IL PAZIENTE COINFETTO HIV/HCV

Strategie terapeutiche

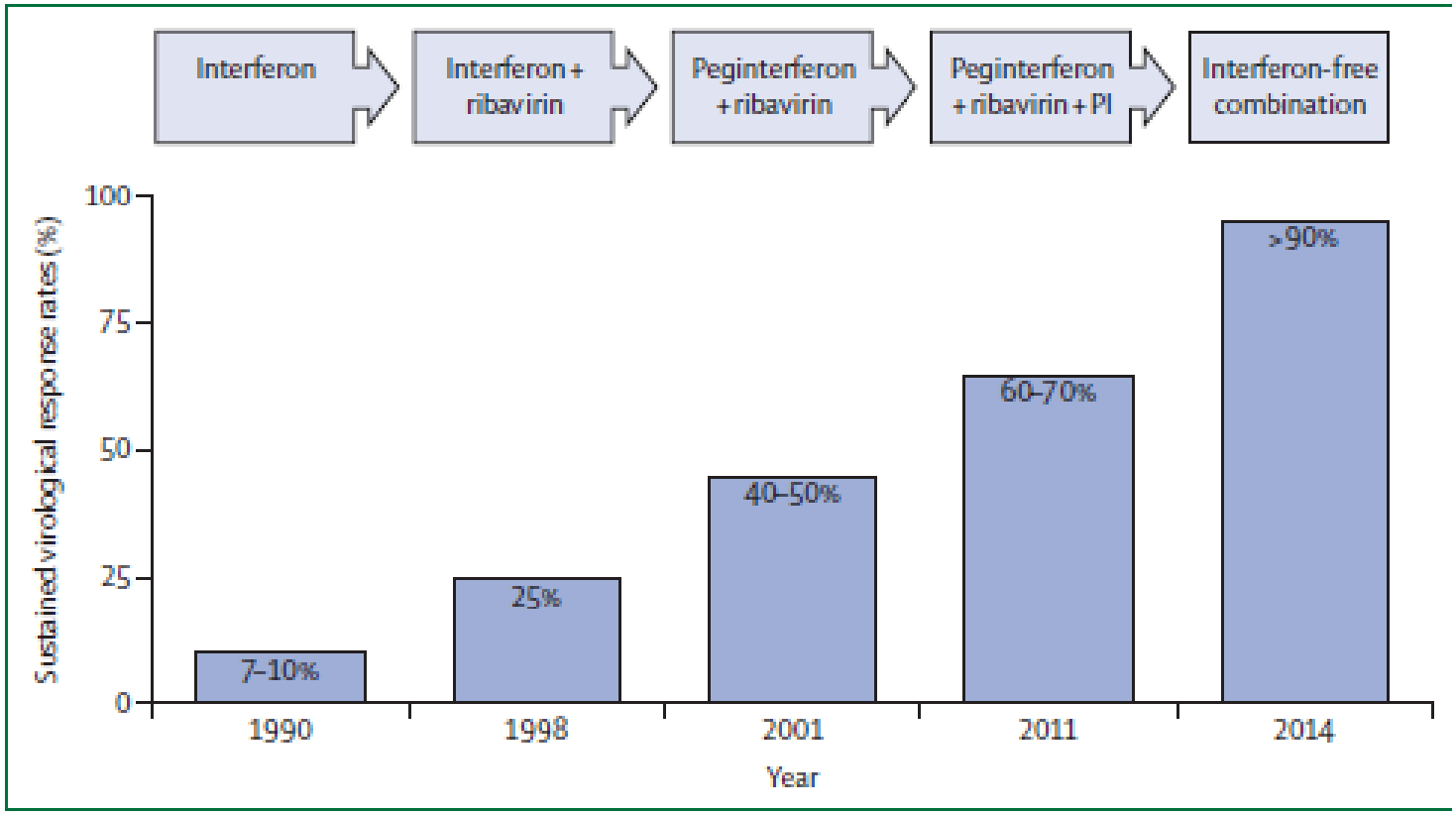
Barbara Menzaghi

Talking about a revolution

Tracy Chapman

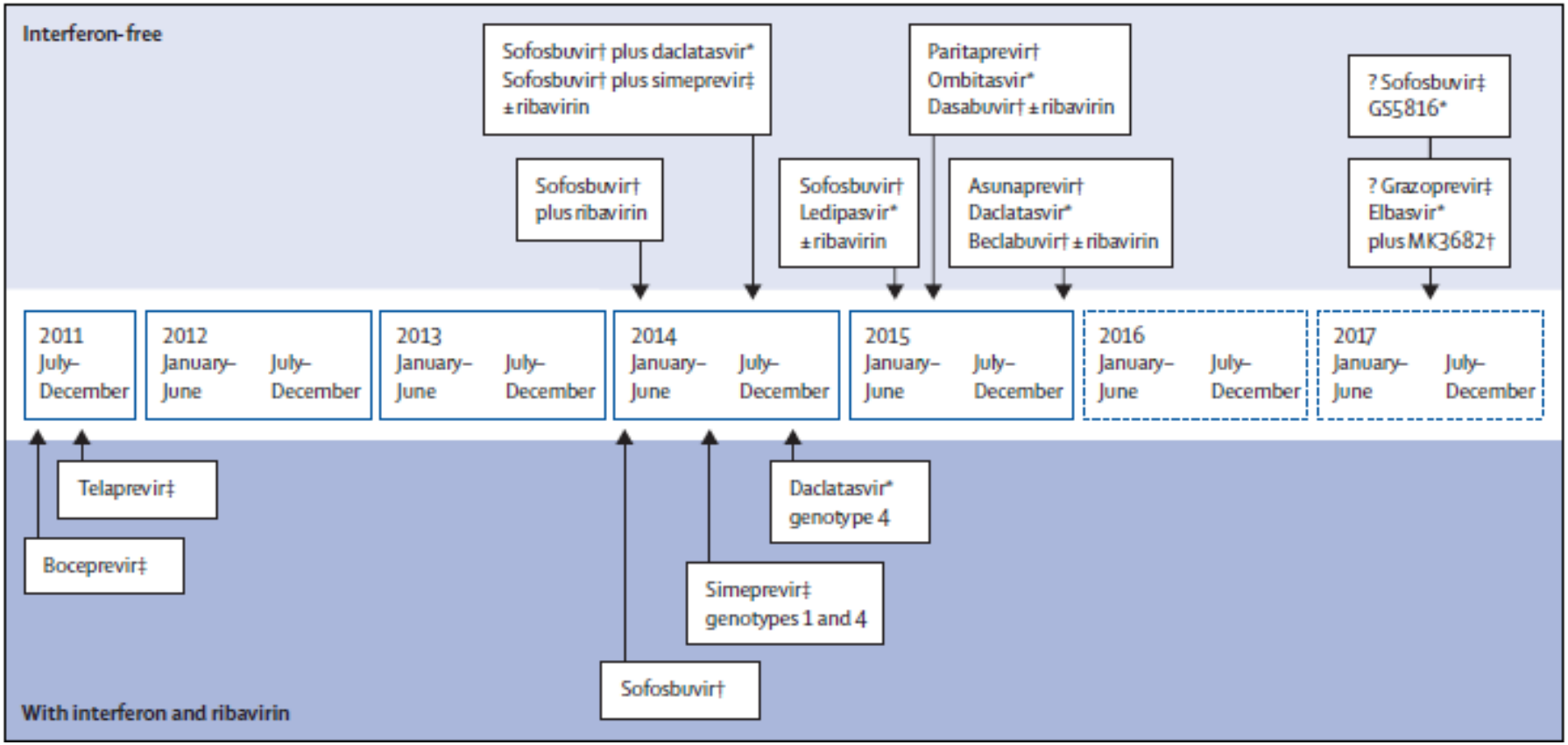
Expo Milano 2015-Padiglione Francia

Changes in standard of care for HCV and increased rate of SVR



Lancet 2015;385:1124-35

Treatment of HCV in 2015



Lancet 2015;385:1124-35

The times they are a-changin'

Bob Dylan

Expo Milano 2015-Padiglione Messico

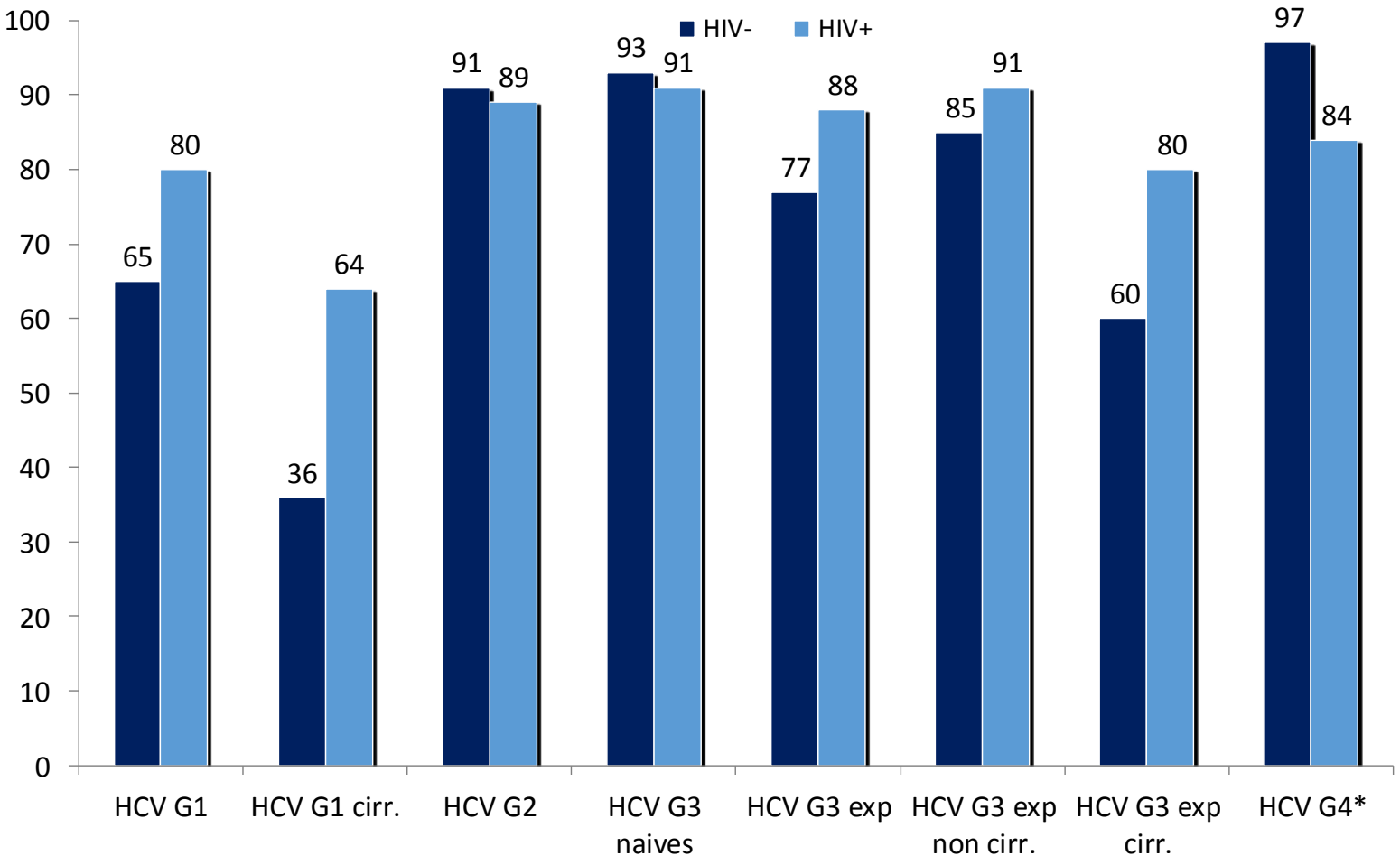
Evoluzione dei trattamenti per HCV nel paziente HIV positivo

Table 1 Sustained virological response rate in human immunodeficiency virus/hepatitis C virus coinfected patients naïve for anti-hepatitis C virus treatment

	Ref.	SVR rate in therapy-naive patients			
		Genotype 1	Genotype 2	Genotype 3	Genotype 4
Peg-IFN plus ribavirin	[85]	35.6% in 191 patients	72.4% in 152 patients		32.6% in 46 patients
Peg-IFN plus ribavirin + boceprevir	[32]	60.7% in 61 patients	-	-	-
Peg-IFN plus ribavirin + telaprevir	[51]	74% in 38 patients	-	-	-
Peg-IFN plus ribavirin + sofosbuvir	[44]		91% in 23 patients		
Peg-IFN plus ribavirin + simeprevir	[55]	79.2% in 52 patients	-	-	-
Peg-IFN plus ribavirin + faldaprevir	[59]	73.7% in 227 patients[1]	-	-	-
Sofosbuvir plus ribavirin	[60]	76% in 114 patients[2]	88% in 26 patients[3]	67% in 42 patients[3]	-
Sofosbuvir plus ribavirin	[62]	84% in 112 patients	90% in 19 patients	91% in 57 patients	84% in 31 patients
Sofosbuvir plus ledipasvir	[63]	100% in 13 patients	-	-	-
Paritaprevir-r/ombitasvir + dasabuvir + ribavirin	[65]	93.5% in 31 patients	-	-	-

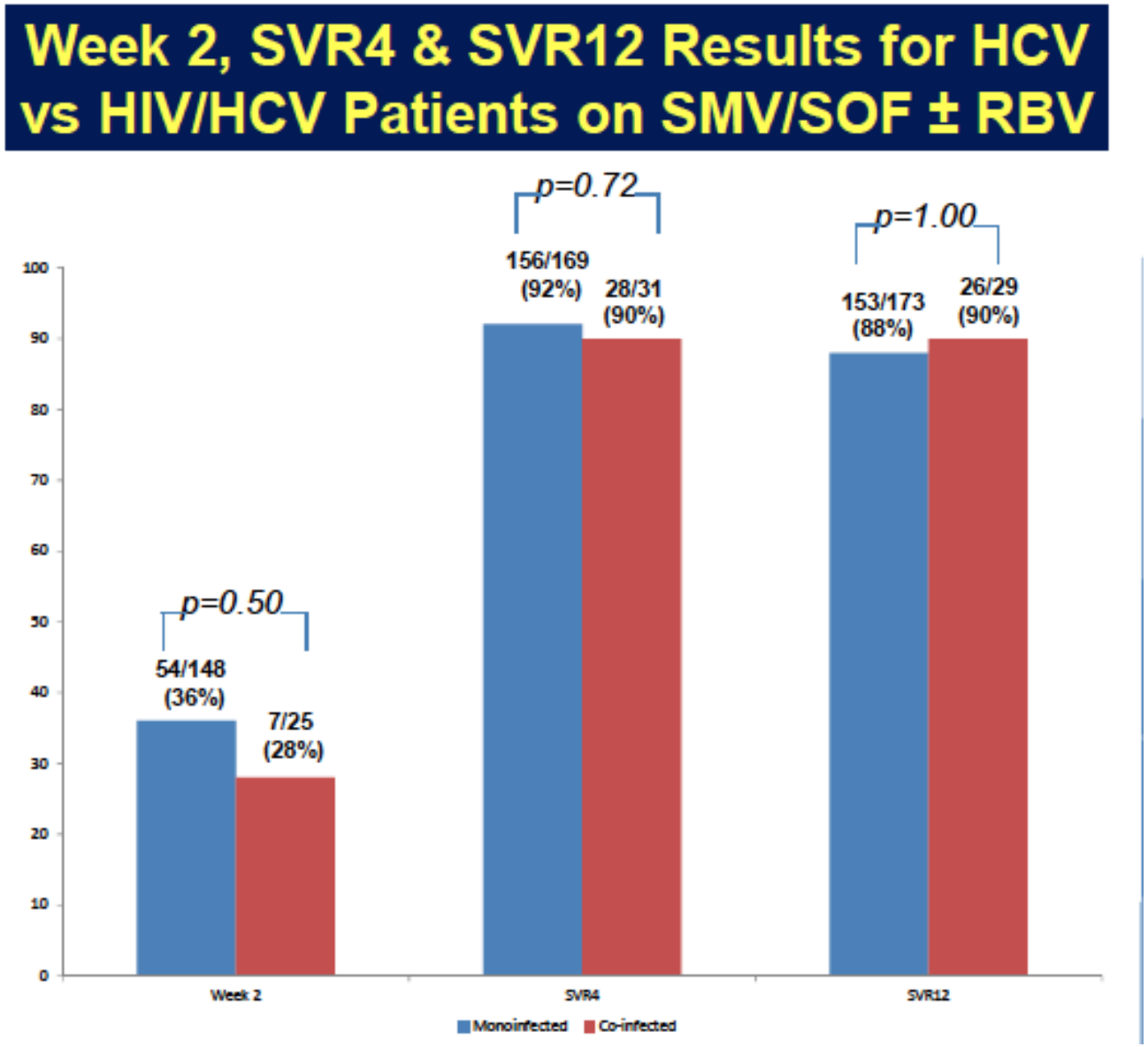
Coppola N, et al. WJG 2015;4:1-12

Efficacy of Sofosbuvir + Ribavirin in HCV G2 (12 weeks) G1 G3 & 4 (24 weeks) stratified according to cirrhosis previous treatment and HIV reactivity



Sovaldi SPC ; Sulkowsky et al. Ann Int Med 2014; Molina JM et al The Lancet 2015

Sofosbuvir + Simeprevir in HIV/HCV vs HCV



Del Bello et al CROI 2015 abstract #45

Real life data on Sofosbuvir + Simeprevir (± RBV) in HIV/HCV : CROI 2015

Author/ Pts Character.	Abstract N	SVR/ total
Grant J all	649	18/20 (90%)
Marks K (PI exp)	644	12/13 (92%)
Gilmore (cirrhotics)	647	22/29 (76%)
Del Bello D (all)	645	26/29 (90%)
All		78/91 (86%)

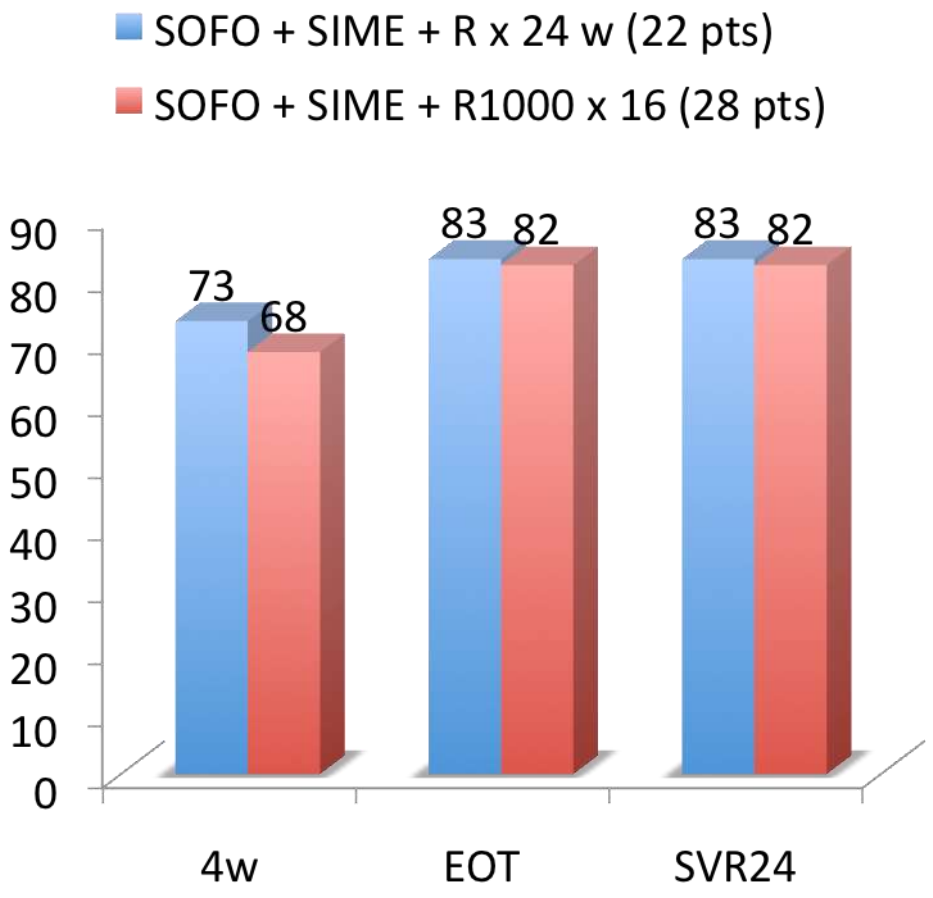
Simeprevir and Sofosbuvir with modified doses of Ribavirin on Telaprevir experienced HIV coinfected cirrhotics with HCV
A randomized open label pilot study: STOP C

Fifty (n=50) co-infected (HIV+CHC, non AIDS) cirrhotics with mean MELD 16, HIV RNA undetectable, mean CD 4 count 439, Hb 10.7, HCV RNA 1.7 million copies, mean platelet count 104, albumin 2.9 and WBC 4600. 18 genotype 1a and 32 genotype 1b. 16 null responders, 12 relapsers while 12 discontinued treatment.

HIV Medications included: Atripla, Reltagavir and Complera.
11/50 patients were on Methadone; mean dose of 40 mg.

Group A: Simeprevir 150 mg + Sofosbuvir 400 mg + RBV for 24 weeks
Group B: Simeprevir 150 mg + Sofosbuvir 400 mg + RBV 1000 mg for 16 weeks

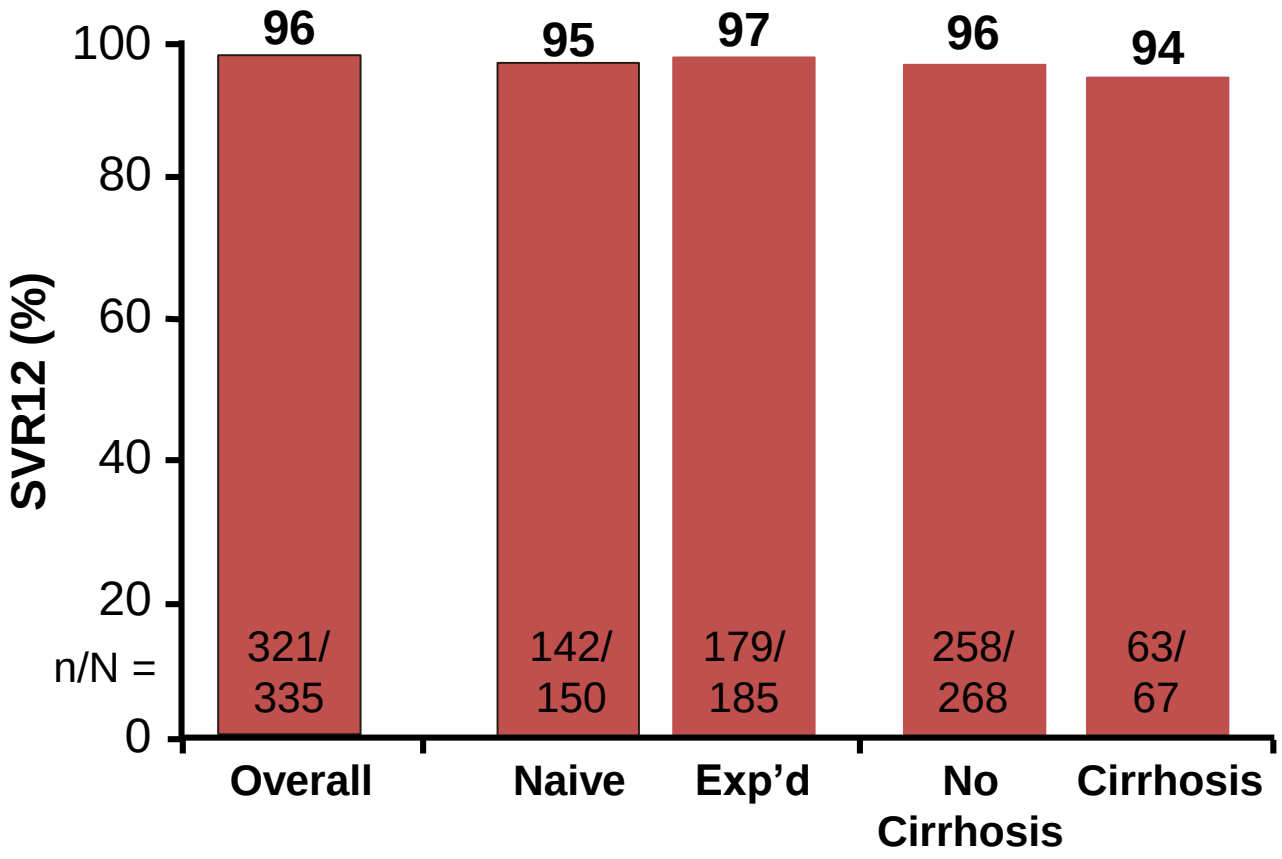
	GROUP A (n=22) Simeprevir 150 mg + Sofosbuvir 400 mg + RBV	GROUP B (n=28) Simeprevir 150 mg + Sofosbuvir 400 mg + RBV 1000 mg
Duration of therapy	24 weeks	16 weeks
Mean age	57	55
M:F	18:4	22:6
BMI	24.6	
Demographics		
Caucasians	0	4
Hispanic	13	14
African American	9	10
Asian	0	0
Null responders	8	8
Partial responders		6
Treatment failure	10	
Relapsers	4	6
Genotype		
1a	9	6
1b	13	22
Mean viral load, k	1,200	1,280
IL28b		
CC	8	11
CT	9	7
TT	5	10
q80k polymorphism	6 (G1a 6)	3 (G1a 3)
Prior Telaprevir resistance	6	3



Basu PP AASLD 2014

ION-4: LDV/SOF for 12 Wks in HCV/HIV-Coinfected Patients

- GT1 or 4 HCV, 20% with compensated cirrhosis, 55% treatment experienced



Naggie S, et al. CROI 2015. Abstract 152LB.

Virologic Response Following Combined Ledipasvir and Sofosbuvir Administration in Patients With HCV Genotype 1 and HIV Co-infection

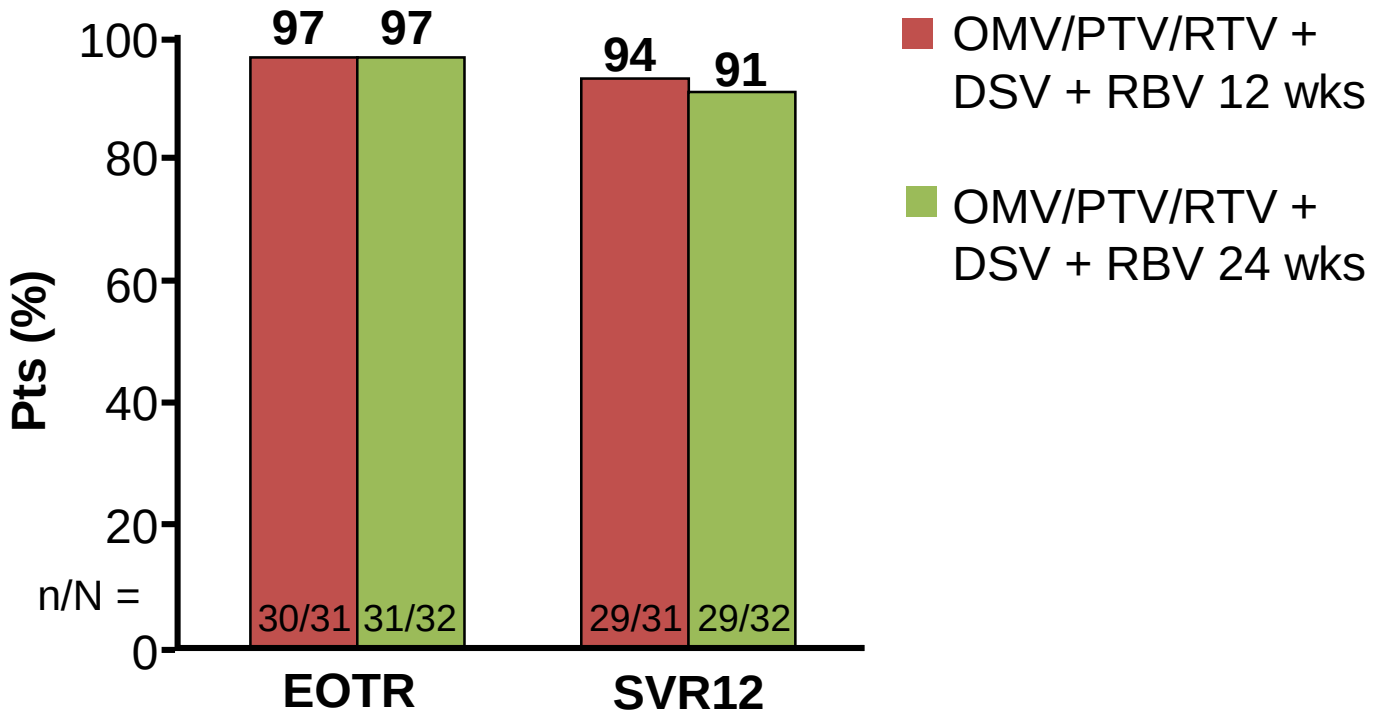
Table 2. Patients With HCV RNA Levels Below the Level of Quantification at Various Times of Treatment and Follow-up[a]

Week	Antiretroviral Therapy, No. (%) [95% CI][b]	
	No (n = 13)	Yes (n = 37)
Treatment Period		
4	13 (100) [75-100]	37 (100) [91-100]
8	13 (100) [75-100]	37 (100) [91-100]
12	13 (100) [75-100]	37 (100) [91-100]
Postttreatment Period		
2	13 (100) [75-100]	37 (100) [91-100]
4	13 (100) [75-100]	36 (97) [89-100]
8	13 (100) [75-100]	36 (97) [89-100]
12 (SVR_{12})	13 (100) [75-100]	36 (97) [89-100]

50 pts
Genotype 1a (78%)
Genotype 1b (22%)
No cirrhosis

Osinusi A, et al. 2015;313:1232-9

TURQUOISE-1: OMV/PTV/RTV + DSV+ RBV for 12 vs 24 Wks in GT1 HCV/HIV Coinfection



- 65% HCV treatment-naive pts in 12-wk arm, 69% in 24-wk arm
- 19% patients with METAVIR F4 fibrosis, Genotype 1a 89%

Sulkowski MS, et al. JAMA 2015;313:1223-31

Non-responders

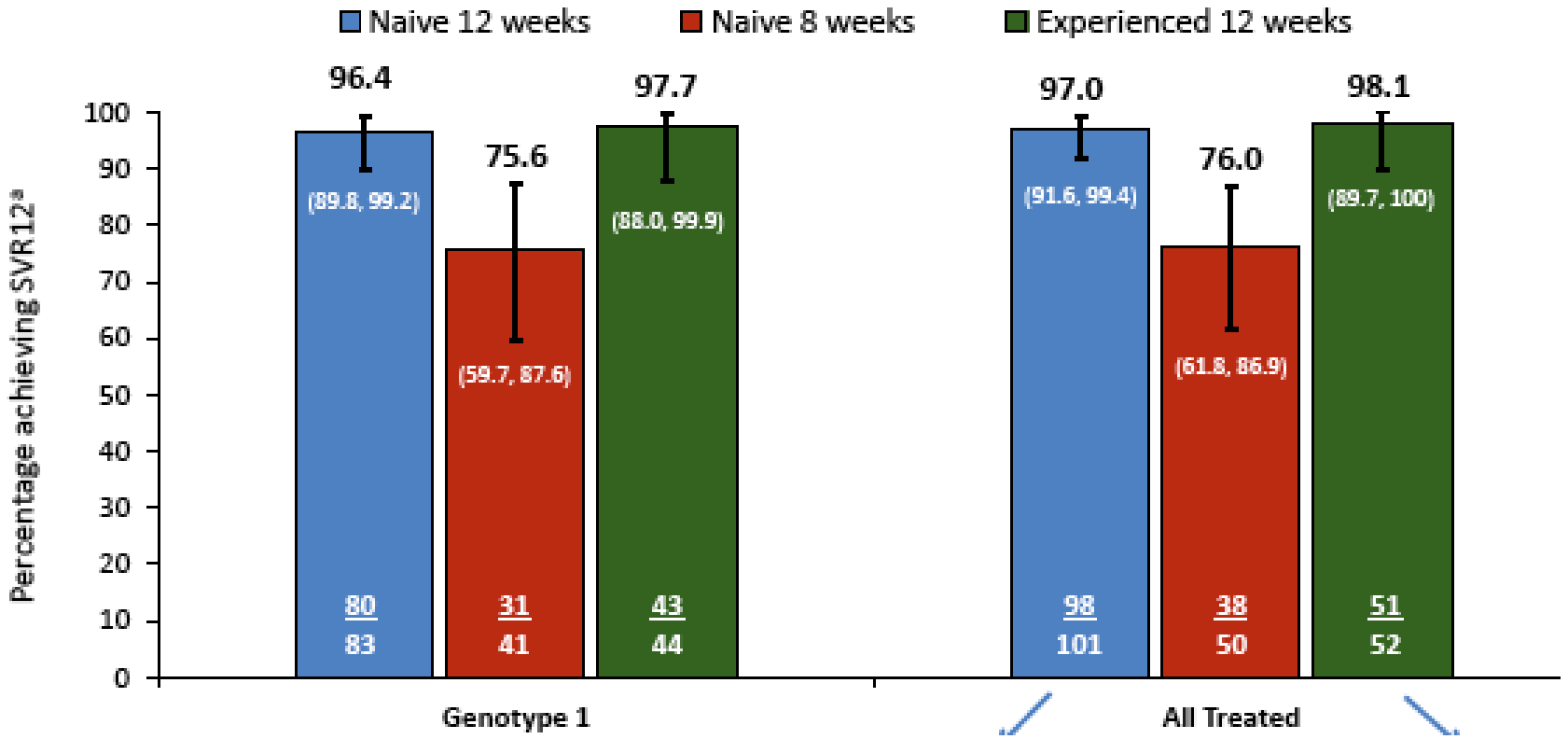
Table 3. Patients Not Achieving Sustained Virologic Response at Posttreatment Week 12: Disease and Virologic Characteristics

		Disease Characteristics						HCV Variants[b]		
Patient	Treatment Group, wk	HCV Genotype	*IL28B* Genotype	Fibrosis Stage[c]	Prior pegIFN Plus Ribavirin[d]	Reason for Nonresponse	Time Point Sequenced[a]	NS3/4A	NS5A	NS5B
1	12	1a	TT	F3	Naive	Withdrawn consent	NA	NA	NA	NA
2	12	1a	TT	F4	Null response	Virologic relapse at PTW4	Baseline	None	None	None
							PTW4	D168V	M28T	S556G
3	24	1a	TT	F4	Null response	Virologic breakthrough during treatment wk 16	Baseline	None	None	None
							PTW2	R155K	Q30R	S556G
4[e]	24	1a	CT	F0-F1	Naive	HCV reinfection	Baseline	None	None	None
							PTW8	None	None	None
5[e]	24	1a	CC	F0-F1	Naive	HCV reinfection	Baseline	None	None	None
							PTW12	None	None	None

Sulkowski MS, et al. JAMA 2015;313:1223-31

Daclatasvir Plus Sofosbuvir for Treatment of HCV Genotypes 1-4 in HIV-HCV Coinfection: The ALLY-2 Study

Figure 3. SVR12 Results

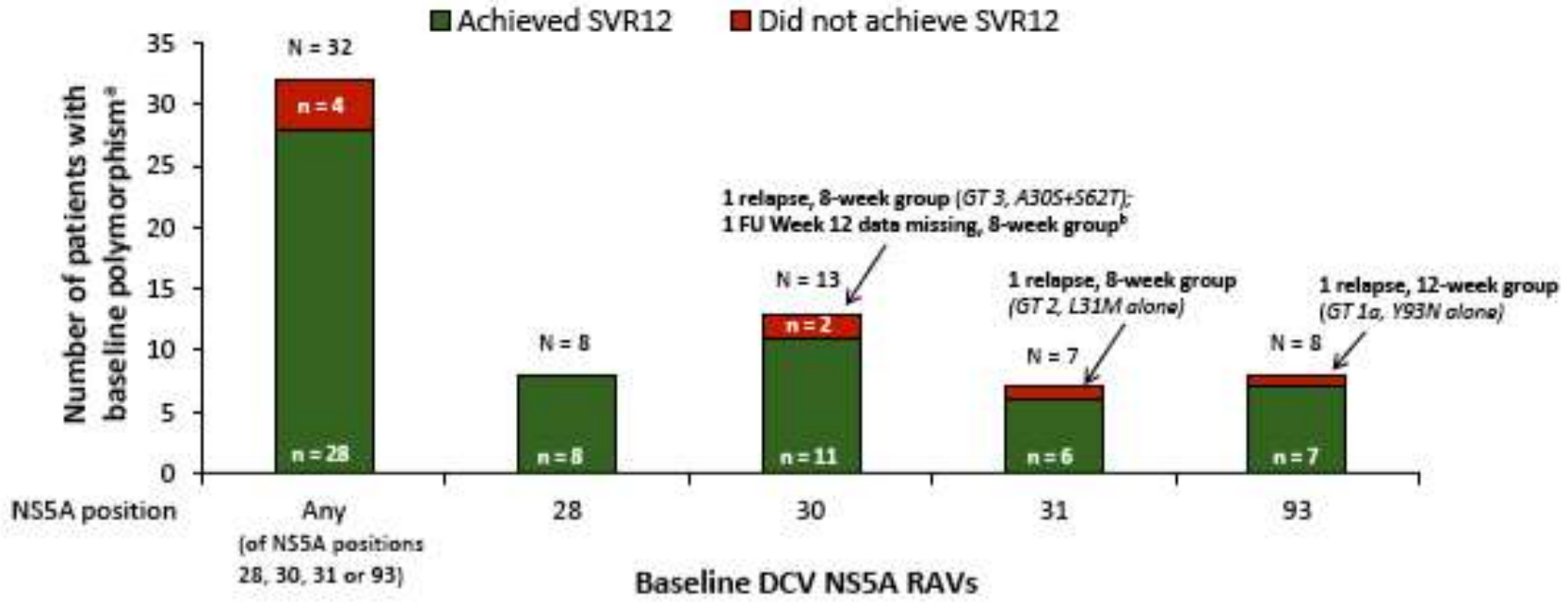


Cirrhosis 16%
Genotype 1a 70%
12 pts with relapse, 10 in 8-wk arm

Wyles DL, et al. EASL 2015

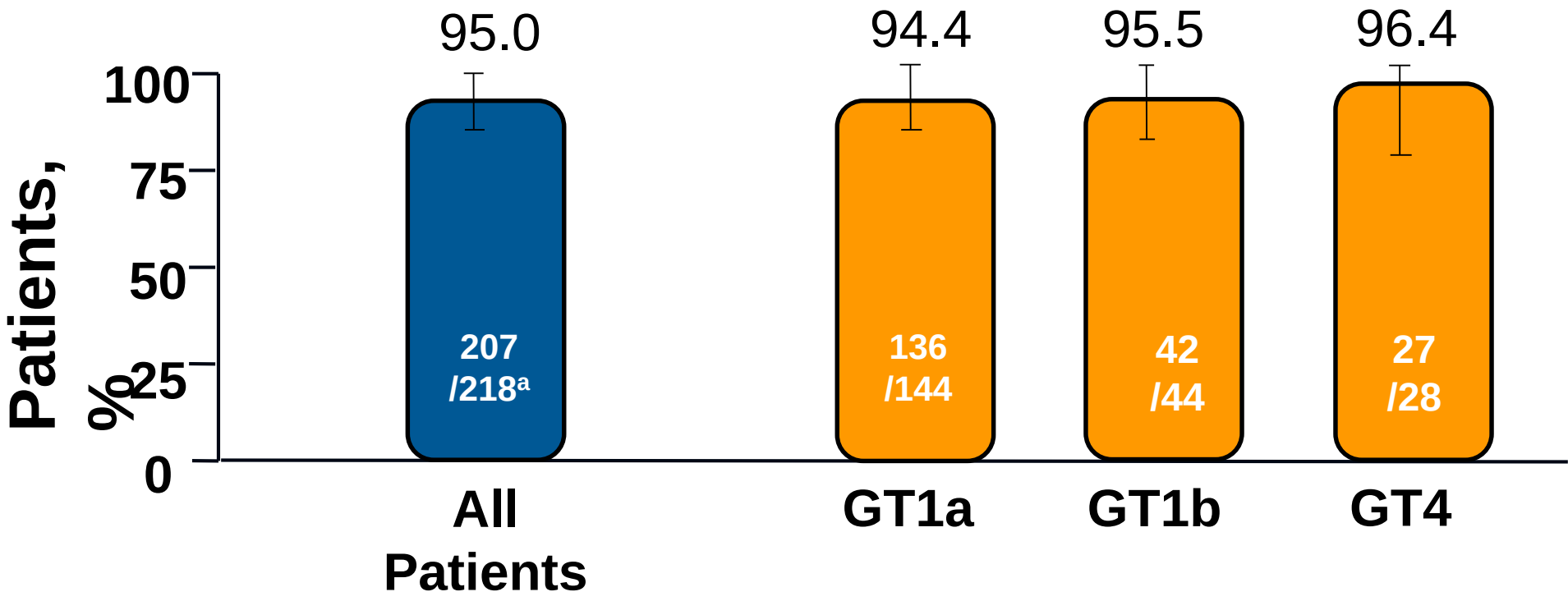
Daclatasvir Plus Sofosbuvir for Treatment of HCV Genotypes 1-4 in HIV-HCV Coinfection: The ALLY-2 Study

Figure 5. Prevalence of Baseline NS5A Resistance-Associated Variants (RAVs) and Treatment Response (All Patients)



Wyles DL, et al. EASL 2015

C-EDGE COINFECTION: PHASE 3 STUDY OF GRAZOPREVIR/ELBASVIR IN PATIENTS WITH HCV/HIV



Rockstroh J et al EASL 2015

All patients are created equal

G.Orwell; cit. modificata

Expo Milano 2015-Padiglione Giappone

EASL Clinical Practice Guidelines: Management of hepatitis C virus infection

European Association for the Study of the Liver*

2014

Treatment of special groups

HIV co-infection

For a given genotype treated with PegIFN/RBV dual therapy, rates of SVR are generally lower for co-infected than for HCV mono-infected patients.

J Hepatol 2014;60:392-420

EASL Clinical Practice Guidelines: Management of hepatitis C virus infection

European Association for the Study of the Liver*

2015

Indications for treatment: who should be treated?

All treatment-naïve and –experienced patients with compensated or decompensated chronic liver disease related to HCV, who are willing to be treated and who have no contra-indications to treatment, should be considered for therapy. Because not every HCV-infected patient can be treated within the next vear or so. prioritization is necessary (Table 2).

High priority groups also include patients with HIV or HBV coinfection, patients in the pre- or post-liver transplant setting, patients with clinically significant extra-hepatic manifestations

J Hepatol. 2015 Apr 21. pii: S0168-8278(15)00208.

EASL Recommendations on Treatment of Hepatitis C 2015

Table 2. Indications for treatment of chronic hepatitis C in 2015: Who should be treated and when?

Treatment priority	Patient group
Treatment is indicated	• All treatment-naïve and treatment-experienced patients with compensated and decompensated liver disease
Treatment should be prioritized	• Patients with significant fibrosis (F3) or cirrhosis (F4), including decompensated cirrhosis • Patients with HIV coinfection • Patients with HBV coinfection • Patients with an indication for liver transplantation • Patients with HCV recurrence after liver transplantation • Patients with clinically significant extra-hepatic manifestations • Patients with debilitating fatigue • 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)
Treatment is justified	• Patients with moderate fibrosis (F2)
Treatment can be deferred	• Patients with no or mild disease (F0-F1) and none of the above-mentioned extra-hepatic manifestations
Treatment is not recommended	• Patients with limited life expectancy due to non-liver related comorbidities

http://www.easl.eu/research/our-contributions/clinical-practice-guidelines

Trattamento del paziente non-cirrotico

Table 5. Treatment recommendations for HCV-monoinfected or HCV/HIV coinfected patients with chronic hepatitis C without cirrhosis, including treatment-naïve patients and patients who failed on a treatment based on PegIFN-α and ribavirin (RBV).

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk (treatment-naïve or relapsers) or 24 wk (partial or null responders)	No	8-12 wk, without RBV	12 wk with RBV	No	12 wk without RBV	12 wk without RBV
Genotype 1b					12 wk without RBV			
Genotype 2	12 wk	No	12 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	24 wk	No	No	No	No	12 wk without RBV
Genotype 4	12 wk	12 wk (treatment-naïve or relapsers) or 24 wk (partial or null responders)	No	12 wk without RBV	No	12 wk with RBV	12 wk without RBV	12 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk without RBV	No	No	No	12 weeks without RBV

Trattamento del paziente con cirrosi compensata

Table 6. Treatment recommendations for HCV-monoinfected or HCV/HIV coinfected patients with chronic hepatitis C with compensated (Child-Pugh A) cirrhosis, including treatment-naïve patients and patients who failed on a treatment based on PegIFN-α and ribavirin (RBV).

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk (treatment-naïve or relapsers) or 24 wk (partial or null responders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	24 wk with RBV	No	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 1b					12 wk with RBV			
Genotype 2	12 wk	No	16-20 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	No	No	No	No	No	24 wk with RBV
Genotype 4	12 wk	12 wk (treatment-naïve or relapsers) or 24 wk (partial or null responders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	24 wk with RBV	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	No	No	12 wk with RBV, or 24 wk without RBV

AASLD/IDSA Guidance for HIV/HCV Coinfection

- Same recommendations as in HCV-monoinfected patients, but consider drug–drug interactions
  - Need to adjust or withhold RTV if receiving a boosted PI with OMV/PTV/RTV + DSV
  - Potential for LDV-mediated increase in tenofovir levels, especially if tenofovir used with RTV
    - Avoid LDV if CrCl < 60 mL/min or if receiving tenofovir with RTV-boosted PI
  - OMV/PTV/RTV + DSV can be used with raltegravir (and probably dolutegravir), enfuvirtide, tenofovir, emtricitabine, lamivudine, atazanavir
  - SMV can be used with: raltegravir (and probably dolutegravir), rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, abacavir
- Other interactions at aidsinfo.nih.gov/guidelines, hiv-druginteractions.org

AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C.

Interazioni farmacologiche con DAAs

Table 4A. Drug-drug interactions between HCV DAAs and HIV antiretrovirals.

		SIM	DCV	SOF	SOF/ LDV	3D
NRTIs	Abacavir	•	•	•	•	•
	Didanosine	•	•	•	•	•
	Emtricitabine	•	•	•	•	•
	Lamivudine	•	•	•	•	•
	Stavudine	•	•	•	•	•
	Tenofovir	•	•	•	•	•
	Zidovudine	•	•	•	•	•
NNRTIs	Efavirenz	•	•	•	•*	•
	Etravirine	•	•	•	•	•
	Nevirapine	•	•	•	•	•
	Rilpivirine	•	•	•	•*	•
Protease inhibitors	Atazanavir; atazanavir/ritonavir	•	•	•	•*	•
	Darunavir/ritonavir; darunavir/cobicistat	•	•	•	•*	•
	Fosamprenavir	•	•	•	•*	•
	Lopinavir	•	•	•	•*	•
	Saquinavir	•	•	•	•*	•
Entry/ Integrase inhibitors	Dolutegravir	•	•	•	•	•
	Elvitegravir/cobicistat	•	•	•	•*	•
	Maraviroc	•	•	•	•	•
	Raltegravir	•	•	•	•	•

DCV+NNRTI= ↓ DCV: **increase to 90 mg**

DCV+PI= DCV+cob= ↑ DCV: **decrease to 30 mg**

LDV+TDF= ↑ TDF

LDV+ELV/COM= ↓ ELV, ↑ COM,LDV

3D+ELV/COM= ↑ 3D

3D+ATV= Only ATV unboosted

3D+DRV= ↓ DRV

Categorie di pazienti affetti da epatite C cronica ammesse alla rimborsabilità in Italia

1) Pazienti con cirrosi in classe di Child A o B e/o con epatocarcinoma 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
2) Recidiva di epatite dopo trapianto di fegato con fibrosi METAVIR[1] ≥2 (o corrispondente Ishack) o fibrosante colestatica
3) Epatite cronica con gravi manifestazioni extra-epatiche HCV-correlate (sindrome crioglobulinemica con danno d'organo, sindromi linfoproliferative a cellule B)
4) Epatite cronica con fibrosi METAVIR ≥3 (o corrispondente Ishack)
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
6) Epatite cronica dopo trapianto di organo solido (non fegato) o di midollo con fibrosi METAVIR ≥2 (o corrispondente Ishack).
7) Pazienti con epatite cronica con fibrosi METAVIR F0-F2 (o corrispondente Ishak)

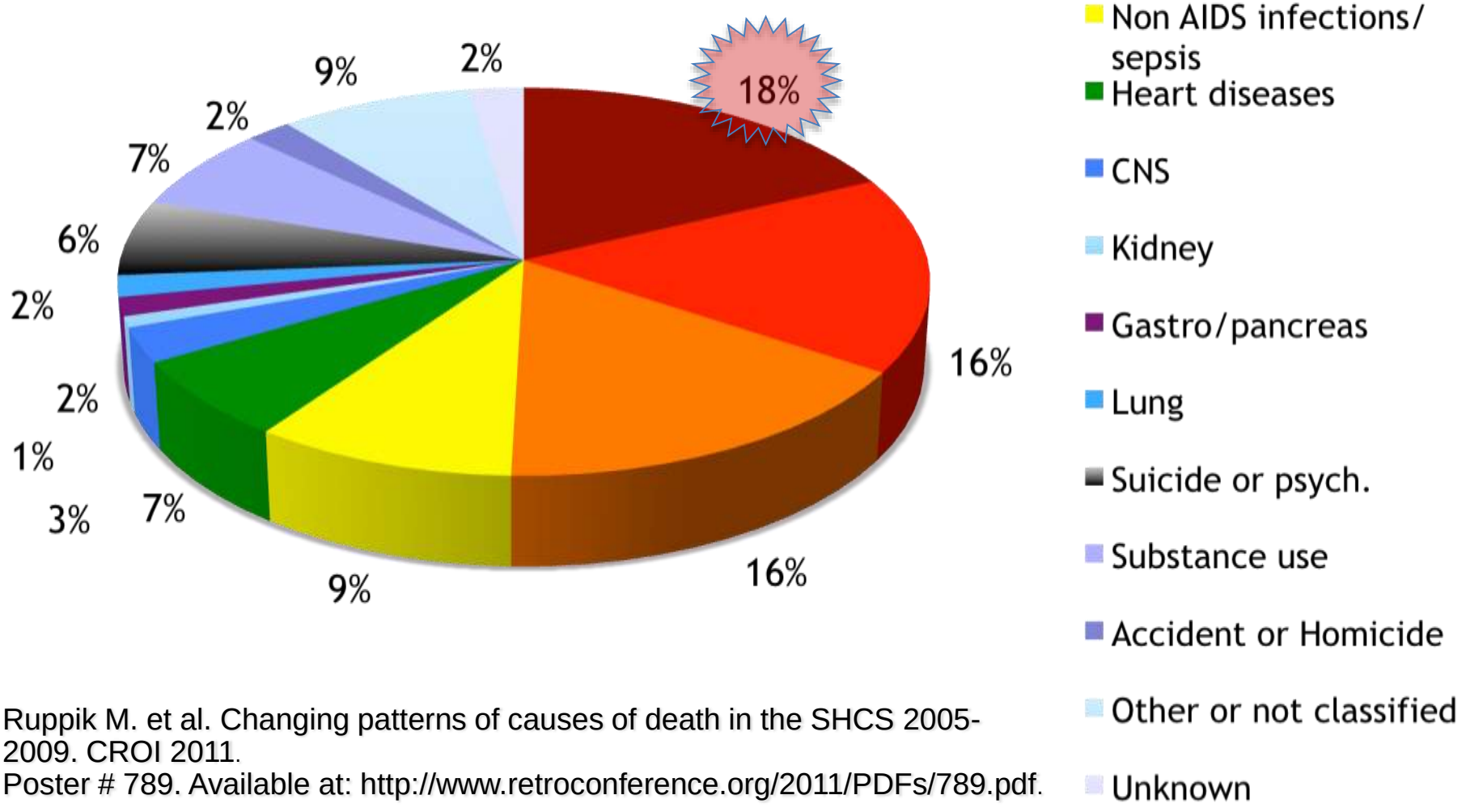
HIV ?

Another brick in the wall

Pink Floyd

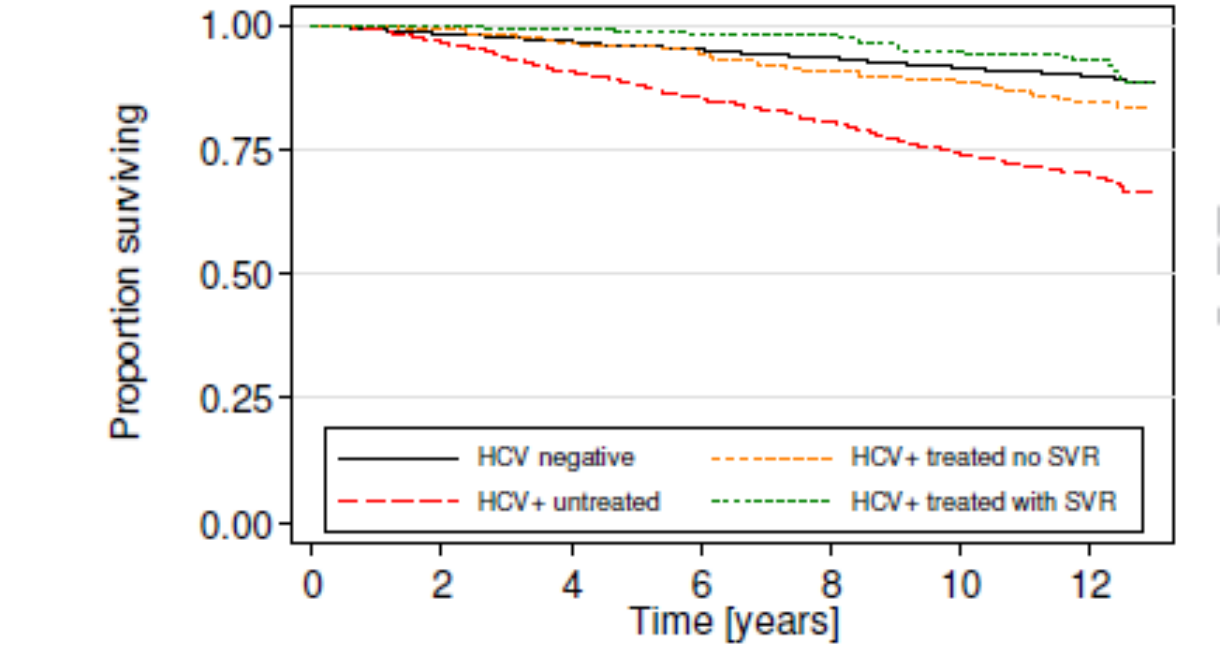
Expo Milano 2015-Padiglione Cina

Causes of death in the Swiss HIV Cohort study 2005-09



Ruppik M. et al. Changing patterns of causes of death in the SHCS 2005-2009. CROI 2011.
Poster # 789. Available at: http://www.retroconference.org/2011/PDFs/789.pdf.

High Hepatic and Extrahepatic Mortality and Low Treatment Uptake in HCV-coinfected Persons in the Swiss HIV Cohort Study between 2001 and 2013



Numbers at risk:

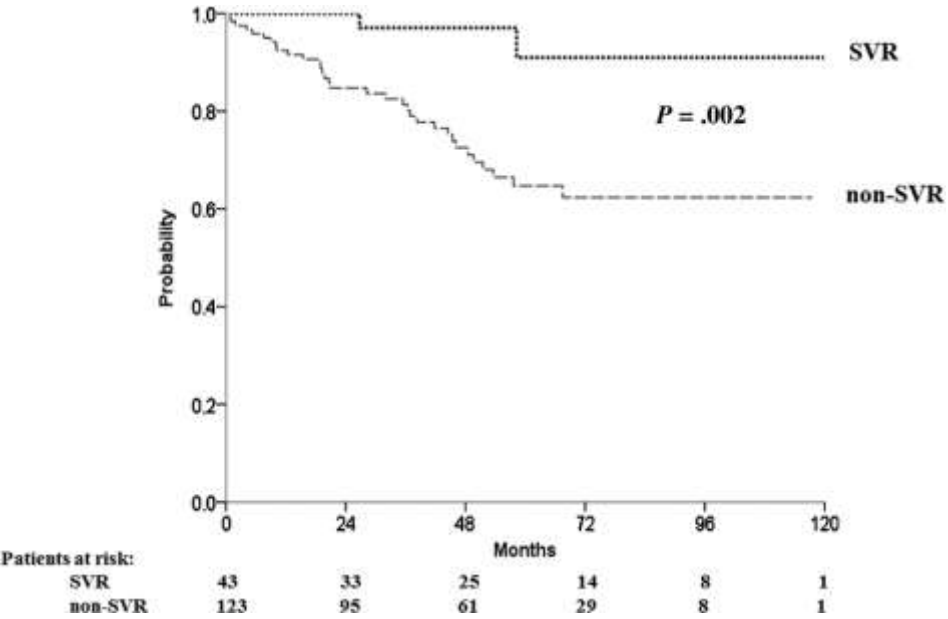
HCV negative	9291	5113	2184
HCV+ untreated	1471	815	345
HCV+ treated no SVR	374	300	162
HCV+ treated with SVR	262	224	124

Figure 2: Kaplan-Meier survival curve of HCV-coinfected untreated, treated, and HIV-monoinfected SHCS participants.

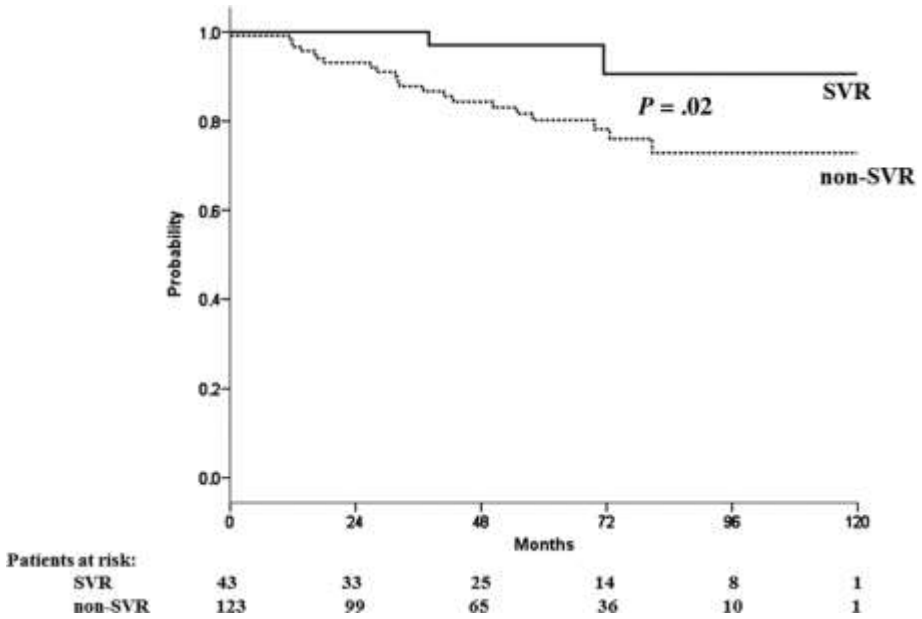
Kovari H, et al. J Hepatol 2015; in press

Benefits From Sustained Virologic Response to Pegylated Interferon Plus Ribavirin in 166 HIV/ Hepatitis C Virus-Coinfected Patients With Compensated Cirrhosis

Incidence of decompensation



Overall mortality



Mira J CID 2013:56: 1646-53

Impact of HCV Exposure/ Coinfection on HIV disease

Issue	HCV exposure (HCVAb+ vs HCVAb-)	HCV active replication (HCVAb+ HCVRNA+ vs HCVAb+ HCVRNA-)
Faster HIV disease progression	Yes[1]	
Impaired CD4 recovery on cART	Yes[2]	Yes[3]
Impaired HIVRNA suppression on cART	Yes [4]	
Worsened renal function	Yes[5]	Yes[6]
Higher incidence of osteopor. fractures	Yes[7]	
Higher incidence of Cardiovascular related events	Yes [8]	
Higher incidence of Diabetes	Yes [9]	
Higher non AIDS non liver related mortality	Yes[10]	Yes[11]

1. *Greub, Lancet, 2000, Piroth, J Viral Hepat, 2000 De Luca et al, Arch Intern Med, 2002), Herrero Martinez E JID 2002, Dorrucci AIDS 2004; Braitsein JID 2006;*
2. *Lincoln, HIV Med, 2003*
3. *Potter M AIDS 2010*
4. *Pulido AIDS Review 2012; Hua L AIDS 2013*
5. *Izzedine AIDS 2009; Lucas JID 2013*
6. *Peters AIDS 2012; Mocroft A PLOS One 2012; Lucas jiD 2013*
7. *Lo Re Hepatology 2012; Maalouf J Bon Min Res 2013, Casado Osteopos Int 2014*
8. *Erqou S CROI 2014*
9. *Howard AA JAIDS 2014; Butt AA AIDS 2009; Jain MK HIV Med 2007; Butt AA Hepatology 2004*
10. *Mallet V CROI 2014*
11. *Grint D CROI 2014*

You can't always get what you want!

The Rolling Stones

Expo Milano 2015-Padiglione Azerbaijan

The price you pay

Drug	US Price $	Estimated Price for Italian NHS €
Sofosbuvir	84-168.000	37.000
Daclatasvir		18.000
Simeprevir	54.000	15.000
Harvoni	94-188.000	40.000
Viekirax Exviera	83-166.000	23.000

Expo Milano 2015-Padiglione Emirati Arabi

…and this is a real life

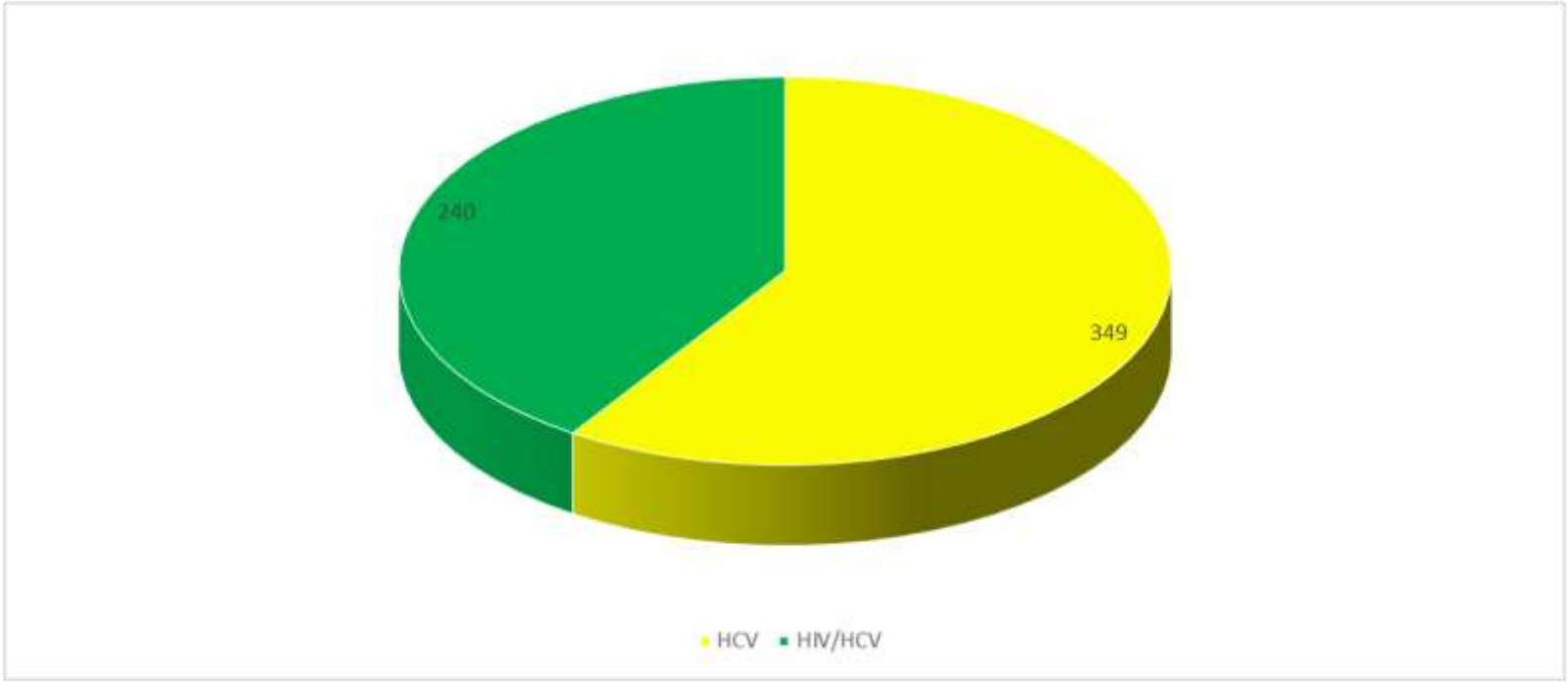
CISAI

Expo Milano 2015-Palazzo Italia

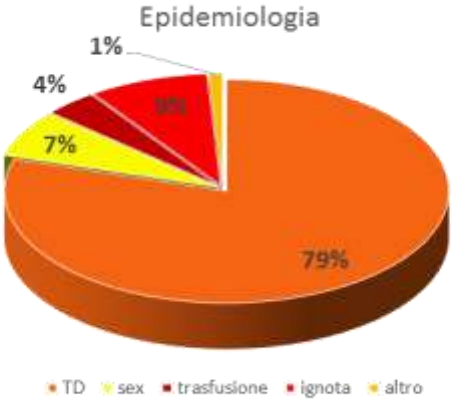
11 Centri

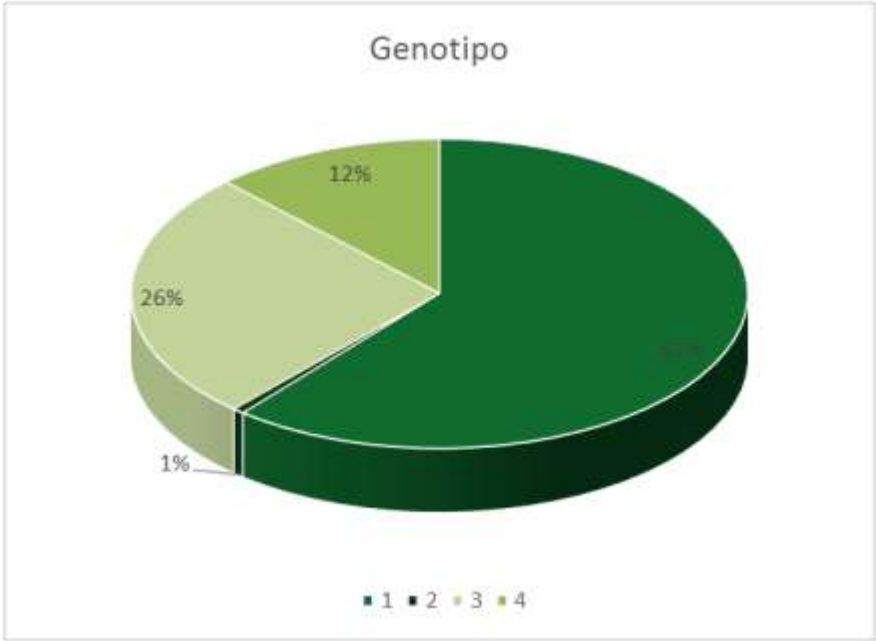
Trattati 589 pz

Coinfetti 240 pz



Coinfetti 240 pz



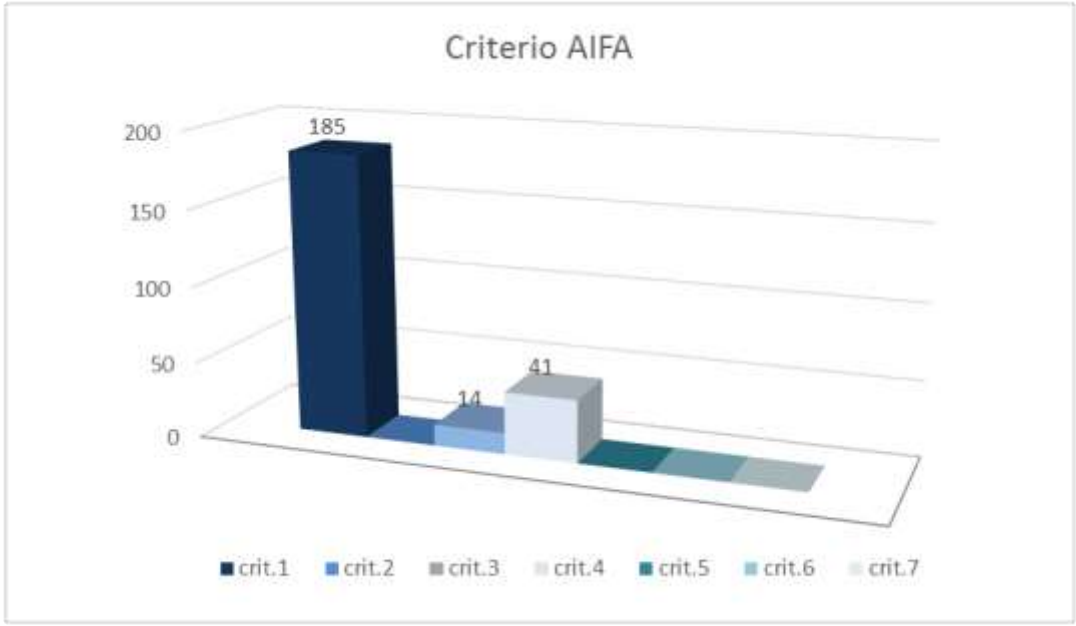


Coinfetti 240 pz

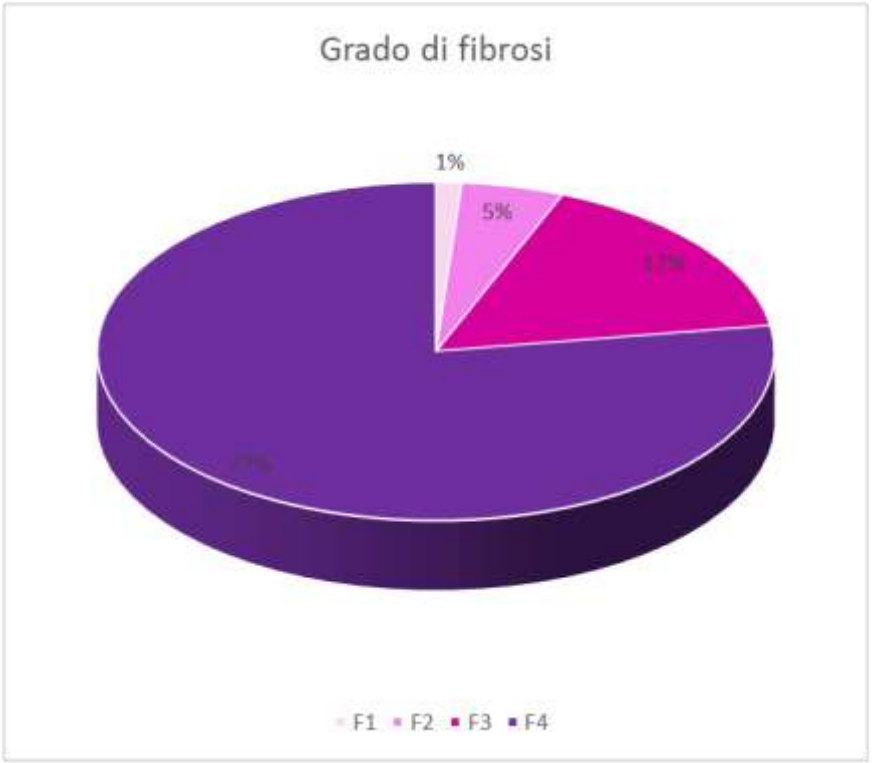
Categorie ammesse alla rimborsabilità

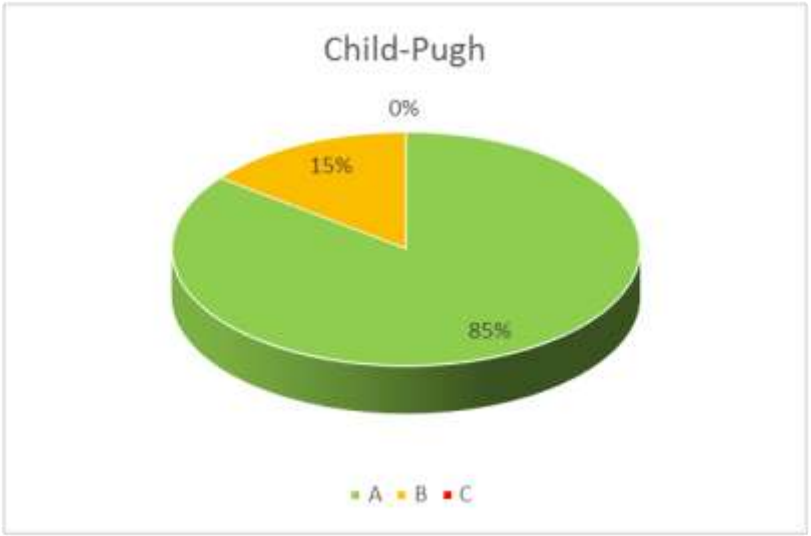
Criteri AIFA

Criterio 1. Pazienti con cirrosi in classe di Child-Pugh 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
Criterio 2. Pazienti con recidiva di epatite dopo trapianto di fegato, con fibrosi METAVIR ≥2 (o corrispondente Ishak) o fibrosante colestatica
Criterio 3. Pazienti con epatite cronica con gravi manifestazioni extra-epatiche HCV-correlate (sindrome crioglobulinemica con danno d'organo, sindromi linfoproliferative a cellule B)
Criterio 4. Pazienti con epatite cronica con fibrosi METAVIR F3 (o corrispondente Ishak)
Criterio 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
Criterio 6. Pazienti con epatite cronica dopo trapianto di organo solido (non fegato) o di midollo con fibrosi METAVIR ≥2 (o corrispondente Ishak)
Criterio 7. Pazienti con epatite cronica con fibrosi METAVIR F0-F2 (o corrispondente Ishak)



Coinfetti 240 pz



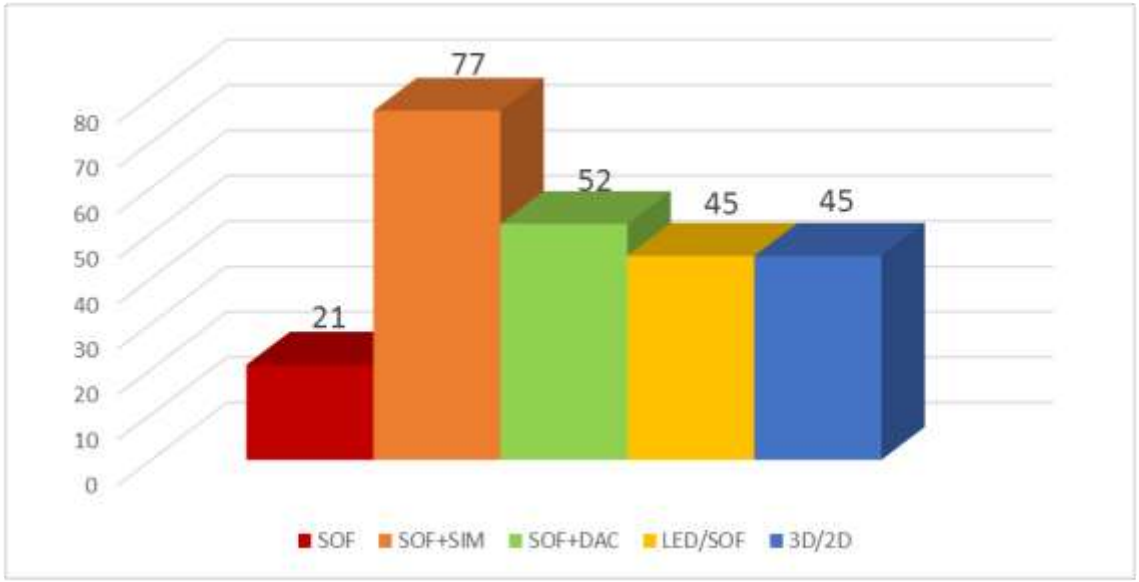


Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3

Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)
Class A = 5 to 6 points (least severe liver disease)
Class B = 7 to 9 points (moderately severe liver disease)
Class C = 10 to 15 points (most severe liver disease)

Coinfetti 240 pz

Regimi di trattamento



190 pz trattati con ribavirina
240 in HAART

Coinfetti 240 pz

2 Sospensioni volontarie, 1 temporanea per iperbilirubinemia

Decessi 0

Eventi avversi seri 1 IMA

SVR??

220 neg durante trattamento

GRAZIE PER L'ATTENZIONE