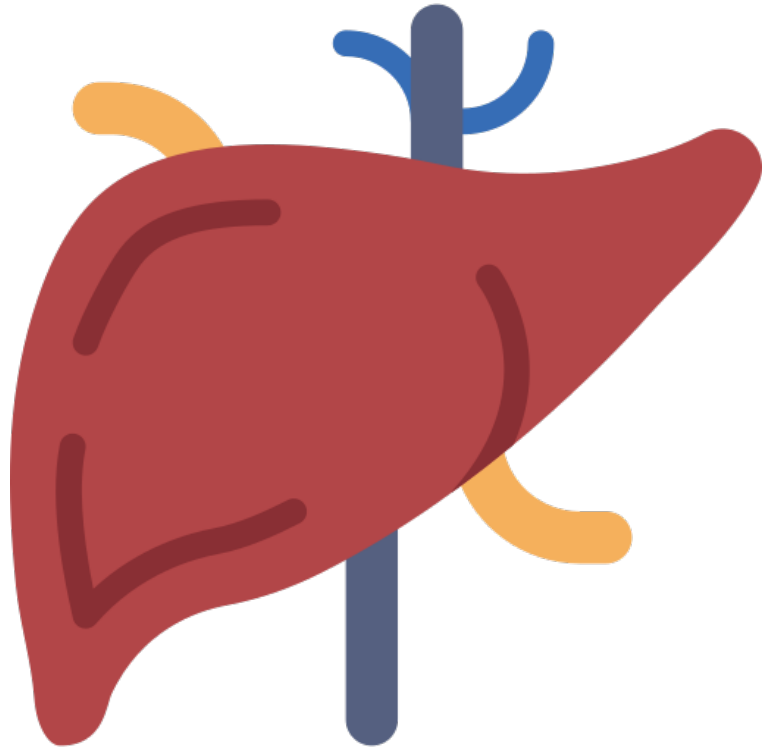


The DAAs: a paradigm shift in chronic Hepatitis C treatment



CASE OUTLINE

- I. **Case for change**
 - *Situation*
 - *Challenge*
 - *Paradigm shift*
 - *Patient population*
- II. **Value to patients**
- III. **Value to the healthcare system**
- IV. **Value to society**
- V. **Annex**
 - *Key assumptions*
 - *Reference list*

Case summary | Hepatitis C

The DAAs: a paradigm shift in chronic Hepatitis C treatment

CASE FOR CHANGE



- **Situation** – Hepatitis C is a cancer-causing virus of growing public health concern that places a large burden on local health systems and economies
- **Challenge** – Early treatment options posed significant efficacy and tolerability challenges for HCPs and patients
- **Paradigm shift** – First- and second-generation direct-acting antivirals (DAAs) have revolutionized HCV treatment
- **Population** – Hepatitis C is a worldwide health challenge, with approx. 14 M patients infected in the European Region

VALUE FOR PATIENTS



- **A cure for most patients** – DAA treatments offer efficacy rates (>98%) approaching cure
- **Prevented disease progression** – Near-curative DAA treatment can prevent advanced liver disease and liver-related death in many patients
- **Improved Quality of Life** – DAA treatment can also reduce the number of patients with additional health problems associated with chronic HCV

VALUE TO THE HEALTHCARE SYSTEM



- **Preventable resource use** – Expanded access to DAA treatment for chronic Hepatitis C could lead to significant savings for EU healthcare systems
- **Averted liver events** – DAA treatment has reduced the proportion of transplants due to HCV-related liver disease

VALUE TO SOCIETY



- **Getting patients able to work again** – DAA treatment improves work productivity and reduces days of sick leave in patients with chronic Hepatitis C
- **Economic gain** – Improved work productivity due to DAA treatment translates to annual savings of €749 to €1,112 per employed patient (deep dive in 4 countries)
- **Benefits outweigh costs** – The DAA list price is offset by a reduction in multiple other healthcare costs, leading to a saving for society of €11,000 per patient (deep dive in Belgium)

TOWARDS THE FUTURE



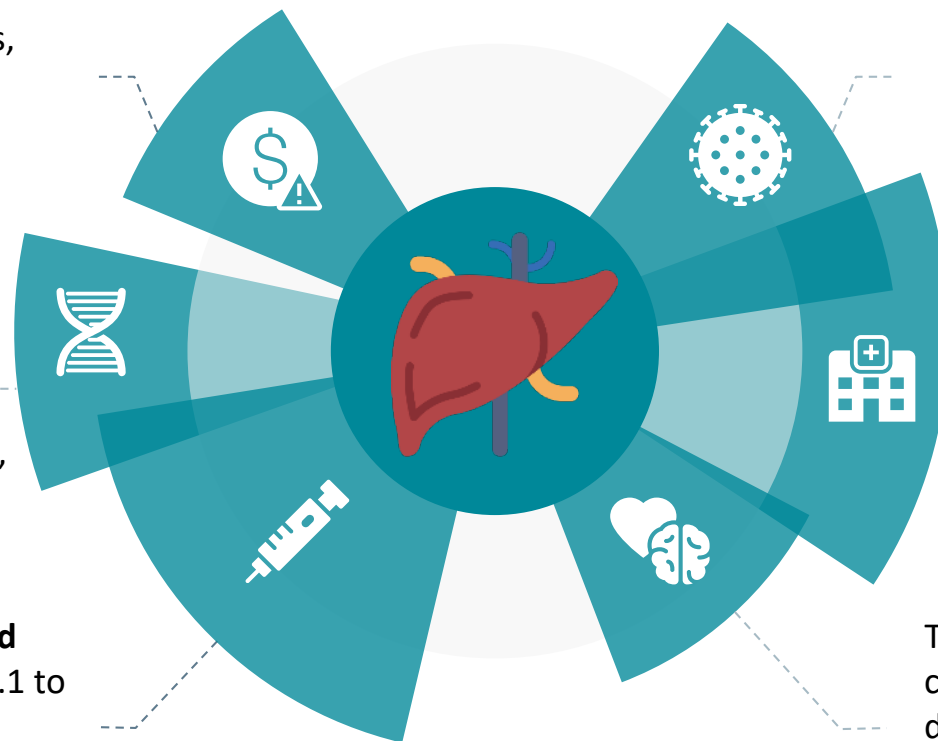
- **Working towards HCV elimination** – The WHO goal of eliminating Hepatitis C by 2030 is now feasible because of DAAs, but the unmet need is now in finding and treating the undiagnosed, thereby maximizing the value of DAA cure

Hepatitis C is a cancer-causing virus of growing public health concern that places a large burden on local health systems and economies

The **burden of Hepatitis C** is influenced by country-specific factors, such as local epidemiology, historical and present risk factors, local screening programs, treatment guidelines and treatment access^{4,5}

There are **6 Hepatitis C virus genotypes**, with G1 and G3 being most common in Western Europe (55% and 29% prevalence, respectively)^{*4}

Hepatitis C is **more commonly reported among men** (male-to-female ratio of 2.1 to 1), and the most affected age group in both sexes is 25–34 years. **Injecting drug use** accounts for 45% of cases with reported transmission mode³



Hepatitis C is a **slow, bloodborne viral disease** that causes **inflammation of the liver**¹. Initial symptoms are vague but could include fatigue, and as the disease progresses, **liver complications** such as cirrhosis (a lengthy process) and liver cancer could arise¹

Hepatitis C is a **leading cause of liver cancer** (hepatocellular carcinoma) and liver transplants worldwide²

The **psycho-emotional impact** of Hepatitis C can be severe, as the fatigue can lead to depression, and on to reduced work productivity and unemployment¹

1. SEBOIO 2020.
2. THE EUROPEAN UNION HCV COLLABORATORS 2017.
3. ECDC 2019.
4. PETRUZZIELLO ET AL. 2016.
5. MENNINI, ET AL. 2021.

*COUNTRIES STUDIED WERE AUSTRIA, BELGIUM, CYPRUS, DENMARK, FINLAND, GERMANY, GREECE, ICELAND, IRELAND, ITALY, LUXEMBOURG, THE NETHERLANDS, NORWAY, PORTUGAL, SPAIN, SWEDEN, SWITZERLAND AND THE UK. NB PREVALENCE FIGURES ARE PRE ARRIVAL OF DAA TREATMENTS.

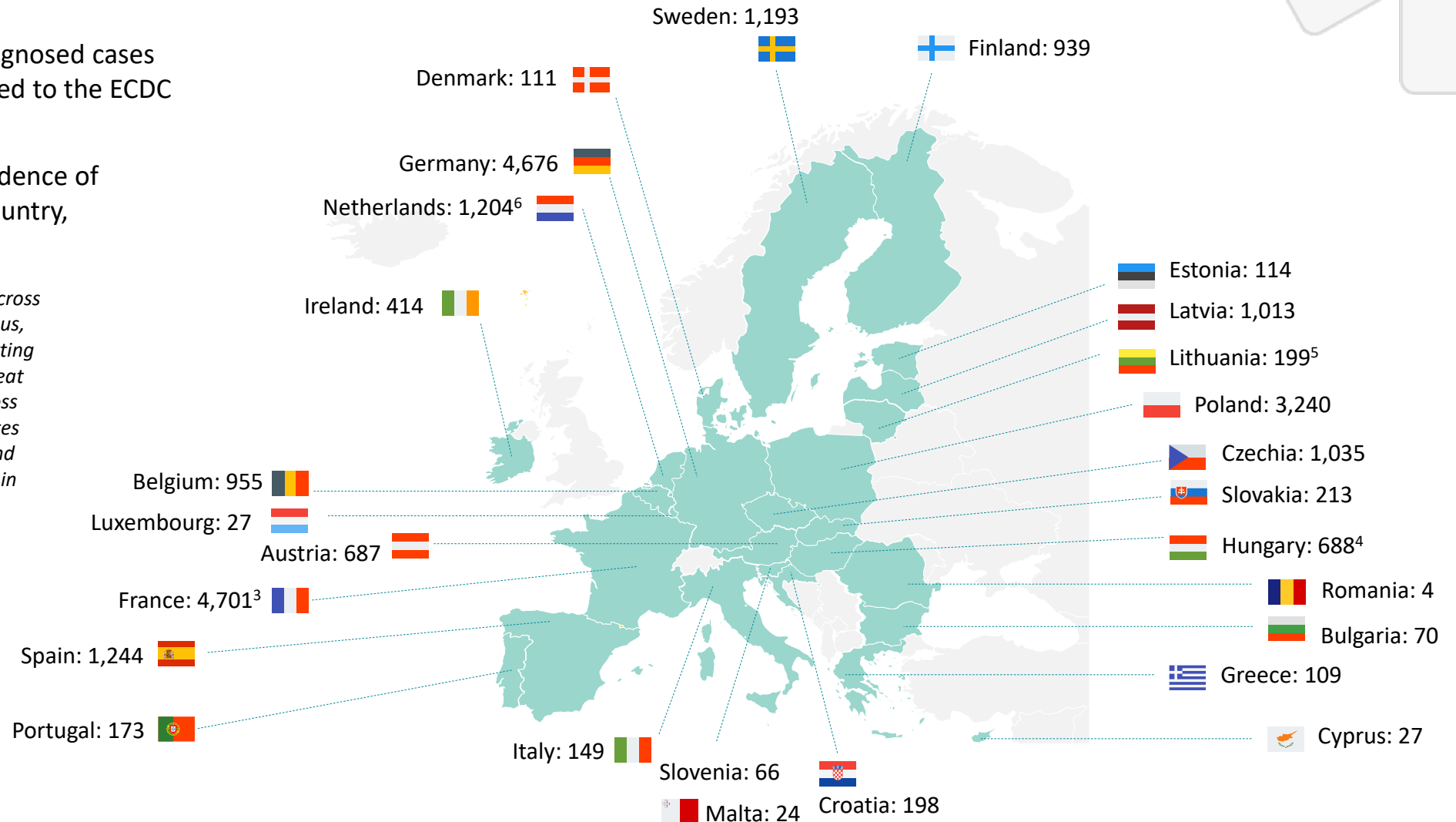
Hepatitis C is a worldwide health challenge, with approx. 14 M patients infected in the European Region¹

The number of newly diagnosed cases (incidence rate) is reported to the ECDC each year²

The map here shows incidence of **chronic HCV** per EU27 country, reported in 2019²

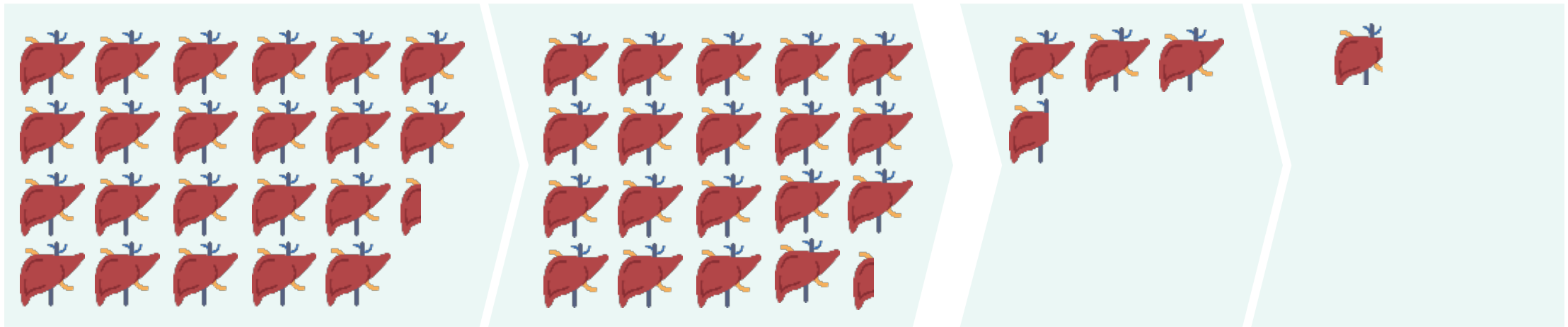
Note: HCV Surveillance systems across the EU countries are heterogeneous, leading to inconsistent case reporting methods. This may explain the great variation in relative numbers across countries. Overall, notification rates were mostly higher in northern and western European countries than in southern European countries⁴

For the purposes of this case study, we will focus on EU27, wherever possible



1. WHO, 2022.
 2. ECDC 2019.
 3. OECD, 2019A.
 4. OECD, 2019B.
 5. OECD, 2019C.
 6. OECD, 2019D.

If left untreated, Hepatitis C can lead to serious health consequences



Chronic Hepatitis C

An estimated **22,379** people per year across EU27 are newly diagnosed per year with chronic Hepatitis C (CHCV)¹⁻⁵

Chronic liver disease

On average, **19,395** of these chronic Hepatitis C patients go on to develop chronic liver disease⁶

Cirrhosis

If left untreated, **3,730** go on to develop cirrhosis over a 20-30 year timeframe⁶

Death due to HCV-related cirrhosis / liver cancer

Of these, if left untreated, **895** die of Hepatitis C-related cirrhosis or liver cancer⁶

“There is the psychological aspect as well. If you’re carrying an infectious virus that is transmitted by contact.. You have a leper feeling that you can’t touch people, share things with people. How you interact as a human becomes very different. You feel you have a blight on your future, as to what’s going to happen – ‘Do I have a life in the future or not? Is this going to kill me? How quickly will it kill me?’”

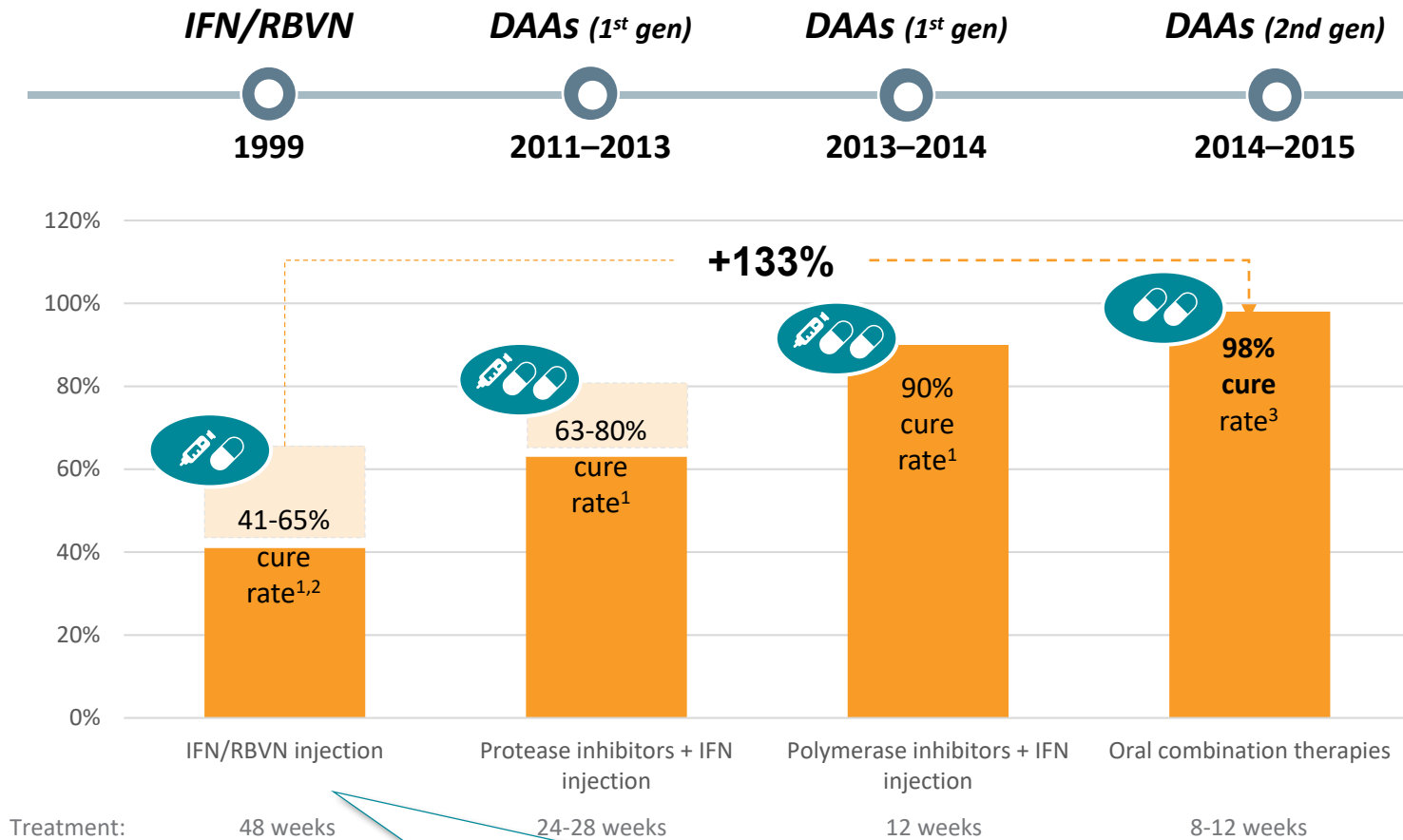
-- Dr John Dillon, University of Dundee, UK

1. ECDC 2019.
2. OECD, 2019A.
3. OECD, 2019B.
4. OECD, 2019C.
5. OECD, 2019D.
6. EMCDDA, 2016.



= 1000 people

Early treatment options posed challenges for HCPs and patients – but DAAs have revolutionized HCV treatment by offering a near-cure



“The big change came when we had interferon-free regimens. They were revolutionary. We could treat almost everybody.”
 -- Dr John Dillon, University of Dundee, UK

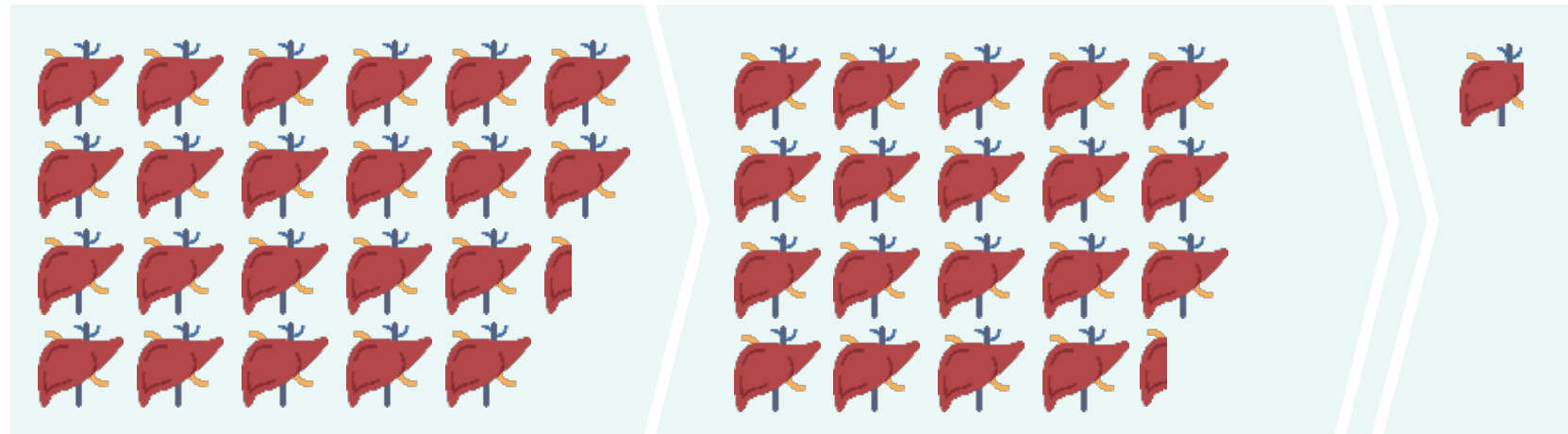
“In 2013, we knew that the cure for more than 90% of the people was there. Not only going from 50% to 95% of cure, but also people who would not respond to interferon were now eligible for these drugs. Disruptive innovation. There was no comparison between what we had and what we got.”
 -- Luís Mendão, Co-Chair, ACHIEVE, Portugal

“We’ve moved to the point where... do I really need to bother to teach the medical students and junior doctors about Hepatitis C because they will never see it!”
 -- Dr John Dillon, University of Dundee, UK

“The physical pain was overwhelming. My body was in pain, sometimes I was losing hair, sometimes my hands were bleeding. It was pretty awful.”
 -- George Kalamitsis, Chairman, Prometheus Hellenic Liver Patient Association, Greece

1. PHRMA, 2017.
 2. LUO, ET AL. 2019.
 3. MANNIS & MAASOUMY, 2022.

Near-curative DAA treatment can prevent the development of advanced liver disease and liver-related death in significant numbers of patients



Chronic Hepatitis C

Of the estimated **22,379** people per year across EU27 who are newly diagnosed per year with chronic HCV, given the DAA 98% cure rate ...¹⁻⁵

If treated with DAAs:

Advanced liver disease

19,007 patients could be prevented from developing advanced liver disease...¹⁻⁶

Death

And **877** could be prevented from dying from Hepatitis C-related cirrhosis or liver cancer¹⁻⁶



Moreover, when patients are diagnosed in a late stadium DAA therapy has been associated with **regression of cirrhosis in >50%**⁷

"It's little short of miraculous. The set of drugs that were so easy to take, so effective, just changed the natural history of this disease completely."

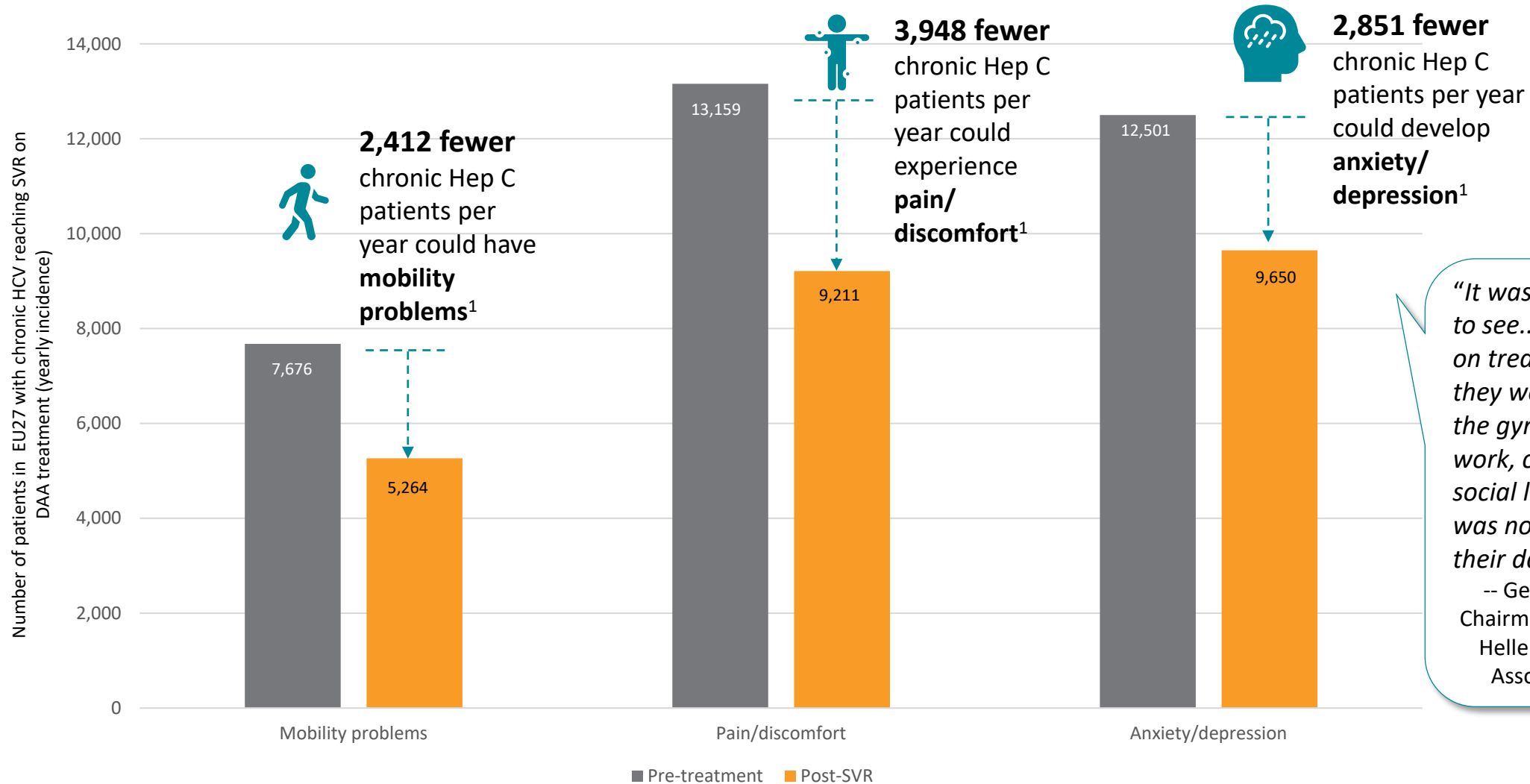
-- Dr John Dillon, University of Dundee, UK

1. ECDC 2019.
2. OECD, 2019A.
3. OECD, 2019B.
4. OECD, 2019C.
5. OECD, 2019D.
6. EMCDDA, 2016.
7. DURAND & FRANCOZ, 2017.



= 1000 people

Near-curative DAA treatment can also reduce the number of patients who have additional health problems associated with chronic HCV



“It was fascinating to see.. people were on treatment and they would go to the gym, go to work, continue their social life. Illness was not affecting their daily routine.”

*-- George Kalamitsis,
Chairman, Prometheus
Hellenic Liver Patient
Association, Greece*

Expanded access to DAA treatment for chronic Hepatitis C could lead to significant savings for healthcare systems across Europe



Deep dive into Romania, Italy and Spain



Expanded access (i.e. without restrictions, so that patients in early stages of infection can receive treatment) to DAA treatment can lead, **over a 20-year time horizon**, to¹:



Over a 20-year time horizon:



Healthcare cost savings

€45M

€63M

€275M

..as a result of avoided hepatocellular carcinoma, decompensated cirrhosis and liver transplants



Time to recovery of investment*

6.7 years

5.4 years

4.5 years

Time to return of investment is generally related to two factors: DAA cost and liver disease costs.

These countries illustrate the varying epidemiological patterns and case reporting of chronic infection across EU27²:

Cases per year	4	149	1,244
% of EU27 (annual incidence)	0.02%	0.7%	5.6%

1. MENNINI, ET AL. 2021.
2. ECDC 2019.

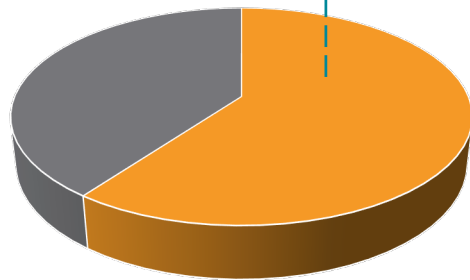
*BREAK-EVEN POINT REALISING RETURN ON INVESTMENT. GENERALLY RELATED TO DAA COST AND LIVER DISEASE COSTS. AVERAGE COST OF DAA TREATMENT WAS ESTIMATED USING EXPERT OPINION AND NON-OFFICIAL SOURCES. SEE SLIDE NOTES FOR COSTS USED IN EACH COUNTRY. NOTE: THE COST OF DAAS ADMINISTERED TO PATIENTS IN 2015-2016 WAS HIGHER THAN THAT ADMINISTERED TO PATIENTS IN 2017-2019, SUGGESTING THAT THE DECREASE IN RETURN ON INVESTMENT OVER TIME WAS ALSO BECAUSE OF THE DECREASING PRICE OF TREATMENT.

DAA treatment has reduced the proportion of transplants due to HCV-related liver disease



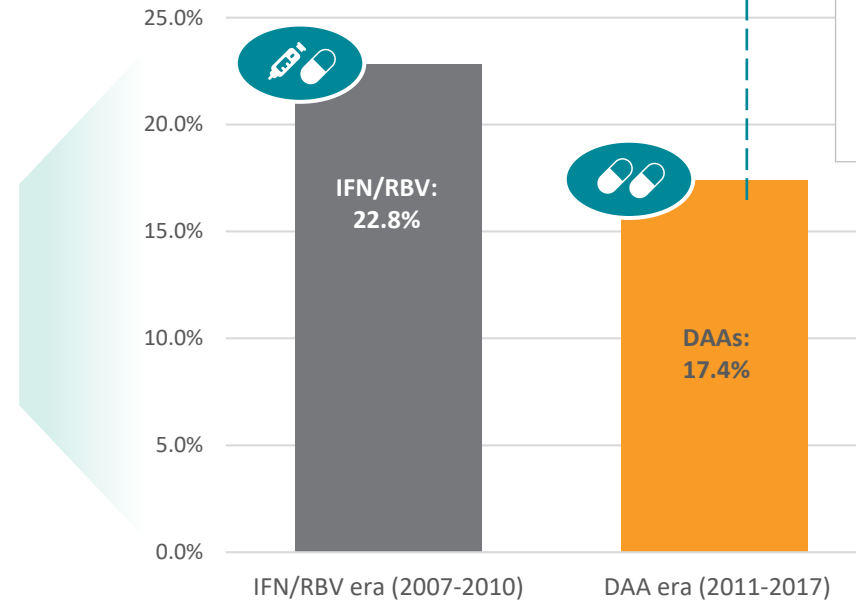
60,527 liver transplants were performed in Europe between 2007 and 2017*¹

Of these, **36,832 (60%)** included patients with chronic HCV**¹

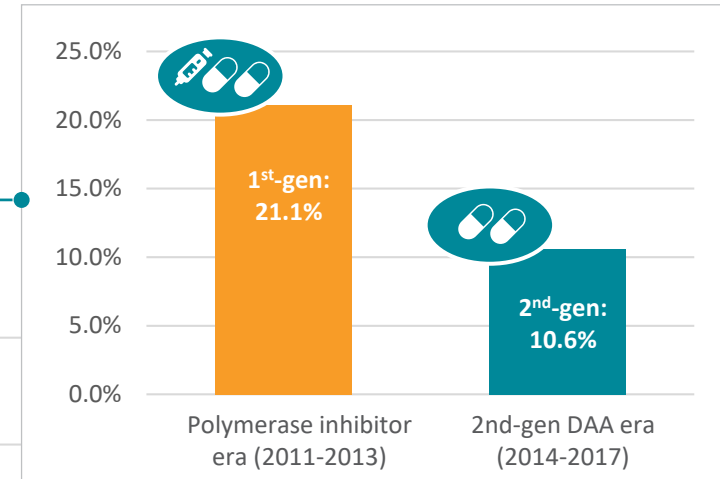


■ Liver transplants incl HCV ■ Other liver transplants

% of liver transplants due to HCV liver disease decreased from 22.8% when IFN/RBV was standard treatment, to 17.4% when DAAs were used¹



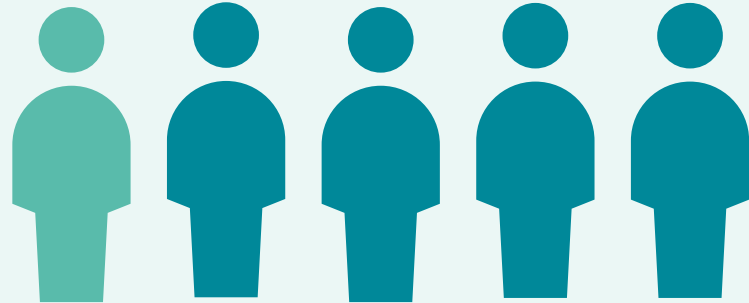
Liver transplants due to HCV-related liver disease during different eras of treatment availability¹



2nd-gen DAAs led to only 10.6% of liver transplants due to HCV[†], compared with 21.1% with polymerase inhibitors¹

*EUROPEAN COUNTRIES IN STUDY WERE NOT NAMED. ASSUME THEY INCLUDE THE UK. **ALSO INCLUDES HEPATITIS B, ALCOHOLIC (ETOH) AND NON-ALCOHOLIC STEATOHEPATITIS (NASH); DATA NOT SEPARATED OUT. †DECOMPENSATED HCV AND HEPATOCELLULAR CARCINOMA INDICATIONS
1. BELLI, ET AL. 2018

DAA's will continue to reduce the need for liver transplants due to HCV-related liver disease



1 in 5 patients with advanced liver disease who are treated with DAAs could be delisted from the liver transplant waiting list¹

DAAs will continue to reduce the need for liver transplants in HCV-infected patients, and the proportion of HCV-infected patients who are candidates for liver transplant will continue to decrease in the future²

"Patients came off transplant lists because their virus went away, their livers got better. Patients that you thought were going to end up transplanted within a year or two were cured."

-- Dr John Dillon, University of Dundee, UK

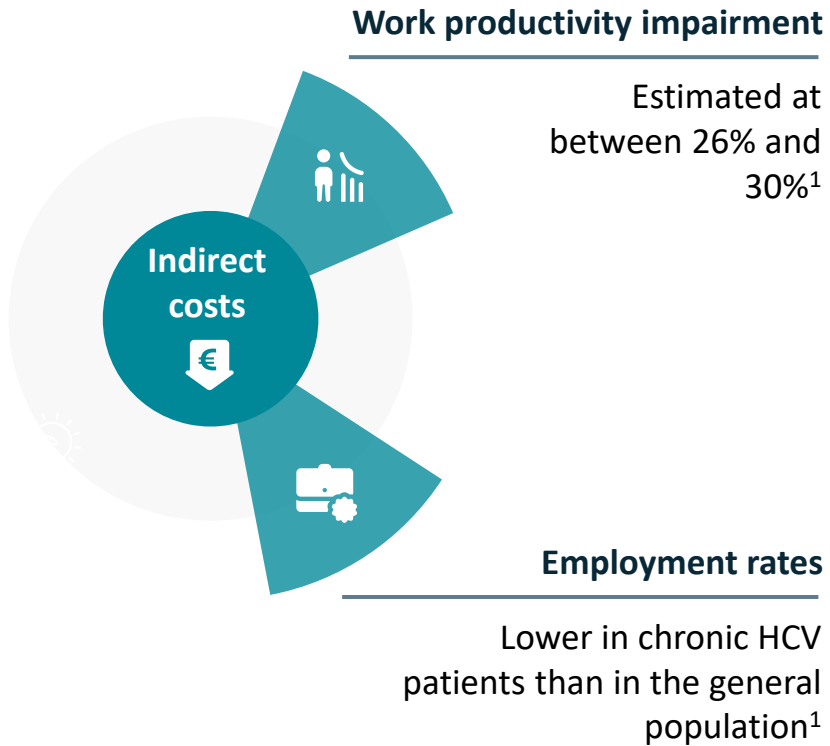


The reduction in HCV-related reasons for liver transplants means **at least 600 more livers per year** could be redistributed to European* patients with indications other than HCV³

1. BELLI, ET AL. 2016.
2. DURAND & FRANCOZ, 2017.
3. BELLI, ET AL. 2018.

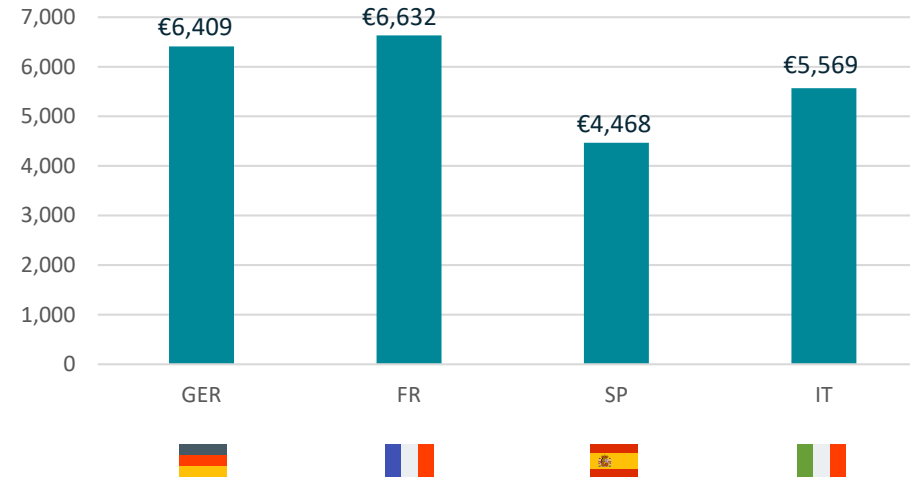
*ANALYSIS BASED ON DATA FROM THE EUROPEAN LIVER TRANSPLANT REGISTRY, WHICH INCLUDES GREAT BRITAIN AND SOME EUROPEAN COUNTRIES OUTSIDE OF EU27

Chronic HCV infection imposes a great economic burden on patients, their employers and society

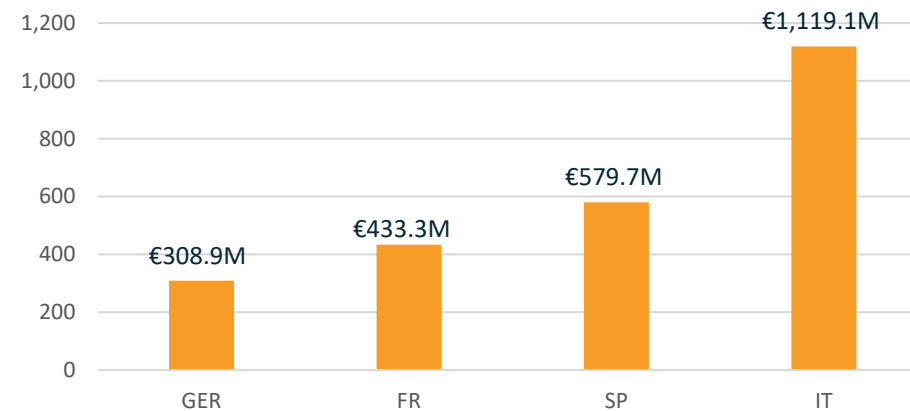


Value of lost production*¹:
Country Deep Dives:

Annualised loss per employed HCV patient (€)

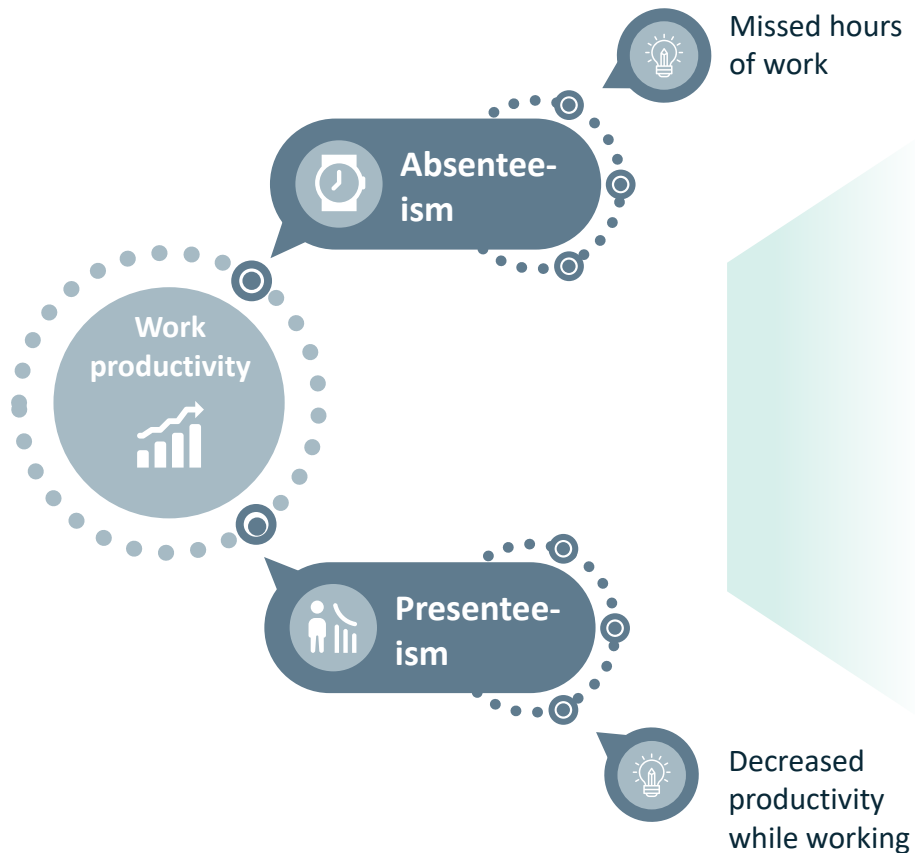


Annual aggregate loss in WP (€)

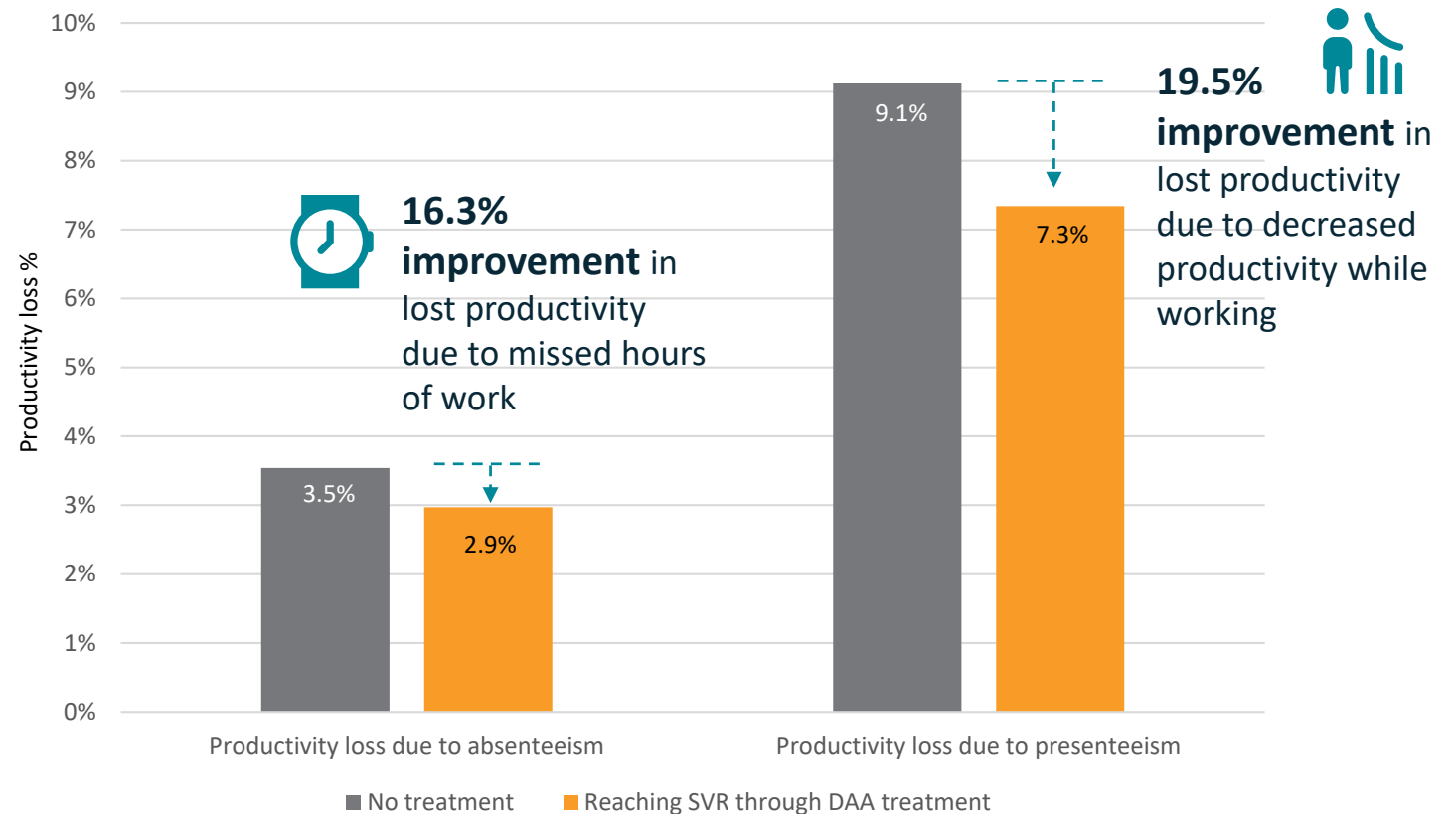


WP: WORK PRODUCTIVITY. *STUDY FOCUSED ON PATIENTS WITH CHRONIC HEPATITIS C GENOTYPE 1
1. YOUNOSSI, ET AL. 2016.

DAA treatment improves work productivity in patients with chronic Hepatitis C by 16-20%



Impact of DAA treatment on work productivity impairment*



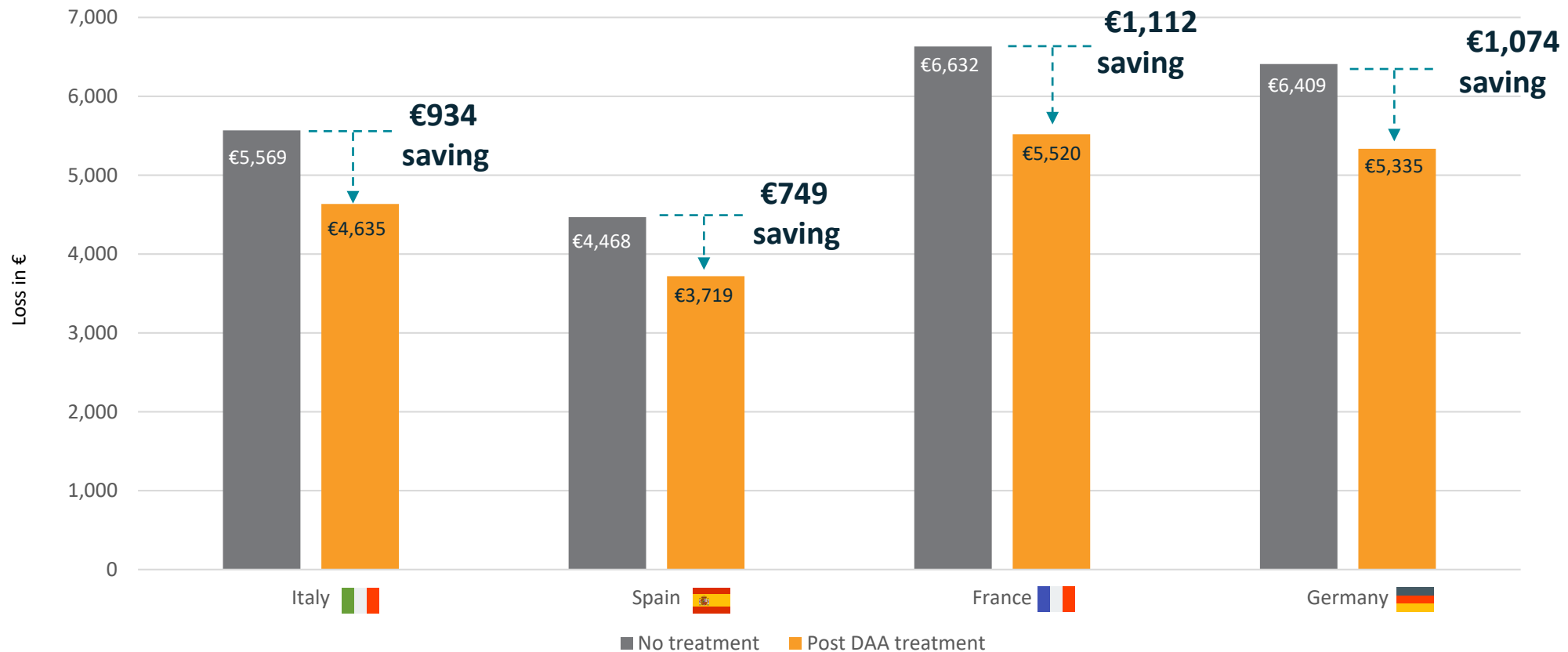
*DATA FROM 5 EU COUNTRIES: ITALY, SPAIN, FRANCE, GERMANY, UK. UK DATA NOT REPORTED SEPARATELY. ACTUAL NUMBERS OF DAYS LOST WERE NOT REPORTED
1. YOUNOSSI, ET AL. 2016.



Deep Dive: Improved work productivity due to DAA treatment translates to annual savings of €749 to €1,112 per employed patient across 4 EU countries

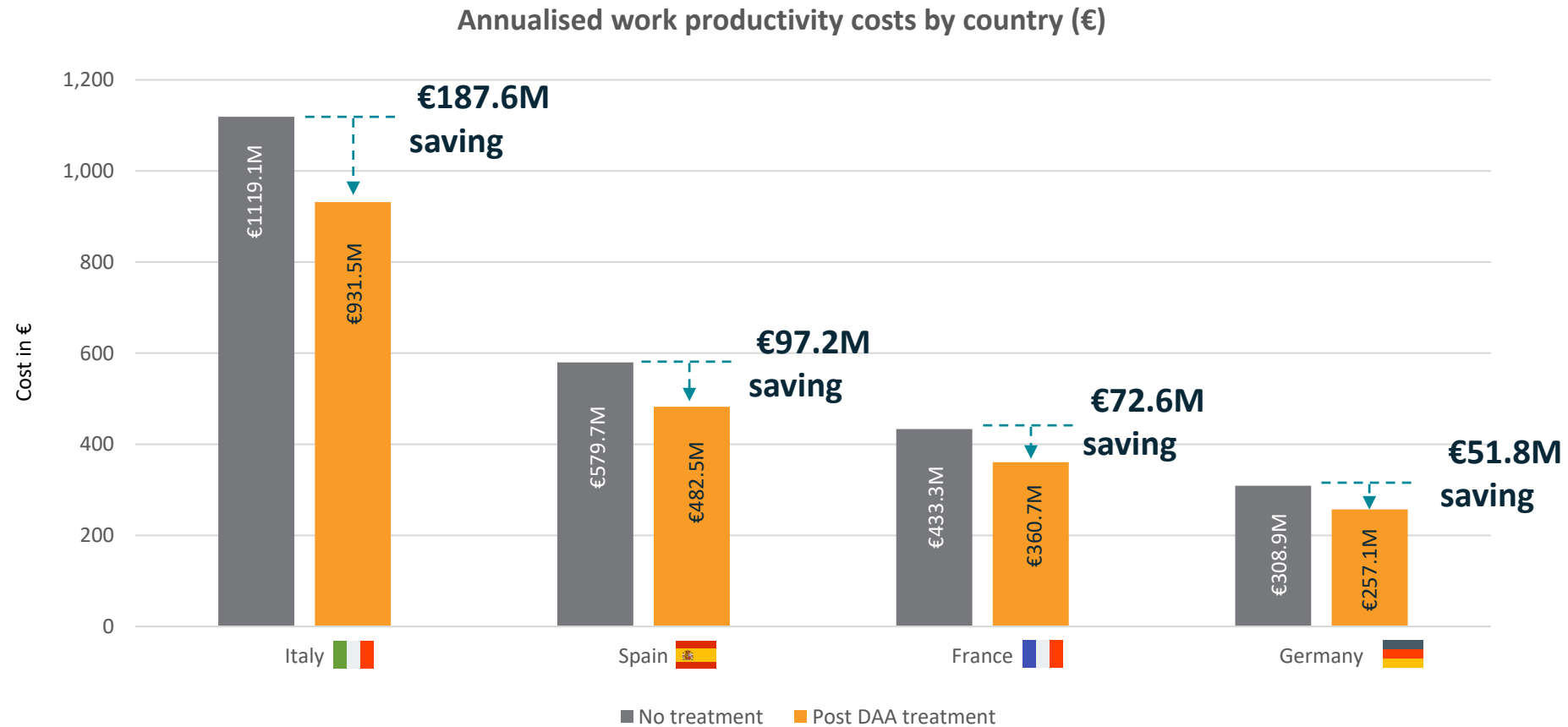


Annualised loss per employed HCV patient by country (€)





Deep Dive: The annualised per-employed-patient savings translate to annual aggregate savings of €52M to €188M across 4 EU countries

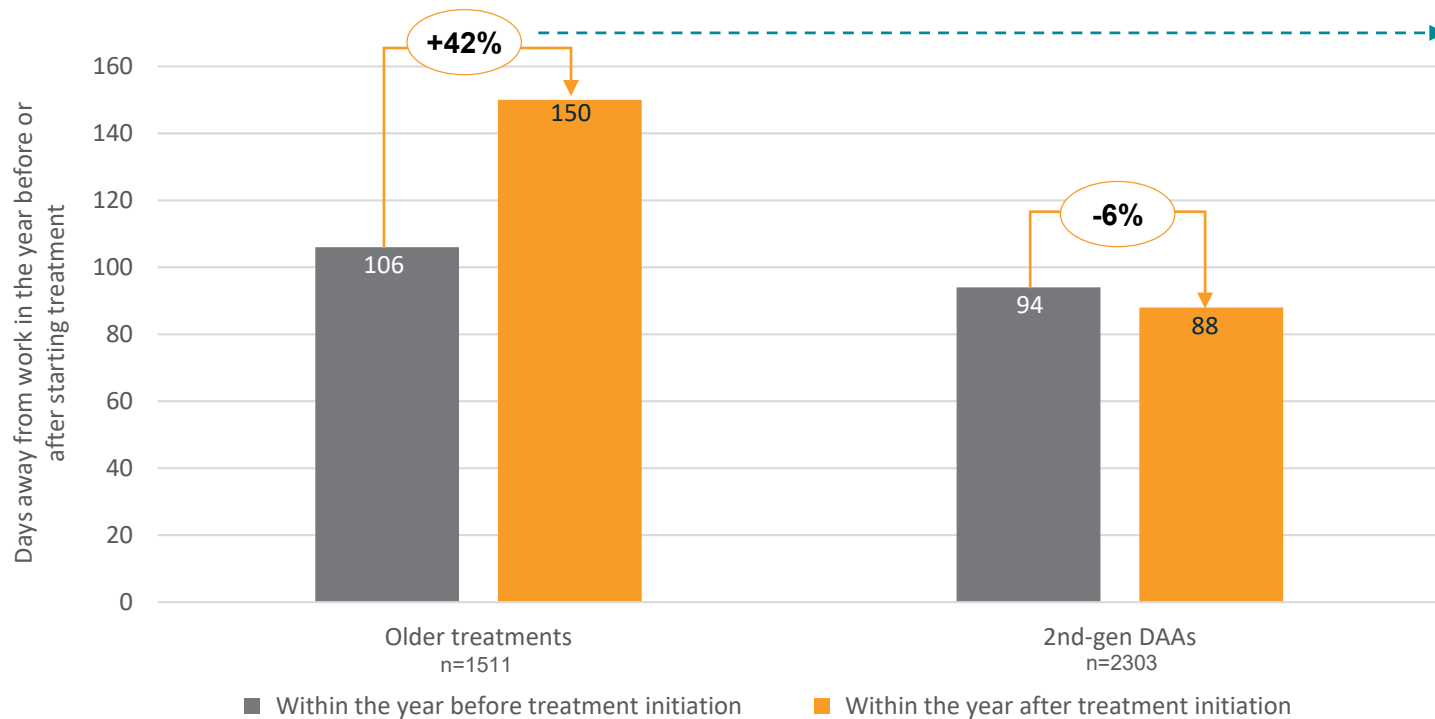


Deep Dive: 2nd-gen DAA treatment reduces days of sick leave



Deep dive into Sweden

Patients treated with 2nd-gen DAAs without peg-IFN experience **fewer days away due to sick leave** in the year after starting treatment, compared with older HCV treatments¹:

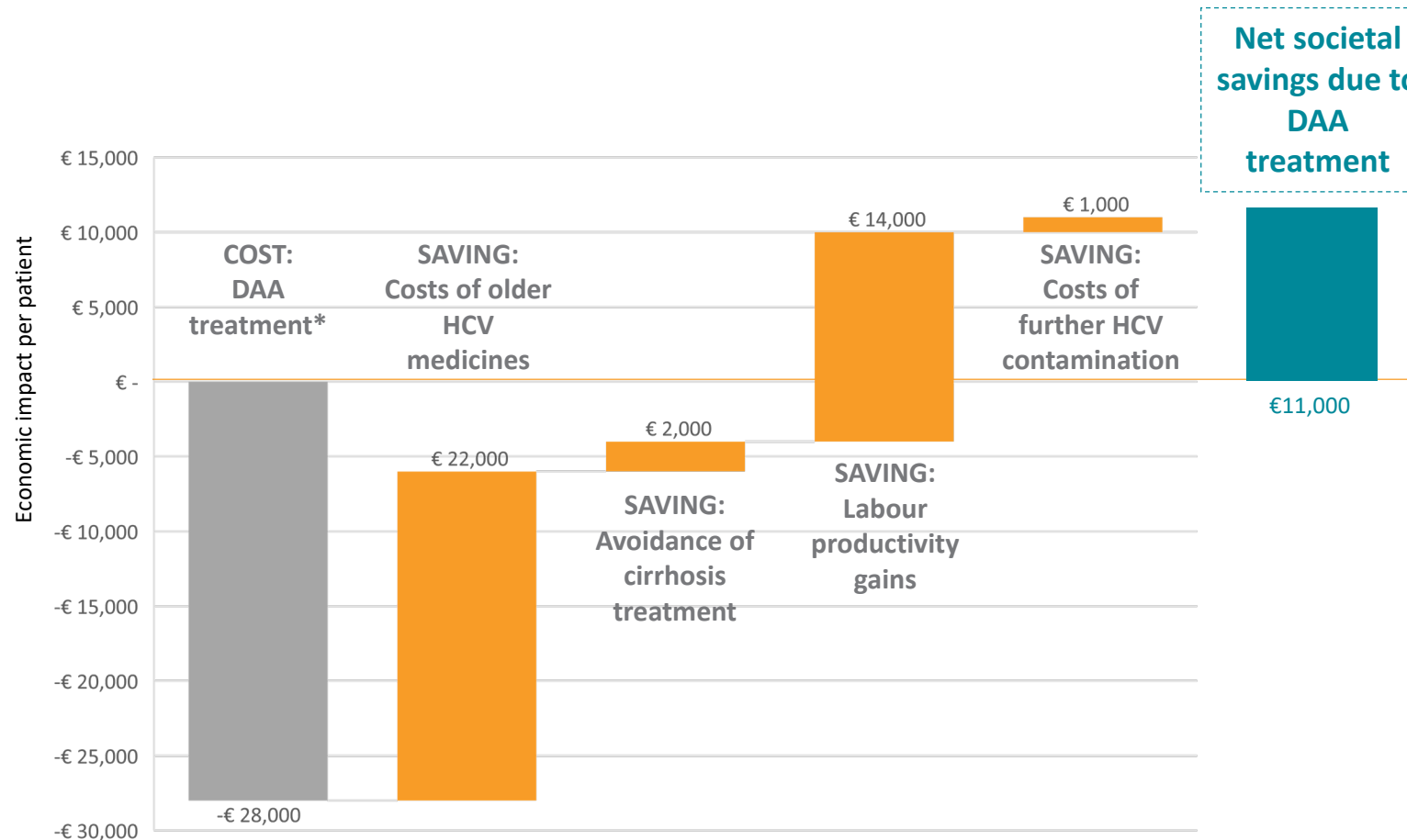


Avoidable 42% increase in number of days away from work in patients treated with 2nd-gen DAAs vs older treatments¹

One possible reason for the reduction in days away from work with DAAs is the reduced burden of adverse events with these drugs¹:

1. LINDGREN, ET AL. 2021.

Deep Dive: The DAA costs is offset by savings made in other healthcare costs, leading to a net saving for society of €11,000 per patient



Net societal savings due to DAA treatment → **€146M** total eventual savings to Belgium society on a population basis¹

“When the DAAs first came out, they were very expensive and there was a big jump in cost. We were treating patients who were about to incur huge health costs. So we were averting substantial costs... Because of countries agreeing to treat larger volumes of patients, the cost fell. For that fixed sum that the healthcare system could invest, they could treat a lot more patients.”

-- Dr John Dillon, University of Dundee, UK

Further, Hepatitis C infections are a driver of liver transplants costs in Belgium – if these could be avoided, **another €6M per year** could be saved for Belgium¹

DEEP DIVE IN BELGIUM. ORANGE LINE MEANS BREAK EVEN POINT. *USES LIST PRICE BETWEEN €24,000 AND €30,000. 1. SEBOIO 2020.

Eliminating Hepatitis C by 2030 is the WHO goal, but the unmet need is in finding and treating the undiagnosed, thereby maximizing the value of DAA cure

World Health Organization Global Health Sector Strategy (GHSS) set goal of eliminating viral hepatitis by 2030¹

- 90% reduction in incidence
- 65% reduction in mortality

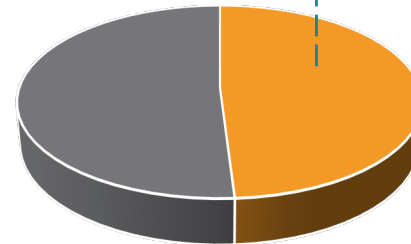
The reduction in liver-related deaths is now feasible because of the availability of DAAs, which have shown a high rate of sustained viral response²

-- The European Union HCV Collaborators

However, the long-term value of the DAAs could be significantly weakened if the undiagnosed population of HCV-infected is not identified and treated

"Globally, we are not on track. We need to estimate how many are not diagnosed. Our struggle now is to get the data right to see what is working.. to not fly blind. We need 90% of the people living with Hep C diagnosed. If we don't have an estimation of how many there are, how can we say that 90% are diagnosed and 90% treated?"

-- Luís Mendão, Co-Chair, ACHIEVE, Portugal



49%

Of HCV-infection injecting drug users have been estimated to be **undiagnosed** in 5 countries*³

The undiagnosed general population must also be considered

For new treatment developments to have any significant impact on HCV mortality and population prevalence, finding and screening HCV cases needs crucially to be improved⁴

1. WHO, 2022.
2. THE EUROPEAN UNION HCV COLLABORATORS, 2017.
3. DILLON, ET AL. 2016.
4. HARRIS, ET AL. 2016.

*DENMARK, FRANCE, POLAND, SPAIN, UK

Hepatitis C case study

Calculation assumptions

Assumption 1

Risk of progression to different disease stages with hepatitis C infection was based on data from the EMCDC¹. Calculations assumed that:

- For every 100 people with Hepatitis C virus, 75-80 will develop chronic infection
- Of the 100 people with Hepatitis C, 60-70 will develop chronic liver disease
- Of the 100 people with Hepatitis C, 5-20 will develop cirrhosis over a period of 20 years
- Of the 100 people with hepatitis C, 1-5 will die of cirrhosis or liver cancer

Assumption 2

Case reporting (incidence) by country was taken from the ECDC². Some countries differentiated their cases into chronic and acute cases, and some also reported unknown cases, whereas other countries reported all cases as an undifferentiated total figure. Overall, the ECDC reported that 6% of cases were reported as acute, 22% as chronic, 69% as unknown, and 3% as unclassified.

In our calculations we have accounted for the Unknown cases, as we must assume that a proportion of them must be chronic cases. We have applied the proportions of acute/chronic etc by scaling them up to the total cases across EU27.

To do this, we took the numbers of known acute and chronic cases to be a 'sample' of the total number of reported cases in EU27, and calculated what the proportions would be scaled-up to that total population. We then applied these scaled-up proportions to the total number of reported cases in EU27. See accompanying Excel calculation sheet for full details.

We also used these scaled-up proportions to calculate the numbers of chronic cases in countries where only unknowns or All cases were reported. In countries where chronic and acute cases were reported alongside unknown cases, to discover the number of unknown cases that should be chronic, we calculated the country-specific proportion of acute and chronic cases from the known case reports, and used that instead. See accompanying Excel calculation sheet for all calculations.

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Interviews

Interviews conducted in July and August 2022 with 2 Patient Experts and 1 Healthcare Professional (KOL)