Società Medico Chirurgica di Ferrara

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

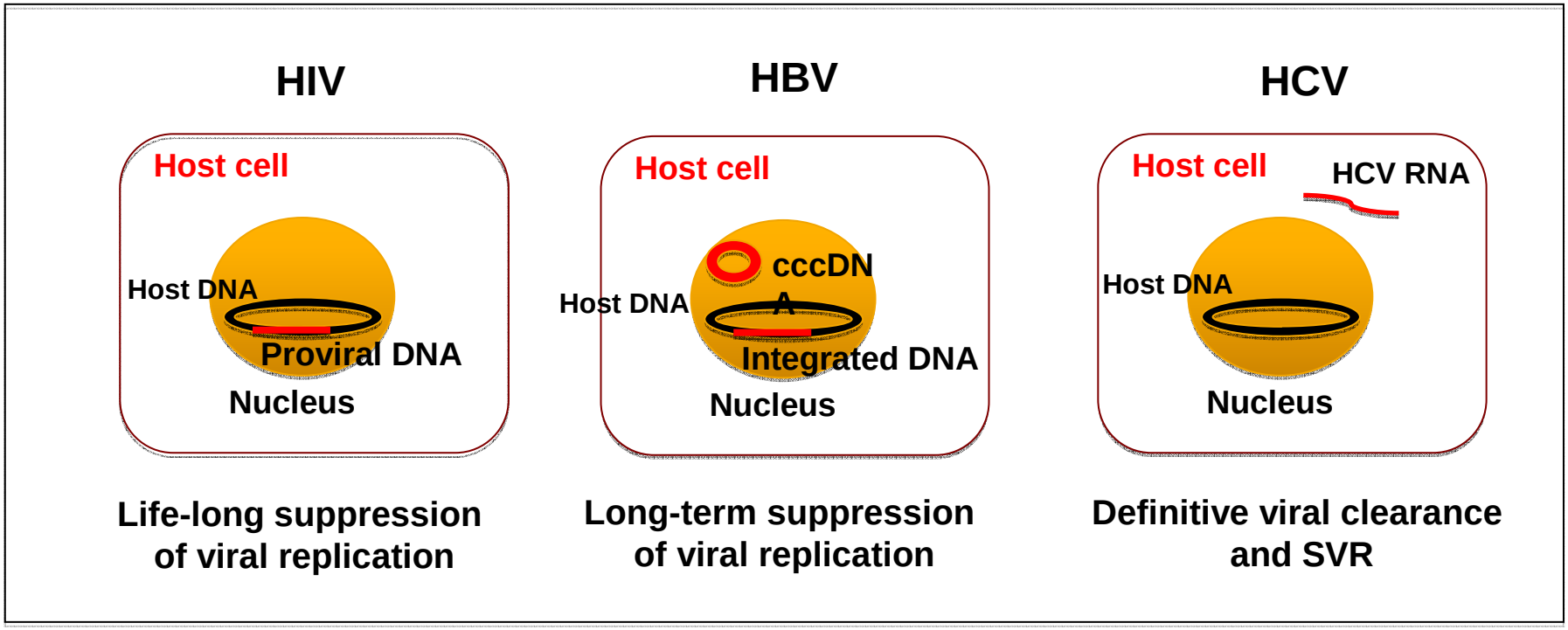
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Ferrara

Terapia dell' epatite virale cronica C: risultati con i nuovi farmaci ad azione antivirale diretta (DAA)

S.Boccia, S.Carradori, A.Grilli, L.Osbello, L.Sighinolfi, L.Simone.

Ferrara 18 marzo 2017

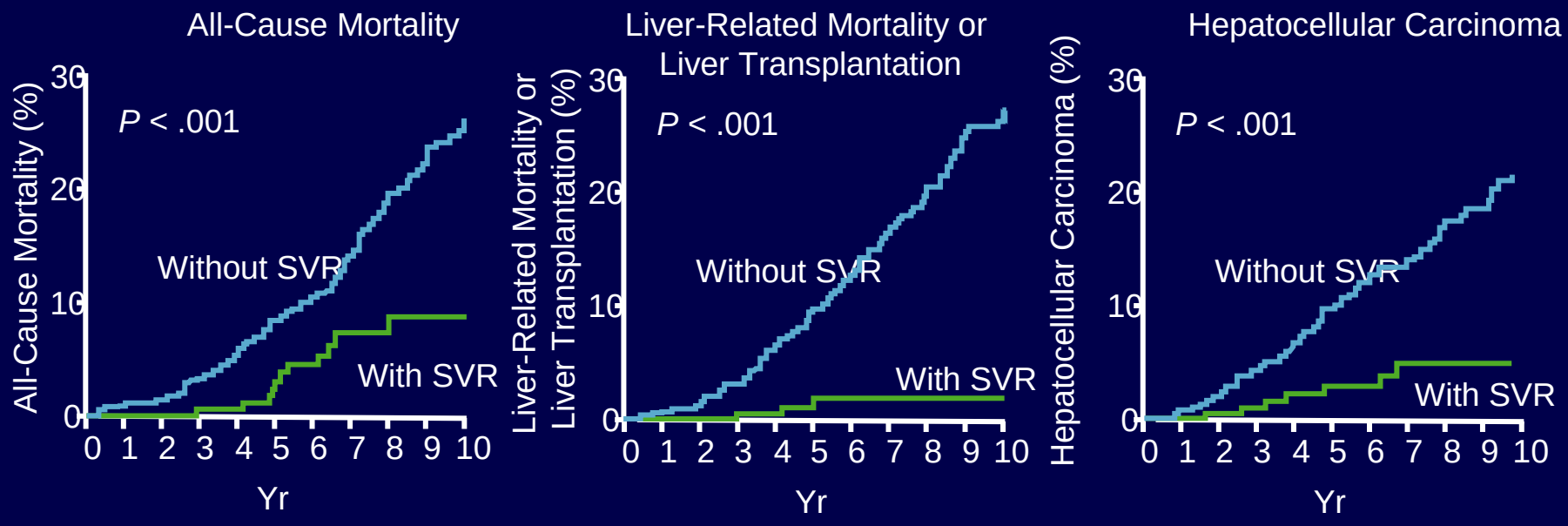
HCV infection is curable!!!!



Obiettivi della Guarigione dall'Epatite C

- Eliminazione di HCV = Cura
- Ridurre la necrosi ed infiammazione nel fegato
- Arrestare la progressione della fibrosi
- Prevenire la cirrosi e le sue complicanze
- Prevenire il carcinoma del fegato
- Ridurre il bisogno di un trapianto nella cirrosi scompensata
- Aumentare la sopravvivenza
- Prevenire la diffusione dell'Infezione (profilassi)

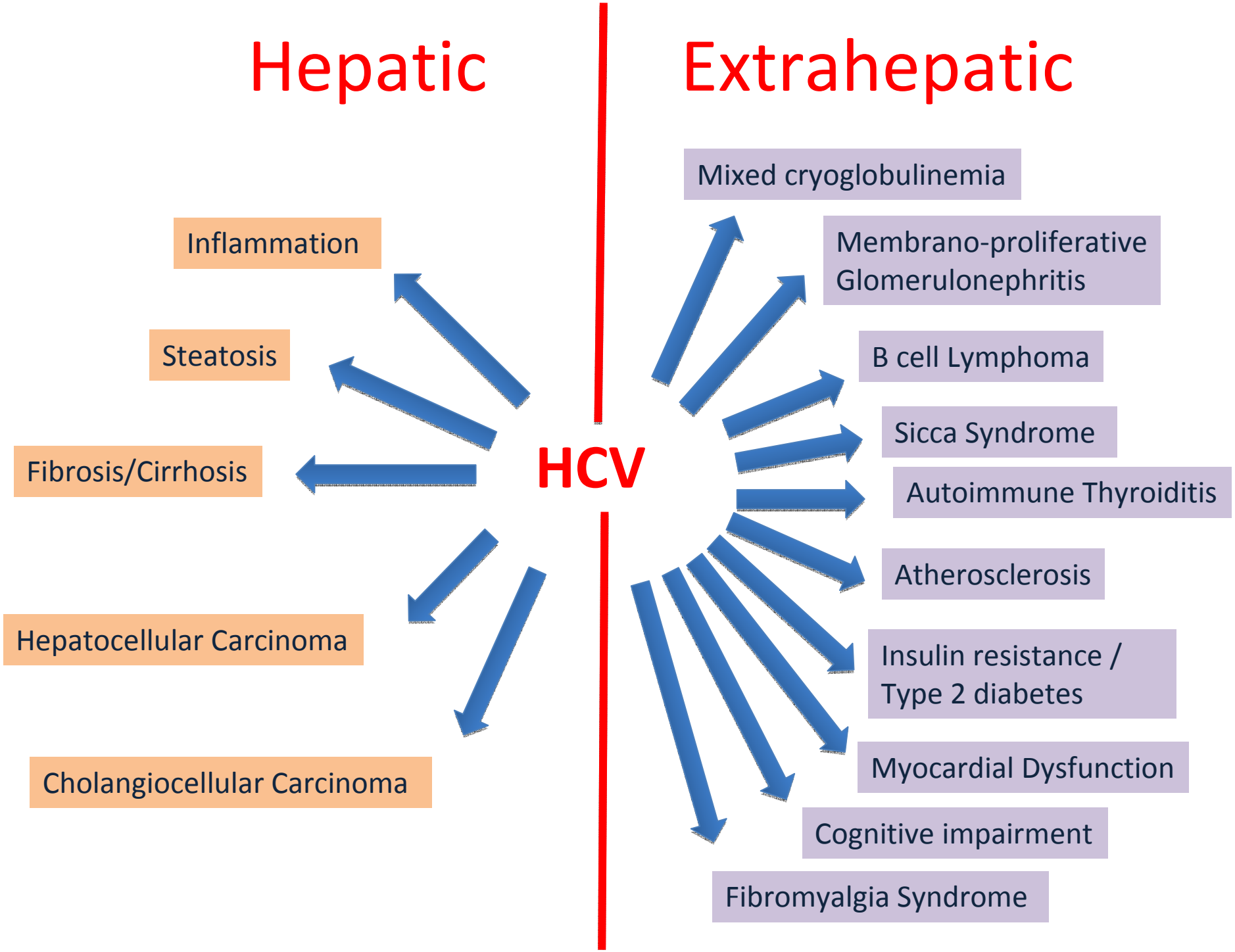
Hepatitis C Virologic Cure Associated With Improved Outcomes



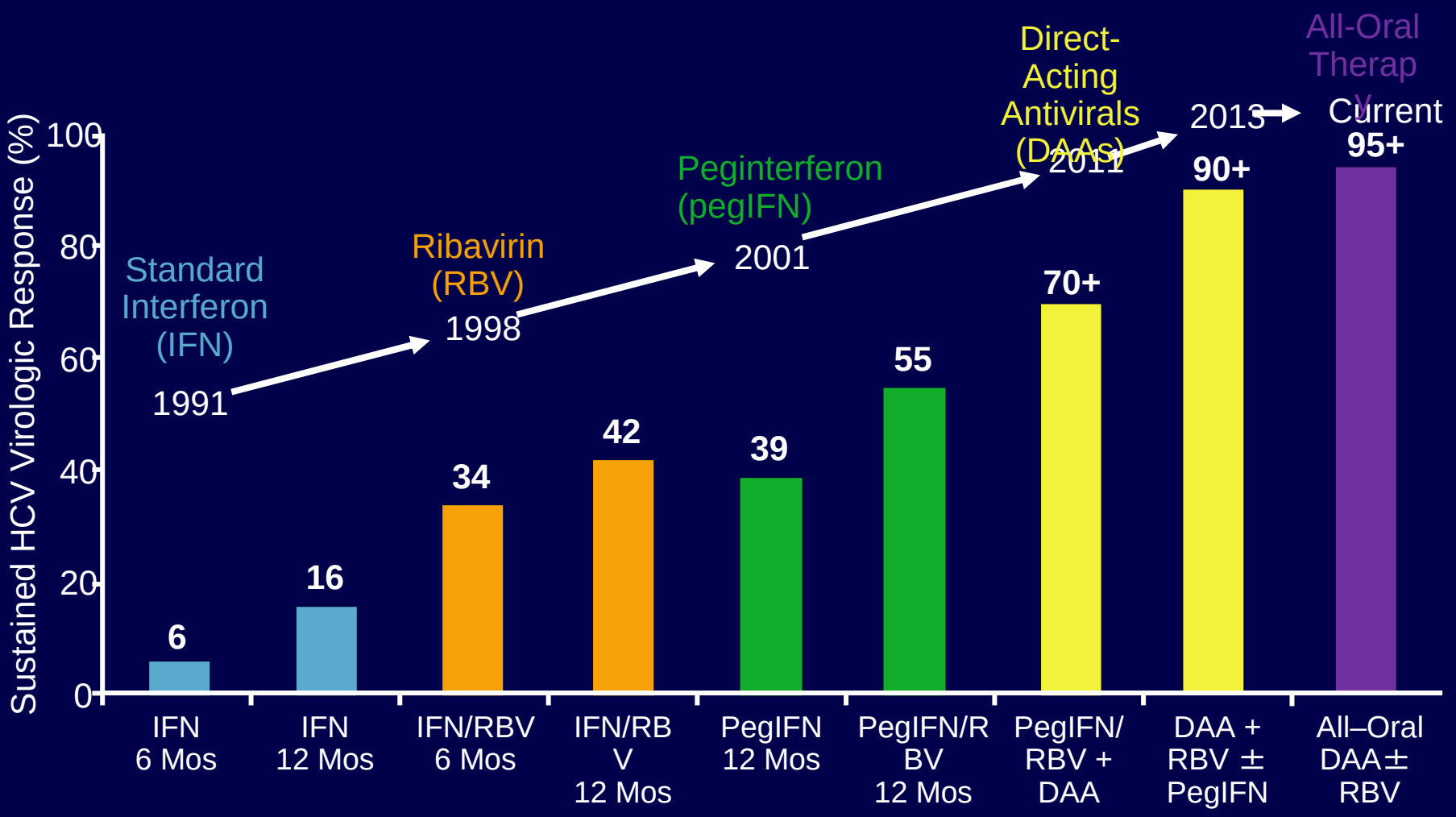
HR: 0.26 (95% CI: 0.14-0.49; *P* < .001)

- Virologic cure does not protect against reinfection

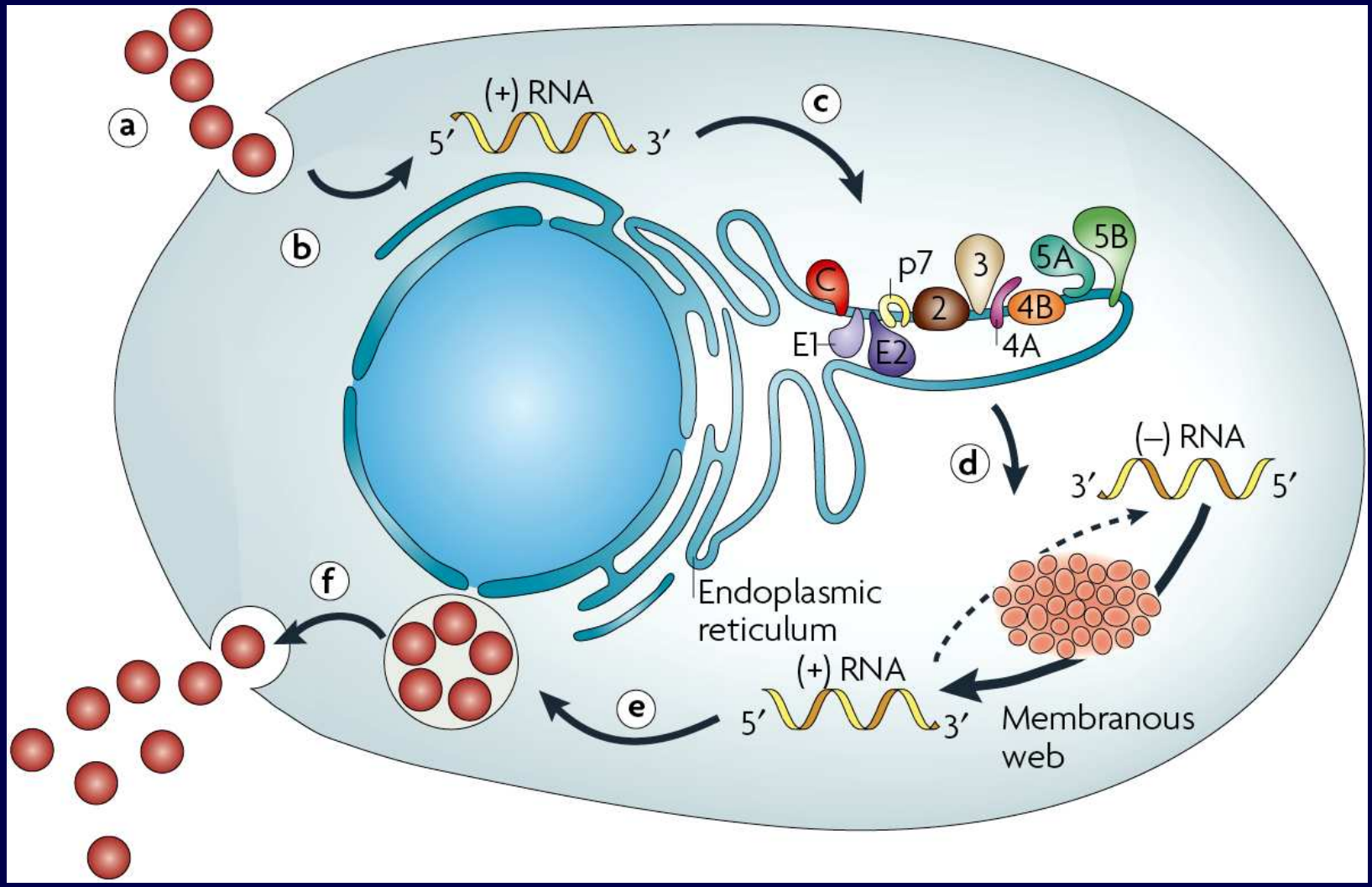
van der Meer AJ, et al. JAMA. 2012;308:2584-2593.


Hepatic
Extrahepatic
HCV
Inflammation
Steatosis
Fibrosis/Cirrhosis
Hepatocellular Carcinoma
Cholangiocellular Carcinoma
Mixed cryoglobulinemia
Membrano-proliferative Glomerulonephritis
B cell Lymphoma
Sicca Syndrome
Autoimmune Thyroiditis
Atherosclerosis
Insulin resistance / Type 2 diabetes
Myocardial Dysfunction
Cognitive impairment
Fibromyalgia Syndrome

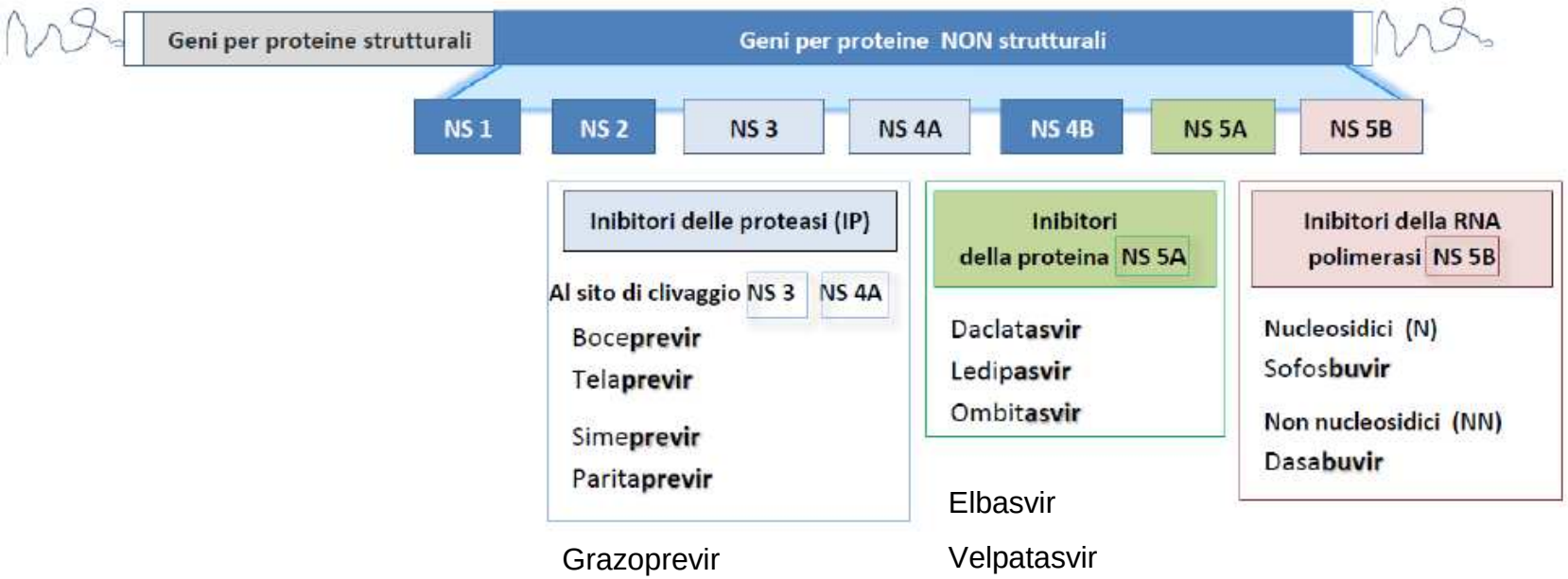
Current All-Oral Therapies Highly Effective, Simple, Well Tolerated



Hepatitis C Virus Life Cycle



FARMACI ANTIVIRALI DIRETTI



HCV Treatment in 2017

- Many highly effective, highly tolerable options
- All-oral therapy for all
- Most pts receive:
  - 12 wks of treatment
  - 1 pill, once per day
  - Ribavirin-free therapy
- Pts with previous pegIFN/RBV treatment easy to cure

Many Options in 2017: Current All-Oral Regimens for Hepatitis C Infection

Regimen	Approved Genotypes
Grazoprevir/elbasvir	1, 4
Ombitasvir/paritaprevir/ritonavir	4
Ombitasvir/paritaprevir/ritonavir + dasabuvir	1
Sofosbuvir + daclatasvir	1, 3
Sofosbuvir/ledipasvir	1, 4, 5, 6
Simeprevir + sofosbuvir	1, 4
Sofosbuvir/velpatasvir	1, 2, 3, 4, 5, 6

- Effective options for every genotype
- Single-pill formulations or 2-pill combinations

- Effective for all genotypes

Farmaci sì, ma… a chi?

1. Pazienti con cirrosi in classe di Child A o B e/o con HCC con risposta completa a terapie resettive chirurgiche o loco-regionali non candidabili a trapianto epatico e nei quali la malattia epatica sia determinante per la prognosi;

2. Pazienti con recidiva di epatite dopo trapianto di fegato con fibrosi METAVIR ≥2 (o corrispondente Ishak) o fibrosante colestatica;

3. Pazienti con epatite cronica con gravi manifestazioni extra-epatiche HCV-correlate (sindrome crioglobulinemica con danno d'organo, sindromi linfoproliferative a cellule B);

4. Pazienti con epatite cronica con fibrosi METAVIR F3 (o corrispondente Ishak);

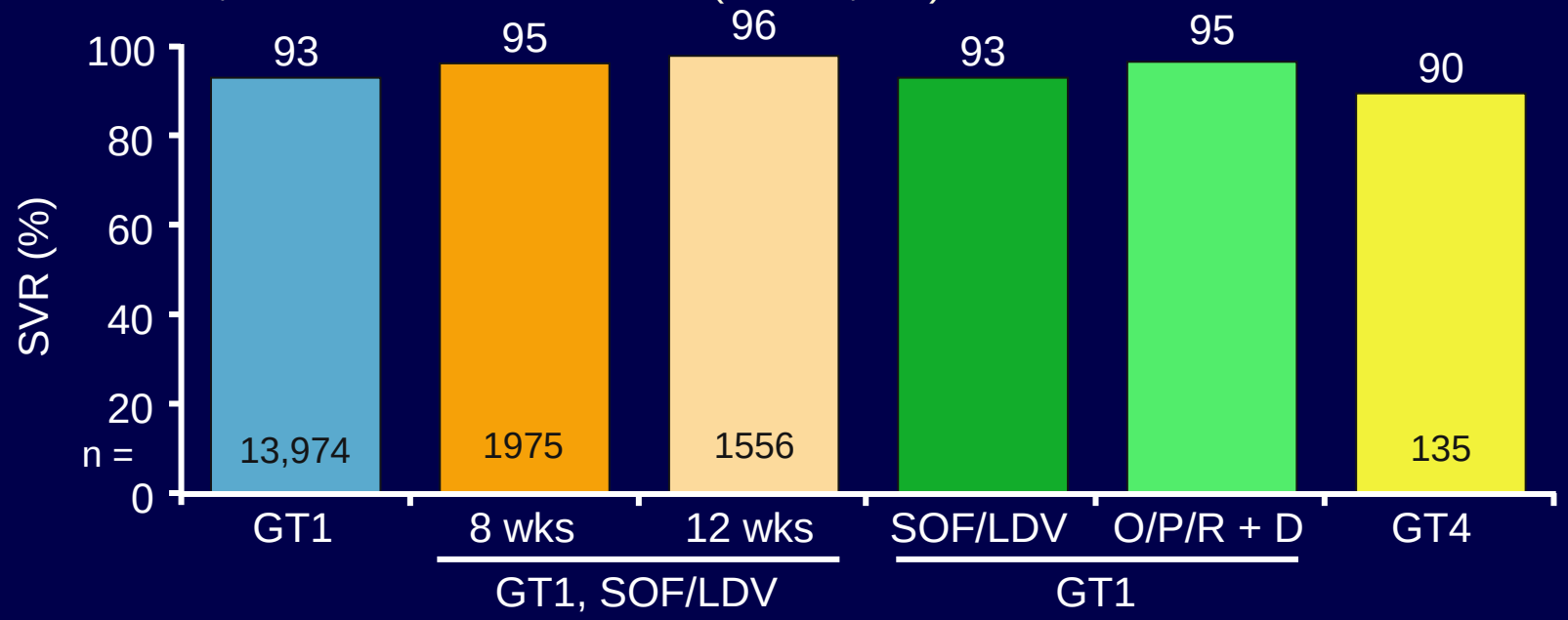
5. Pazienti in lista per trapianto di fegato con cirrosi MELD <25 e/o con HCC all'interno dei criteri di Milano con la possibilità di un'attesa in lista di almeno 2 mesi;

6. Pazienti con epatite cronica dopo trapianto di organo solido (non fegato) o di midollo con fibrosi METAVIR ≥2 (o corrispondente Ishak).

7. Pazienti con epatite cronica con fibrosi METAVIR F0-F2 (o corrispondente Ishak)

Real-World HCV Treatment in the US VA Healthcare System

- Analysis of real-world SVR for pts with GT1-4 HCV treated with SOF + RBV ± pegIFN, SOF/LDV, or OBV/PTV/RTV + DSV (N = 17,487)[1]



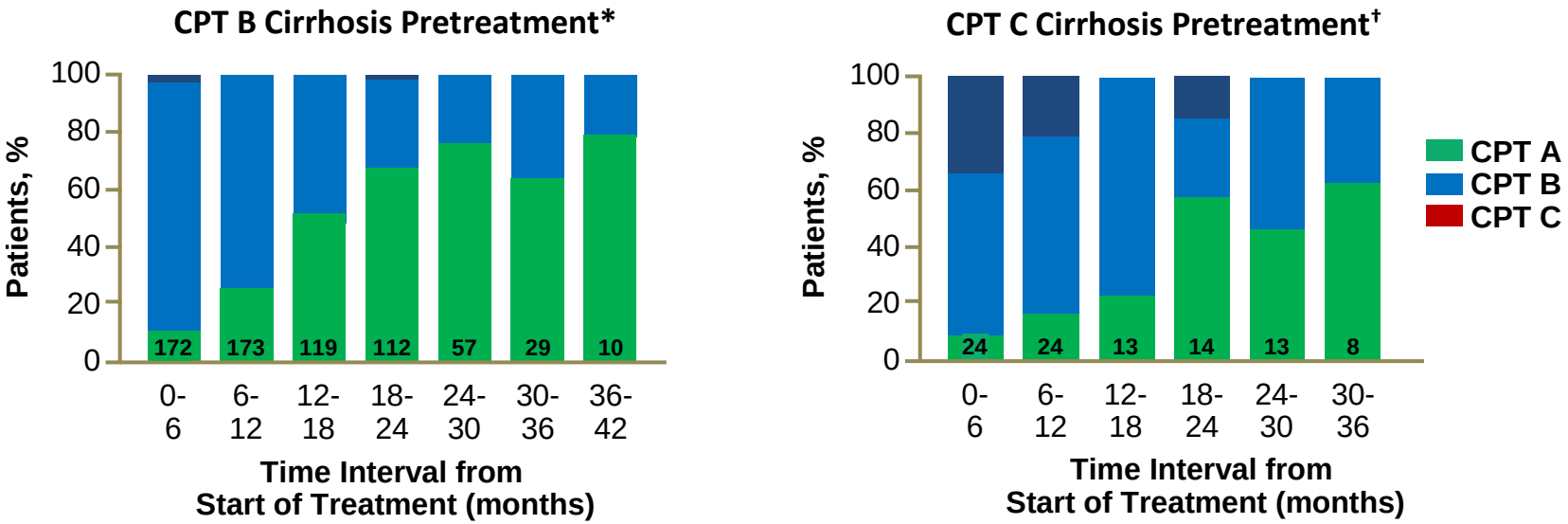
- Analysis of HCV treatment in VA healthcare system (N = 107,079)[2]
  - Dramatic increases in HCV treatment in 2014-2015 vs 1999-2013 (1999-2011, 1989 to 7196 treatments/yr; 2014, 9180 treatments; 2015, 31,028 treatments)
  - Related to improved antiviral efficacy and availability of funding

1. Ioannou GN, et al. AASLD 2016. Abstract 21. Reproduced with permission.
2. Moon AM, et al. AASLD 2016. Abstract 227.

‡

Long-term Follow-up of >1,000 HCV Patients With Compensated or Decompensated Cirrhosis Who Achieved SVR Following Treatment With Sofosbuvir-Based Regimens

Shift in CPT Classification



- The majority of patients maintained or improved their CPT category relative to pretreatment through up to 36 (CPT C) or 42 (CPT B) months relative to treatment start
- Overall improvements in key laboratory components such as mean bilirubin and mean albumin were observed

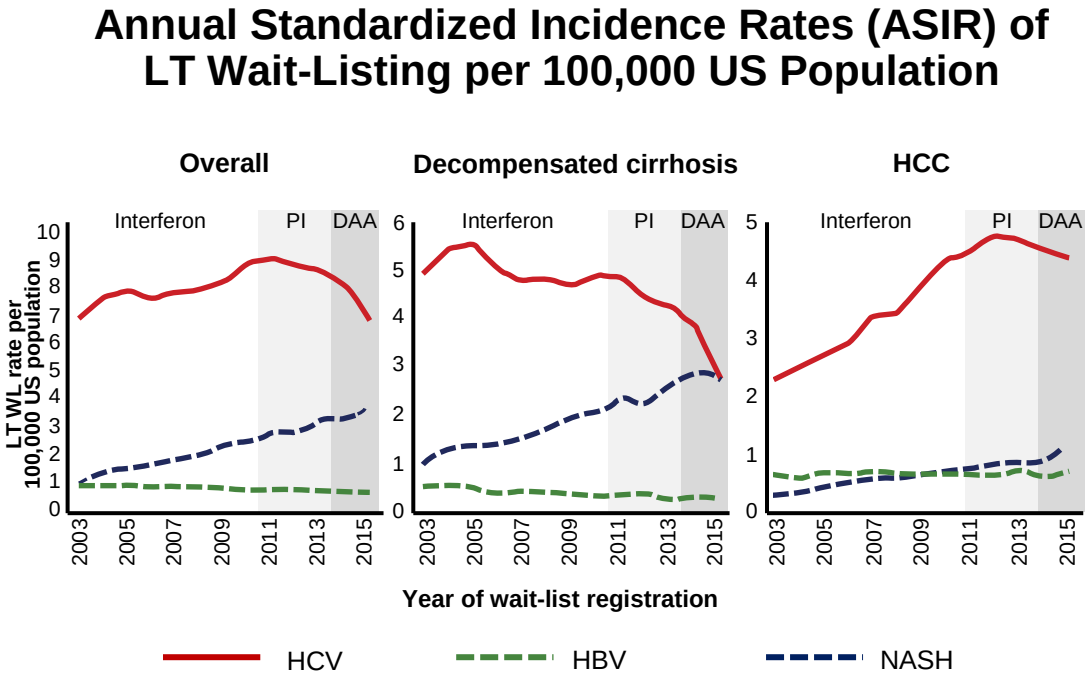
*Only 1 patient with CPT B cirrhosis prior to treatment has reached >42 mo since start of treatment; this patient had CPT A cirrhosis at last assessment.
†Only 1 patient with CPT C cirrhosis prior to treatment has reached >36 mo since start of treatment; this patient had CPT A cirrhosis at last assessment.

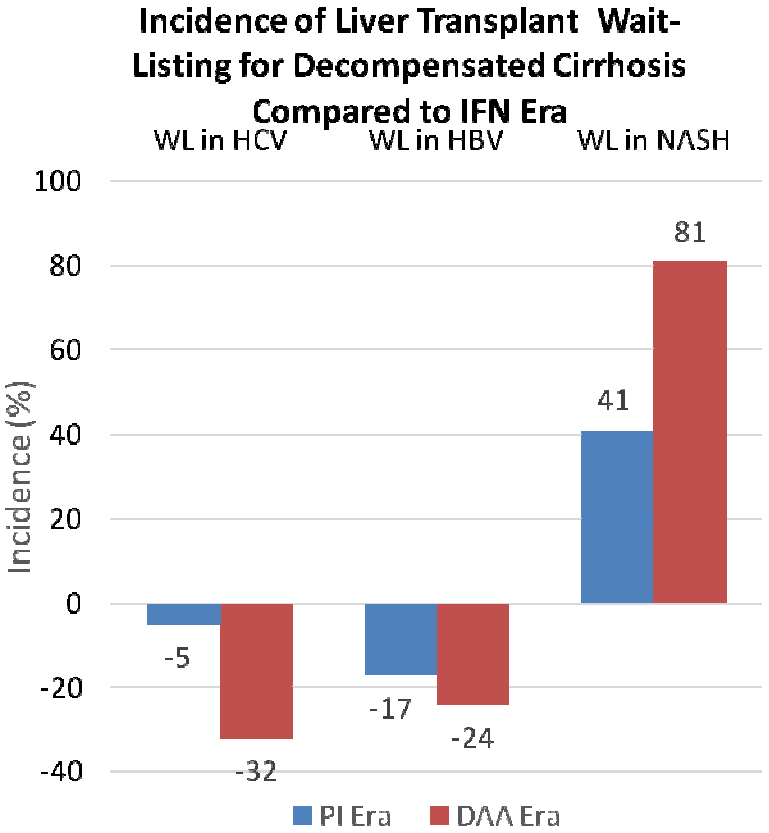
Muir A, AASLD, 2016, #880

Reduction in Liver Transplant Waitlist in the Era of HCV DAAs

‡

Cohort study of 47,591 adults wait-listed for liver transplant (LT WL) using the Scientific Registry of Transplant Recipients database from 2003–2015

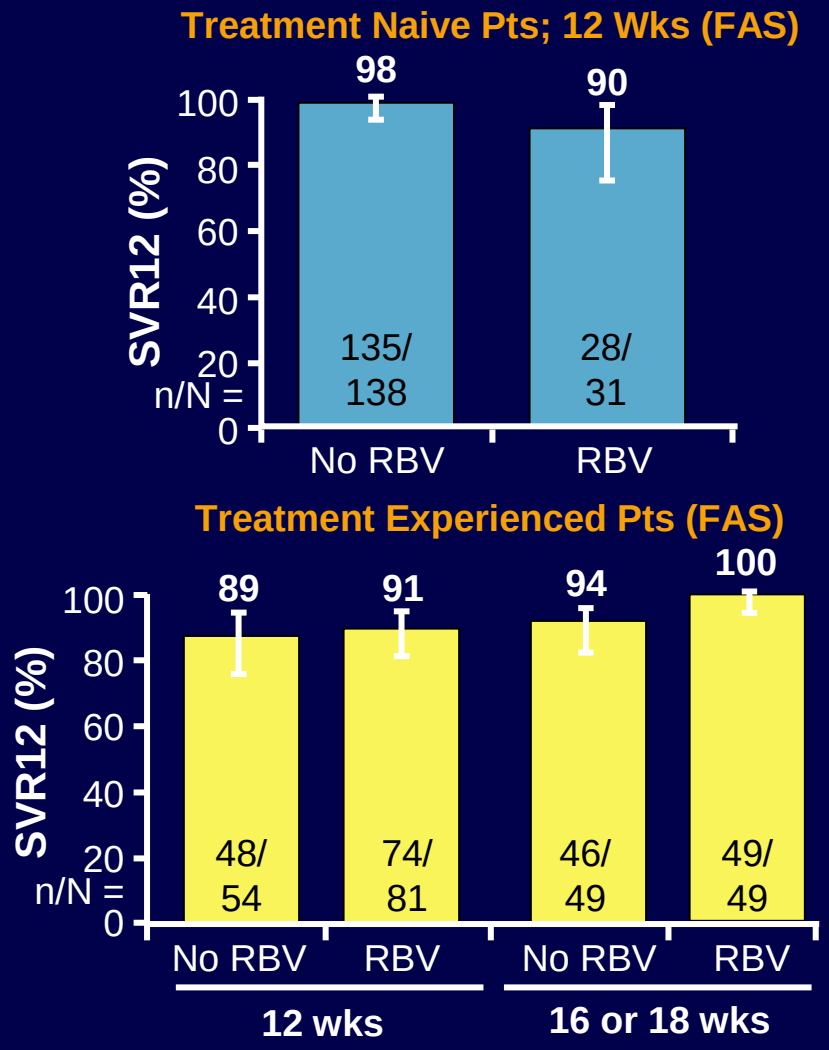




The rate of liver transplant wait-listing for HCV secondary to decompensated cirrhosis has decreased by 32% in the era of DAA therapy as compared to the IFN era and is now equal to that of NASH

Flemming JA, AASLD 2016, Poster LB-23

Elbasvir/Grazoprevir in Compensated Cirrhosis: SVR12

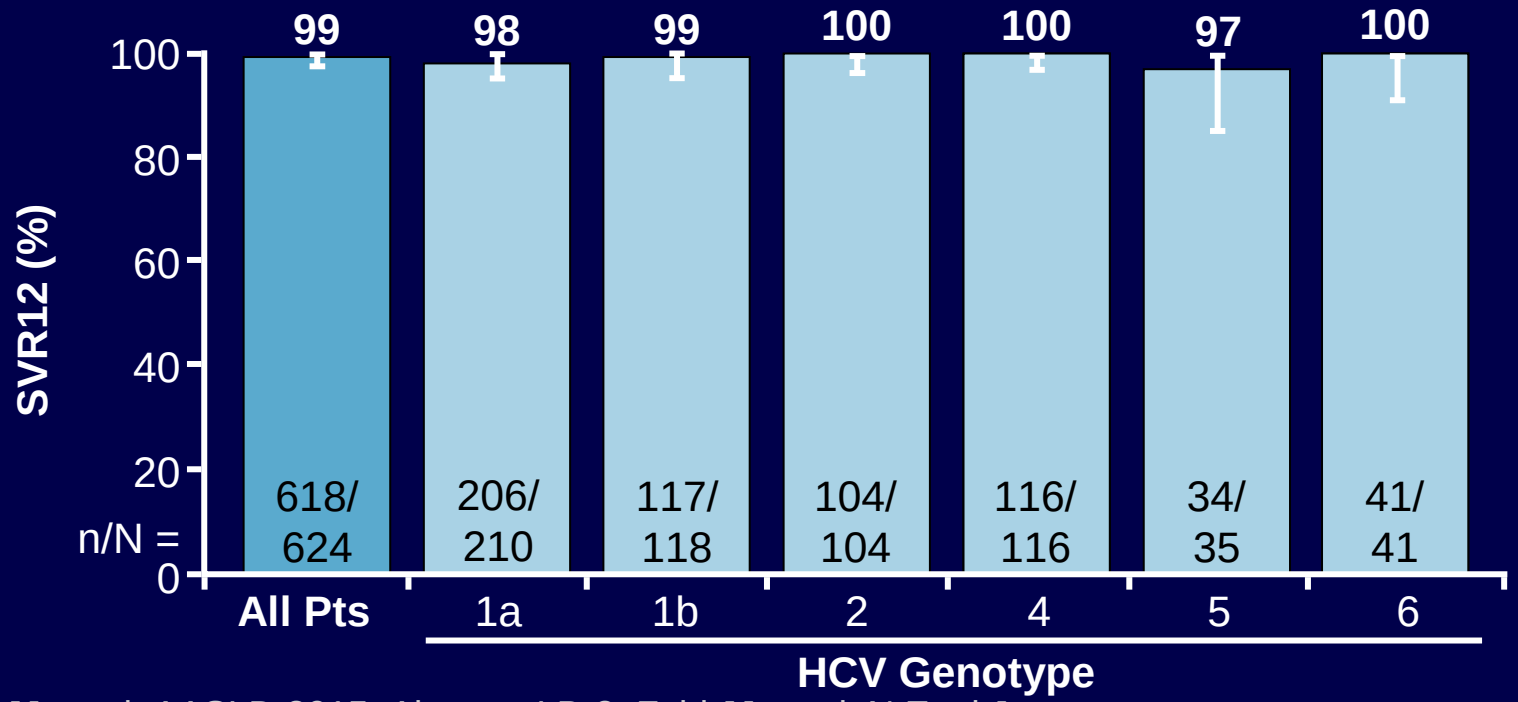


- **Treatment-naive pts**: SVR12 rates similar regardless of RBV use, HCV subtype in FAS and regardless of platelets, cirrhosis determination method, *FibroScan* score in mFAS
  - SVR12 rate range across subgroups treated without RBV: 96% to 100%
- **Previous relapsers (mFAS)**: SVR12 rates not affected by treatment duration or RBV use
- **Previous nonresponders (mFAS)**: SVR12 rates lower with 12-wk, no RBV vs 16/18-wk, + RBV treatment
  - GT1: 92% vs 100%
  - GT4: 67% vs 100%

Jacobson IM, et al. AASLD 2015. Abstract 42. Reproduced with permission.

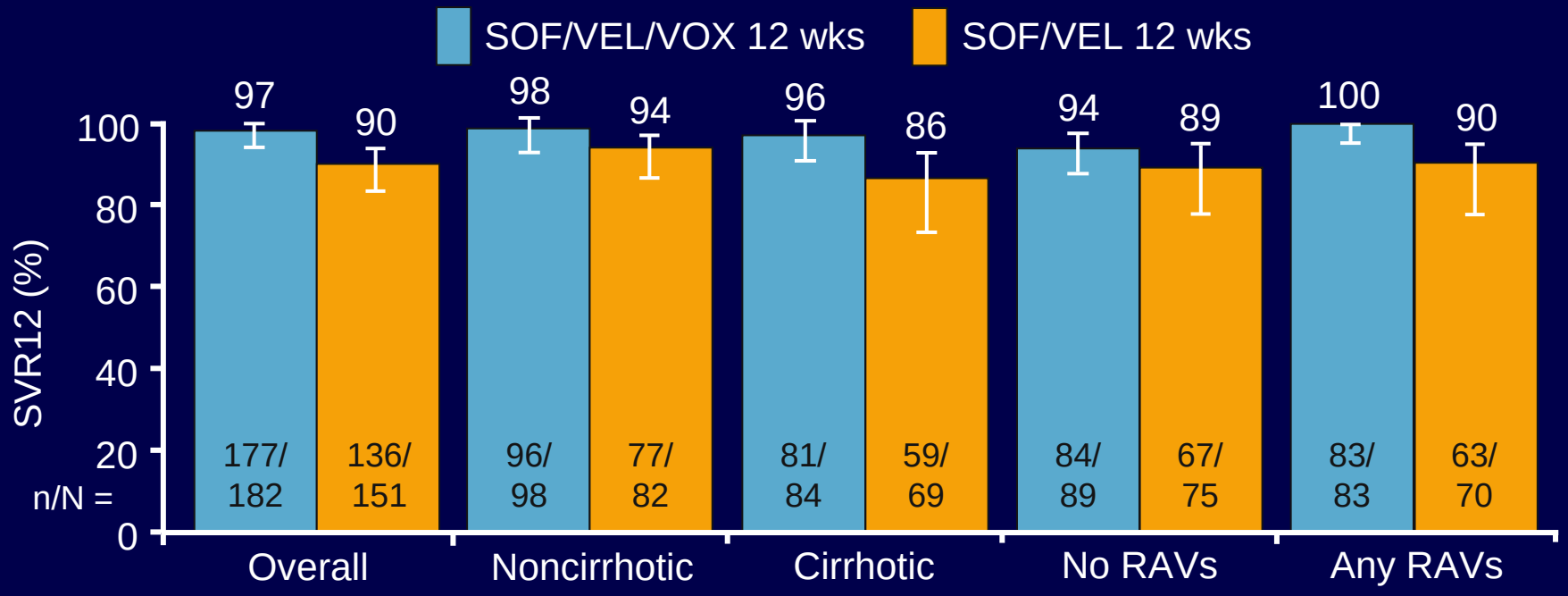
ASTRAL-1: SVR12 With Sofosbuvir/ Velpatasvir in GT1, 2, 4, 5, 6 HCV

- Double-blind, placebo-controlled trial
  - All pts with GT5 HCV allocated to active Tx because few pts in this group (n = 35)
  - Key baseline characteristics: cirrhosis 19%; Tx exp'd 32%; BL NS5A RAVs 42%
- No impact of cirrhosis, Tx experience, BL NS5A RAVs on SVR rates



Feld JJ, et al. AASLD 2015. Abstract LB-2. Feld JJ, et al. N Engl J Med. 2015;[Epub ahead of print]. Reproduced with permission.

POLARIS-4: Efficacy of SOF/VEL/VOX for DAA-Exp'd, NS5A Inhibitor Naive HCV Pts



- SOF/VEL/VOX: *P* < .001 for superiority vs prespecified 85% goal; SOF/VEL: *P* = .092
- Overall, reduced SVR12 rate for SOF/VEL driven by increased number of relapses
  - SOF/VEL/VOX (n = 182): 1 relapse, 1 death, 3 LTFU
  - SOF/VEL (n = 151): 14 relapses, 1 breakthrough

Zeuzem S, et al. AASLD 2016. Abstract 109. Reproduced with permission.

ENDURANCE Studies: Efficacy of glecaprevir/pibrentasvir for Treating GT1, 2, 4, 5, 6 HCV

Outcome	ENDURANCE-1[1] (GT1)		ENDURANCE-2[2] (GT2)	ENDURANCE-4[3] (GT4-6)
	GLE/PIB 8 Wks	GLE/PIB 12 Wks	GLE/PIB 12 Wks	GLE/PIB 12 Wks
SVR12, % (n/N)	99.1* (332/335)	99.7* (331/332)	99† (195/196)	99‡ (120/121)
Relapse/ on-treatment failure, n	1§	0	0	0

*ITT-PS analysis: included all pts receiving ≥ 1 dose of study drug; excluded pts with HIV coinfection or SOF experience. †ITT analysis: excluded pts with SOF experience. ‡ITT analysis. §On-treatment virologic failure at Day 29 in pt with GT1a HCV.

1. Zeuzem S, et al. AASLD 2016. Abstract 253.
2. Kowdley KV, et al. AASLD 2016. Abstract 73.
3. Asselah T, et al. AASLD 2016. Abstract 114.

Treatment Context

Treatment prioritisation summary

- All treatment-naive and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV must be considered for therapy (**A1**).
- Treatment should be considered without delay in patients with significant fibrosis or cirrhosis (METAVIR score F2, F3 or F4), including decompensated (Child-Pugh B or C) cirrhosis, in patients with clinically significant extra-hepatic manifestations (e.g. symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia, HCV immune complex-related nephropathy and non-Hodgkin B cell lymphoma), in patients with HCV recurrence after liver transplantation, and in individuals at risk of transmitting HCV (active injection drug users, men who have sex with men with high risk sexual practices, women of child-bearing age who wish to get pregnant, haemodialysis patients, incarcerated individuals) (**A1**).
- Patients with decompensated cirrhosis and an indication for liver transplantation with a MELD score ≥18-20 should be transplanted first and treated after transplantation. If the waiting time is more than 6 months, these patients can be treated before transplantation (**B1**)

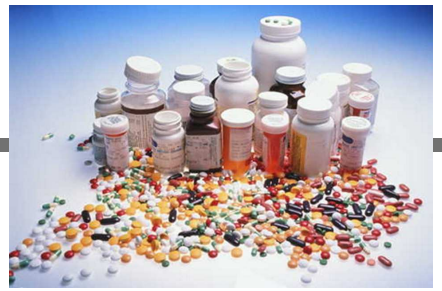
EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016
http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

IFN-free combination treatment regimens available as valuable options for each HCV genotype

Combination regimen	SOF + RBV	LDV/SOF ± RBV	SOF/VEL ± RBV	OBV/PTV/ RTV+ DSV ± RBV	OBV/PTV/ RTV ± RBV	GZR/ EBR	SOF + DCV ± RBV	SOF + SMV ± RBV
GT1	✗	✓	✓	✓	✗	✓	✓	Suboptimal
GT2	Suboptimal	✗	✓	✗	✗	✗	✓	✗
GT3	Suboptimal	✗	✓	✗	✗	✗	✓	✗
GT4	✗	✓	✓	✗	✓	✓	✓	✗
GT5	✗	✓	✓	✗	✗	✗	✓	✓
GT6	✗	✓	✓	✗	✗	✗	✓	✗

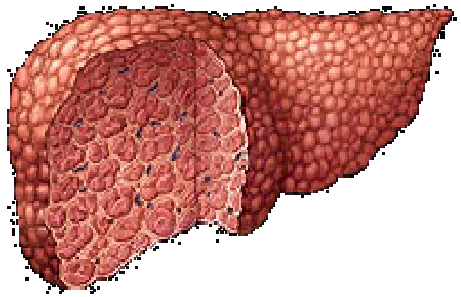
▪EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016
http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

Ribavirina



Interazioni

Scelta del Trattamento

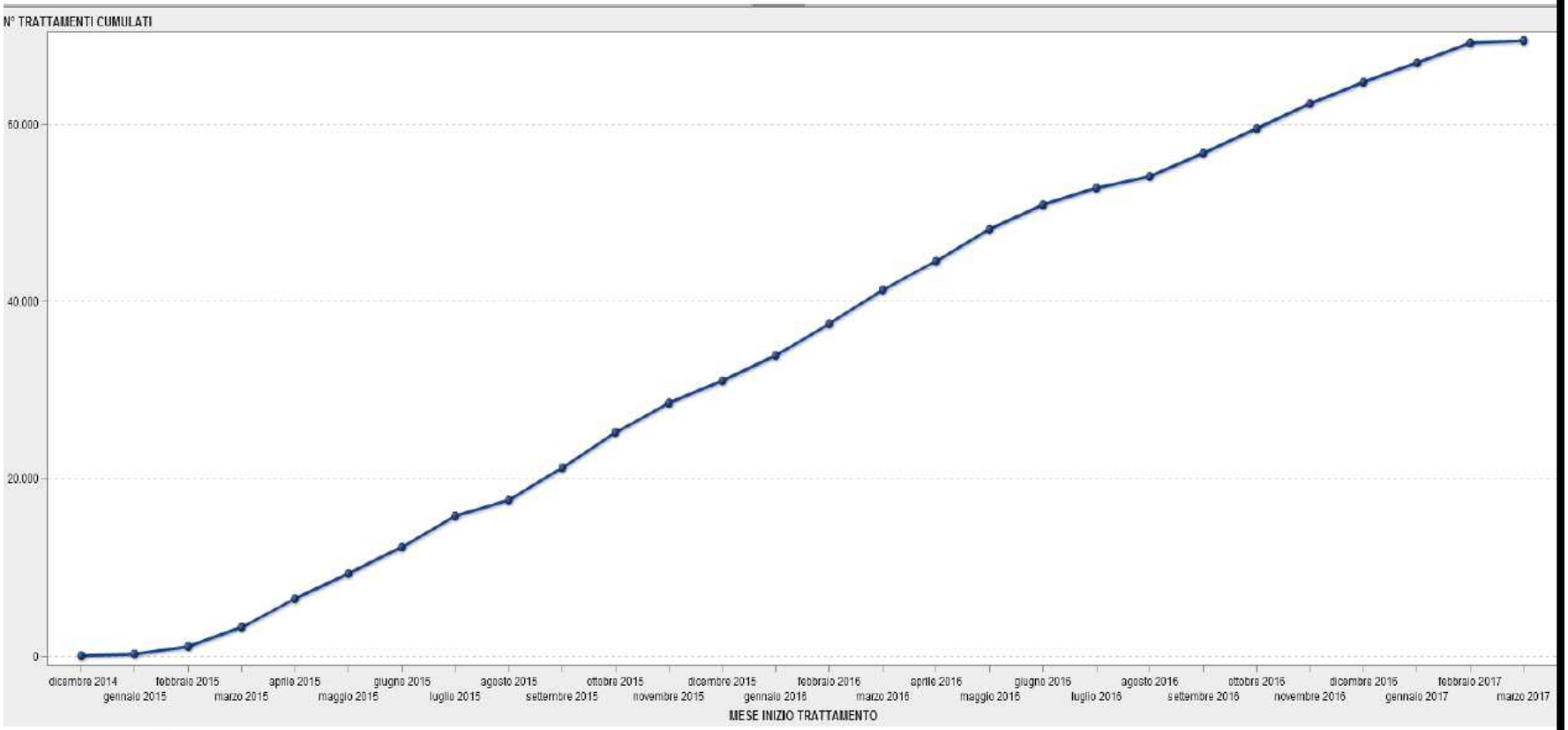


Cirrosi

Durata del trattamento

Costi

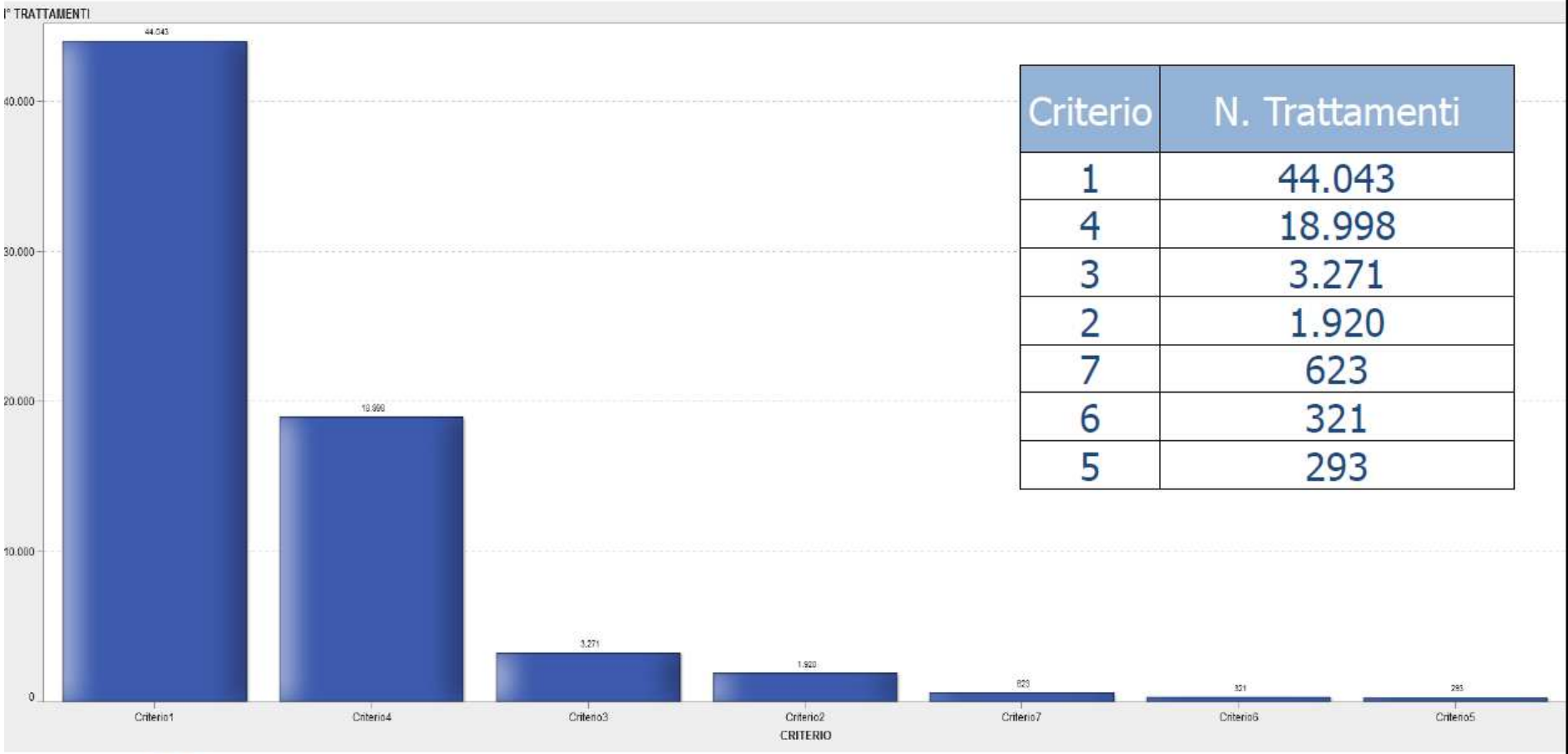
Trend cumulativo dei trattamenti avviati



Agenzia Italiana del Farmaco
AIFA

69.469 «avviati» sono i trattamenti (solo pazienti eleggibili) con almeno una scheda di Dispensazione farmaco

Trattamenti avviati per criterio



Criterio	N. Trattamenti
1	44.043
4	18.998
3	3.271
2	1.920
7	623
6	321
5	293

Azienda Ospedaliera Universitaria di Ferrara: Andamento della numerosità pz in trattamento con i nuovi DAA febbraio 15 – mar 2017

Dati al 27/02/17

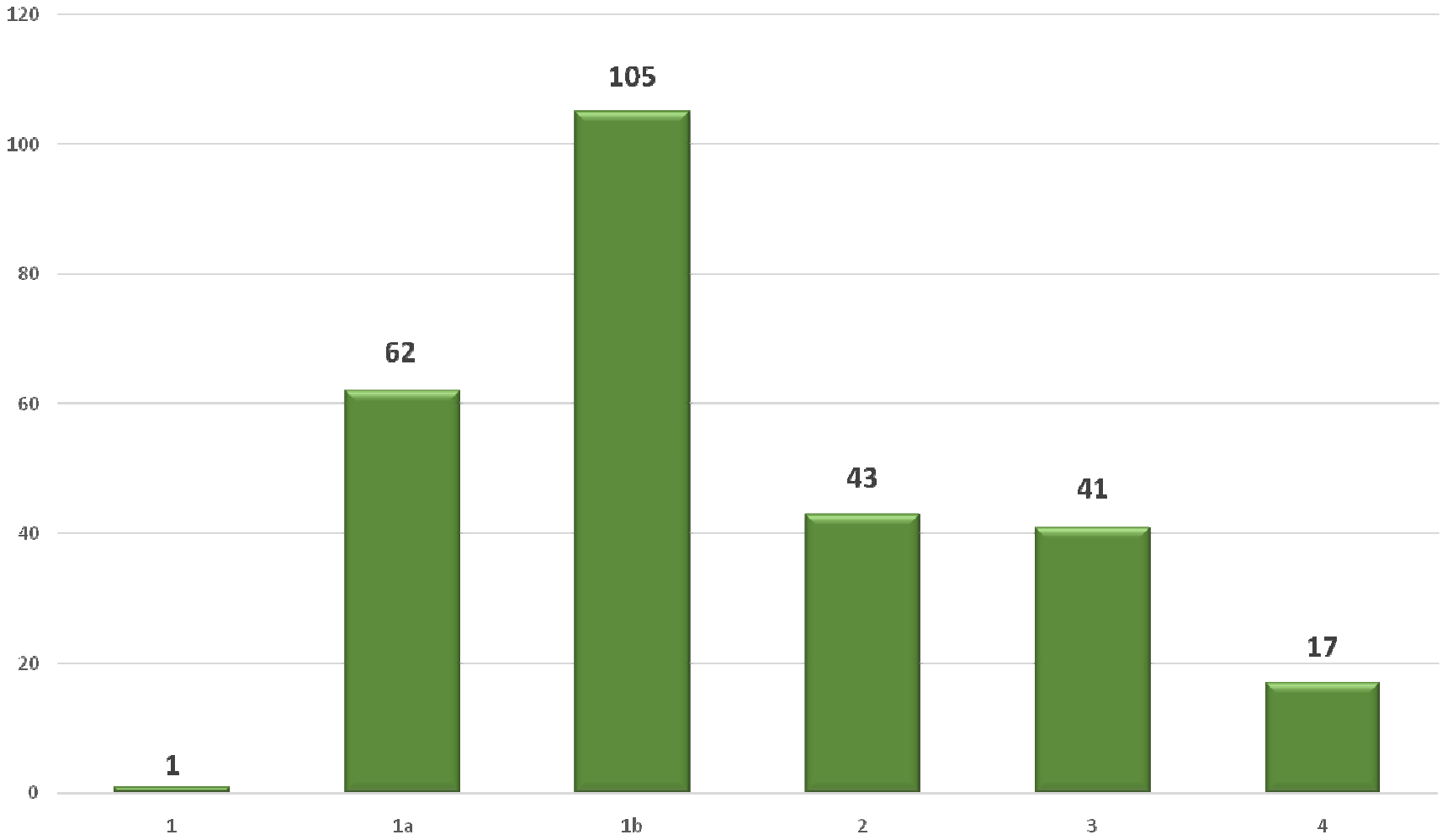
Numero trattamenti gen 2015 - dic 2016			Totale pz AOU FE per farmaco	% di utilizzo del farmaco sul totale dei trattamenti
DAKLINZA	Dac + Sof +/- Riba 12 SETT	**11**	**44**	**16%**
	Dac + Sof +/- Riba 24 SETT	**33**		
HARVONI	Led/Sof ± Riba 12 SETT	**42**	**106**	**39%**
	Led/Sof ± Riba 24 SETT	**64**		
OLYSIO	SimPR24	**4**	**24**	**9%**
	SimSof12	**4**		
	SimSofR12	**16**		
SOVALDI	SOF + RIBA per 24 sett	**35**	**50**	**19%**
	SOF + RIBA per 12 sett	**15**		
VIEKIRAX	Omb/Par/RTV+Das12	**16**	**46**	**17%**
	Omb/Par/RTV+Das12+Riba	**20**		
	Omb/Par/RTV+Das24+Riba	**8**		
	Omb/Par/RTV+Riba12	**1**		
	Omb/Par/RTV+Riba24	**1**		
Totale pz AOU FERRARA	**125 pazienti: 12w** **145 pazienti: 24w**		**270**	

FASCIA DI ETÀ	N.ro Pazienti	UOMINI	DONNE
20- 30	2	2	0
31 - 40	6	6	0
41 – 50	61	43	18
51 - 60	92	74	18
61 - 70	56	24	32
71 - 80	49	23	26
> 80	4	3	1

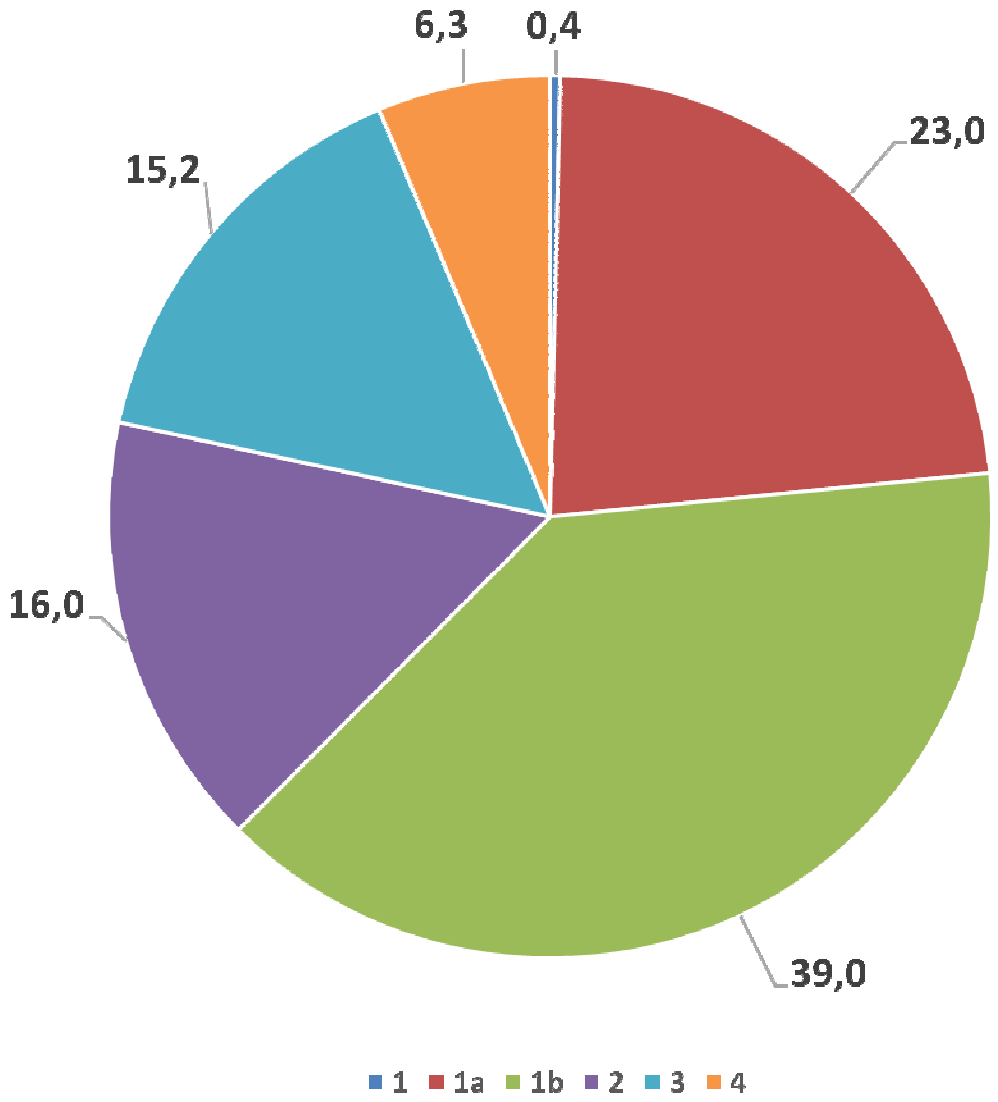
175 UOMINI

95 DONNE

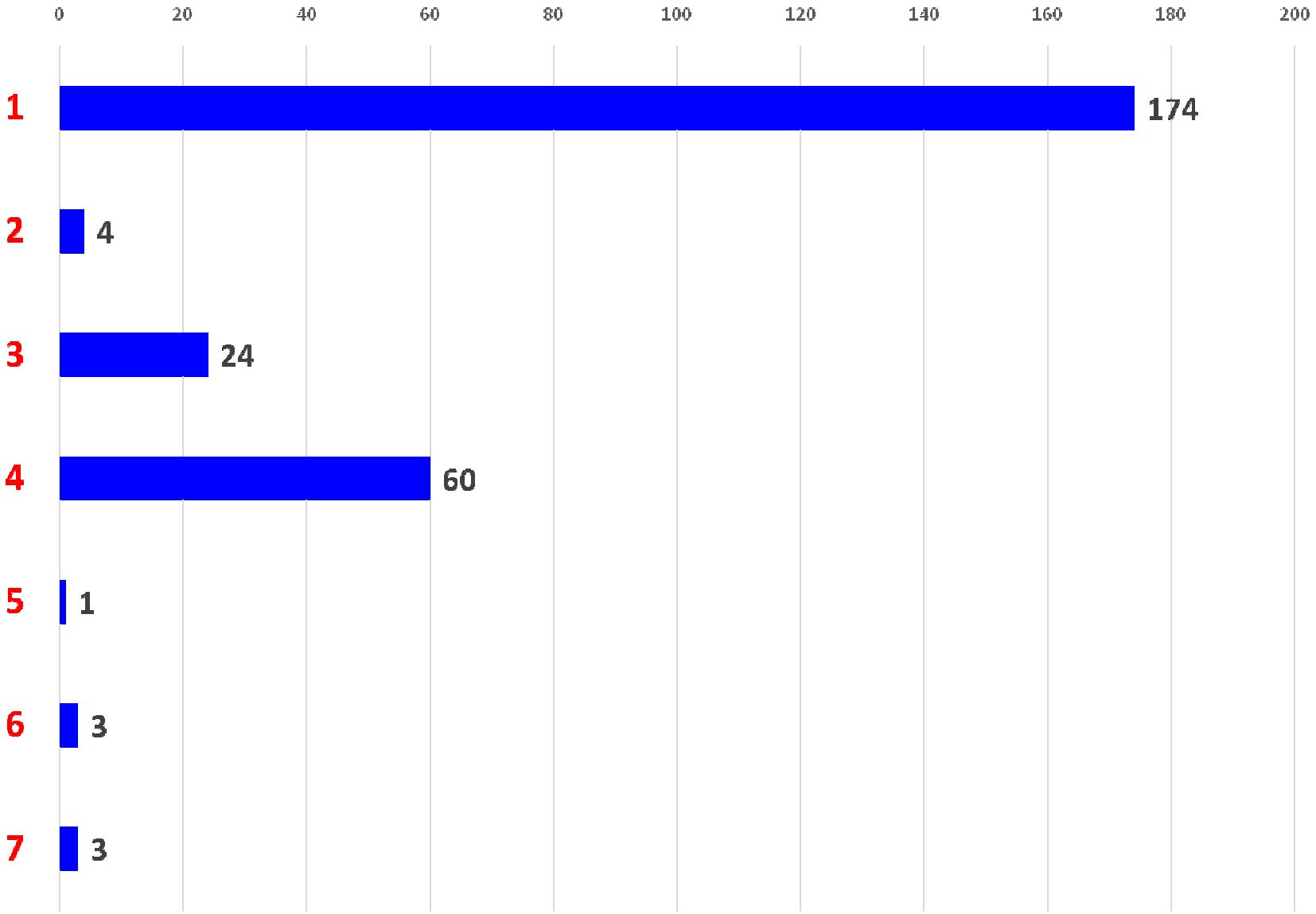
Distribuzione pazienti per genotipo
AOU FERRARA 2015 - 2016



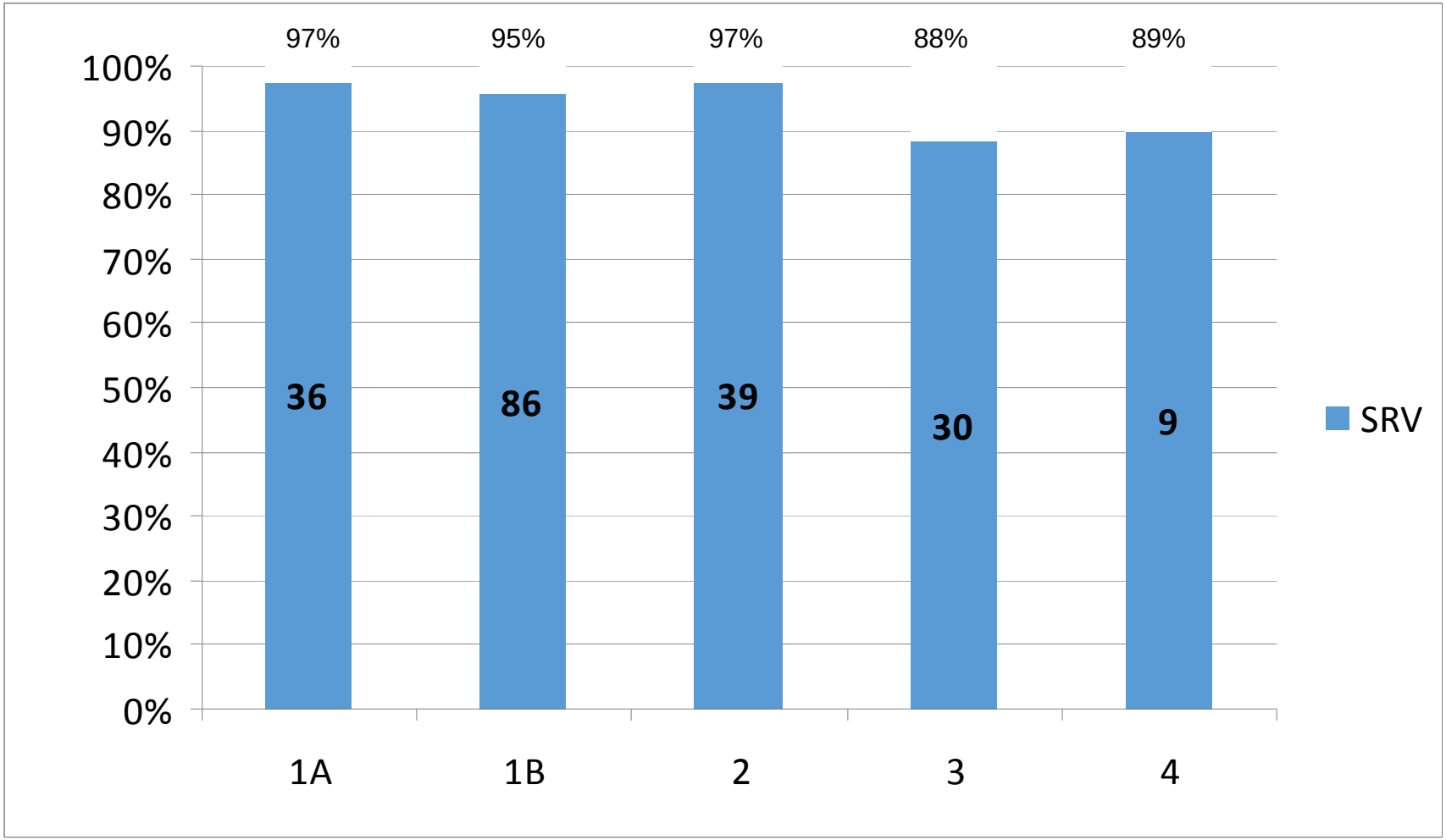
Distribuzione pazienti per genotipo AOU FERRARA (%)



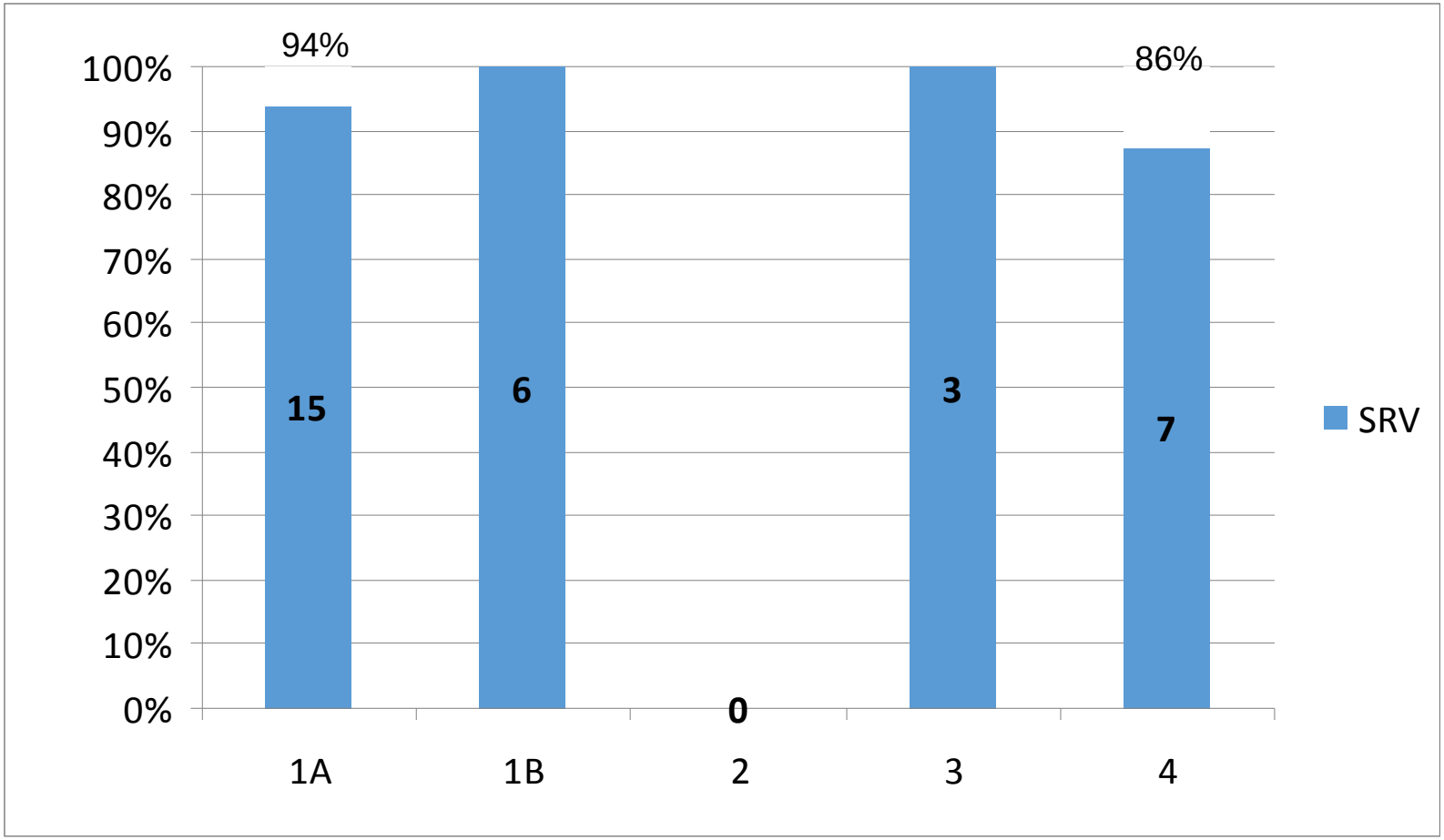
Distribuzione pazienti per criterio AOU FERRARA



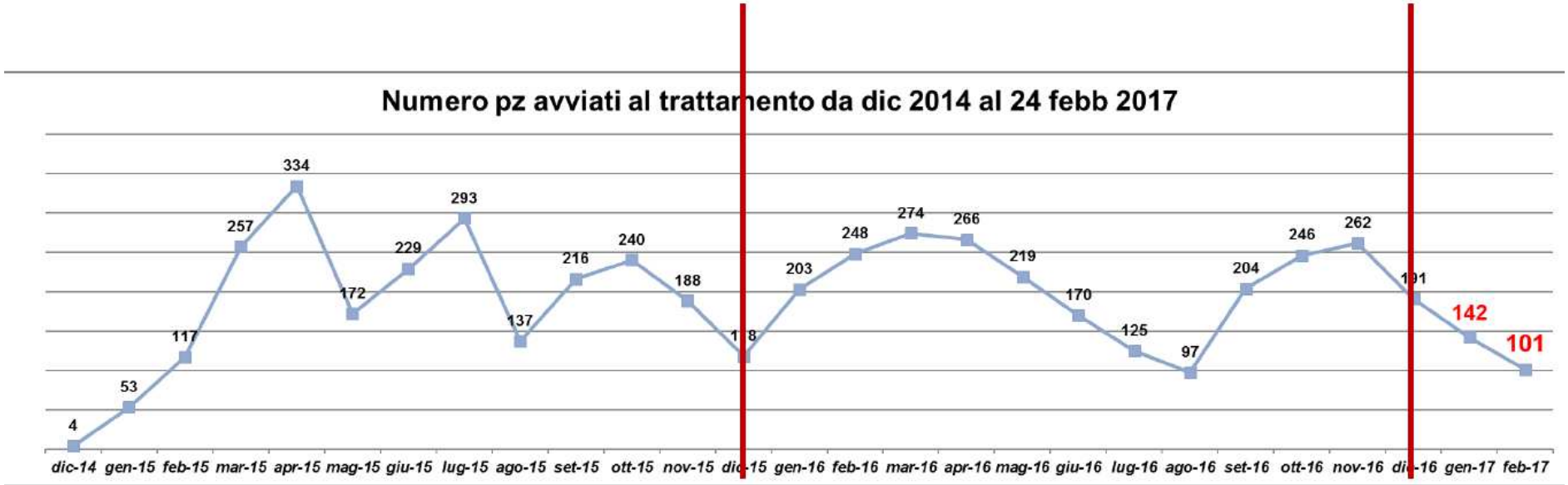
RISPOSTA SOSTENUTA A 24 SETTIMANE 200 pz



RISPOSTA SOSTENUTA 24 SETTIMANE HIV/ HCV 31 PZ



N. di pazienti in trattamento con i nuovi DAA per l'epatite C
Dic 2014 a febbraio 2017



2015: **2.358**

2016: **2.505**

243

AIFA Agenzia Italiana del Farmaco

TOTALE: 5.106

Farmaci prescritti per ogni criterio AIFA da dicembre 2014 a febbraio 2017

	MEDICINALE					tot per Criterio AIFA
	DAKLINZA	HARVONI	OLYSIO	SOVALDI	VIEKIRAX	
Criterio1	667	1012	376	553	756	***3364***
Criterio2	35	53	24	29	5	***146***
Criterio3	42	94	34	77	81	***328***
Criterio4	176	349	115	154	367	***1161***
Criterio5	7	14	5	12	1	***39***
Criterio6	11	21	3	6	3	***44***
Criterio7			24			***24***
Totale RER	***938***	***1543***	***581***	***831***	***1213***	***5106***

AIFA
Agenzia Italiana del Farmaco

Distribuzione pazienti per farmaco, schema terapeutico

Numero trattamenti avviati dal 2014 al 24 febbraio 2017				
Farmaco	**Schema Terapeutico**	**N trattamenti avviati**	**Totale pz RER per farmaco**	**% di utilizzo del farmaco sul totale dei trattamenti**
DAKLINZA	Dac + Sof +/- Riba 12 SETT	**327**	**938**	**18%**
	Dac + Sof +/- Riba 24 SETT	**611**		
HARVONI	Led/Sof ± Riba 12 SETT	**699**	**1.543**	**30%**
	Led/Sof ± Riba 24 SETT	**841**		
	Led/Sof ± Riba 8 SETT	**3**		
OLYSIO	SimPR24	**21**	**581**	**11%**
	SimPR48	**4**		
	SimSof12	**282**		
	SimSofR12	**274**		
SOVALDI	SOF + PEG-IFN + RIBA per 12 SETT	**48**	**831**	**16%**
	SOF + RIBA per 24 sett	**619**		
	SOF-RIBA per 12 sett	**152**		
	SOF-RIBA sino al trapianto o al massimo per 48 sett	**12**		
VIEKIRAX	Omb/Par/RTV+Das12	**419**	**1.213**	**24%**
	Omb/Par/RTV+Das12+Riba	**463**		
	Omb/Par/RTV+Das24+Riba	**189**		
	Omb/Par/RTV+Riba12	**54**		
	Omb/Par/RTV+Riba24	**88**		
Totale pz RER		**5.106**		

TOTALE Pazienti ritrattati in SOLE

Az sanitaria	Pz Ritrattati in Sole
OSPEDALE DI PIACENZA	5
AZIENDA OSPEDALIERO UNIVERSITARIA DI PARMA	6
ARCISPEDALE S. MARIA NUOVA	3
OSPEDALE DI BAGGIOVARA	5
POLICLINICO DI MODENA	5
ARCISPEDALE S. ANNA	10
POLICLINICO BOLOGNA	25
OSPEDALE BENTIVOGLIO	5
OSPEDALE IMOLA	1
OSPEDALE FAENZA	2
OSPEDALE RAVENNA	1
OSPEDALE RIMINI	5
RER	**73**

SOLE
sanità online

TOTALE Pazienti ritrattati in SOLE per GENOTIPO

GENOTIPO	Pz Ritrattati in Sole	% sul totale dei trattati
1	1	3,8
1a	8	0,9
1b	23	1,1
2	3	0,5
3	26	3,1
4	12	3,1
totale	**73**	**1,5**

SOLE
sanità online

Nota: di cui 6 con genotipo diverso tra primo e secondo trattamento

Prezzi aggiornati dei trattamenti con DAA al 2 marzo 2017
La tabella dei costi

Trattamento	Costo (+ IVA) di un trattamento con DAA (12 sett.) €	Sconto P/V calcolato al 02.03.2017 in RER	Costo finale (+ IVA) di un trattamento con DAA (12 settimane) al 02.03.2017 in RER €
SOF + (RBV±PIFN)	40.700		< 16.500*
SOF + (RBV)	40.700		< 16.500*
SOF+LDP ± (RBV)	44.770		< 18.260
SOF+DCV ± (RBV)	55.000/69.300 [se 90mg/die]	---	< 26.400* < 36.300 [se 90mg/die]
PTVr/OBV+DSV ± (RBV)	29.700	66,67%	9.899
PTVr/OBV + (RBV)	27.324	66,67%	9.107
SOF+SIM ± (RBV)	51.700	---	< 27.500*
SIM + (RBV+PIFN)	11.000	---	11.000
ELB/GRAZ	44.673,75	primi 15.000 paz.	9.900

azienda	Ripartizione stanziamento per FARMACI HCV	Stima spesa anno	Assegnato con DGR 2411 del 28.12.2016
AUSL PC	€ 3.566.563	€ 4.156.008	€ 4.756.000
AUSL PR	€ 390.093	€ 4.076.495	€ 4.076.500
AOSP PR	€ 4.012.384		
AUSL RE			€ 4.983.000
AOSP RE	€ 7.188.854	€ 4.982.806	
AUSL MO	€ 1.448.916	€ 7.370.652	€ 7.370.500
AOSP MO	€ 7.913.313		
AUSL BO	€ 2.061.920	€ 1.386.455	€ 1.386.500
AOSP BO	€ 14.767.802	€ 10.957.831	€ 10.958.000
IOR			
Imola	€ 724.458	€ 597.543	€ 597.500
AUSL FE			
AOSP FE	€ 2.730.650	€ 1.563.662	€ 1.863.500
AUSL ROMAGNA	€ 9.195.046	€ 7.338.265	€ 7.338.000
IRST			
RER	**€ 54.000.000**	**€ 42.429.718**	**€ 43.329.500**

NUOVI CRITERI AIFA MARZO 2017

Criterio 1: Pazienti con cirrosi in classe di Child A o B e/o con HCC con risposta completa a terapie resettive chirurgiche o loco-regionali non candidabili a trapianto epatico nei quali la malattia epatica sia determinante per la prognosi.

Criterio 2: Epatite ricorrente HCV-RNA positiva del fegato trapiantato in paziente stabile clinicamente e con livelli ottimali di immunosoppressione.

Criterio 3: Epatite cronica con gravi manifestazioni extra-epatiche HCV-correlate (sindrome crioglobulinemica con danno d'organo, sindromi linfoproliferative a cellule B, insufficienza renale).

Criterio 4: Epatite cronica con fibrosi METAVIR F3 (o corrispondente Ishak).

Criterio 5: In lista per trapianto di fegato con cirrosi MELD <25 e/o con HCC all'interno dei criteri di Milano con la possibilità di una attesa in lista di almeno 2 mesi.

Criterio 6: Epatite cronica dopo trapianto di organo solido (non fegato) o di midollo in paziente stabile clinicamente e con livelli ottimali di immunosoppressione.

Criterio 7: Epatite cronica con fibrosi **METAVIR F2**.

Criterio 8: Epatite cronica con fibrosi **METAVIR F0-F1** (o corrispondente Ishak) e/o comorbilità a rischio di progressione del danno epatico [coinfezione HBV, coinfezione HIV, malattie croniche di fegato non virali, diabete mellito in trattamento farmacologico, obesità (body mass index ≥30 kg/m2), emoglobinopatie e coagulopatie congenite].

Criterio 9: Operatori sanitari infetti.

Criterio 10: Epatite cronica o cirrosi epatica in paziente con insufficienza renale cronica in trattamento emodialitico.

Criterio 11: Epatite cronica nel paziente in lista d'attesa per trapianto di organo solido (non fegato) o di midollo