MÁSTER EN HEPATOLOGÍA

Universidad Autónoma de Madrid

Universidad de Alcalá

Asignatura: Hepatitis virales

“New scenario in Hepatitis C treatment”

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Agenda

- Revolution in treatment of Hepatitis C
  - Real World Evidence
- Impact of treatment in long term outcomes
- The time for a Elimination Plan
  - Microelimination in risk groups
  - Macroelimination
- Simplification in the management of patients
- Conclusions

HCV Therapy Has Evolved Substantially over the Past 30 Years

Interferon Based

Injection-based
up to 72 weeks treatment

1984

Early DAAs

Oral and injection-based
up to 48 weeks treatment

2011

1st-Generation DAAs

First all oral regimens
up to 24 weeks treatment

2014

Pan-genotypic

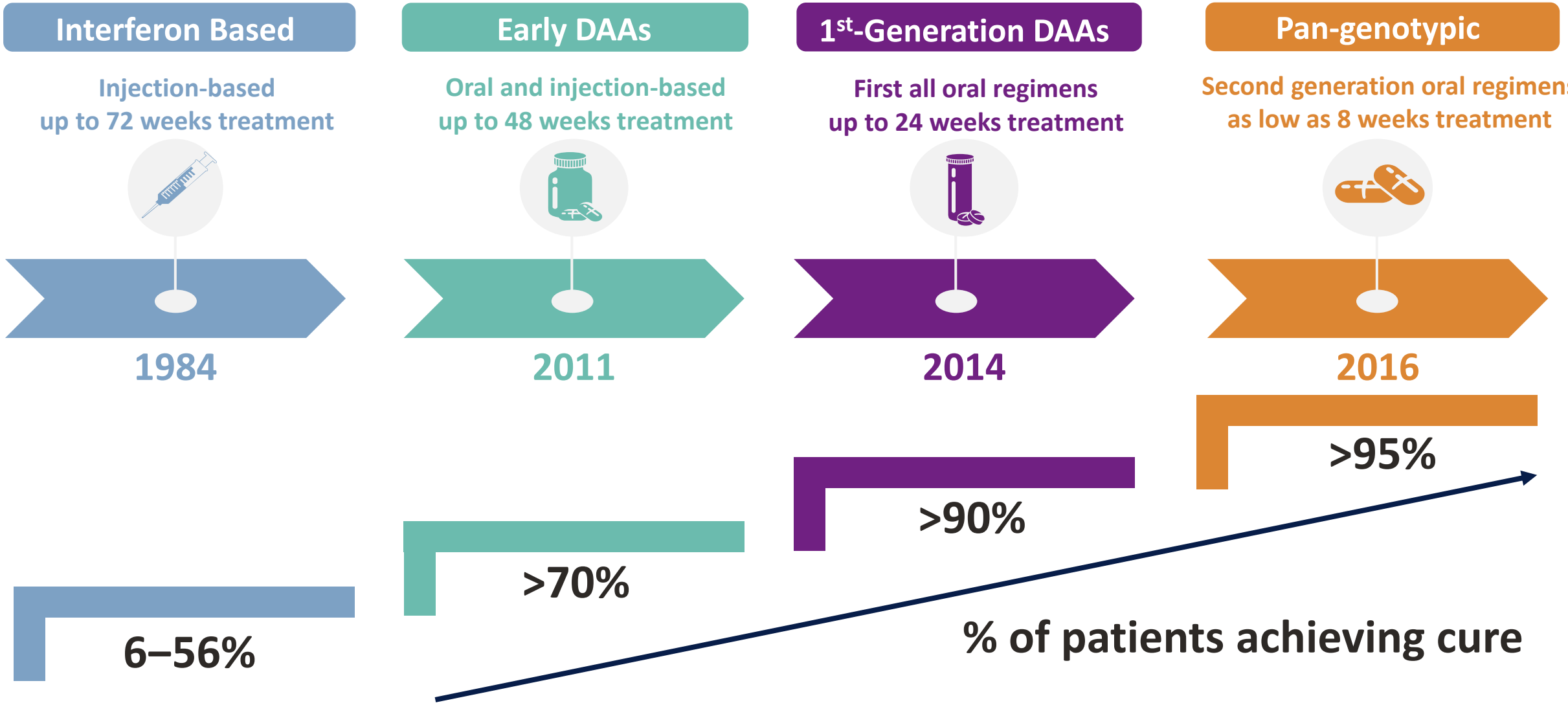
Second generation oral regimens
as low as 8 weeks treatment

2016

DAAs, direct-acting antivirals.

1. Pawlotsky JM, *et al. J Hepatol* 2016; **62:**S87–99; 2. Manns M, *et al. Nat Rev Dis Primers* 2017; **3:**1–19.

There Has Been An Unprecedented Improvement in Cure Rates



DAAs, direct-acting antivirals.

1. Pawlotsky JM, *et al. J Hepatol* 2016; **62:**S87–99; 2. Manns M, *et al. Nat Rev Dis Primers* 2017; **3:**1–19.

Treatment Simplification is a Key Attribute of Pan-genotypic Regimens

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up to 72 weeks treatment

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Second generation oral regimens
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2016

Long treatment durations → Short treatment durations

Injectable → All oral, once-daily dosing

Frequent monitoring → Minimal monitoring

DAAs, direct-acting antivirals.

1. Pawlotsky JM, *et al. J Hepatol* 2016; **62:**S87–99; 2. Manns M, *et al. Nat Rev Dis Primers* 2017; **3:**1–19.

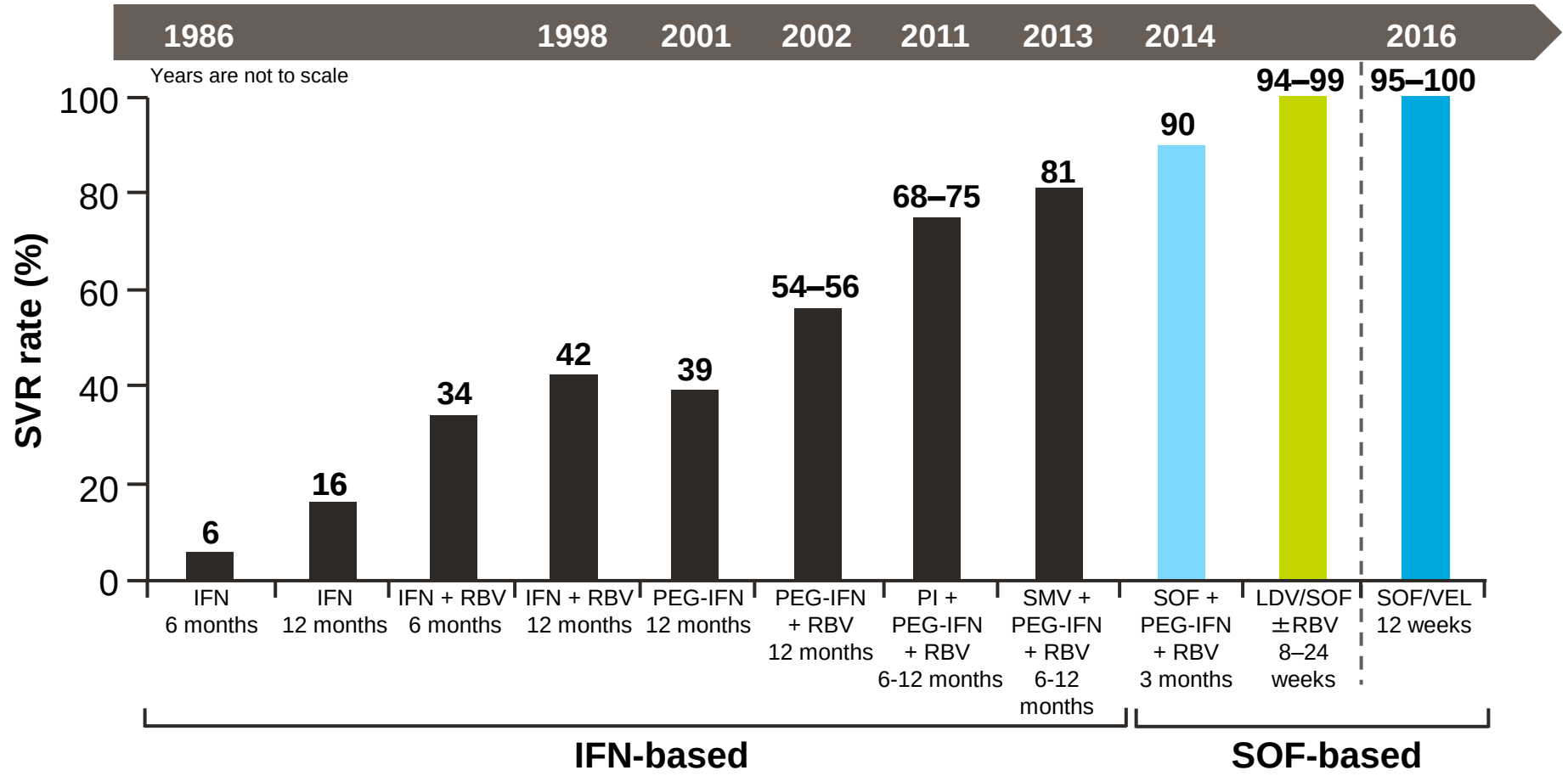
Single tablet regimens are also available, meaning that chronic HCV has become simpler to treat

High pill burden
Multiple clinic visits

vs.

Simpler regimen

Treatment with DAAs achieves SVR in >90% patients



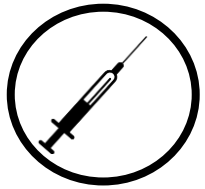
Adapted from Strader DB, et al. Hepatology 2004;39:1147–71; Vertex Pharmaceuticals. INCIVO (telaprevir) SmPC, October 2016; Merck & Co. VICTRELIS (boceprevir) SmPC, May 2017; Manns M, et al. Lancet 2014;384:414–26; Lawitz E, et al. APASL 2013; Oral #LB-02; Afdhal N, et al. N Engl J Med 2014;370:1889–98; Kowdley K, et al. N Engl J Med 2014;370:1879–88; Agarwal K, et al. ILC 2016; Poster #SAT-195

Not head to head studies hence a direct comparison between studies is not possible

Telaprevir is no longer authorized for use in the EU.

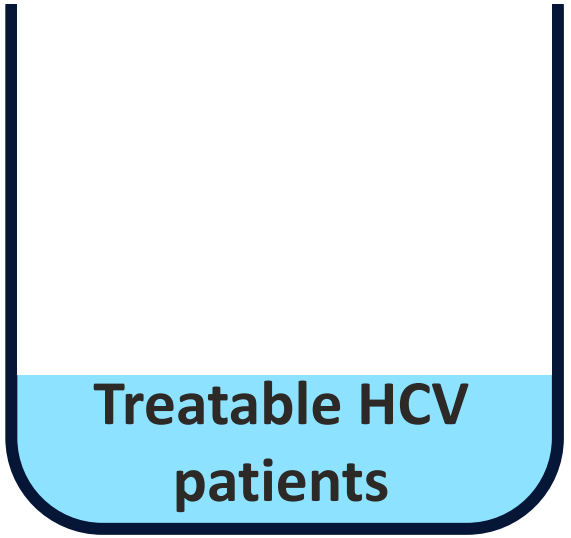
LDV: ledipasvir; PEG-IFN: pegylated interferon; PI: protease inhibitor; SMV: simeprevir; SOF: sofosbuvir; SVR: sustained virological response; VEL: velpatasvir

In the IFN era, a large number of patients were ineligible for treatment



IFN-based therapy era

- Intolerant to IFN
- Intolerant to RBV
- Autoimmune conditions
- Hepatic dysfunction or decompensated cirrhosis
- Severe heart disease
- Pregnant
- Mental health risk



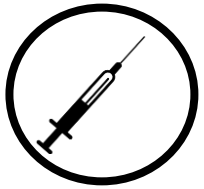
Chronic HCV -infected patients

Roche. PEGASYS (peginterferon alfa-2a) SmPC, November 2016

IFN: interferon; RBV: ribavirin

We are now in the era where the majority of HCV-infected patients can be treated

2013 → **2017**



IFN-based therapy era

- Tolerant to IFN
- Tolerant to RBV
- No autoimmune conditions
- No severe hepatic dysfunction or decompensated cirrhosis
- No severe heart disease
- Not pregnant
- No mental health risk

Treatable HCV patients

Chronic HCV -infected patients

DAA therapy era

- Cirrhotic
- Decompensated cirrhotic
- Co-morbidities
- Renal impairment
- Psychiatric
- Transplant
- PWID

Roche. PEGASYS (pegylated interferon alfa-2a) SmPC, November 2016;

DAAs are now approved in Europe to cure patients with HCV in 8–24 weeks

Nucleotide-based regimens

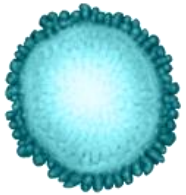
Ledipasvir/sofosbuvir
± ribavirin
Genotypes 1, 3, 4, 5, 6

Sofosbuvir/velpatasvir
± ribavirin
Genotypes 1, 2, 3, 4, 5, 6

Sofosbuvir/velpatasvir /voxilaprevir
Genotypes 1, 2, 3, 4, 5, 6

Sofosbuvir + daclatasvir
± ribavirin
Genotypes 1, 3, 4

HCV



8–24 weeks' treatment

CURE

Non-nucleotide-based regimens

Ombitasvir/paritaprevir/ ritonavir + dasabuvir
± ribavirin
Genotype 1

Ombitasvir/paritaprevir/ ritonavir + ribavirin
Genotype 4

Grazoprevir/elbasvir
± ribavirin
Genotypes 1, 4

Glecaprevir/pibrentasvir
Genotypes 1, 2, 3, 4, 5, 6

Gilead Sciences Europe Ltd. HARVONI▼ (ledipasvir/sofosbuvir) SmPC, September 2017; Gilead Sciences Europe Ltd. EPCLUSA▼ (sofosbuv
June 2017; Gilead Sciences Europe Ltd. VOSEVI▼ (sofosbuvir/velpatasvir/voxilaprevir) SmPC, July 2017;
Bristol-Myers Squibb Pharma EEIG. DAKLINZA▼ (daclatasvir) SmPC, March 2017; AbbVie Ltd. VIEKIRAX▼ (ombitasvir/paritaprevir/ritonavir) SmPC, April 2017;
AbbVie Ltd. EXVIERA▼ (dasabuvir) SmPC, April 2017; Merck Sharp & Dohme Ltd. ZEPATIER▼ (grazoprevir/elbasvir) SmPC, May 2017; AbbVie Ltd. MAVIRET
▼(glecaprevir/pibrentasvir) SmPC August 2017

Guias AEEH : Pacientes no cirroticos

Pacientes no cirroticos					
Pacientes	**Experiencia tratamiento previo**	**SOF/VEL**	**GLE/PIB**	**LDV/SOF**	**EBR/GZR**
Gen 1a	naives	12 sem	8 sem	8-12 sem *	12 sem (RNA-VHC< 800.000 IU/ml)
	Experimentados a IFN	12 sem	8 sem	No	12 sem (RNA-VHC< 800.000 IU/ml)
Gen 1b	naives	12 sem	8 sem	8-12 sem *	12 sem
	Experimentados a IFN	12 sem	8 sem	12 sem	12 sem
Gen 2	naives	12 sem	8 sem	No	No
	Experimentados a IFN	12 sem	8 sem	No	No
Gen 3	naives	12 sem	8-12 sem **	No	No
	Experimentados a IFN	12 sem	8-12 sem **	No	No
Gen 4	naives	12 sem	8 sem	12 sem	12 sem
	Experimentados a IFN	12 sem	8 sem	12 sem	No
Gen 5	naives	12 sem	8 sem	12 sem	No
	experimentados a IFN	12 sem	8 sem	12 sem	No
Gen 6	naives	12 sem	8 sem	12 sem	No
	Experimentados a IFN	12 sem	8 sem	12 sem	No

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Guias AEEH :Pacientes cirroticos

Pacientes con cirrosis compensada					
Pacientes	**Experiencia tratamiento previo**	**SOF/VEL**	**GLE/PIB**	**LDV/SOF**	**EBR/RZR**
Gen 1a	naives	12 sem	12 sem	12 sem	12 sem (RNA-VHC< 800.000 IU/ml)
	Experimentados a IFN	12 sem	12 sem	No	12 sem (RNA-VHC< 800.000 IU/ml)
Gen 1b	naives	12 sem	12 sem	12 sem	12w
	experimentados a IFN	12 sem	12 sem	12 sem	12w
Gen 2	naives	12 sem	12 sem	No	No
	Experimentados a IFN	12 sem	12 sem	No	No
Gen 3	naives	12 sem	12 sem	No	No
	Experimentados a IFN	12 sem	16 sem	No	No
Gen 4	naives	12 sem	12 sem	12 sem	12 sem
	Experimentados a IFN	12 sem	12 sem	12 sem	No
Gen 5	naives	12 sem	12 sem	12 sem	No
	Experimentados a IFN	12 sem	12 sem	12 sem	No
Gen 6	naives	12 sem	12 sem	12 sem	No
	Experimentados a IFN	12 sem	12 sem	12 sem	No

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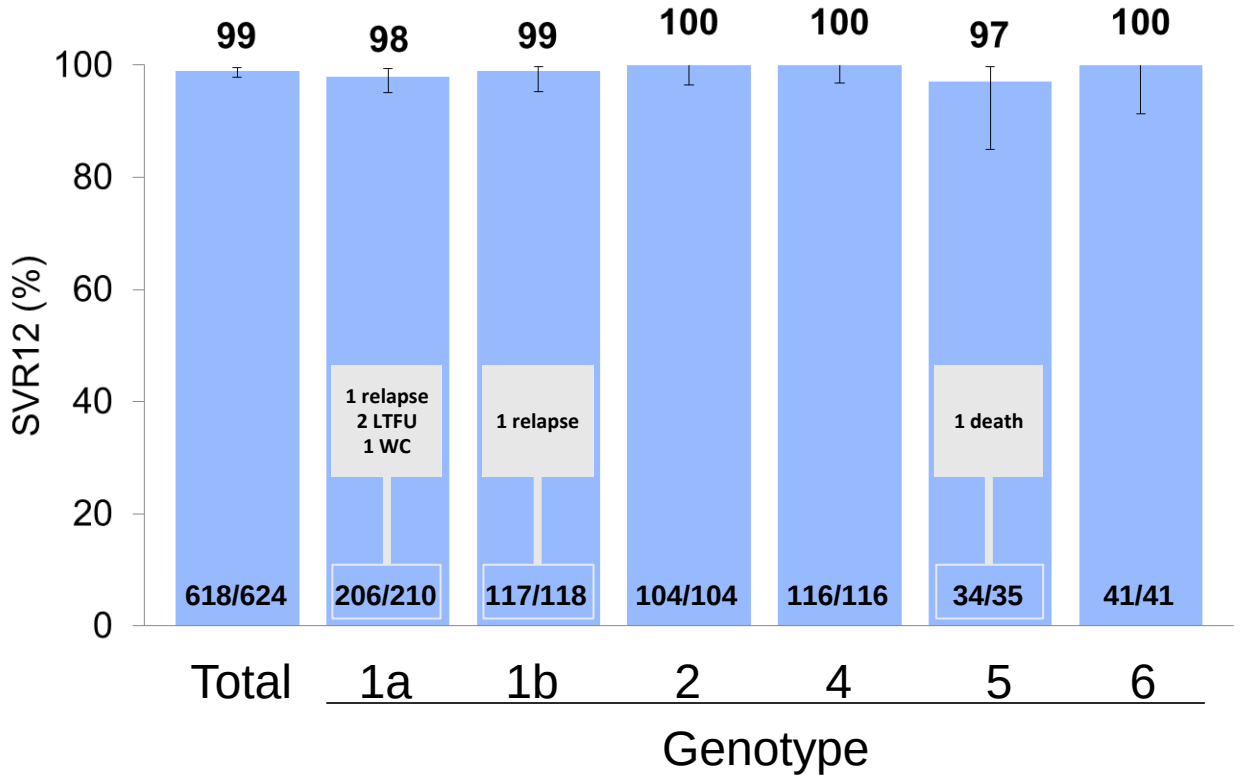
Sofosbuvir/Velpatasvir

ASTRAL-1: SOF/VEL STR for 12 Weeks in GT 1, 2, 4, 5, 6 HCV-Infected Patients ‡

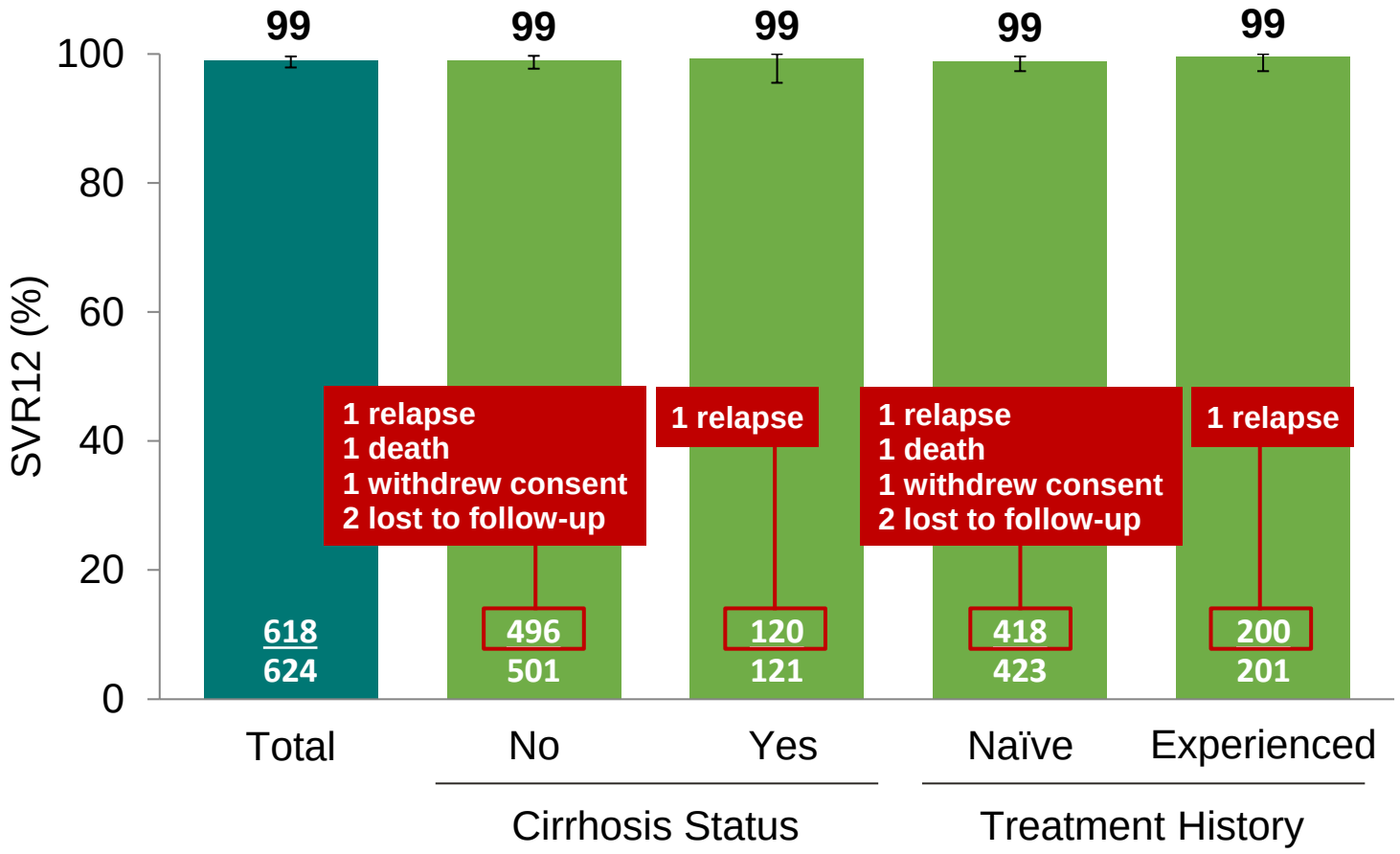


LTFU=lost to follow up; WC=withdrew consent

Feld, AASLD, 2015, LB-2. Feld JJ, et al. *N Engl J Med*. 2015. DOI: 10.1056/NEJMoa1512610

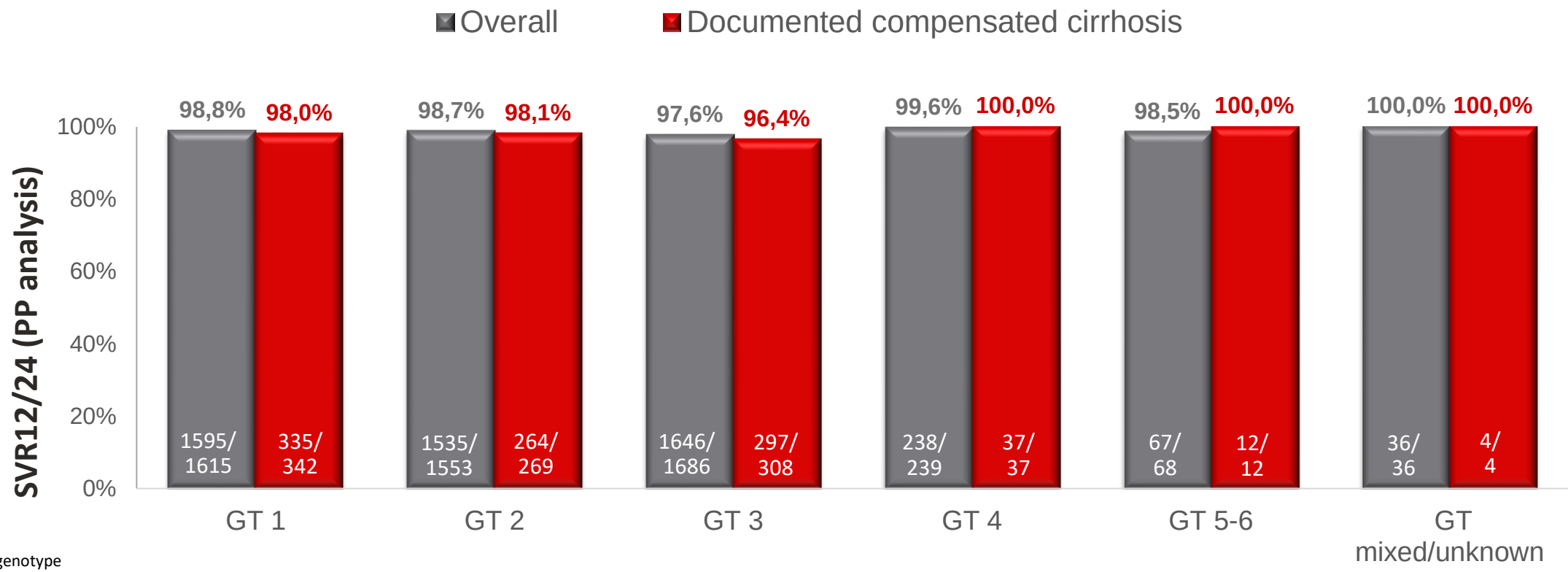
Sofosbuvir/Velpatasvir : SVR12 by Cirrhosis or Prior Treatment

ASTRAL-1, SOF/VEL



Error bars represent 95% confidence intervals.

High efficacy of SOF/VEL in a large, real-world multinational cohort (N=5214)

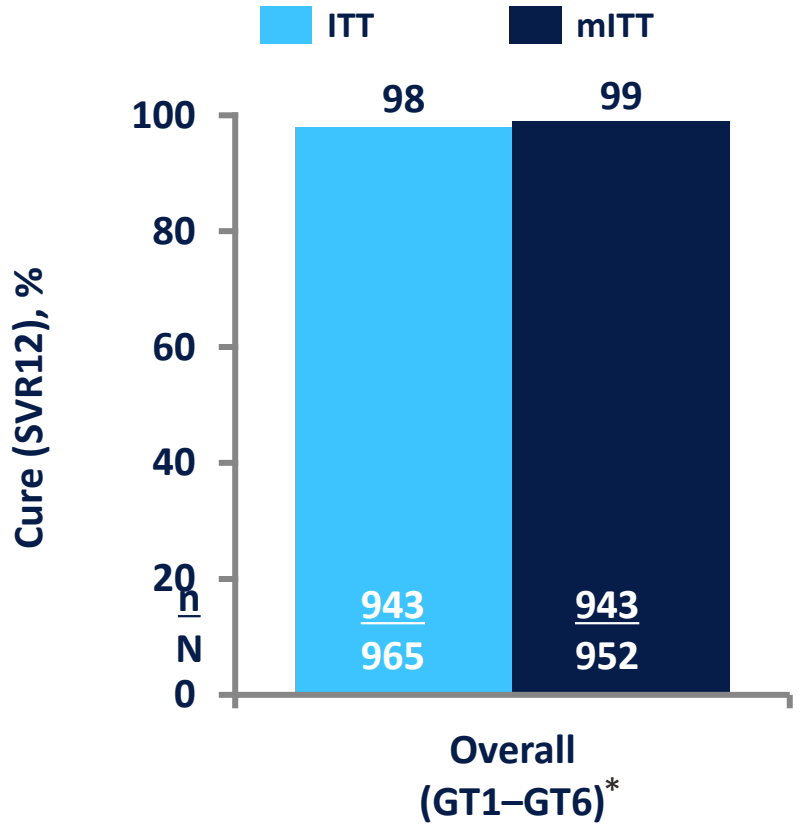


GT = genotype

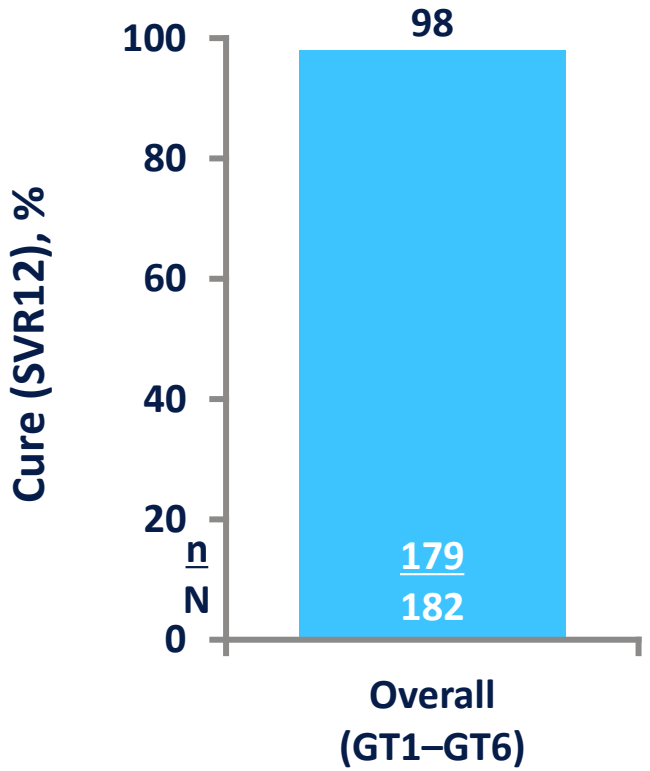
17 patients with missing GT information
Information about presence of cirrhosis in each GT was available for 4557 patients (PP)

G/P for 8 or 12 Weeks is an Effective Treatment Regimen for HCV-Infected Patients With or Without Cirrhosis

G/P for 8 weeks in patients without cirrhosis[1]



G/P for 12 weeks in treatment-naive patients with cirrhosis[2]



* GT3 patient were treatment-naive only; GT1, 2, 4-6 had prior experience with peg-IFN + ribavirin +/- sofosbuvir, or sofosbuvir + ribavirin
ITT, intent-to-treat; Mitt, modified intent-to-treat; TE, treatment-experienced; TN, treatment-naïve.

1. Puoti M, et al. J Hepatol 2018; 69:293–300;
2. Krishnan P, et al. J Hepatol 2017; 66(Suppl):S500 (poster presentation FRI-205).

▼Este medicamento está sujeto a seguimiento adicional, es prioritaria la notificación de sospechas de reacciones adversas asociadas a este medicamento.

Effectiveness and Safety of ▼Glecaprevir/Pibrentasvir for the Pangenotypic Treatment of Chronic Hepatitis C: Results from a Spanish Cohort (Hepa-C)

Dr. Marc Puigvehi, Dr. Agustin Albillos, Ms. Ana Viu, Manuel Nicolas Hernandez Guerra, Dr. Inmaculada Fernandez, Dr. Martín Prieto, Dr. Xavier Torras Collell, Dr. Jose Miguel Rosales Zabal, Dr. Lourdes Grande, Dr. Rosa Morillas, Dr. Moises Diago, Dr. Beatriz De Cuenca, Dr. Manuel Delgado, Dr. Lucia Bonet, Dr. Juan Turnes, Dr. Javier Crespo, Dr. Carme Baliellas, Dr. Jose Luis Calleja, Dr. Ester Badia, Dr. Juan Manuel Pascasio, Dr. Jose Maria Moreno Planas, Dr. Vanesa Bernal, Dr. Isabel Carmona, Dr. Miguel Fernandez, Javier Salmeron, Pablo Bellot, Dr. Jesus M. Gonzalez-Santiago, Dr. Maria Luisa Gutierrez, Dr. J.Javier Moreno, Dr. Maria Dolores Anton, Dr. Juan De La Vega, Dr. Desamparados Escudero-Garcia, Dr. Juan Arenas and Dr. Jose Antonio Carrion.

Hospital del Mar (1), H. U. Ramón y Cajal (2), Hospital Universitario de Canarias (3), H. U. 12 Octubre (4), HU La Fe (5), Hospital de la Santa Creu i Sant Pau (6), Hospital Costa del Sol (7), Hospital Virgen de Valme (8), H. Germans Trias i Pujol (9), Hospital General Universitario de Valencia (10), Hospital Universitario de Getafe (11), Hospital Universitario La Coruña (12), Hospital Universitario Son Espases (13), Complejo Hospitalario de Pontevedra (14), Hospital Marqués de Valdecilla (15), Hospital Universitari de Bellvitge (16), HU Puerta de Hierro Majadahonda (17), Hospital Universitario de Burgos (18), H. U. Virgen del Rocío (19), C. H. U. de Albacete (20), Hospital Miguel Servet (21), Hospital Virgen Macarena (22), H. San Pedro de Alcantara (23), H. U. San Cecilio (24), Hospital General y Universitario de Alicante (25), Complejo Asistencial Universitario de Salamanca (26), H. U. Fundacion Alcorcon (27), H. General de Segovia (28), Hospital Dr. Peset (29), H. San Agustin de Avilés (30), Hospital Clínico de Valencia (31), Hospital Universitario Donostia (32).

The Liver Meeting (AASLD)
• San Francisco, United States •
9th November 2018

abbvie

HEPC-ES-00019-FM (noviembre'18)

Puigvehi M. et al. AASLD 2018, San Francisco 9-13 nov, P#601

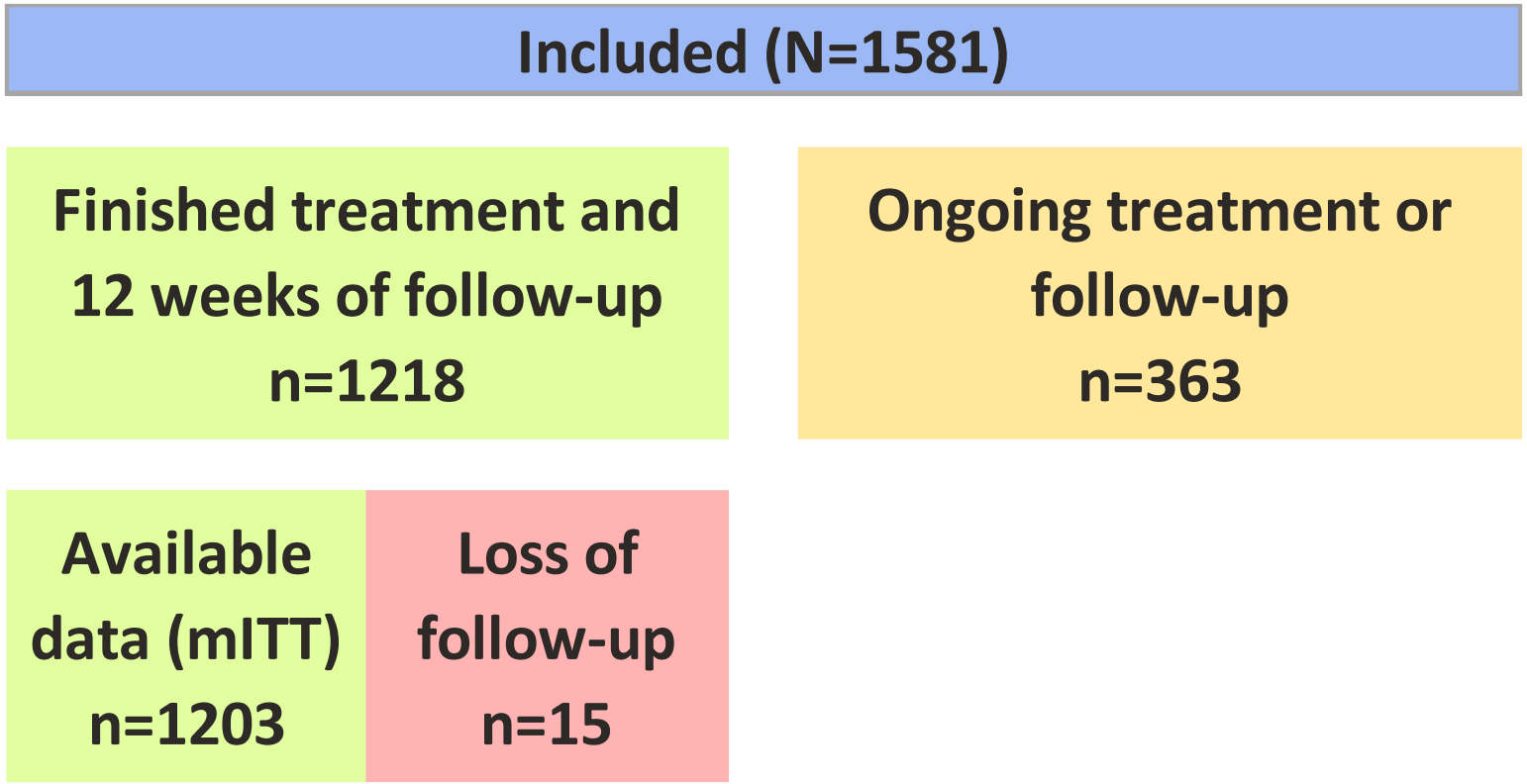
Baseline characteristics:

Characteristics	N=1581
Gender (male,%)	883 (55.9)
Age (years)	54 (48-61)
Caucasian (n,%)[†]	1249 (94.7)
BMI (Kg/m2)[§]	25.1 (22.7-27.9)
LSM (kPa)	5.8 (4.8-7.5)
<9.6 kPa[3]	1339 (86.3)
>12.5 kPa[4]	112 (7.2)
Former i.v. drug user (n,%)	294 (18.6)
Treatment naïve (n,%)	1362 (86.1)
HCV-RNA (log10 IU/ml)	6.3 (5.8-6.7)

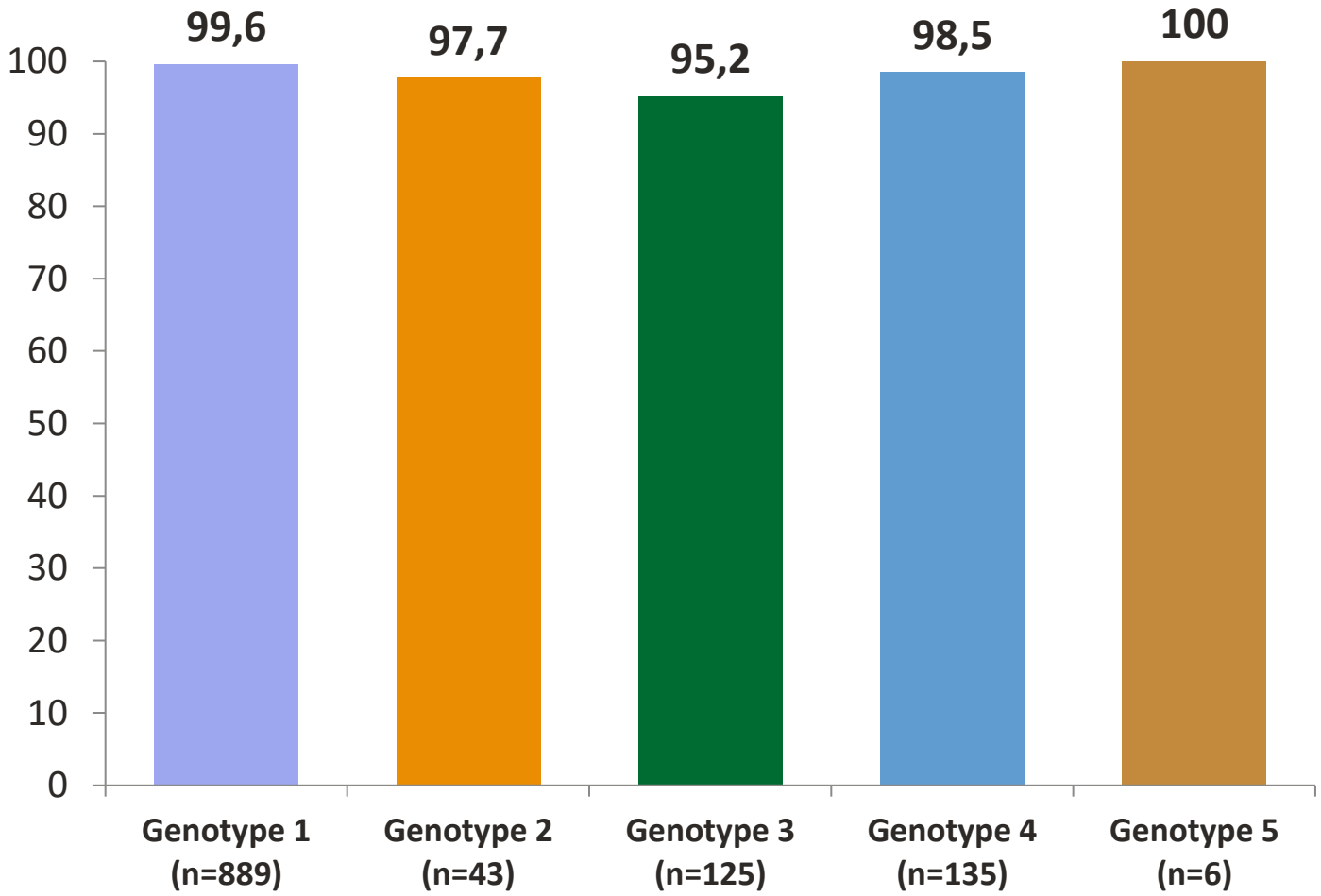
Characteristics	N=1581
Genotype:	
1a (n,%)	420 (26.9)
1b (n,%)	706 (45.1)
3 (n,%)	205 (13.1)
Bilirubin (mg/dL)	0.6 (0.5-0.8)
ALT (IU/mL)	47 (32-74)
Albumin (g/L)	43 (41-46)
Hemoglobin (g/dL)	15 (13.9-15.9)
Platelets (10^9)	211 (177-253)

[†] Data available in 1319 (83.4%) patients
[§] BMI available in 947 (59.9%) patients

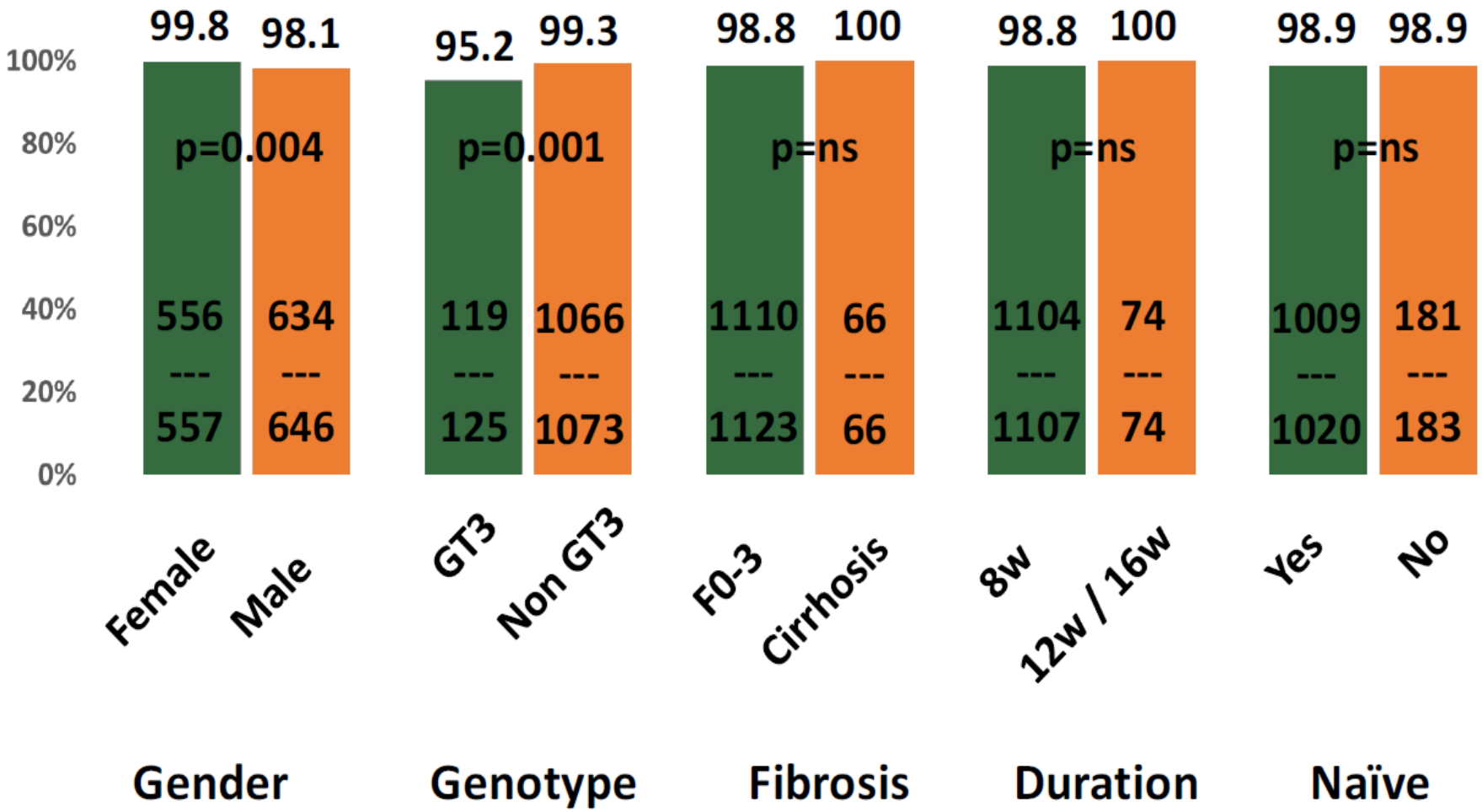
Study flowchart:



SVR (%) according to genotype (mITT)



Subgroup SVR12 analysis (%):



Safety and lab. abnormalities:

Adverse events	N=1203
Any adverse event (n,%)	53 (4.4)
Severe adverse events (n,%)	1(<0.1)
Treatment discontinuation (n,%)	0 (0)
Hb < 10 g/dl (n%)	1(<0.1)
AST or ALT > 5 ULN (n,%)	0 (0)
Bilirubin > 3 ULN (n,%)	3 (0.2)
Exitus (n,%)	1(<0.1)

P#601
Effectiveness and Safety of Glecaprevir/Pibrentasvir for the Pangenotypic Treatment of Chronic Hepatitis C: Results from a Spanish Cohort (Hepa-C)

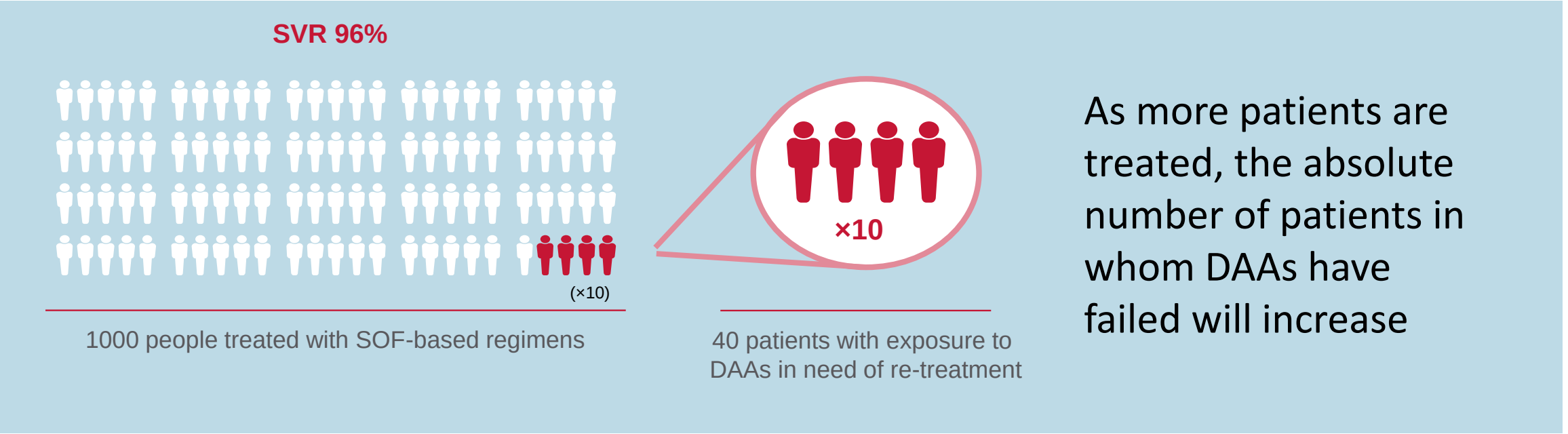
CONCLUSIONS

- The pangenotypic combination of glecaprevir and pibrentasvir shows, in clinical practice, very high SVR rates (>95%) in all subgroups of patients with chronic hepatitis C, regardless of treatment duration, fibrosis stage, and prior antiviral treatment.

- Treatment safety profile is excellent, with a very low rate (%) of severe adverse events and discontinuations.

- Real-world results of the present study are comparable to those obtained in clinical trials.

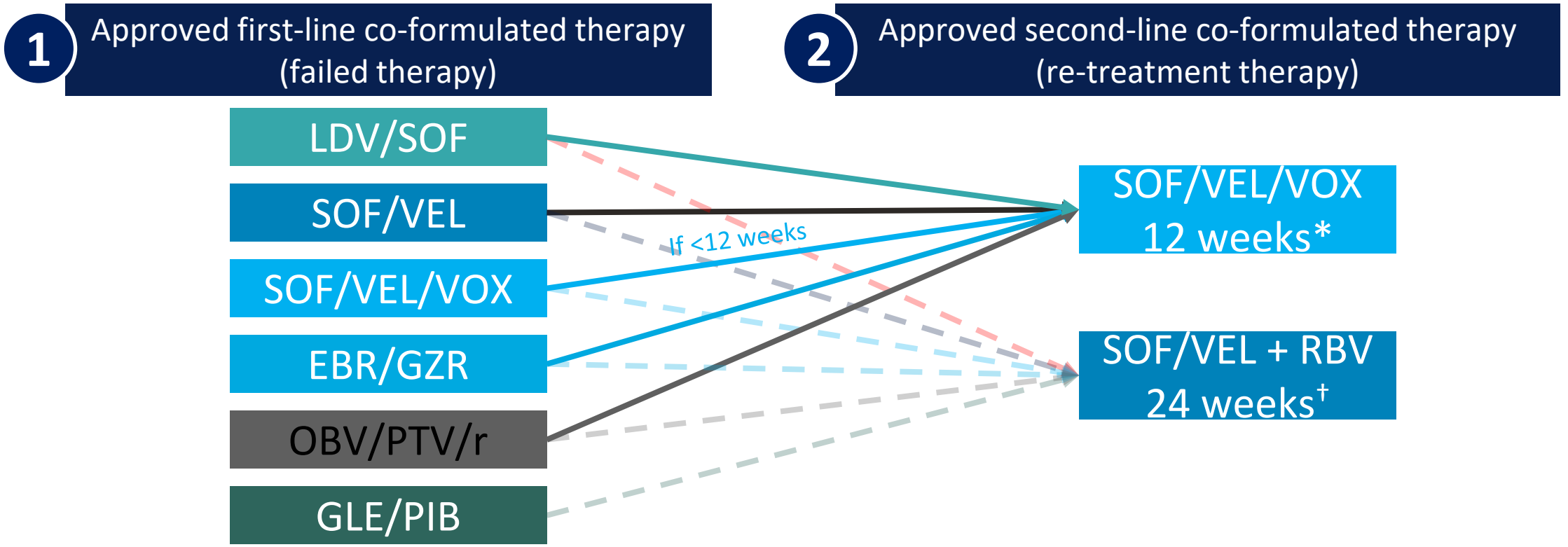
Even with an Effective First-line Therapy, Treatment Will Fail in a Small Proportion of Patients



This is a concept slide based on a real-world SVR of 96% calculated from 9391 patients treated with LDV/SOF ± RBV and SOF/VEL ± RBV in the TRIO, HCV-TARGET and DHC-R cohorts.

Curry M, et al. ILC 2017; Oral #102; Flamm S, et al. ILC 2017; Poster #SAT-279; Khalili M, et al. ILC 2017; Poster #SAT-222; Roberts S, et al. ILC 2017; Poster #SAT-280; Terrault N, et al. Gastroenterology 2016;151:1131–40; Vermehren J, et al. ILC 2017; Poster #FRI-247; Welzel TM, et al. ILC 2016; Poster #SAT-274.

What Are the Licensed Options in the EU for Patients in Whom Treatment Has Failed?



AbbVie Ltd. EXVIERA▼ (dasabuvir), SmPC, March 2018; AbbVie Ltd. MAVIRET▼ (glecaprevir/pibrentasvir), SmPC, February 2018; AbbVie Ltd. VIEKIRAX▼ (ombitasvir/paritaprevir/ritonavir), SmPC, March 2018; Bristol-Myers Squibb Pharmaceuticals Ltd. DAKLINZA▼ (daclatasvir), SmPC, January 2018; Gilead Sciences Ltd. EPCLUSA▼ (sofosbuvir/velpatasvir), SmPC, March 2018; Gilead Sciences Ltd. HARVONI▼ (ledipasvir/sofosbuvir), SmPC, December 2017; Gilead Sciences Ltd. SOVALDI▼ (sofosbuvir), SmPC, October 2017; Gilead Sciences Ltd. VOSEVI▼ (sofosbuvir/velpatasvir/voxilaprevir), SmPC, September 2017; Merck Sharp & Dohme Ltd. ZEPATIER▼ (elbasvir/grazoprevir), SmPC, July 2017.

*SOF/VEL/VOX has not been tested in patients who have experienced treatment failure with GLE/PIB; †SOF/VEL + RBV for 24 weeks can be considered for patients at high risk of clinical disease progression without alternative treatment options.

EU: European Union

With an Effective Treatment and Re-treatment Strategy, the Vast Majority of Patients Could Achieve an SVR

SVR 96%

1000 people treated with SOF-based regimens

SVR 97%

Treat 40 who require re-treatment with SOF/VEL/VOX*

Overall

Up to 999/1000 eligible patients could potentially achieve an SVR

Based on eligibility to SOF/VEL/VOX treatment*

*SOF/VEL/VOX is not recommended in patients with moderate or severe hepatic impairment (CTP B or CTP C). This is a concept slide based on a real-world SVR of 96% calculated from 9391 patients treated with LDV/SOF ± RBV and SOF/VEL ± RBV in the TRIO, HCV-TARGET and DHC-R cohorts. Re-treatment SVR of 97% with SOF/VEL/VOX is reported in the POLARIS-1–4 integrated analysis.

Curry M, et al. ILC 2017; Oral #102; Flamm S, et al. ILC 2017; Poster #SAT-279; Khalili M, et al. ILC 2017; Poster #SAT-222; Roberts S, et al. ILC 2017; Poster #SAT-280; Terrault N, et al. Gastroenterology 2016;151:1131–40; Vermehren J, et al. ILC 2017; Poster #FRI-247; Welzel TM, et al. ILC 2016; Poster #SAT-274.

Recomendaciones para el tratamiento de la hepatitis C[1]

Monoinfectados o coinfectados VIH (≥18 años) o adolescentes (12-17 años) con **hepatitis C crónica sin cirrosis o con cirrosis compensada** (Child-Pugh A), incluyendo **pacientes naïve** (nunca han sido tratados para el VHC) o con **tratamiento previo** (han sido previamente tratados para el VHC con IFN-α pegilado y ribavirina; IFN-α pegilado, ribavirina y sofosbuvir; o sofosbuvir y ribavirina).

Tipo de tratamiento	Genotipo	Cirrosis	Experiencia tratamiento previo	Sofosbuvir/ velpatasvir	Glecaprevir/ pibrentasvir	Sofosbuvir/ velpatasvir/ voxilaprevir	Grazoprevir/ elbasvir
Tratamiento simplificado, sin determinación del genotipo/ subtipo[a]	Todos los genotipos	Sin cirrosis	Naïve	12 semanas	8 semanas	No	No
			Tratamiento previo				
		Compensada (cirrhosis Child-Pugh A)	Naïve				
			Tratamiento previo		12 semanas		
Genotype/subtype determination-based treatment	Genotipo 1a, 1b, 2, 4, 5 y 6	Sin cirrosis	Naïve	12 semanas	8 semanas	No	12 semanas (solo genotipo 1b)
			Tratamiento previo				
		Compensada (cirrhosis Child-Pugh A)	Naïve				
			Tratamiento previo		12 semanas		
	Genotipo 3	Sin cirrosis	Naïve	12 semanas	8 semanas	No	No
			Tratamiento previo		12 semanas		No
		Compensada (cirrhosis Child-Pugh A)	Naïve	12 semanas con ribavirina en función del peso[b]*	8-12 semanas[c]	12 semanas[b]	No
			Tratamiento previo		16 semanas		No
	Subtipo 1l, 4r, 3b, 3g, 6u, 6v o cualquier otro subtipo que contenga de forma natural una o varias RASs[d] en NS5A	Sin cirrosis	Naïve	Desconocido	Desconocido	12 semanas	No
			Tratamiento previo				
		Compensada (cirrhosis Child-Pugh A)	Naïve				
			Tratamiento previo				

IFN: interferón; **RASs**: sustituciones asociadas a resistencia. [a]Siempre que la determinación del genotipo y subtipo del VHC no esté disponible, no sea asequible y/o limite el acceso al tratamiento. [b]Si se lleva a cabo un test de resistencias, solo los pacientes con RAS en NS5A Y93H deberían ser tratados con sofosbuvir/velpatasvir y ribavirina o con sofosbuvir/velpatasvir/voxilaprevir, meintras que los pacientes sin RAS en Y93H deberían ser tratados con sofosbuvir/velpatasvir solo. [c]En pacientes naïve infectados con el genotipo 3 con cirrosis compensada (Child-Pugh A), el tratamiento con glecaprebir/pibrentasvir puede ser acortado a 8 semanas, pero se necesitan más datos para consolidar esta recomendación. [d]Determinada mediante análisis de secuencia de la región NS5A por medio de secuenciación poblacional o secuenciación profunda (valor de corte 15%).

*Según FT, se puede contemplar la adición de ribavirina en pacientes infectados con GT3 con cirrosis compensada. En pacientes con cirrosis descompensada, la pauta es Epclusa® con ribavirina 12 semanas.

1. EASL Clinical Practice Guidelines. EASL recommendations on treatment of hepatitis C – Final update of the series. J Hepatol. 2020. DOI:https://doi.org/10.1016/j.jhep.2020.08.018.

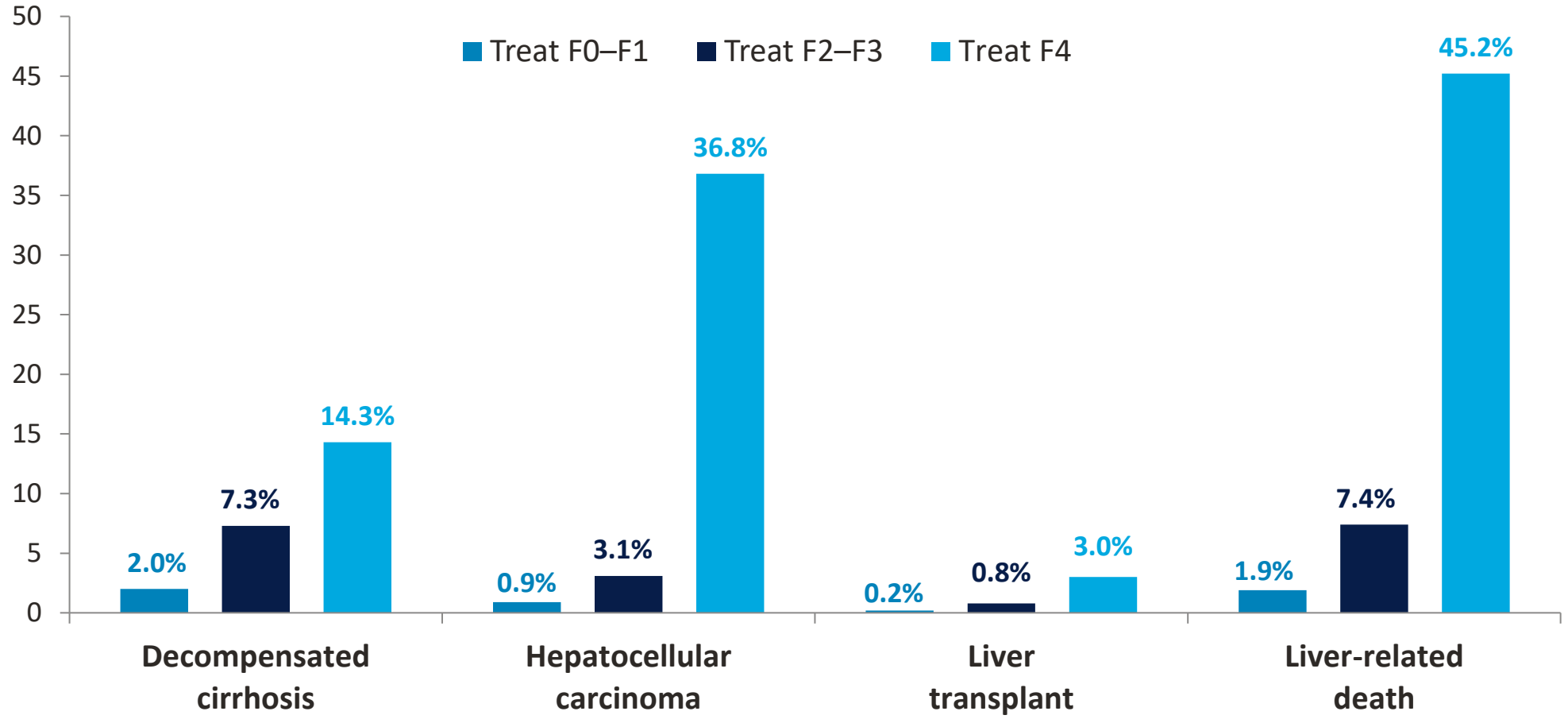
Agenda

- Revolution in treatment of Hepatitis C
  - Real World Evidence
- Impact of treatment in long term outcomes
- The time for a Elimination Plan
  - Microelimination in risk groups
  - Macroelimination
- Simplification in the management of patients
- Conclusions

Treatment at Early Stages of HCV Infection Reduces the Likelihood of Liver-Related Morbidity and Mortality

METAVIR score:

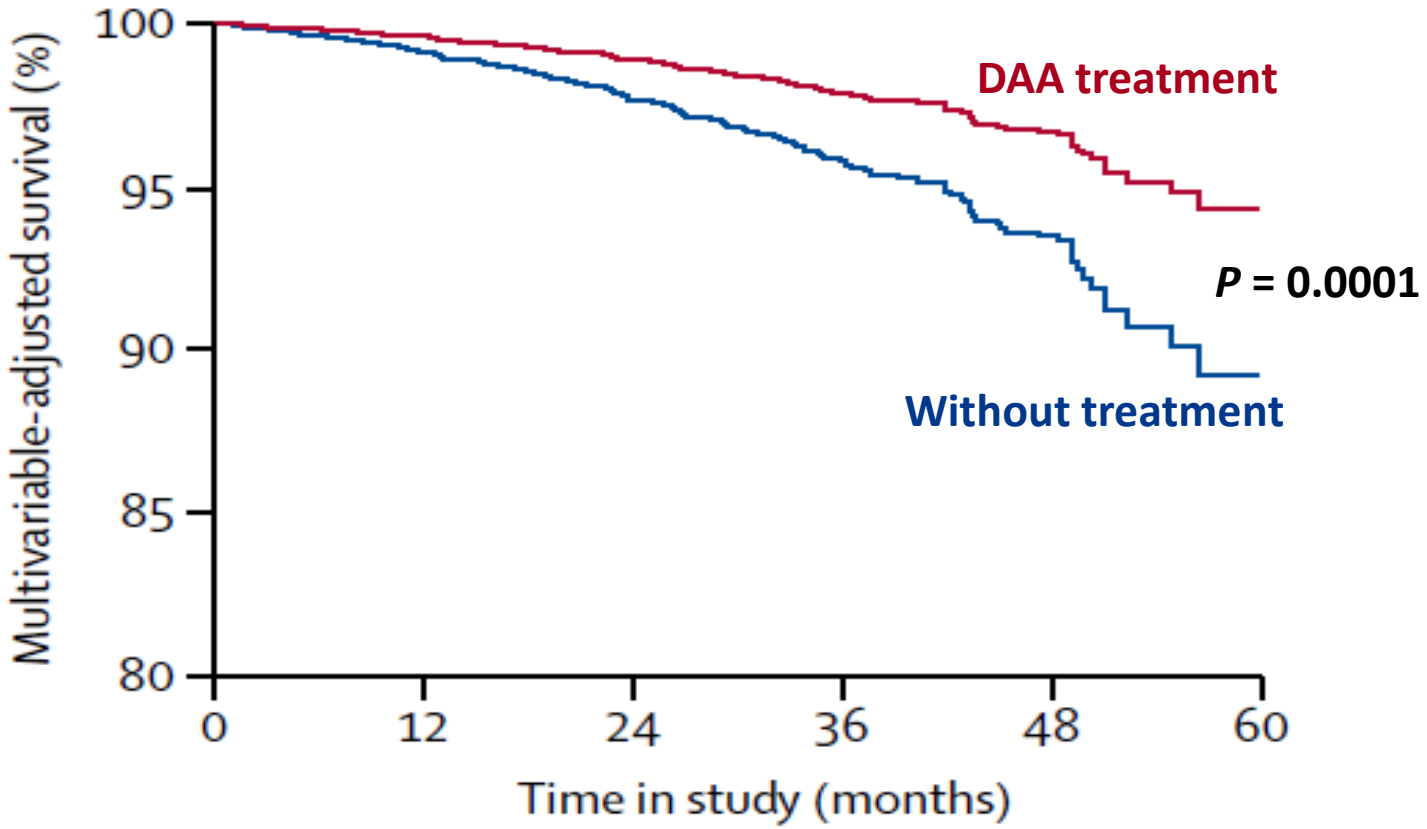
- F0 = No fibrosis
- F1 = Minimal fibrosis
- F2 = Significant fibrosis
- F3 = Advanced fibrosis
- F4 = Cirrhosis



Sanchex Gonzales Y, et al. J Hepatology 2017.

First Prospective Evidence for All Oral HCV Regimens Demonstrated a Decrease in Mortality Rate Associated with Treatment

French ANRS CO22 HEPATHER cohort
All-cause deaths in chronic HCV patients: weighted survival curves (IPTW)

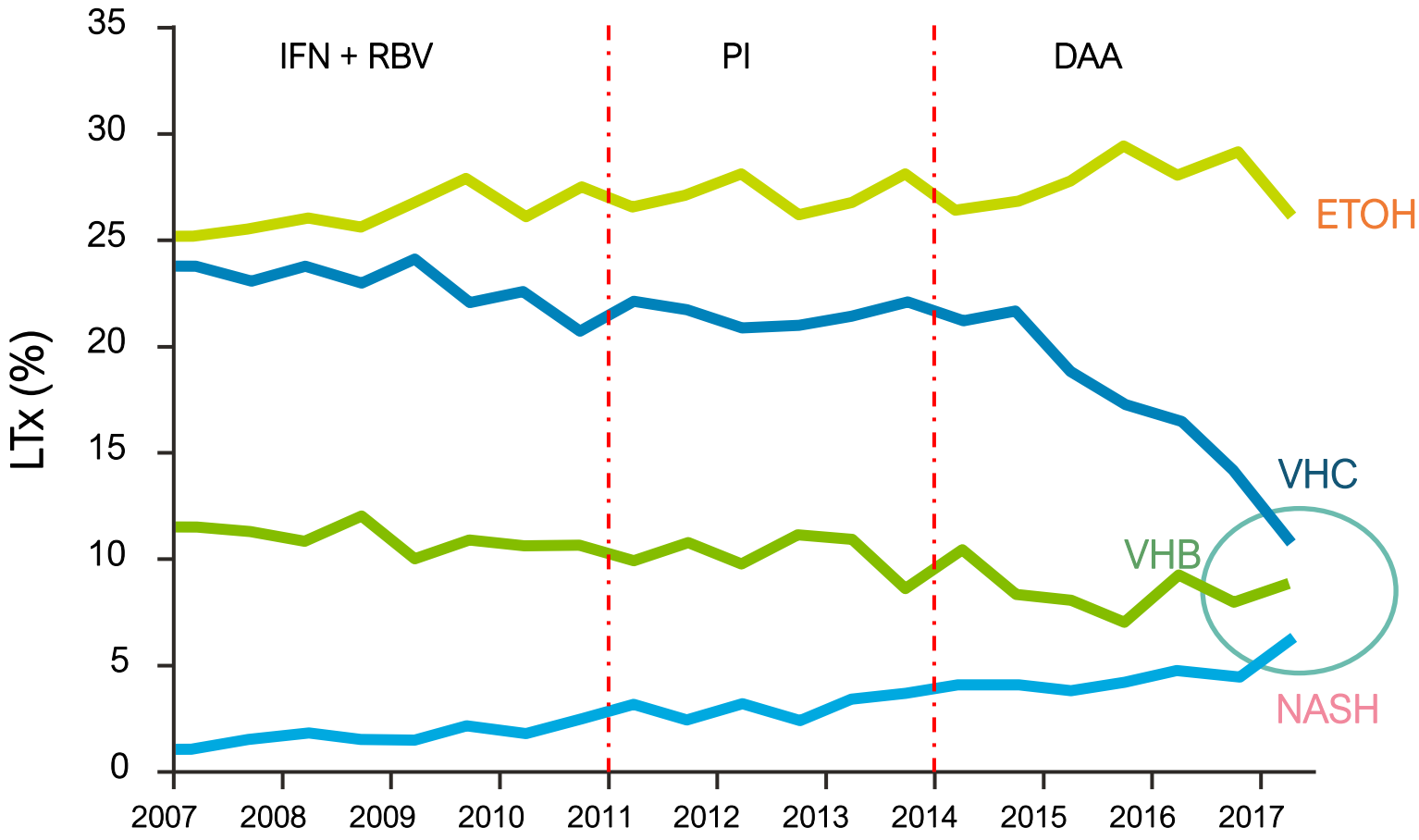


DAA treatment was associated with a decreased risk of death (HR = 0.48; 95% CI: 0.33–0.70)

IPTW, Inverse probability of Treatment Weighting (Cox proportional hazard model).

Carrat F, *et al*. *Lancet* 2019; **393:**1453–64.

Change in indications for Liver Trasplantation

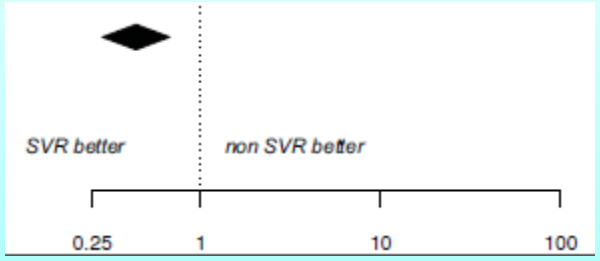


Indications LTx (%)	DCC	HCC
ETOH	74,5	25,5
VHC	53,6	46,4
VHB	62,9	37,1
NASH	75,3	24,7

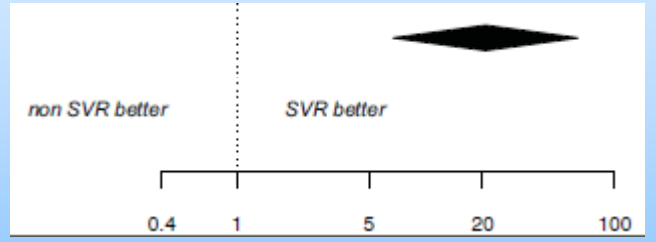
Achieving Cure is Associated with a Reduction in Extrahepatic Mortality

Systematic review and meta-analysis of 48 studies analysing the impact of achieving cure (versus not achieving cure) on extrahepatic manifestations of CHC

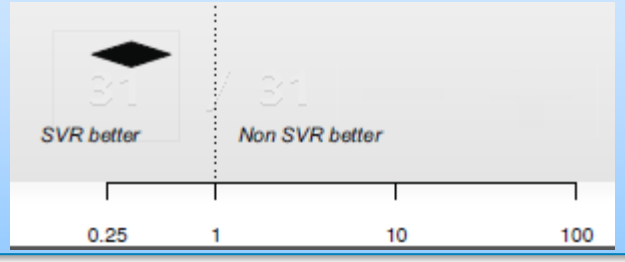
Reduction in extrahepatic mortality

Studies	Odds ratio	OR [95% CI]
N = 4		0.44 [0.28–0.67]
		Overall effect P>0.001

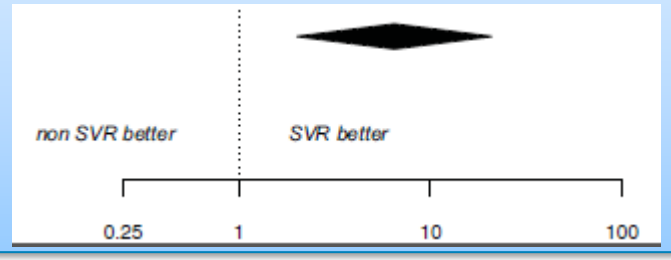
Higher complete remissions in patients with cryoglobulinemia vasculitis

Studies	Odds ratio	OR [95% CI]
N = 16		20.76 [6.73–64.05]
		Overall effect P=0.01

Protective effect on the incidence of diabetes

Studies	Odds ratio	OR [95% CI]
N = 7		0.34 [0.21–0.56]
		Overall effect P<0.001

Higher objective response in patients with malignant B-cell lymphoproliferative disease

Studies	Odds ratio	OR [95% CI]
N = 5		6.49 [2.02–20.85]
		Overall effect P=0.0017

CHC, chronic hepatitis C; CI, confidence interval; OR, odds ratio.

Cacoub P, et al. Gut 2018;**67**:2025–2034.

Agenda

- Revolution in treatment of Hepatitis C
  - Real World Evidence
- Impact of treatment in long term outcomes
- The time for a Elimination Plan
  - Microelimination in risk groups
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The Spanish National Strategic Plan 2015: a pioneer in Europe

The **Spanish National Strategic Plan** has allowed Spain to be recognised as one of the countries that has advanced the most towards the objectives set by the WHO for the elimination of hepatitis C by 2030

Strategic aims

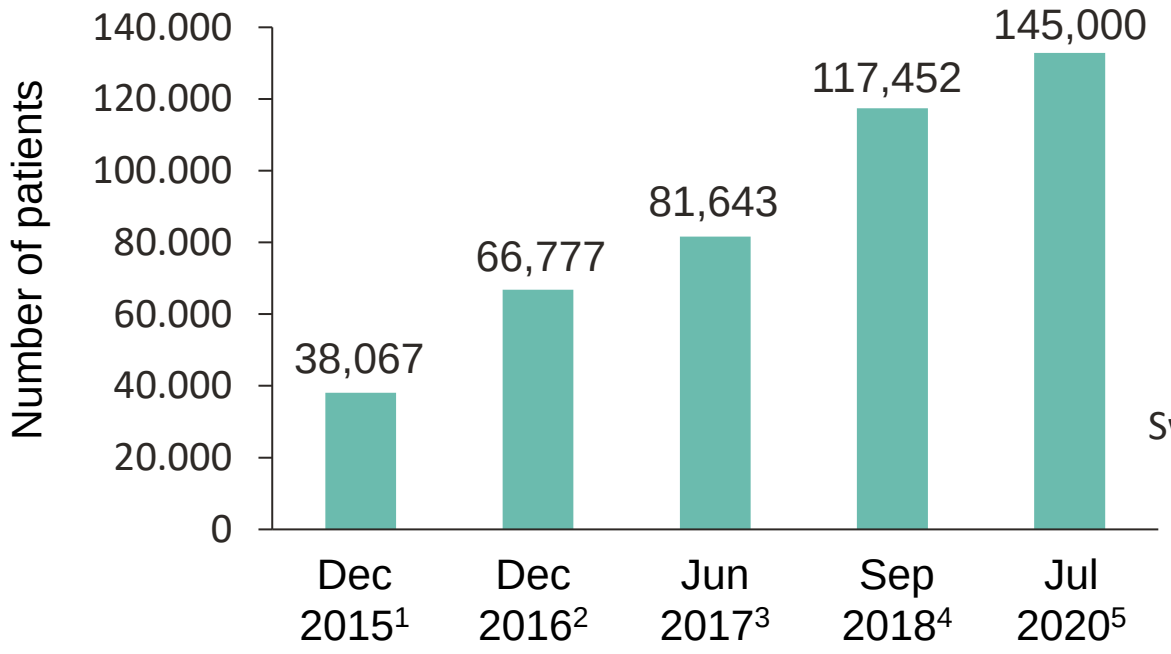
- **Quantifying the problem and determining measures for prevention**
- **Defining the scientific-clinical criteria to determine when to use DAA drugs**
- **Co-ordinating implementation throughout the healthcare system**
- **Advancing knowledge of prevention, diagnosis and treatment through research and development**

Policy approaches to tackling hepatitis C in Spain. Available at: https://eiuperspectives.economist.com/sites/default/files/Gilead%20Hep%20C%20report%20WEB%20%281%29.pdf (accessed February 2020)

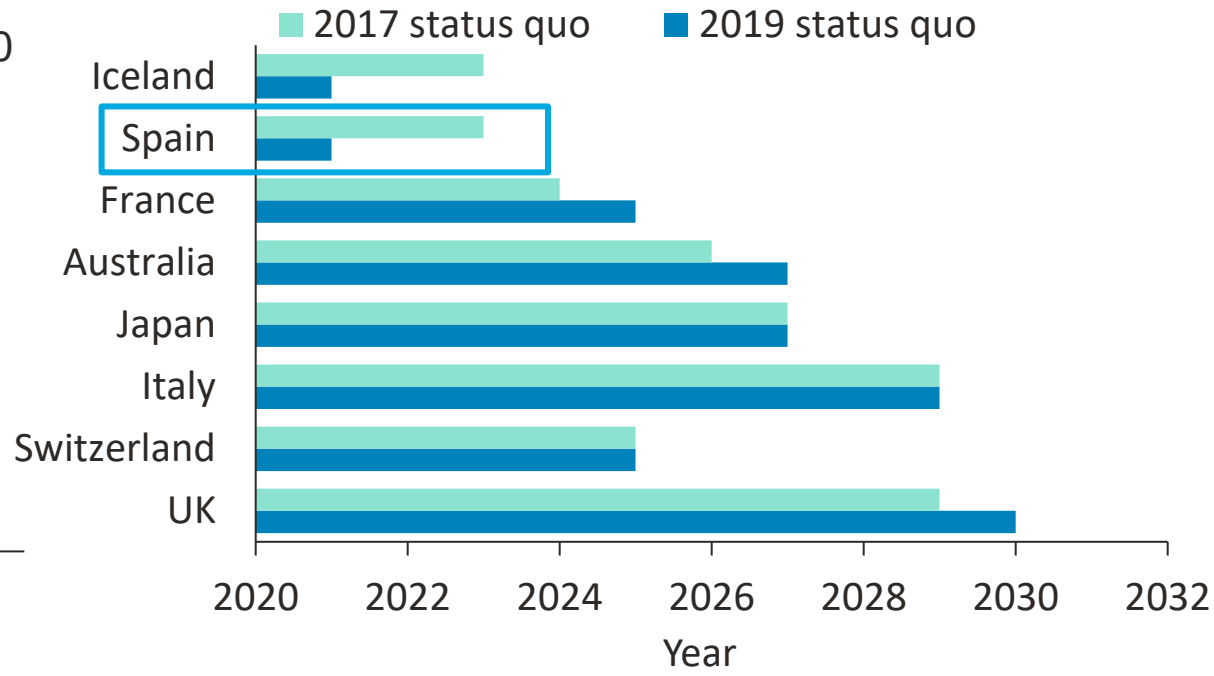
DAA: direct-acting antiviral

Spain's Progress in HCV Elimination

Patients Treated with DAAs since 2015



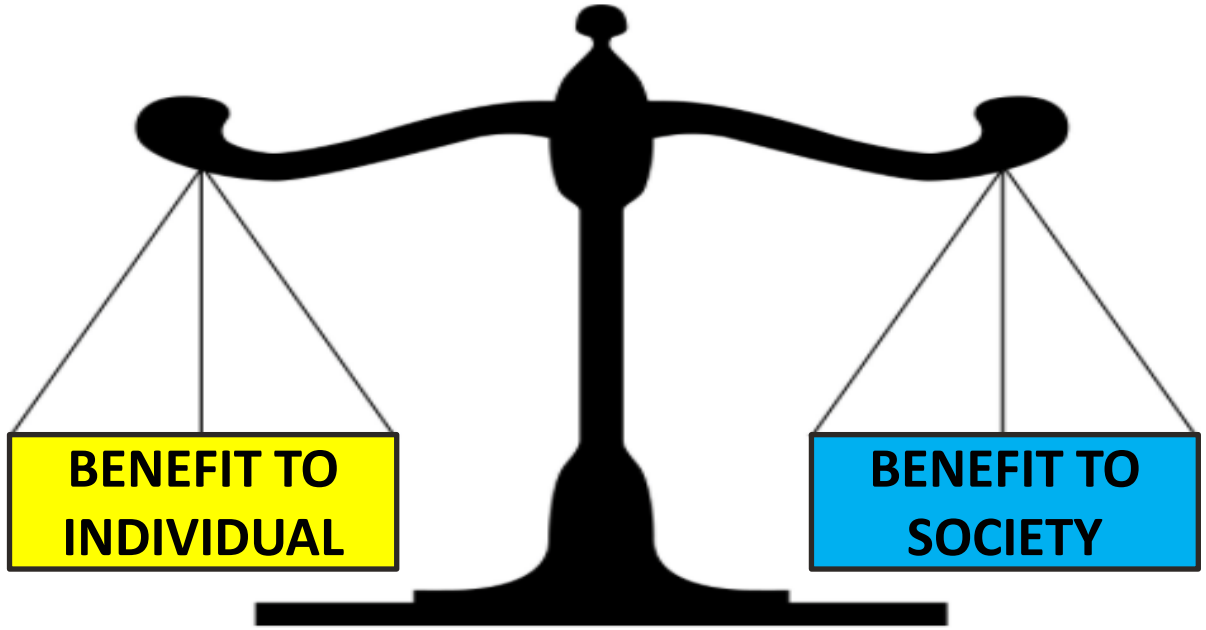
Estimated Year of HCV Elimination by Country[6]



In 4 years (2015–2019), over 126,000 patients with HCV have been treated and cured

1. La Moncloa. Available at: https://www.lamoncloa.gob.es/serviciosdeprensa/notasprensa/msssi/Paginas/2016/230216reunionhepatitisc.aspx (Accessed February 2020); 2. Ministry of Health. Available at: https://www.mscbs.gob.es/ciudadanos/enfLesiones/enfTransmisibles/hepatitisC/PlanEstrategicoHEPATITISC/docs/informeSituacionPEAHCPresentadoCISNS_Jun2017.pdf (Accessed February 2020); 3. dariofarma. Available at: https://www.diariofarma.com/2017/09/03/hepatitis-c-81-643-pacientes-tratados-9552-respuesta-positive (Accessed February 2020); 4. Ministry of Health. Available at: https://www.mscbs.gob.es/ciudadanos/enfLesiones/enfTransmisibles/hepatitisC/PlanEstrategicoHEPATITISC/docs/Plan_Estrategico_Abordaje_Hepatitis_C_(PEAHC).pdf (Accessed February 2020); 5. La Moncloa. Available at: https://www.lamoncloa.gob.es/serviciosdeprensa/notasprensa/sanidad/Paginas/2019/011019-hepatitis.aspx (Accessed February 2020); 6. Gamkrelidze I et al. Liver Int. 2021;41(3):456–63.

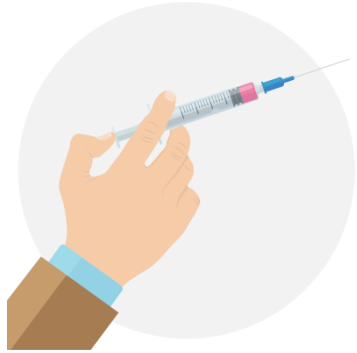
A Shift in Emphasis



- Prevention of cirrhosis, HCC and premature death
- Alleviation of extra-hepatic symptoms

- Prevention of transmission to others
- Achievement of elimination

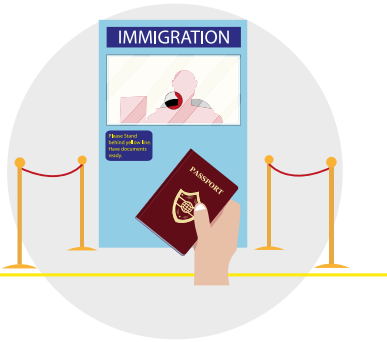
Risk population : Local aspects



PWIDS

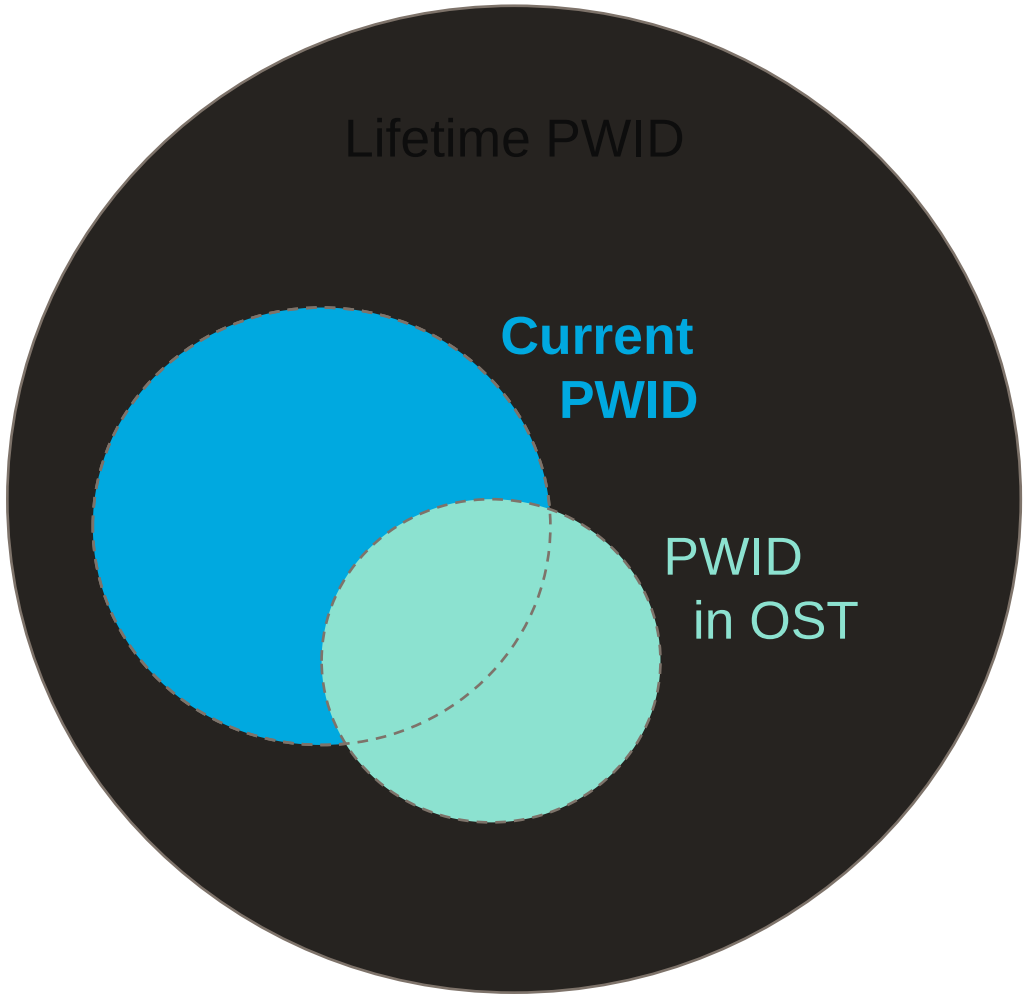
Prisoners

MSM



Inmigrants

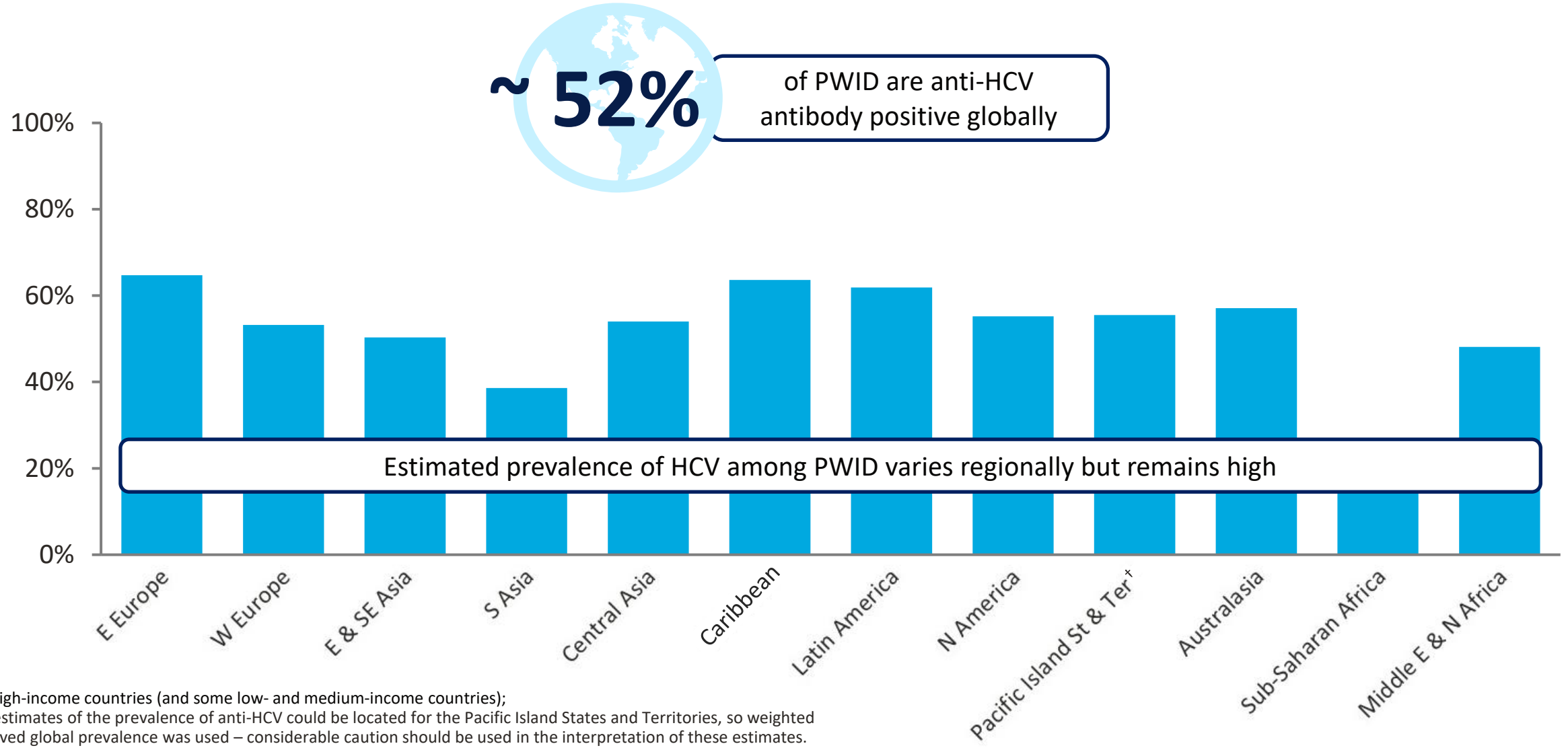
PWID Population Definitions



Marginalized:
- Socioeconomic
- Prisoners
- Homeless

Slide credit: clinicaloptions.com

HCV is Endemic among PWID



* In high-income countries (and some low- and medium-income countries);
† No estimates of the prevalence of anti-HCV could be located for the Pacific Island States and Territories, so weighted observed global prevalence was used – considerable caution should be used in the interpretation of these estimates.
PWID, people who inject drugs.

Degenhardt L. *Lancet Glob Health* 2017; **5:**e1192–e1207.

Treating PWID Will be Critical to Reduce Transmission of HCV

of existing infections occur among PWID

of new infections occur among PWID*

As a great proportion of HCV infections occur among PWID or former PWID, it will be critical to focus on treatment of this population to reduce transmission and overall HCV prevalence

* In high-income countries (and some low- and medium-income countries).

Grebely J, et al. Antiviral Res 2014; 104:62–72.

HCV Treatment Guidelines Now Recommend the Treatment of PWID

EASL[1]

*"Treatment must be considered without delay in individuals at risk of transmitting HCV (**PWID**) (A1)"*

AASLD[2]

*"**Active or recent drug use** or a concern for re-infection is **not a contraindication** to HCV treatment (Class IIA, Level B)"*

WHO[3]

*"All adults and adolescents (aged 12–17 years) with chronic HCV infection, **including PWID**, should be assessed for antiviral treatment"*

INHSU[4]

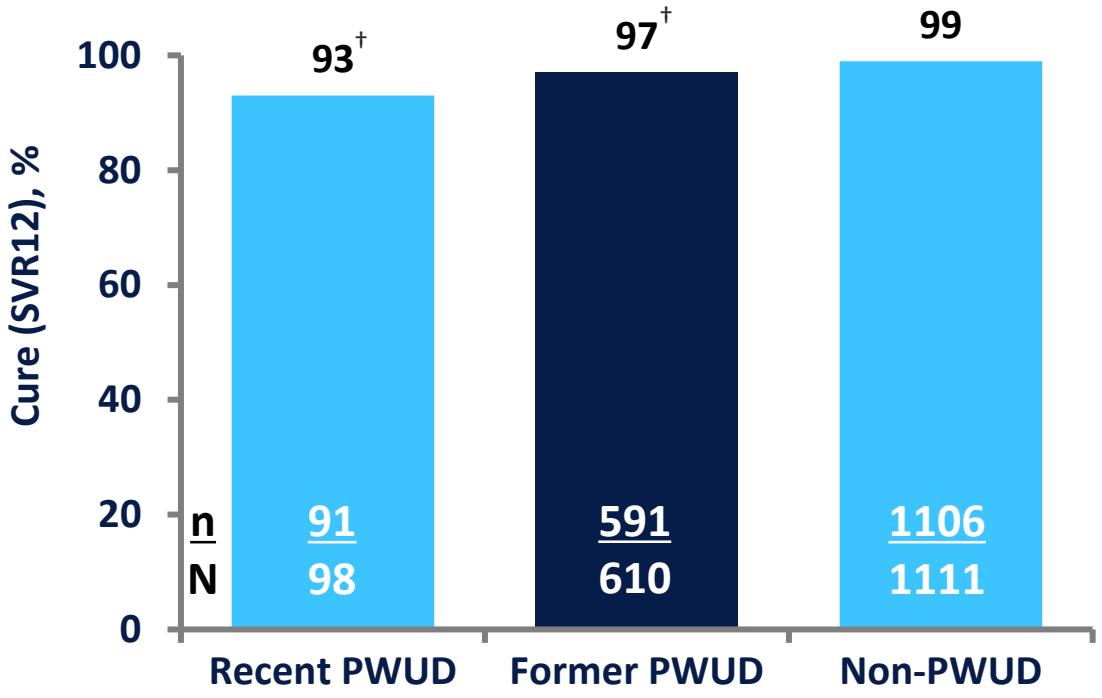
*"Treatment is recommended for **PWID** with chronic HCV infection (Class I, Level A)"*

International guidelines recommend regular HCV testing for PWID and, if HCV positive, PWID should start HCV therapy

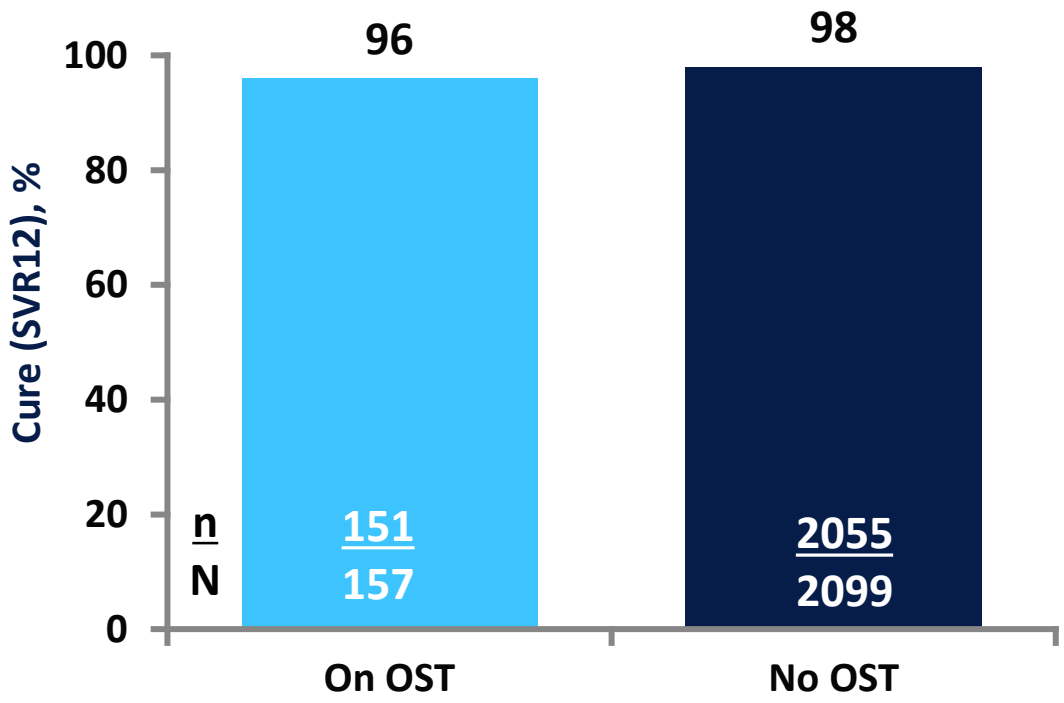
1. EASL recommendations on the treatment of hepatitis C 2018. *J Hepatol* 2018; **69:**461–511;
2. AASLD Management of unique and key populations with HCV infection 2018. Available at: https://www.hcvguidelines.org/unique-populations/pwid (accessed September 2018);
3. WHO Guidelines for Care and Treatment of Persons Diagnosed with Chronic Hepatitis 2018. Available at: http://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf?ua=1 (accessed September 2018);
4. Grebely J, *et al. Int J Drug Policy* 2015; **26:**1028–1038.

G/P Achieved High Cure Rates in Patients with HCV Infection and Recent Drug Use or On OST

G/P for 8 or 12 weeks in HCV-infected patients with a recent history of drug use*[1]



G/P for 8, 12 or 16 weeks in HCV-infected PWID on OST[2]

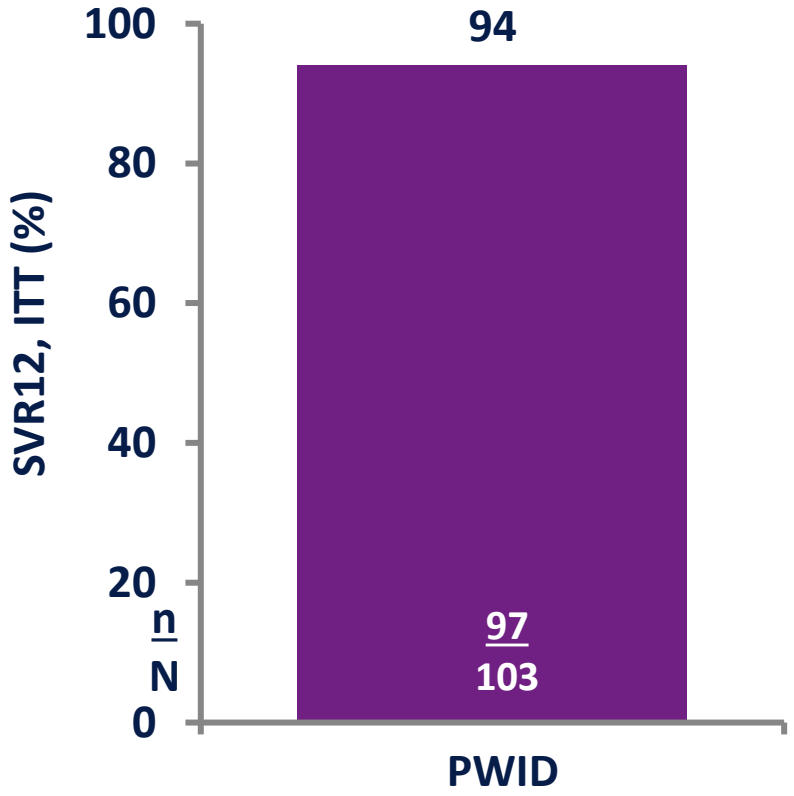


* Recent PWUD defined as self-reported injection drug use within 12 months prior to screening and/or positive urine drug screen; Former PWUD defined as self-reported injection drug use more than 12 months prior to screening and negative urine drug screen; †p<0.0001 compared to non-PWUD.

1. Foster GR, *et al*. *Drug Alcohol Depend* 2019; **194:**487–494.
2. Grebely J, *et al*. *Int J Drug Pol* 2019; **66:**73–79.

SOF/VEL for 12 Weeks Achieved High Cure Rates in Patients with HCV Infection and Recent Injecting Drug Use

SIMPLIFY study: SOF/VEL for 12 weeks in patients with HCV infection and recent injecting drug use



Grebely J, *et al. Lancet Gastroenterol Hepatol* 2018; **3:**153–161.

▼Este medicamento está sujeto a seguimiento adicional, es prioritaria la notificación de sospechas de reacciones adversas asociadas a este medicamento.

Efficacy and Safety of ▼glecaprevir/pibrentasvir for the Pangenotypic Treatment of Chronic Hepatitis C in former intravenous drug users: Subanalysis from a Spanish Real-World Cohort (Hepa-C)

Broquetas T.[1], Mateos B.[2], Puigvehí M.[1], Hernández-Guerra M.[3], Fernández I.[4], Prieto M.[5], Torras X.[6], Rosales J.M.[7], Figueruela B.[8], Morillas R.M.[9], Diago M.[10], de Cuenca B.[11], Delgado M.[12], Bonet L.[13], Turnes J.[14], Crespo J.[15], Marquez Rodriguez P.[16], Calleja J.L.[17], Badia E.[18], Pascasio J.M.[19], Moreno J.M.[20], Bernal V.[21], Bellido F.[22], Fernandez M.[23], Salmerón J.[24], Bellot P.[25], González-Santiago J.M.[26], Gutierrez M.L.[27], Moreno J.J.[28], Antón M.D.[29], De la Vega J.[30], Escudero D.[31], Arenas J.[32], Carrión J.A.[1]

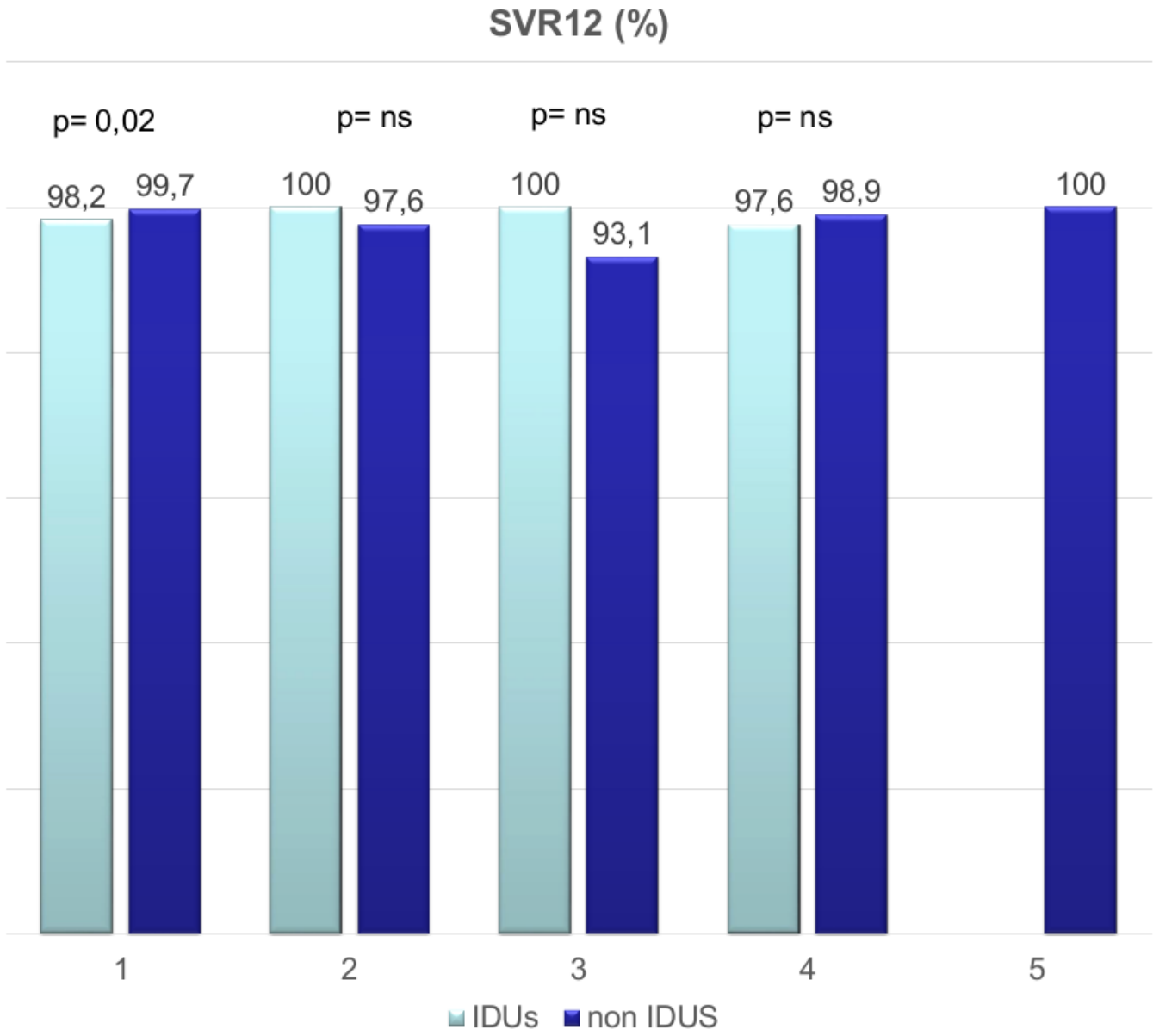
Hospital del Mar (1), H. U. Ramón y Cajal (2), Hospital Universitario de Canarias (3), H. U. 12 Octubre (4), HU La Fe (5), Hospital de la Santa Creu i Sant Pau (6), Hospital Costa del Sol (7), Hospital Virgen de Valme (8), H. Germans Trias i Pujol (9), Hospital General Universitario de Valencia (10), Hospital Universitario de Getafe (11), Hospital Universitario La Coruña (12), Hospital Universitario Son Espases (13), Complejo Hospitalario de Pontevedra (14), Hospital Marqués de Valdecilla (15), Hospital Universitari de Bellvitge (16), HU Puerta de Hierro Majadahonda (17), Hospital Universitario de Burgos (18), H. U. Virgen del Rocío (19), C. H. U. de Albacete (20), Hospital Miguel Servet (21), Hospital Virgen Macarena (22), H. San Pedro de Alcantara (23), H. U. San Cecilio (24), Hospital General y Universitario de Alicante (25), Complejo Asistencial Universitario de Salamanca (26), H. U. Fundacion Alcorcon (27), H. General de Segovia (28), Hospital Dr. Peset (29), H. San Agustin de Avilés (30), Hospital Clínico de Valencia (31), Hospital Universitario Donostia (32).

Presented at the European Association for the Study of the Liver's 54th Annual International Liver Congress, 10–14 April 2019, Vienna, Austria

abbvie

HEPC-ES-00029-FM (abril 2019)

Results – SVR according to genotype (mITT)



Adverse Events

	IDUs	Non IDUs
Any adverse event, n (%)	2 (1)	51 (5)
Serious AE, n (%)	0 (0)	1 (0,1)
Treatment discontinuation, n (%)	0 (0)	0 (0)
Hb <10 g/dl, n (%)	0 (0)	1 (0,1)
AST or ALT >5 ULN, n (%)	0 (0)	0 (0)
Bilirubin > 3 ULN, n (%)	0 (0)	3 (0,3)
Exitus, n (%)	0 (0)	1 (0,1)*

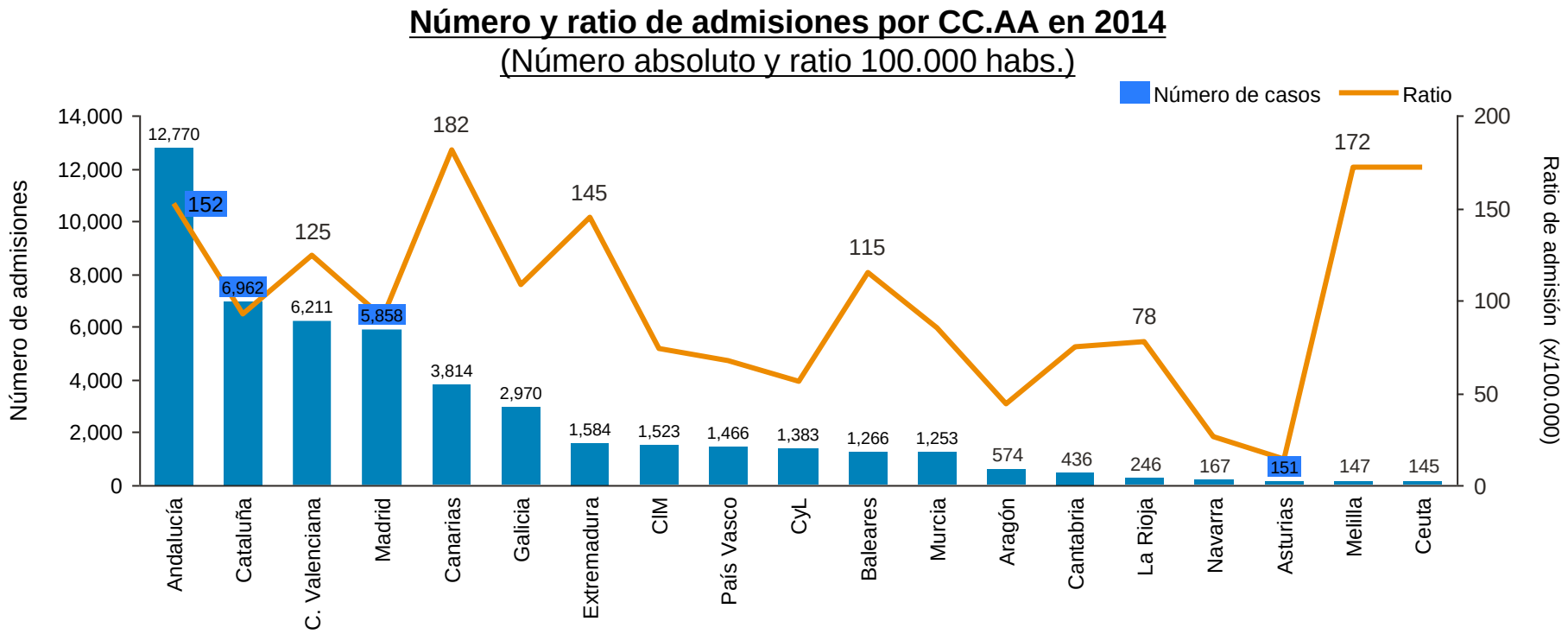
* Death not related with treatment

THU-124
Efficacy and Safety of glecaprevir/pibrentasvir for the Pangenotypic Treatment of Chronic Hepatitis C in former intravenous drug users: Subanalysis from a Spanish Real-World Cohort (Hepa-C)

CONCLUSIONS

Our real-world data confirm that G/P is an effective and save pangenotypic therapy for patients with chronic hepatitis C and prior IDU, similarly to the general population.

Addiction Center in Spain : Admisions



Números de centros	155	62	41	40	30	17	26	11	38	20	17	8	10	3	9	3	4	1	1
Admisiones por centro [1]	82	**112**	**151**	**146**	**127**	**174**	60	**138**	38	69	74	**157**	57	**145**	27	56	37	**147**	**145**

Fuente: Informe 2016 del Observatorio Español de la Droga y las Toxicomanías (OEDT); IQVIA Analysis
Note (1): Total admissions divided by number of second level centers

The Role of the Specialised Nurse for Patients Unable to Visit the Hospital

Patients

Weekly

Specialised nurse

Onsite:
Medical history
Blood sample
FibroScan®

1 Virtual evaluation by hepatologist

2 Hepatologists

HOSPITAL

3 Take medication from hospital

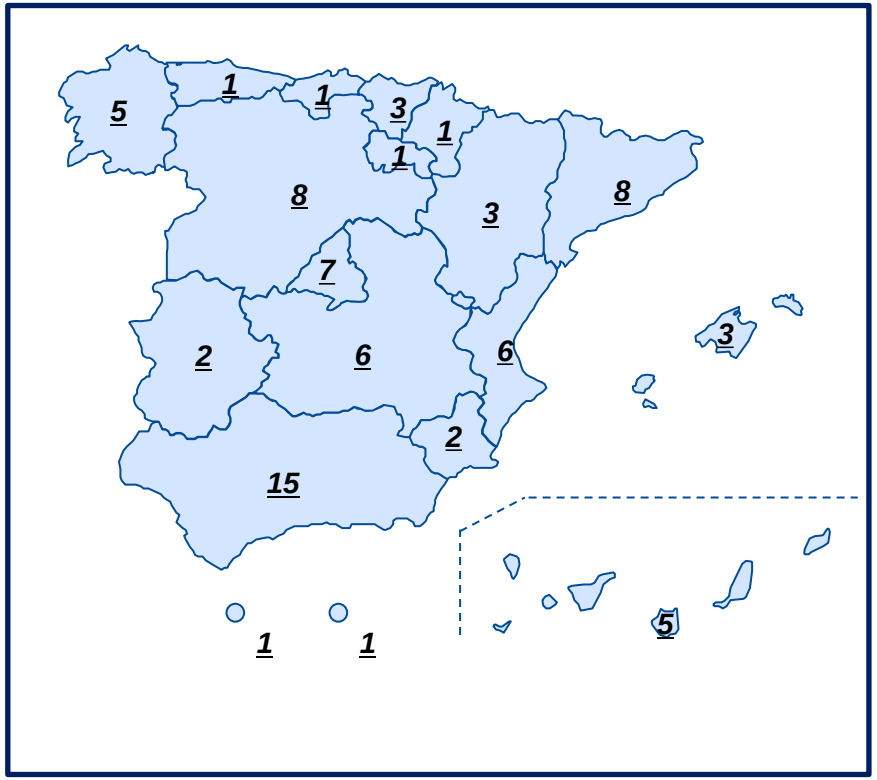
4 Follow-up under protocol

5 SVR visit

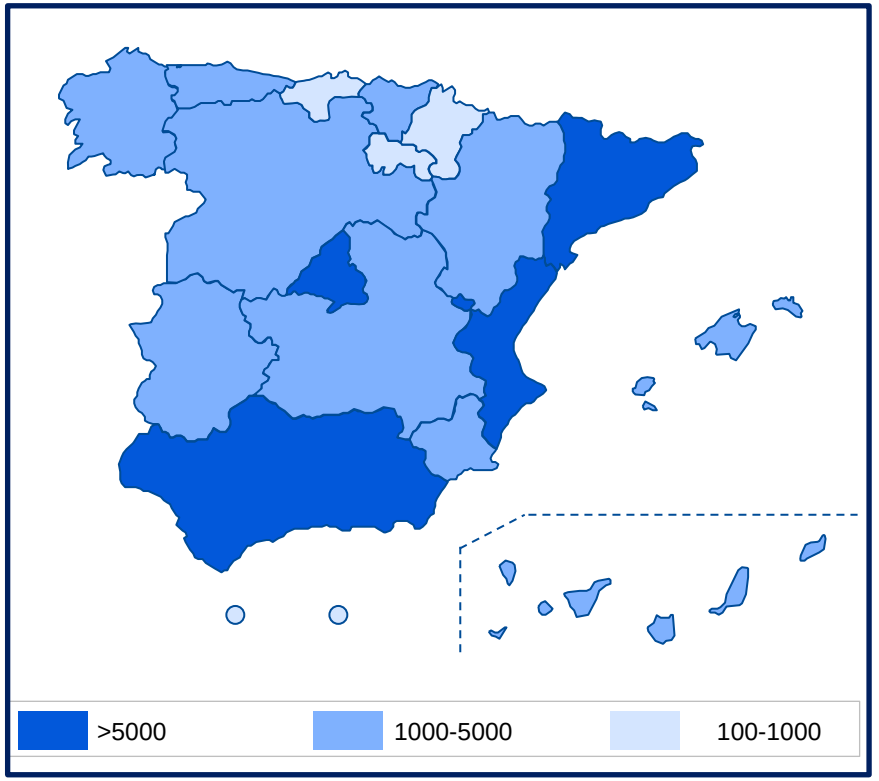
ADDICTION CENTRE

Prisons in Spain

Número de centros penitenciarios

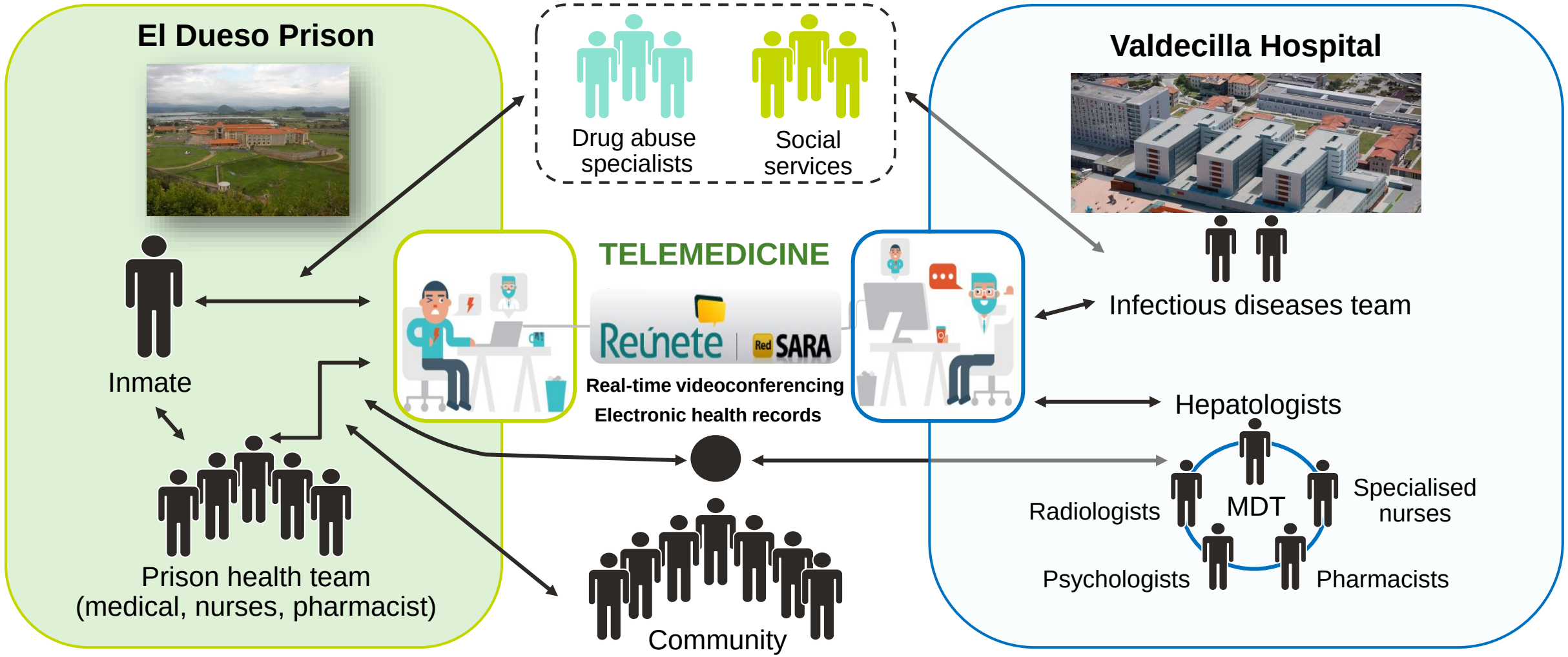


Número de presos por región



Fuente: Secretaria general de instituciones penitenciarias; análisis IQVIA

JAILFREE C: A programme of testing and treatment



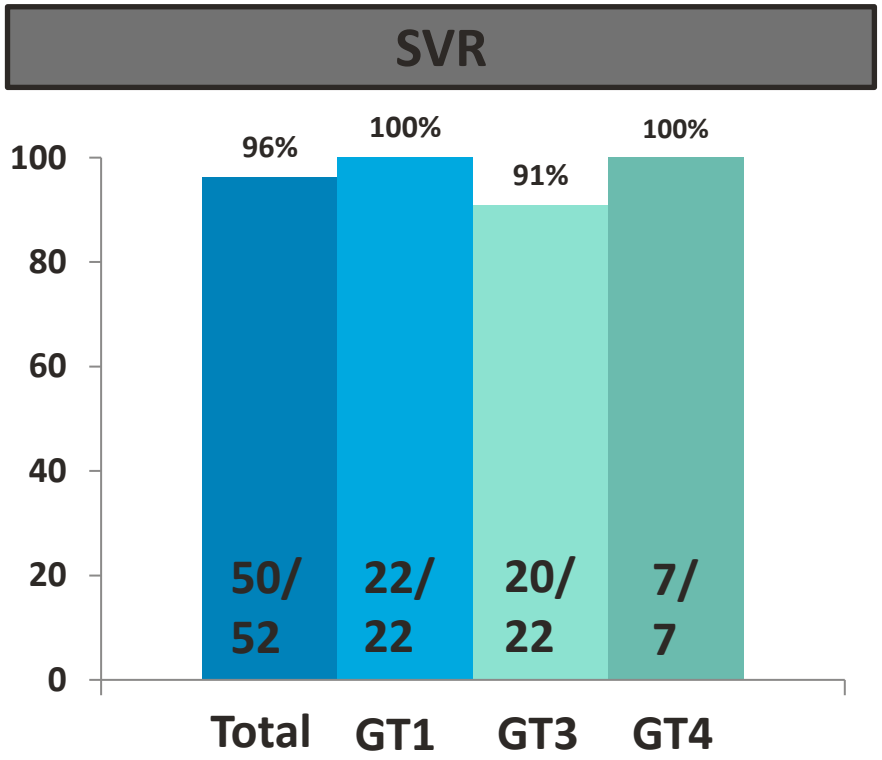
The JAILFREE Study: A Program of Testing and Treatment Intended to Eliminate HCV in a Prison

HCV screening and treatment : Micro-elimination Model in El Dueso Prison, Cantabria (Spain)

687 screened → **82 (13%) anti HCV +** → **66 (10%) RNA VHC +** → **DAA**

Comorbidities	
VIH	7 (13%)
VHB	0 (0%)
exADVP	30 (58%)

Liver Fibrosis	
F0-F1	29 (56%)
F2	5 (10%)
F3	5 (10%)
F4	13 (25%)



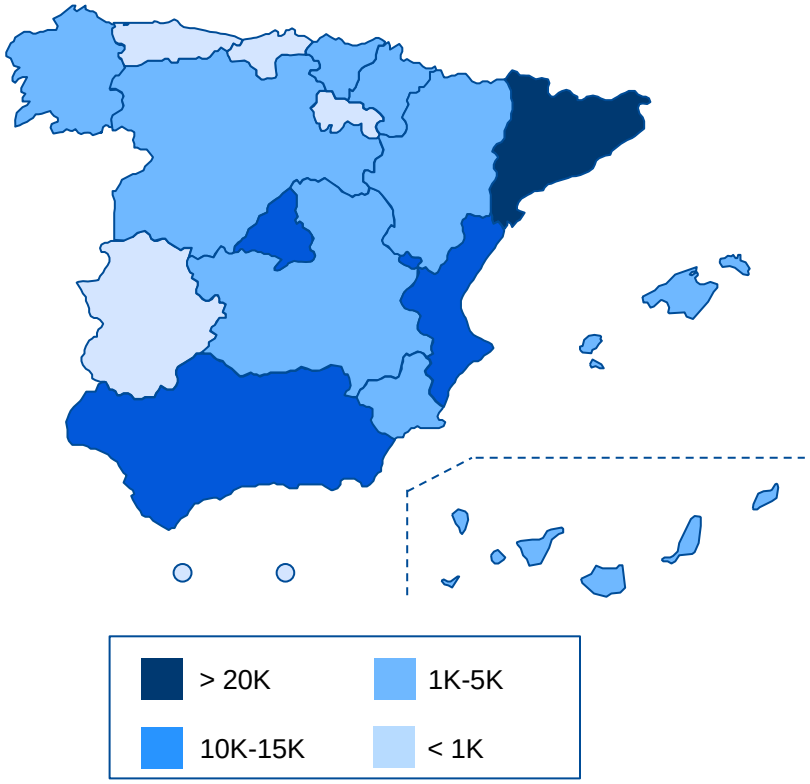
Cuadrado A., Calleja JL et al. *Am J Gastroenterol* (2018) 113:1639–1648

MSM : Specific locations

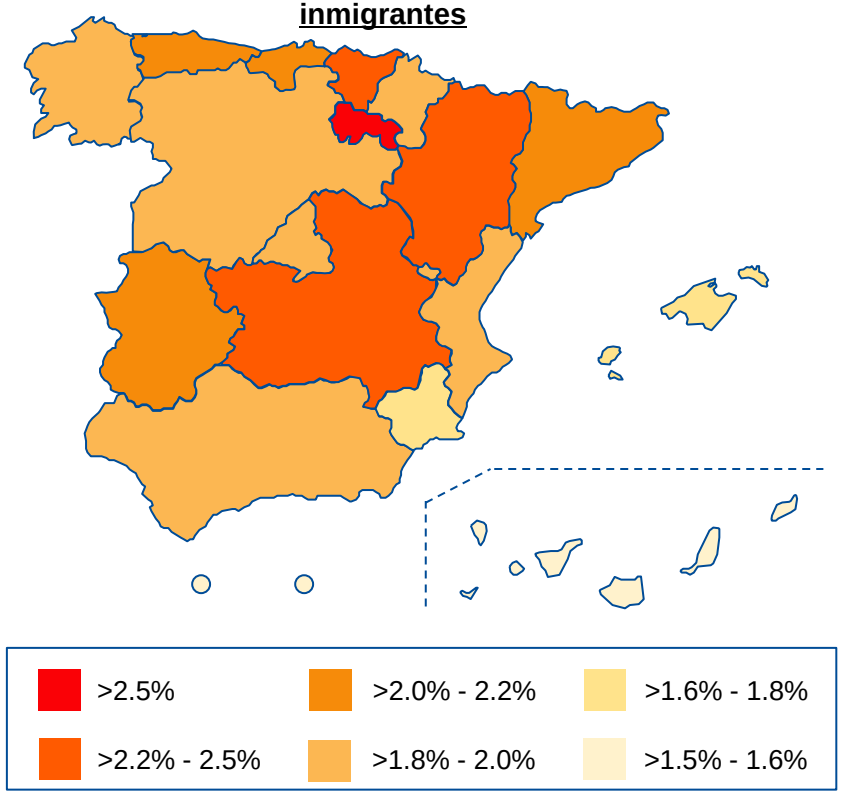
Fuente: Desk Research; IQVIA Analysis
Note: LGTB stands for Lesbian, Gay, Bisexual and Transgender

Inmigrants in Spain

Distribución de inmigrantes HCV + en España



Prevalencia regional de VHC + entre los inmigrantes



Fuente: Global epidemiology and genotype distribution of the hepatitis C virus infection, Journal of Hepatology, Instituto nacional de Estadística; IQVIA Analysis

Potential Populations for Micro-elimination

Majority population
Treatment naive non-cirrhotic with no social or economic disadvantages
Example patient populations to be prioritized for HCV micro-elimination[1]
Prisoners
Chaotic/active PWUDs
Former PWUDs/on-OST
MSM
Migrant communities from high prevalence regions
Generational cohorts of high prevalence
Hemophilia patients
Children
Geographically defined areas
Patients with advanced liver disease

MSM, men who have sex with men; OST, opioid substitution therapy; PWUD, people who use drugs.

Agenda

- Revolution in treatment of Hepatitis C
  - Real World Evidence
- Impact of treatment in long term outcomes
- The time for a Elimination Plan
  - Microelimination in risk groups
  - Macroelimination
- Simplification in the management of patients
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Recomendaciones para el abordaje simplificado del paciente VHC[1]

Un **ABORDAJE SIMPLIFICADO** es la opción preferida para pacientes:

- PWID
- Presos
- Sin hogar
- Migrantes
- Con enfermedad mental
- HSH
- Trabajadores/as del sexo

Las **interacciones farmacológicas** deben ser cuidadosamente **revisadas antes de iniciar el tratamiento** y han de seguirse las recomendaciones.

Para **iniciar el tratamiento solo es necesario conocer la carga viral** y chequear muy bien las interacciones farmacológicas.

- Se puede **iniciar el AAD sin conocer GT**
- **No se recomienda** hacer **test de resistencias basales** en pacientes **naïve**
- En el caso de **no conocer el grado de fibrosis** se recomienda la **Duración Universal de 12 semanas**.

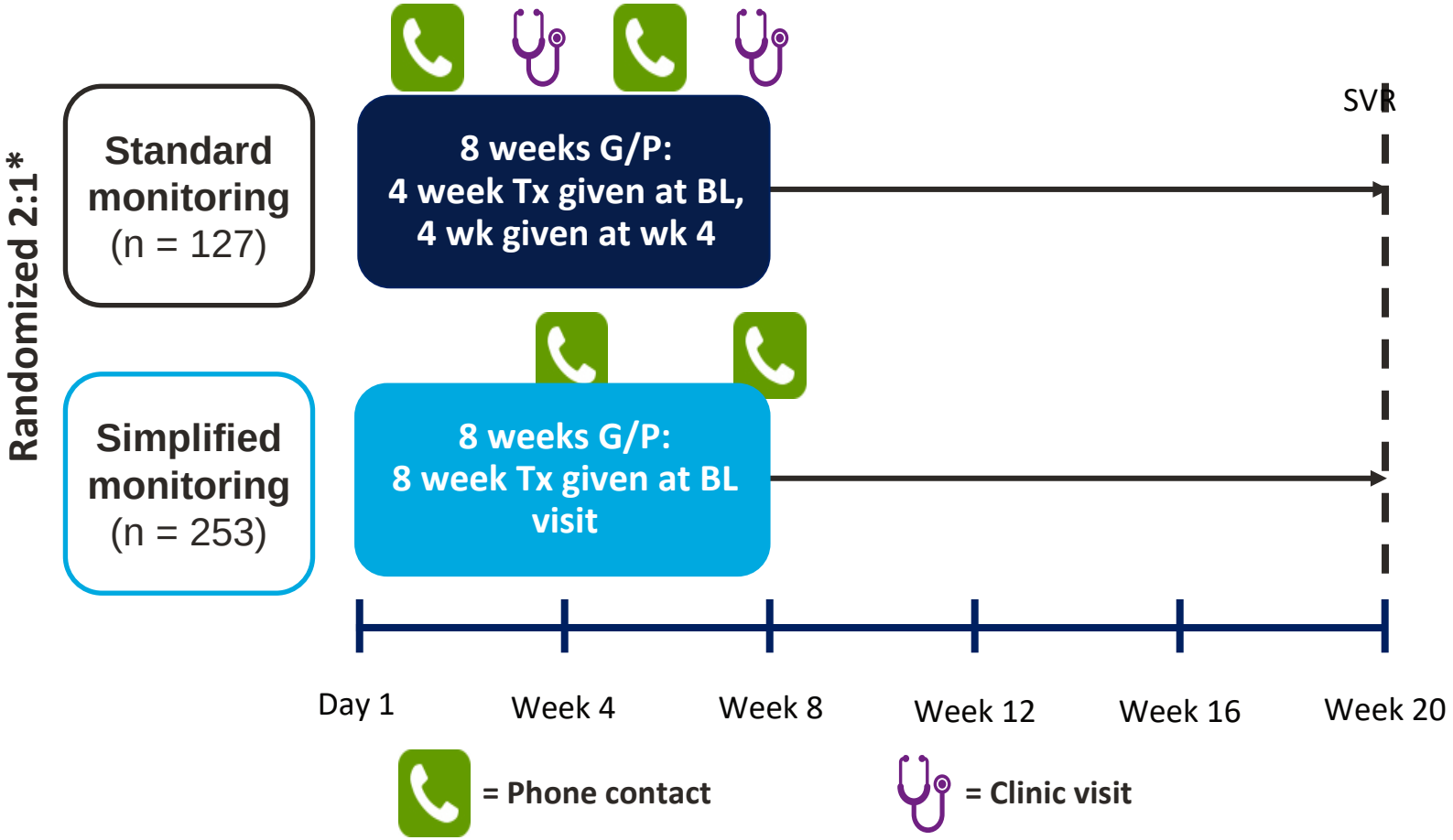
La **RVS12 puede ser omitida** (excepto en pacientes con riesgo de reinfección)

PWID: usuarios de drogas inyectables; **HSH**: hombres que tienen sexo con otros hombres; **AAD**: antivirales de acción directa; **RVS**: respuesta viral sostenida.

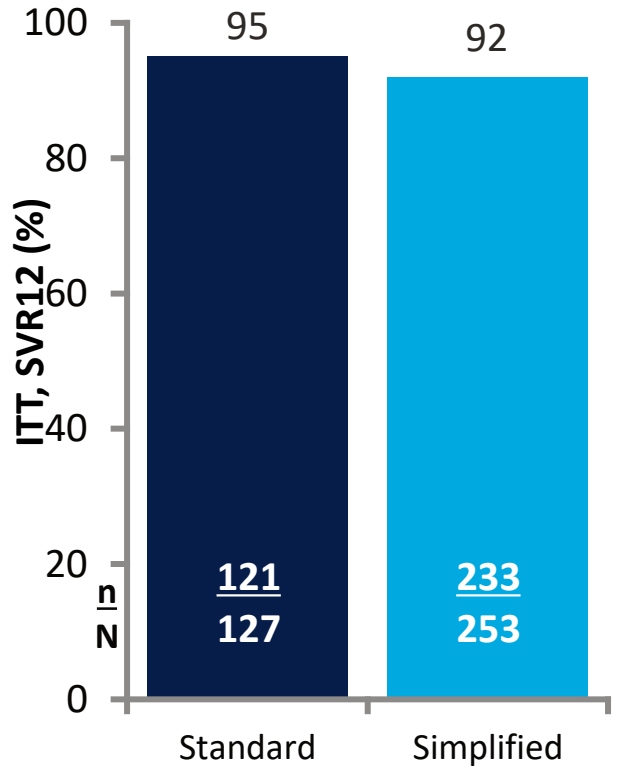
1. EASL Clinical Practice Guidelines. EASL recommendations on treatment of hepatitis C – Final update of the series. J Hepatol. 2020. DOI:https://doi.org/10.1016/j.jhep.2020.08.018.

Simplified Monitoring for May Also Be Possible With G/P

Study Design



Results



*Patients were excluded if they had anticipated poor adherence, recent IDU (last 6 months), positive urinary drug screens;
BL, baseline; IDU, injection drug use; Tx, treatment.

Dore G, et al. EASL 2019; oral presentation (PS-178).

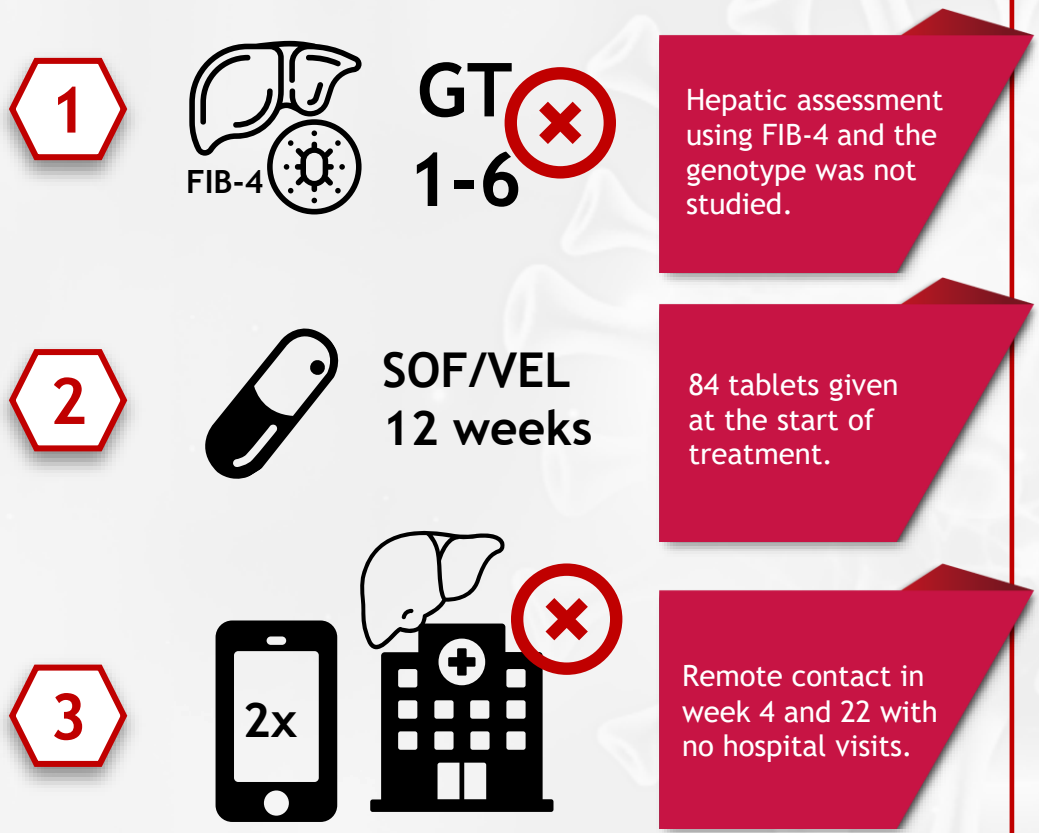
SOF/VEL enables a simple and safe approach for patients with HCV, using a minimally monitoring strategy

A phase 4, multinational, open, prospective and interventional study of patients who received SOF/VEL for 12 weeks as part of a strategy involving minimal monitoring.

- 400 patients in 5 countries (USA, Brazil, Uganda, Thailand and South Africa)
- 9% with compensated cirrhosis.
- 34% PWID.
- 42% Coinfected with HIV.

SOF/VEL, the only DAA that has shown that a MINIMUM approximation in the treatment of HCV was SIMPLE and SAFE, thus achieving a SVR (more tha 95%) comparable with the clinical treatment standard in naive persons with no cirrhosis.*

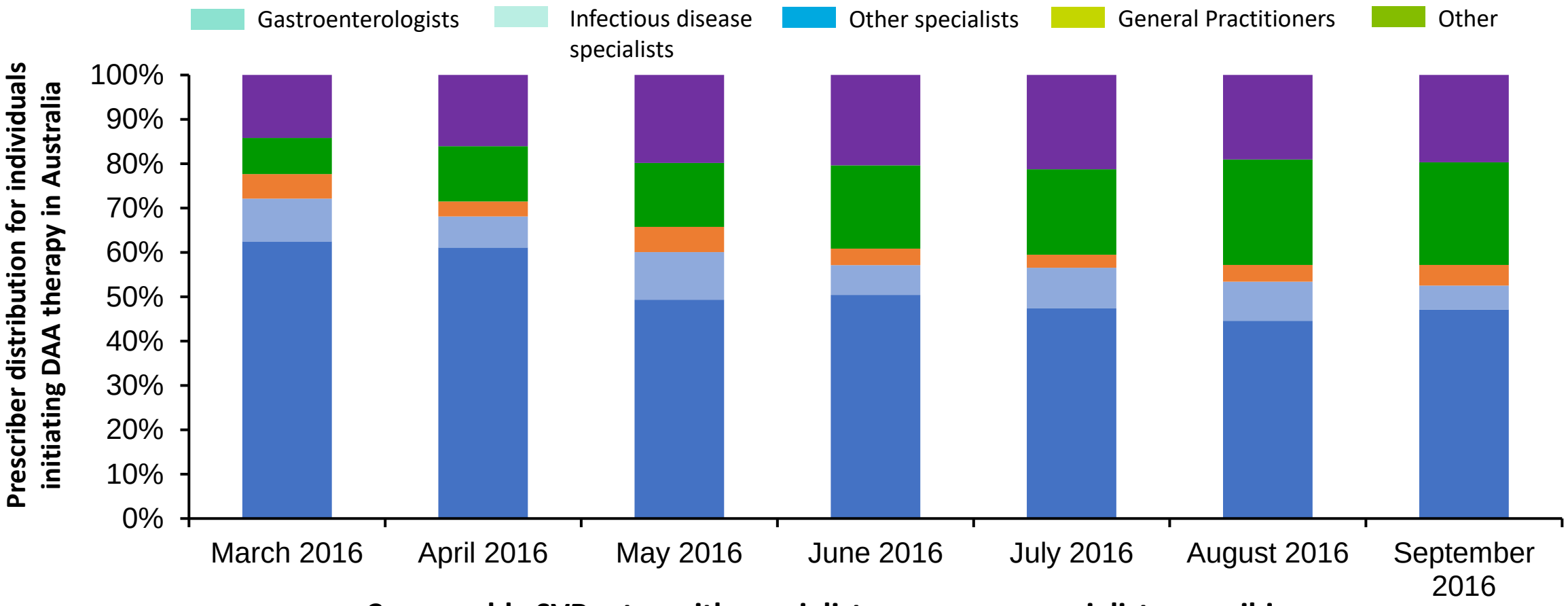
Treatment with SOF/VEL for 12 weeks with a simplified strategy involving minimal monitoring



*The results of this study cannot be generalised outside of the scope of investigation.

Solomon S. The "Keep it Simple and Safe" Approach to HCV Treatment: Primary Outcomes form the ACTG A5360 (MINMON) Study. AASLD 2020.

Increasing involvement of non-specialists in HCV care in Australia

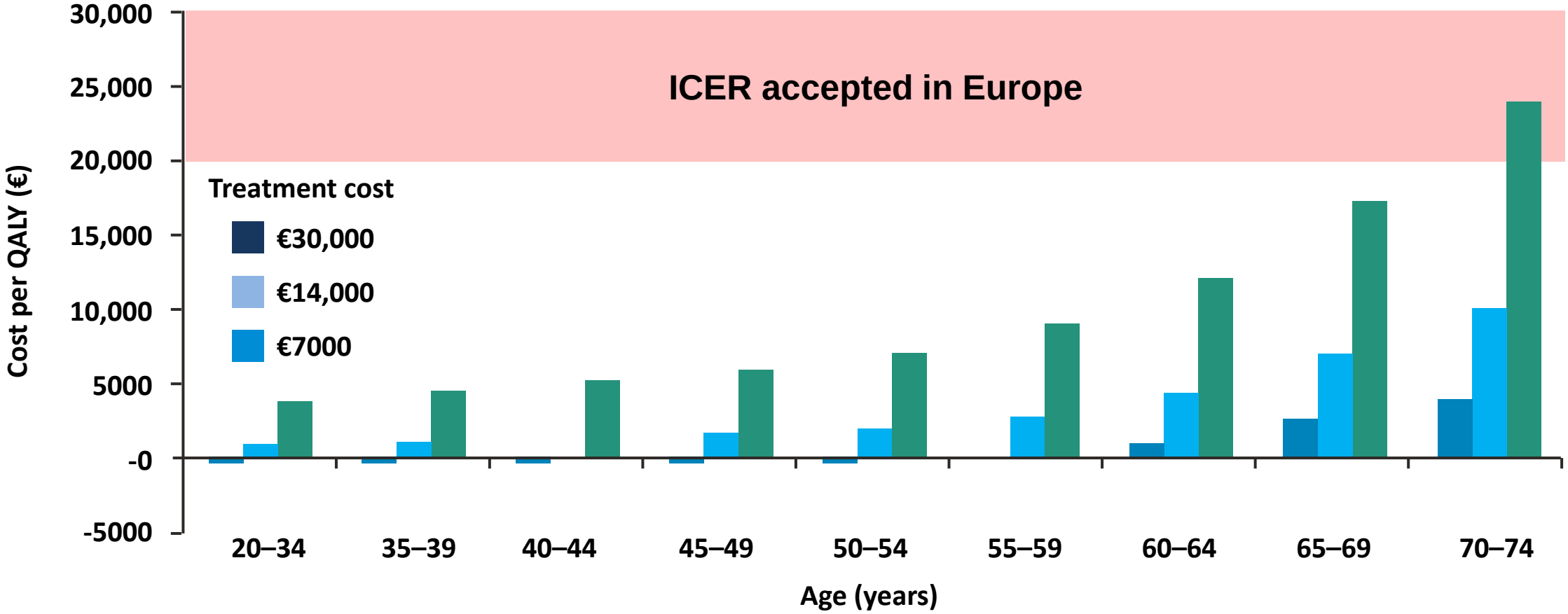


Comparable SVR rates with specialist versus non-specialist prescribing have previously been reported in the USA[2]

1. Hajarizadeh B, et al. ILC 2017. Poster #THU-232; 2. Kattakuzhy S, et al. Ann Intern Med 2017;167:311–8

HCV Treatment by GPs – An Easy-to-use Tutorial on YouTube

New Epidemiological Data in Spain Show that Universal Screening Is Cost Effective



ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

Cuadrado AEEH 2018; Crespo, et al. manuscript submitted. Data courtesy of Calleja JL.

AFEF Recommends Universal Screening for France

Rapid diagnostic

Universal screening

1 Every adult should be screened once during their life

2 Screening of HCV, HBV and HIV should be combined

3 All screening tests should be free and covered by the National Health Service

AFEF
SOCIETÉ FRANÇAISE D'HÉPATOLOGIE

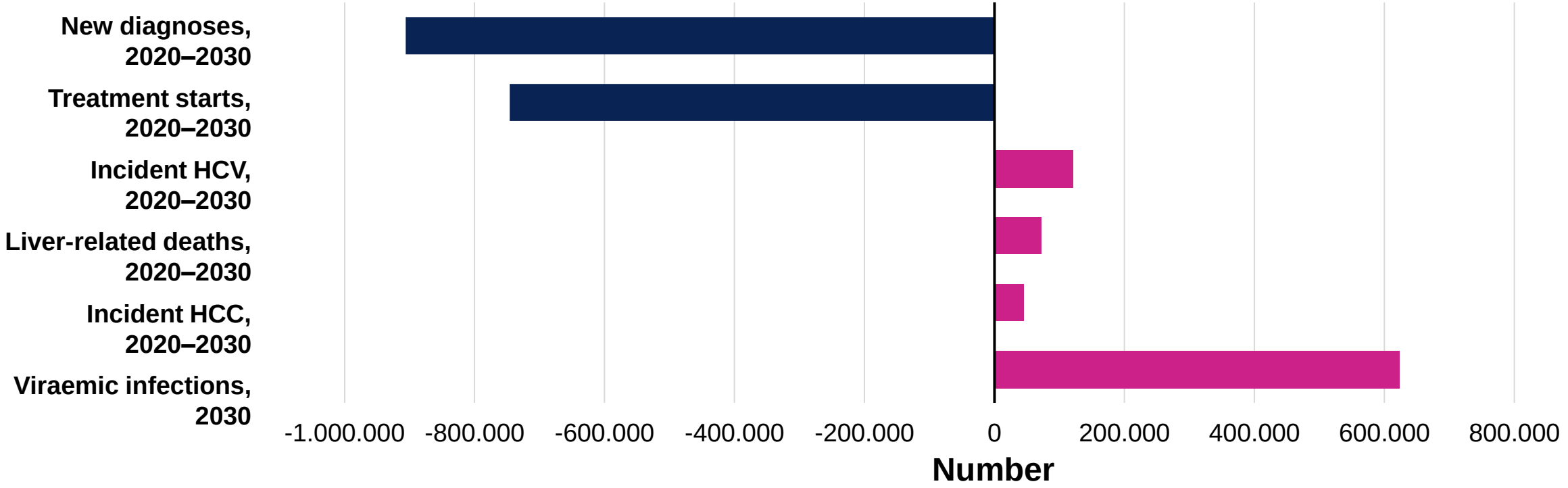
AFEF. Recommandations AFEF pour l'élimination de l'infection par le virus de l'hépatite C en France. Available at: http://www.afef.asso.fr/ckfinder/userfiles/files/recommandations-textes-officiels/recommandations/VF%20INTERACTIF-%20RECO-VHC%20AFEF%20v2103.pdf (accessed April 2018).

The COVID-19 pandemic has brought additional challenges to HCV care

Modelling study to analyse the global impact of a 1-year delay in HCV programming (relative to the status quo with no delay)

Reduced touchpoints for HCV care

Increased acquisition of HCV and excess LVD mortality



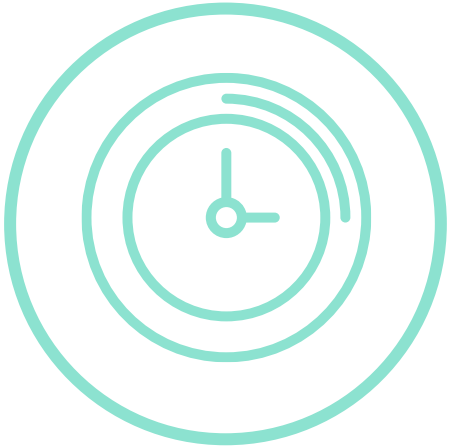
Blach S, et al. J Hepatol 2020; doi: 10.1016/j.jhep.2020.07.042

HCC: hepatocellular carcinoma; LVD: liver disease

New Opportunities with COVID-19 to Eliminate Hepatitis C

“Virus awareness” in the general population

Third dose of vaccine based on serology

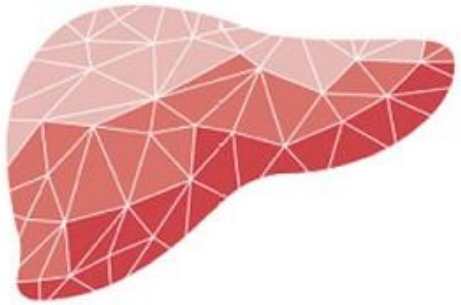


New autotest for hepatitis C

Expert opinion.

Summary

- The introduction of DAAs has had a significant impact on the HCV treatment environment
- Clinical studies have demonstrated that there are now effective and generally well-tolerated DAA treatment options for the majority of patients
- Real-world data confirm the data from clinical trials
- SVR is associated to a decrease of hepatic and extrahepatic morbidity and mortality
- Is now time to consider Hepatitis C from a Public Health perspective
- Optimal approach includes a National Elimination Plan :
  - Macroelimination : screening programs
  - Microelimination : risk populations
  - Consider expansion of treaters
  - Awareness



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