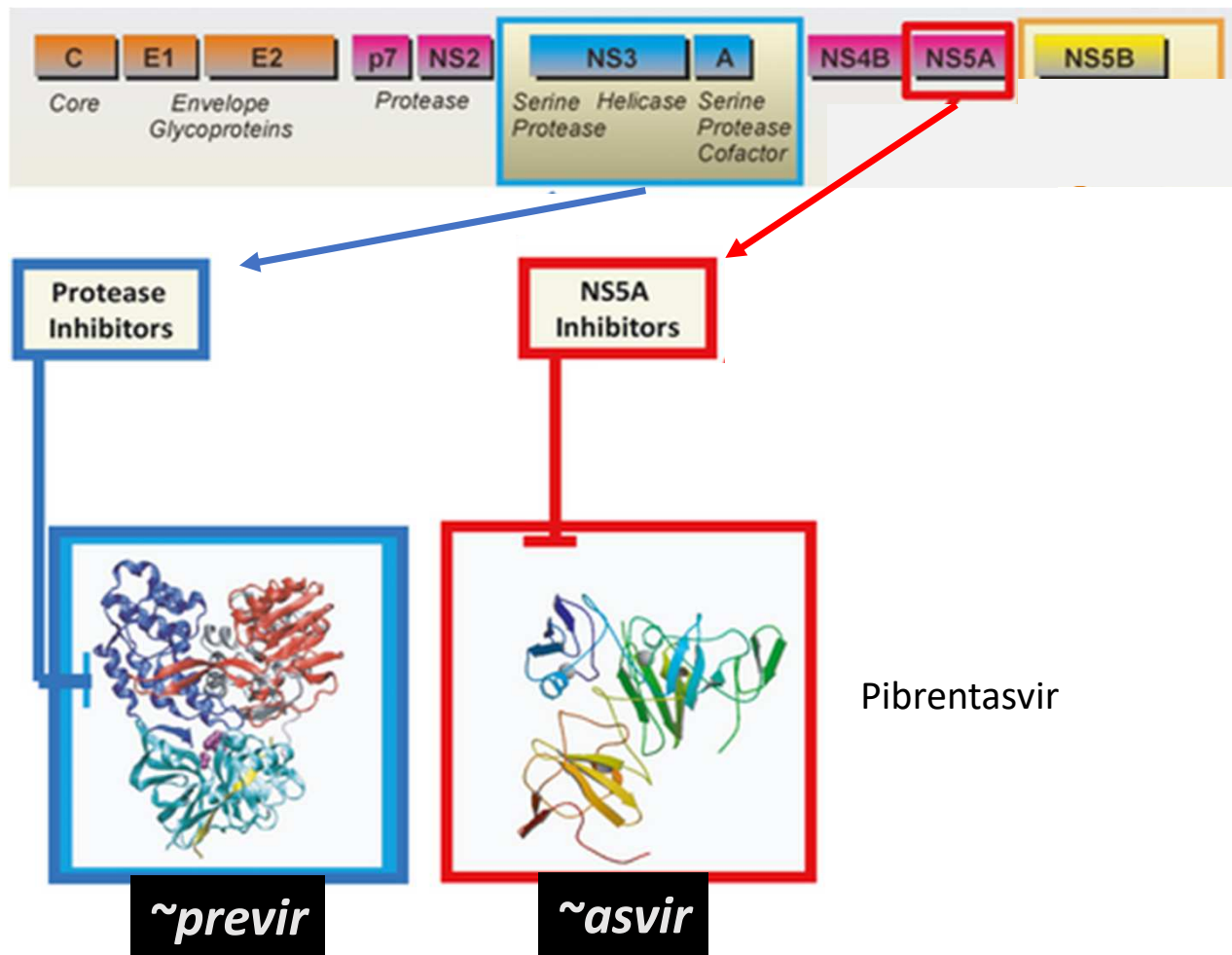


Sources: GBI Analysis (August 4, 2010), Pipeline Sources, Company Press Releases, Reuters Knowledge Analyst Reports

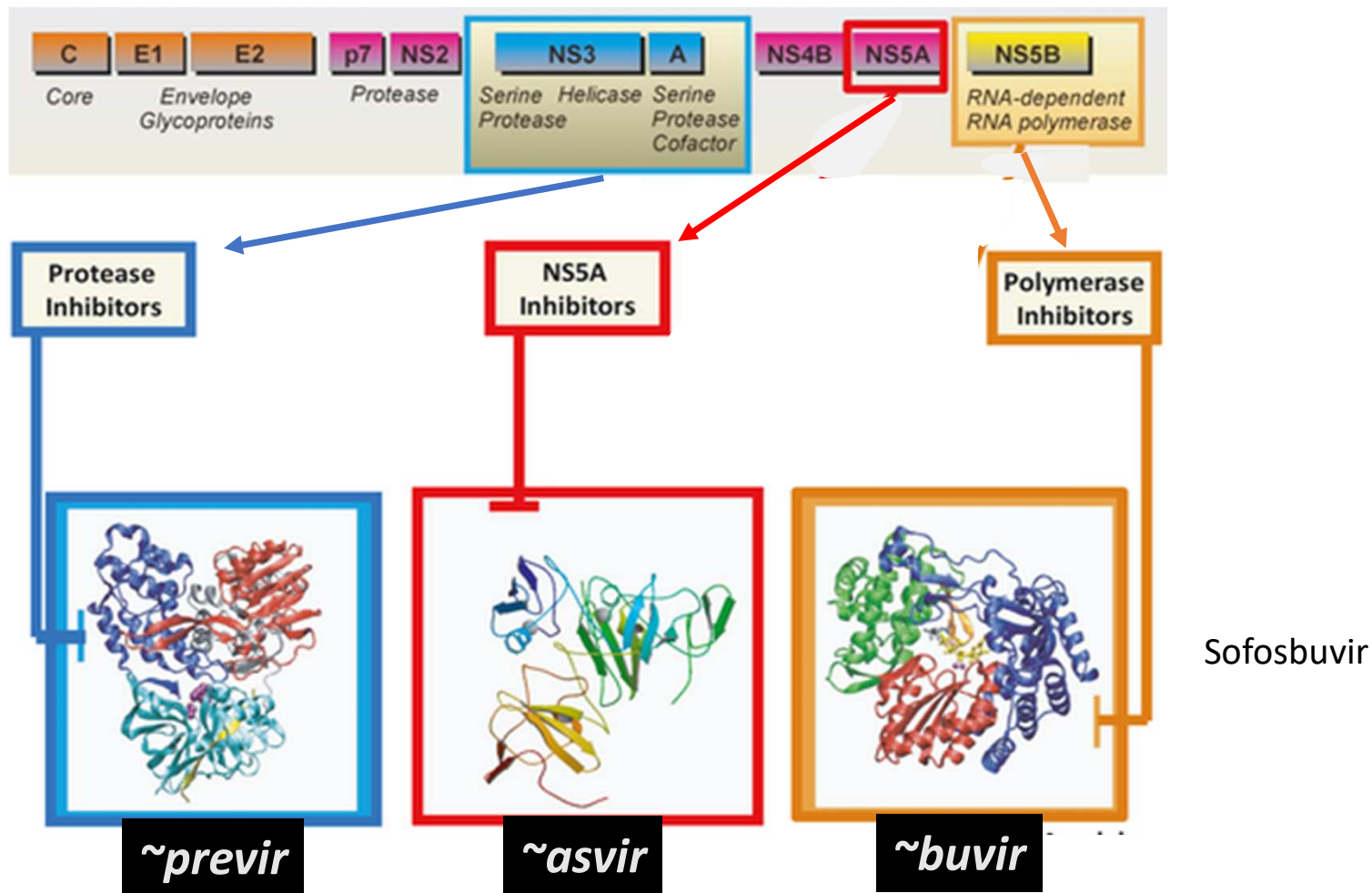
Different classes of direct acting antiviral agents (DAA)



Different classes of direct acting antiviral agents (DAA)



Different classes of direct acting antiviral agents (DAA)



ORIGINAL ARTICLE

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Ledipasvir and Sofosbuvir for Chronic HCV Genotype 1

Treatment of HCV with ABT-450/r–Ombitasvir and Dasabuvir with Ribavirin

Nezam Afdhal, M.D., Stefan Zeuzem, M.D., Paul Norman Gitlin, M.D., Massimo Puoti, M.D., Manuel Romero-Gomez, M.D., Ph.D.

Jordan J. Feld, M.D., M.P.H., Kris V. Kowdley, M.D., Eoin Coakley, M.D.,

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

ESTABLISHED IN 1812

APRIL 17, 2014

Ledipasvir and Sofosbuvir for Prevalent Genotype 1 Infection

Retreatment of HCV with ABT-450/r–Ombitasvir and Dasabuvir with Ribavirin

Nezam Afdhal, M.D., K. Rajender Reddy, M.D., David R. Nelson, M.D.,

Stefan Zeuzem, M.D., Ira M. Jacobson, M.D., Tolga Baykal, M.D.,

ORIGINAL ARTICLE

ORIGINAL ARTICLE

Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis

ABT-450/r–Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis

Kris V. Kowdley, M.D., Stuart C. Gordon, M.D., K. Rajender Reddy, M.D.,

Fred Poordad, M.D., Christophe Hezode, M.D., Roger Trinh, M.D., M.P.H.,

Lorenzo Burgaz, M.D., David E. Bernstein, M.D., Eric Lewitz, M.D.

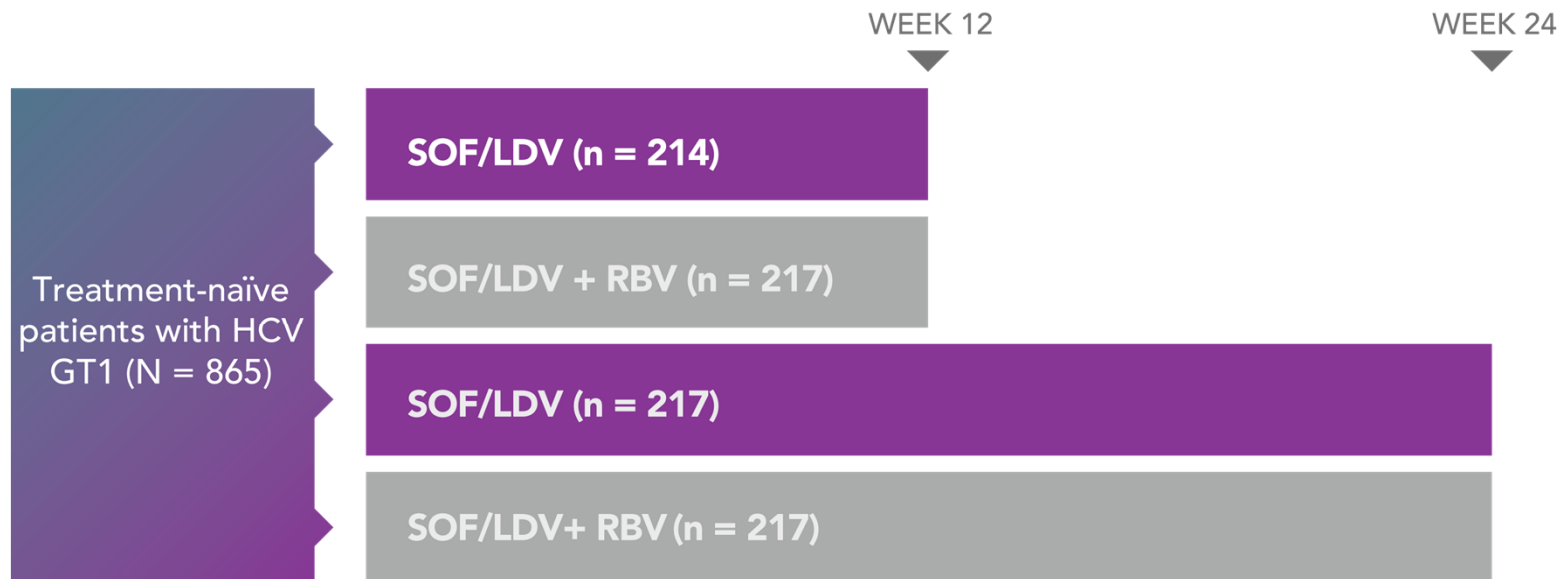
Kris V. Kowdley, M.D., Stefan Zeuzem, M.D., Mark A. Aronoff, M.D.,

Study Design – ION-1¹

Randomised clinical trial in treatment-naïve patients with HCV infection

Primary endpoint: How many patients achieve SVR when tested 12 weeks after end of therapy?

SOF = Sofosbuvir; LDV = Ledispavir; SOF/LDV = Harvoni RBV = Ribavirin



ION-1

Cure
rate

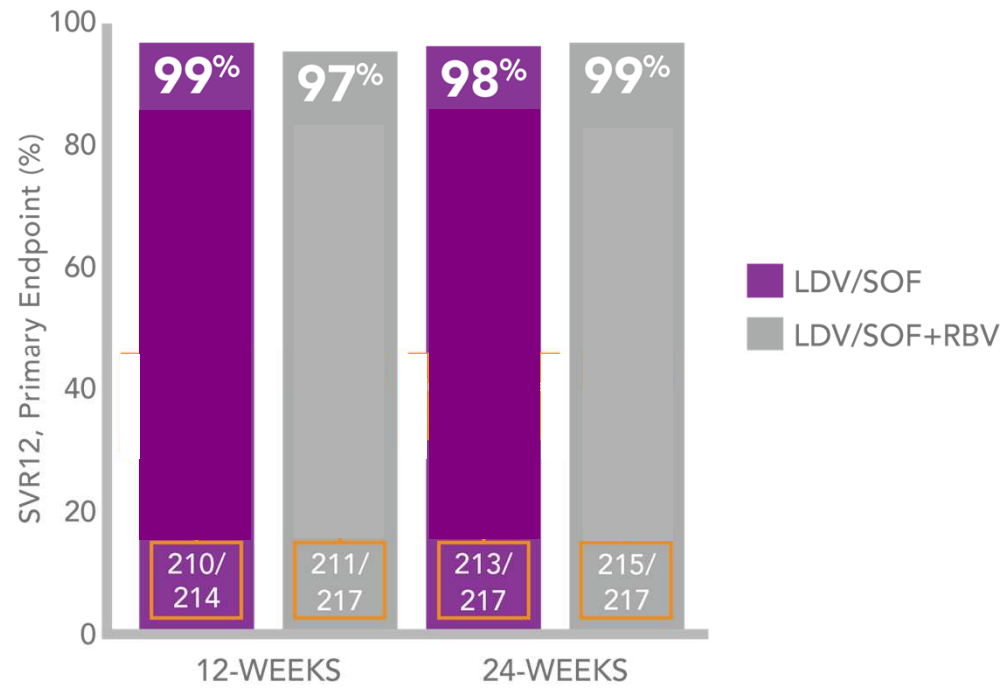
■ LDV/SOF
■ LDV/SOF+RBV

12-WEEKS

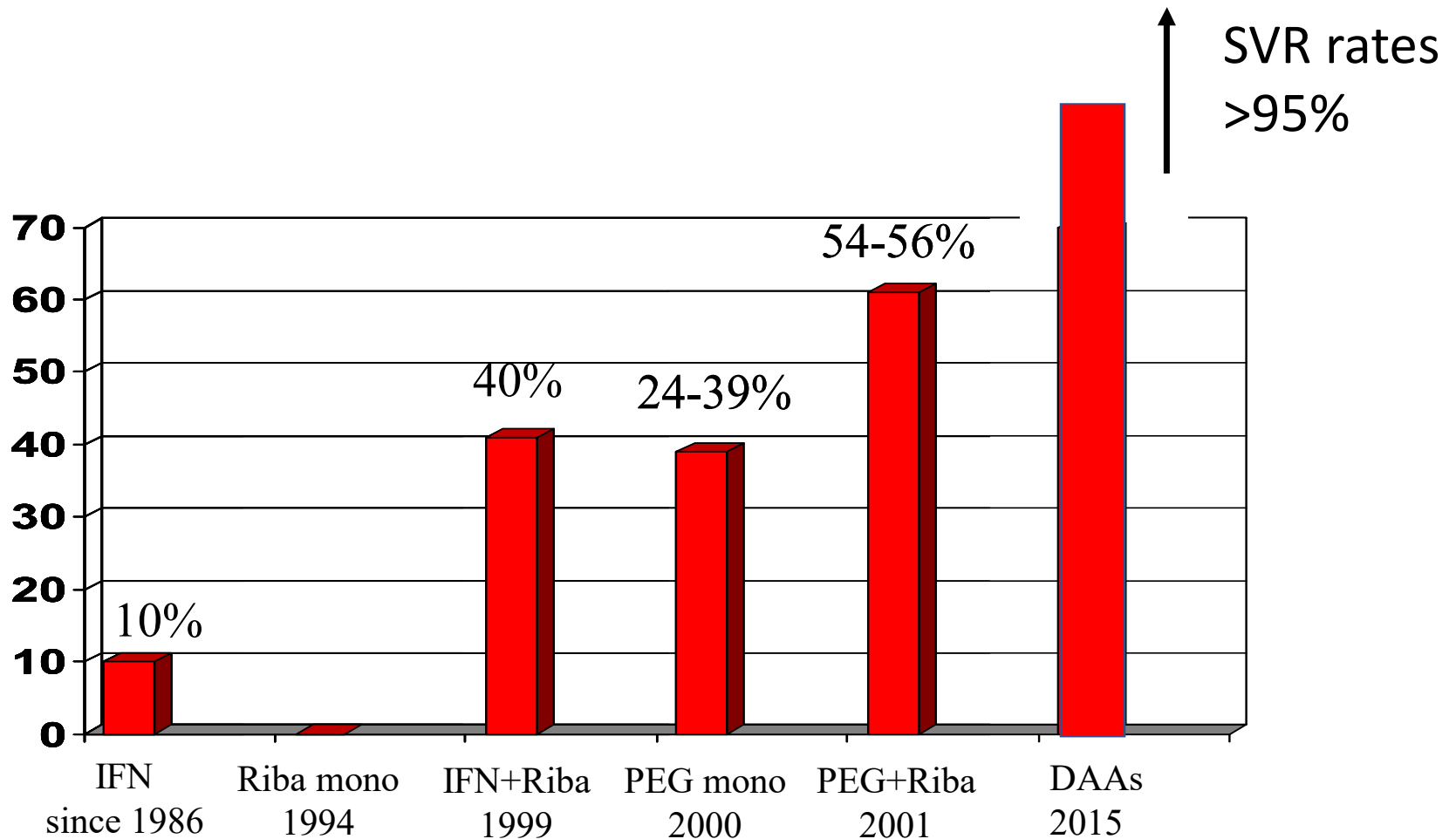
24-WEEKS

ION-1

Cure
rate



Treatment of Hepatitis C



Hoofnagle et al. NEJM 1986

McHutchison et al., NEJM 1998

Manns et al., Lancet 2001

Brillanti et al. Gastroenterology 1994

Zeuzem et al., NEJM 2000

Fried et al., NEJM 2002

May 2016:



Make the elimination of viral hepatitis our next greatest achievement

Video animation rallying for the first ever Global Viral Hepatitis Strategy
May 2016 | Video, [duration 01:59]


On 28 May, 194 Member States made a historic commitment to eliminate viral hepatitis by 2030. At the 69th World Health Assembly, governments unanimously voted to adopt the first ever Global Viral Hepatitis Strategy, signalling the greatest global commitment in viral hepatitis to date. The Strategy sets a goal of eliminating hepatitis B and C by 2030 and includes a set of prevention and treatment targets which, if reached, will reduce annual deaths by 65% and increase treatment to 80%, saving 7.1 million lives globally by 2030.

<https://www.who.int/hepatitis/news-events/ghss-hepatitis-video/en/>



News

NHS England sets out plans to be first in the world to eliminate Hepatitis C

 29 January 2018

Medicine

Patient care

England could be the first country in the world to eliminate Hepatitis C, under ambitious plans announced by the NHS today.

<https://www.england.nhs.uk/2018/01/hepatitis-c-2/>

Definitions: Elimination versus Eradication

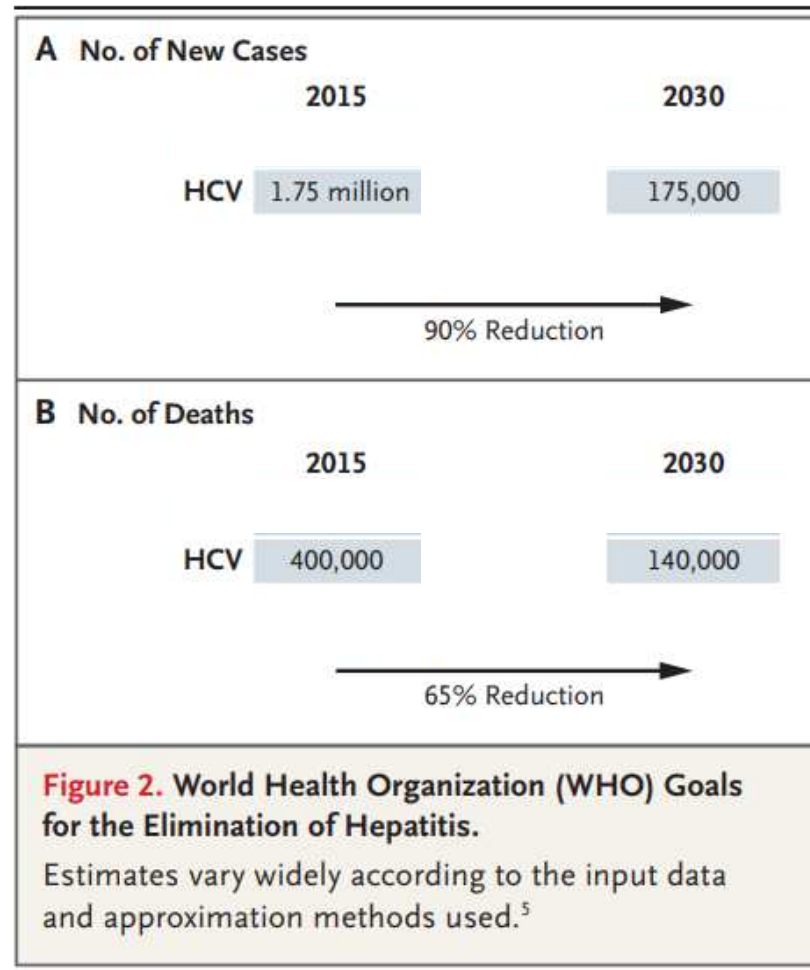
A lesson in WHO-speak

- Eradication: refers to the complete and permanent worldwide reduction to zero new cases of the disease through deliberate efforts.
 - e.g.



A lesson in WHO-speak

- Elimination:
 - As a public health threat
 - Is defined as 90% reduction in incidence and 65% reduction in number of related deaths from a 2015 baseline



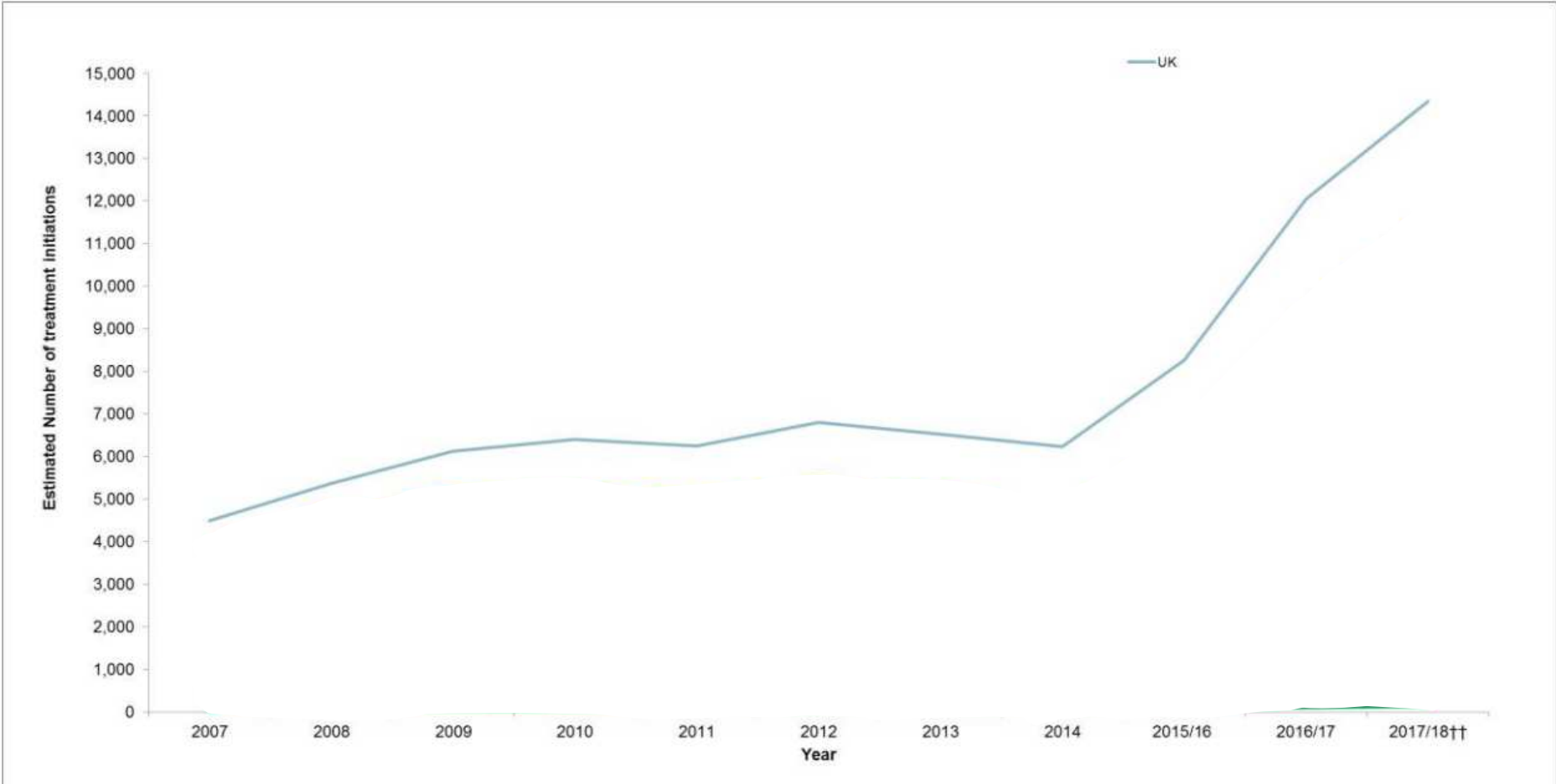
Thomas DL. New England Journal of Medicine 2019; 380: 2041-50

Progress towards elimination of hepatitis C in England

The good news

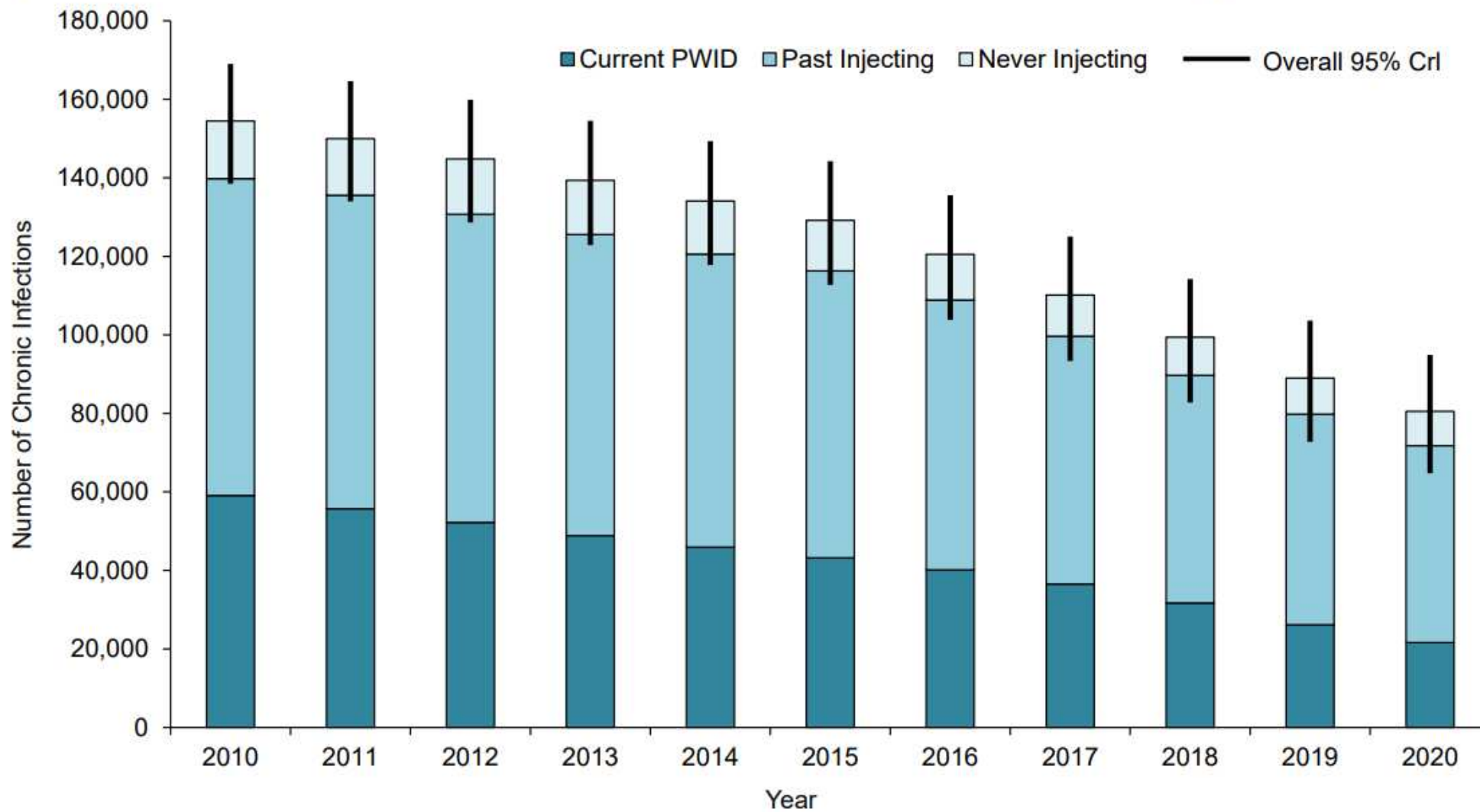
- DAAs cure >95% of patients with chronic HCV infection
- NHSE have committed funding to purchase these DAAs (>£200 million)
- So “all” we have to do is diagnose the infected patients and cure them

Figure 3. UK-wide estimates of numbers initiating HCV treatment, calendar years 2007 to 2014 and financial years 2015 to 2016 – 2017 to 2018^{*,}**



Hepatitis C in the UK 2018 Report (PHE)

Figure 1. Estimates of chronic prevalence of HCV in England, 2010 to 2020 (bars represent 95% CrI) (9)



The bad news (1)

- We don't know who the patients are:
- As of 2020, it is estimated that there are 89,000 individuals in England with chronic HCV infection
- Of these, 30% are diagnosed and therefore “awaiting treatment”
- Therefore 70% are currently undiagnosed

The missing 70%

- Who are they?
 - People who inject drugs (PWID)
 - Ex-PWID
 - Ethnic minority populations
 - Babies of carrier mothers
 - Sexual partners of PWID
 - Blood/blood product recipients
- Where are they?
 - Addiction treatment services, prisons
 - Primary care

Some more bad news

- We don't have a vaccine
- It is questionable whether, in the long-term, we can achieve global elimination without one

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Trial of a Vaccine Regimen to Prevent Chronic HCV Infection

Kimberly Page, Ph.D., M.P.H., Michael T. Melia, M.D., Rebecca T. Veenhuis, Ph.D.,
Matthew Winter, D.D.S., Kimberly F. Rousseau, B.S., Guido Massaccesi, B.S.

N ENGL J MED 384;6 NEJM.ORG FEBRUARY 11, 2021

Vaccine development – an aside

Virus	First identified	First vaccine trials	Vaccine adopted for global clinical use
HIV	1983	1990s	No effective vaccine
HCV	1989	2017 (phase 3 trial)	No effective vaccine
SARS-CoV-2	2020	2020	2020

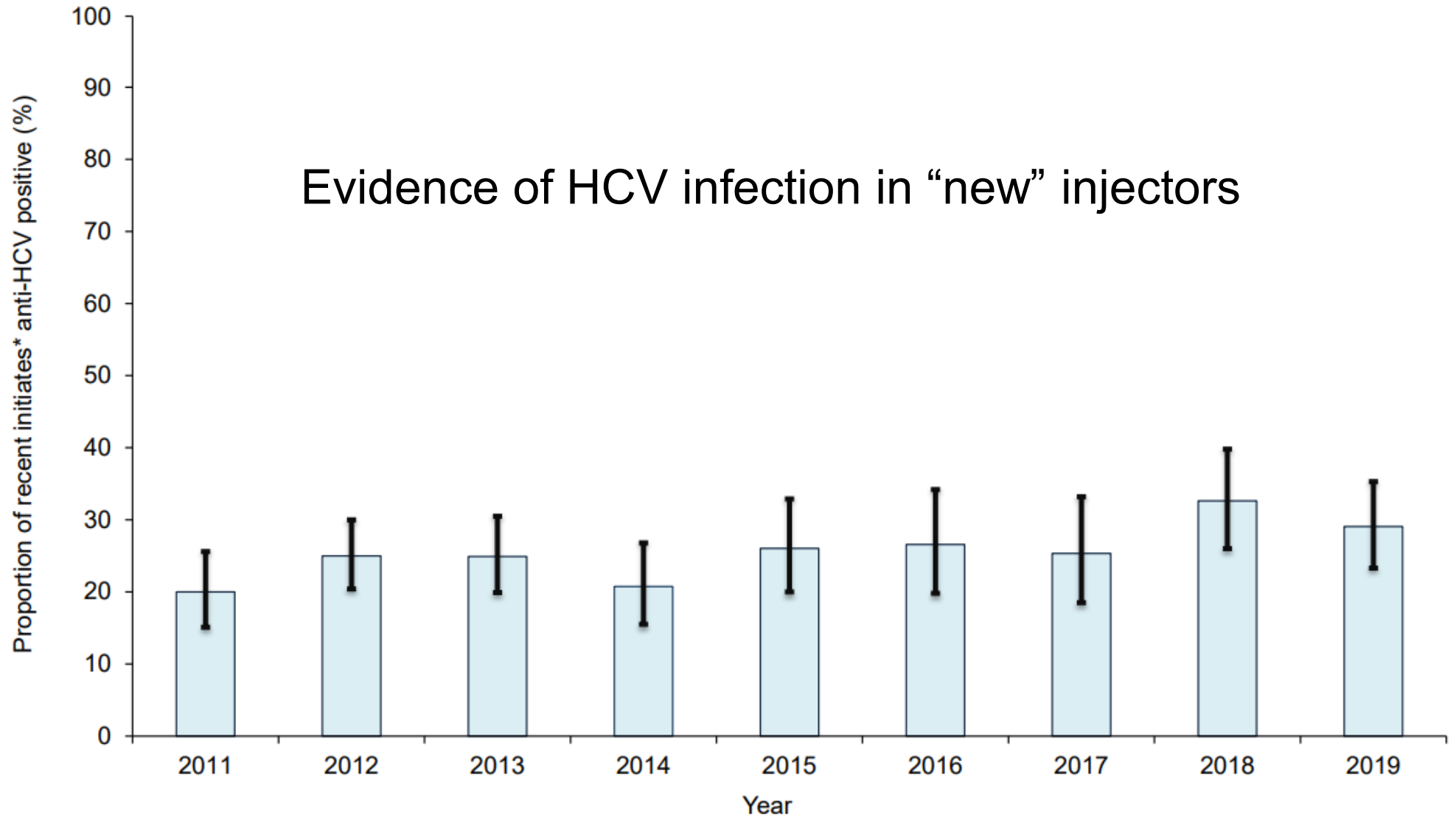
WHO Elimination Targets: Hepatitis C

TARGET AREA	2020 TARGETS^[8]	2030 TARGETS^[1]
Impact targets		
Incidence: New cases of chronic viral hepatitis C infection	30% reduction	80% reduction

Incidence of new infections

- A **MAJOR** challenge!
- There is no single diagnostic test for incident HCV infection

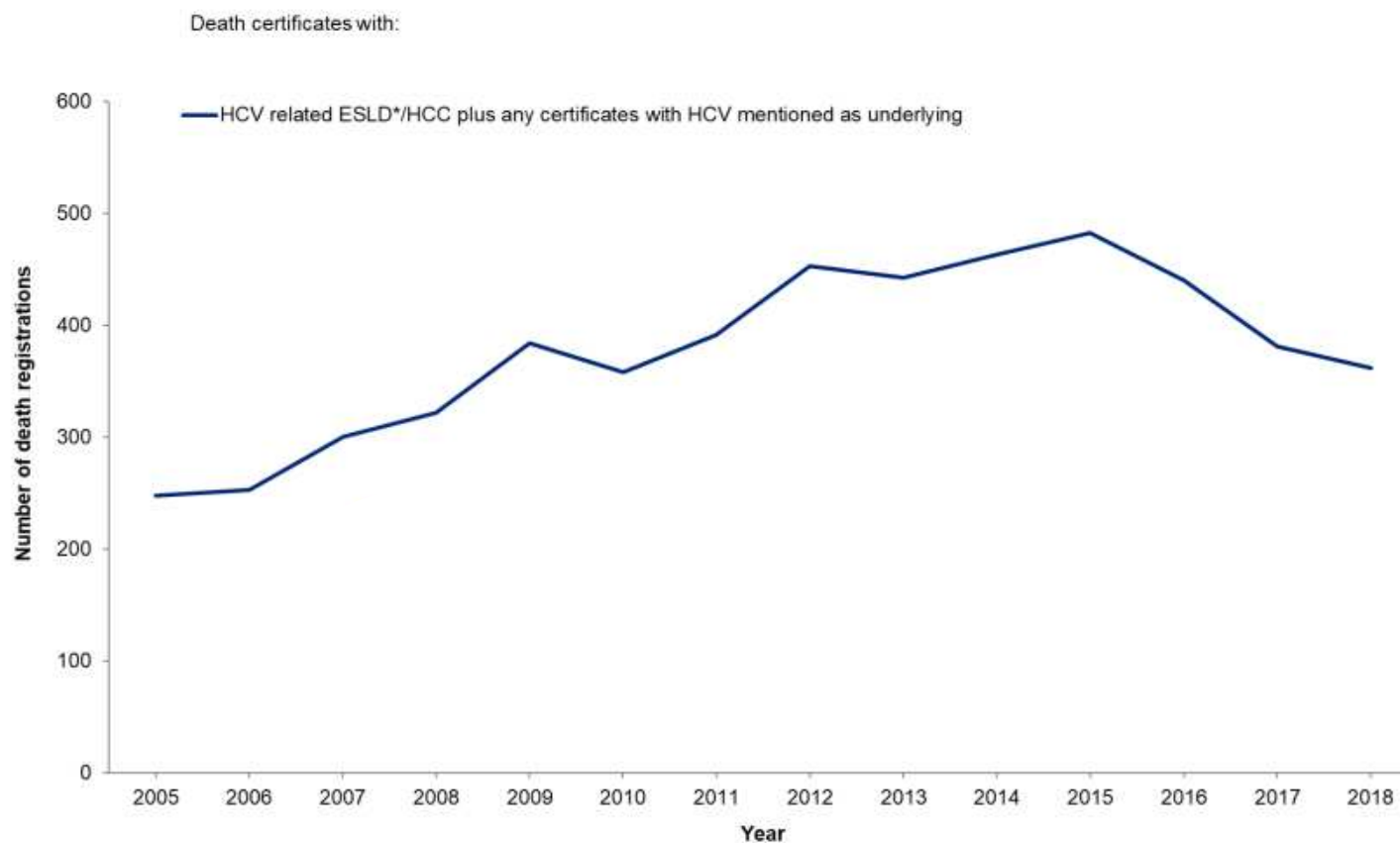
Figure 34. Prevalence of anti-HCV among recent initiates to injecting* in England 2011 to 2019 (bars represent 95% CI)



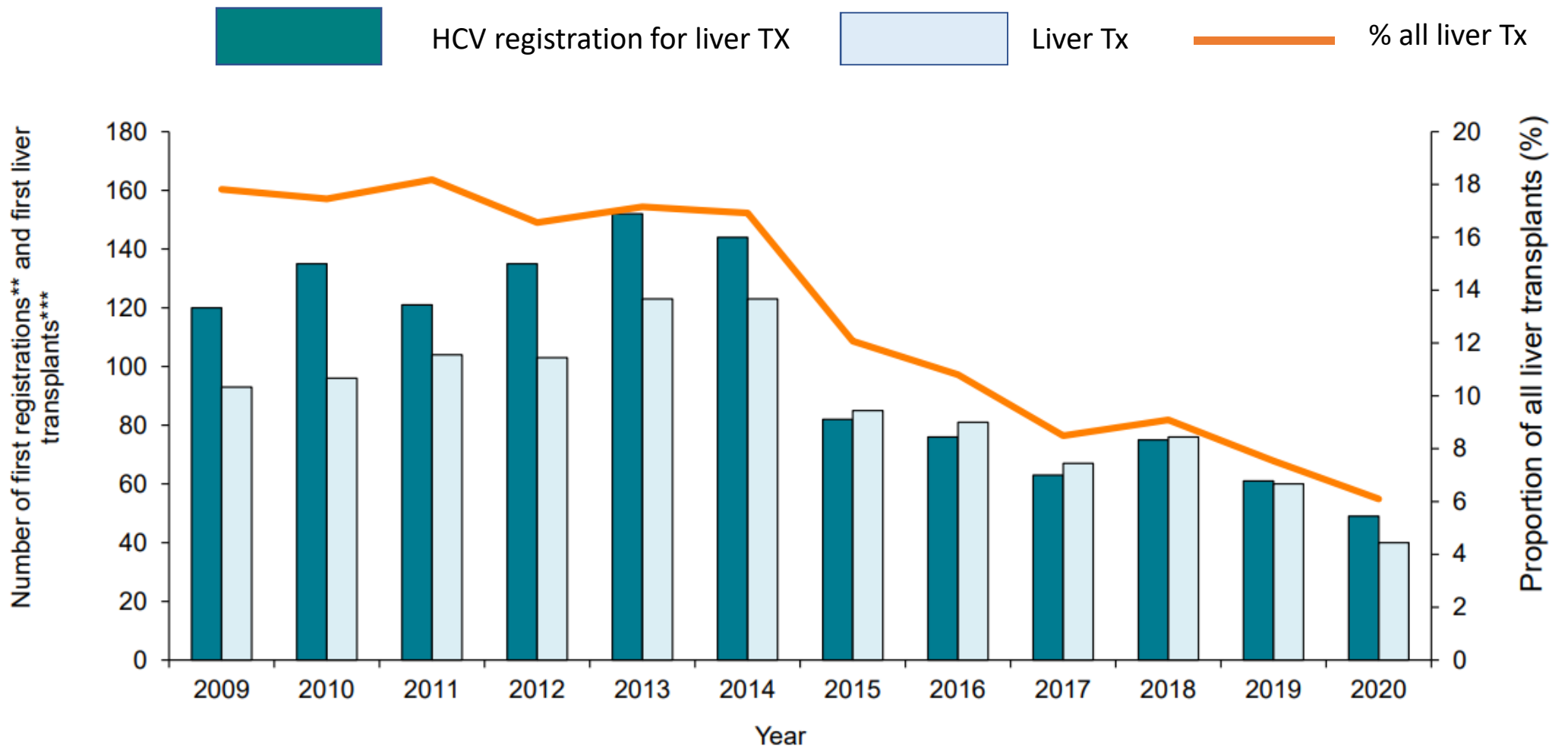
WHO Elimination Targets: Hepatitis C

TARGET AREA	2020 TARGETS ^[8]	2030 TARGETS ^[1]
Impact targets		
Incidence: New cases of chronic viral hepatitis C infection	30% reduction	80% reduction
Mortality: Viral hepatitis C deaths	10% reduction	65% reduction

Figure 4: Death registrations for ESLD* or HCC in those with HCV mentioned on their death certificate in England: 2005 to 2018**



Liver transplantation data



Hepatitis C: from pandemic to elimination in 40 years?

- Virus identified in 1989
- Current estimates – 71 million people are infected
- Curative DAAs with >95% cure rates licensed for clinical use 2015
- WHO set elimination target of 2030

- In England: Current diagnosis rates ~ 10-15,000 per year
- 89,000 untreated patients in England of whom 60,000 are undiagnosed
- Current treatment rates ~ 12-15,000 per year

Hepatitis C: from pandemic to elimination in 40 years?

- The challenge has shifted from molecular virology
 - What kind of virus?
 - How can we diagnose infection?
 - What viral targets are there for antiviral drugs?
- To public health medicine
 - How can we find the infected patients?
 - And link them in to care pathways for treatment?



Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis

Michelle C.M. Cheung¹, Alex J. Walker², Benjamin E. Hudson³, Suman Verma⁴, John McLauchlan⁵, David J. Mutimer⁶, Ashley Brown⁷, William T.H. Gelson⁸, Douglas C. MacDonald⁹, Kosh Agarwal⁴, Graham R. Foster^{10,*}, William L. Irving¹¹, HCV Research UK

¹Liver Unit, Blizard Institute, Queen Mary University of London, United Kingdom; ²Faculty of Medicine & Health Sciences, University of Nottingham, United Kingdom; ³University Hospitals Bristol NHS Trust, United Kingdom; ⁴Institute of Liver Studies, King's College London, United Kingdom; ⁵MRC-University of Glasgow Centre for Virus Research, United Kingdom; ⁶Centre for Liver Research and NIHR Biomedical Research Unit, Queen Elizabeth Hospital, Birmingham, United Kingdom; ⁷Department of Hepatology, St Mary's Hospital, Imperial College London, United Kingdom; ⁸Department of Hepatology, Cambridge University Hospitals NHS Foundation Trust, United Kingdom; ⁹UCL Institute for Liver and Digestive Health, University College London, United Kingdom; ¹⁰Queen Mary University of London, United Kingdom; ¹¹NIHR Nottingham Digestive Diseases Biomedical Research Unit, United Kingdom

See Editorial, pages 663–665

Nobel Prize for Medicine October 2020

Harvey Alter

Mike Houghton

Charlie Rice

