La gestione dei pazienti HIV con infezione cronica da HCV: le nuove terapie

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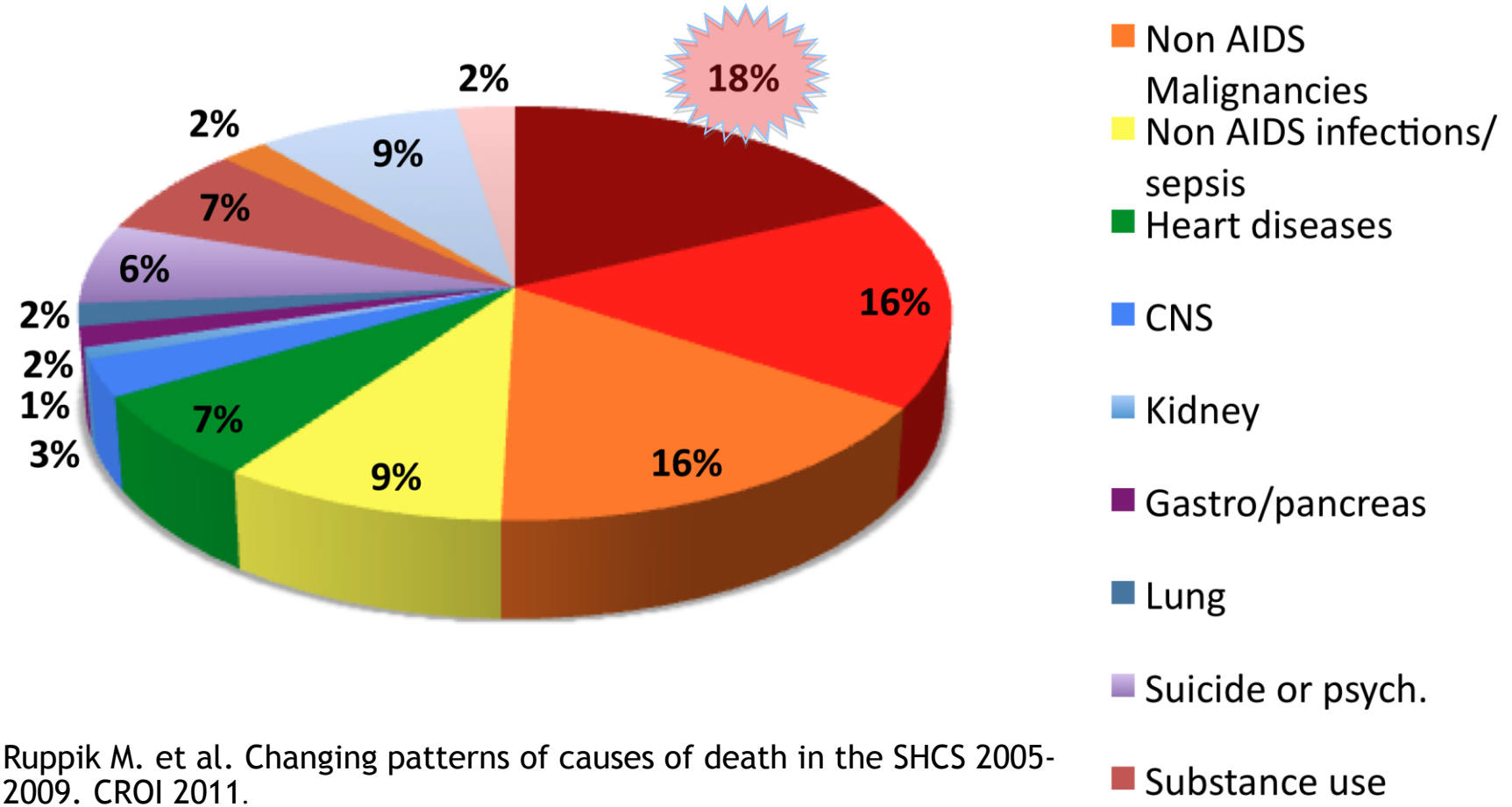
Estimates of HCV co-infection in PLHIV in Italy from cohorts' data

Cohort	Icona[1] (%)	Master[2] % (N)	Estimated data in 94.146 PLHIV linked to care[3]
PLHIV **tested for HCV**		75% (11.203)	70.609
PLHIV with anti HCV reactivity	29% (11241)	34% (8439)	21.791
PLHIV with HCV and cirrhosis in the cohorts (HCVAb+ & FIB4 > 3.25)	7.7% (3061)	7.8% (3475)	7.390

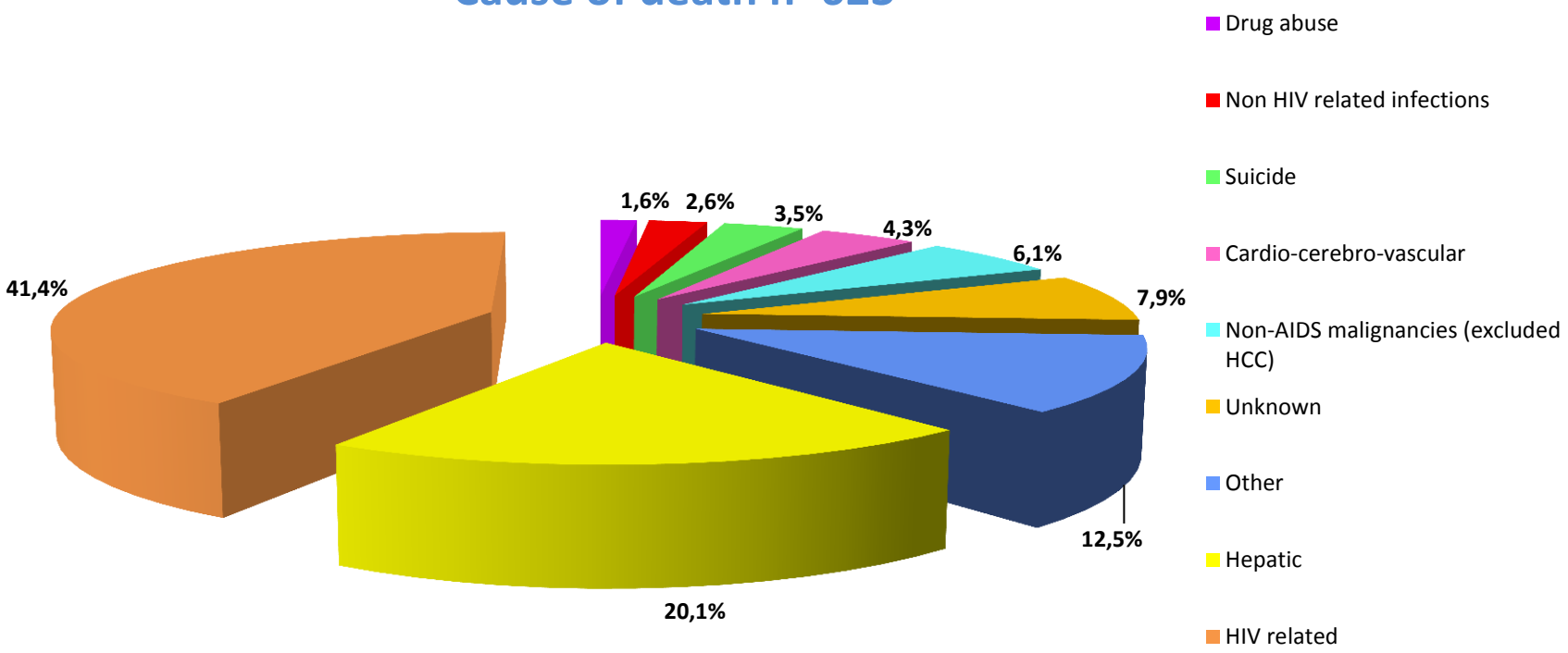
1. De Luca a et al CROI 2014, 2. Motta et al AIDS Res Ther 2012, 3. Notiziario ISS 2013

Causes of death in the Swiss HIV Cohort study
459 deaths between 2005 and 2009



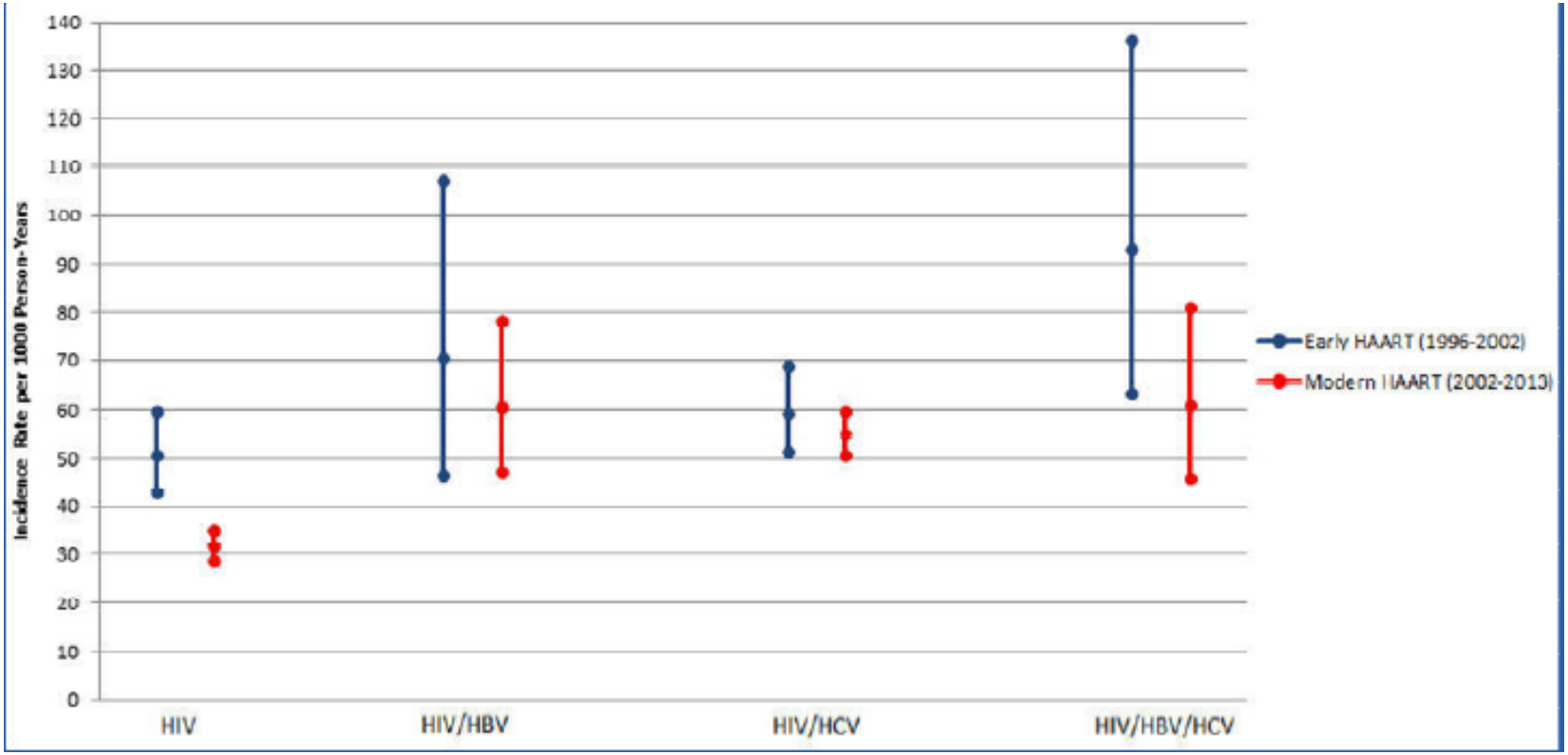
Ruppik M. et al. Changing patterns of causes of death in the SHCS 2005-2009. CROI 2011.

Cause of death n=623



Association of Co-Infection with HBV, HCV or both on survival among HIV infected adults

Prospective cohort study of 4819 patients with HIV and known HBV and HCV status receiving care at the Johns Hopkins HIV Clinic from 1996 to March 2013



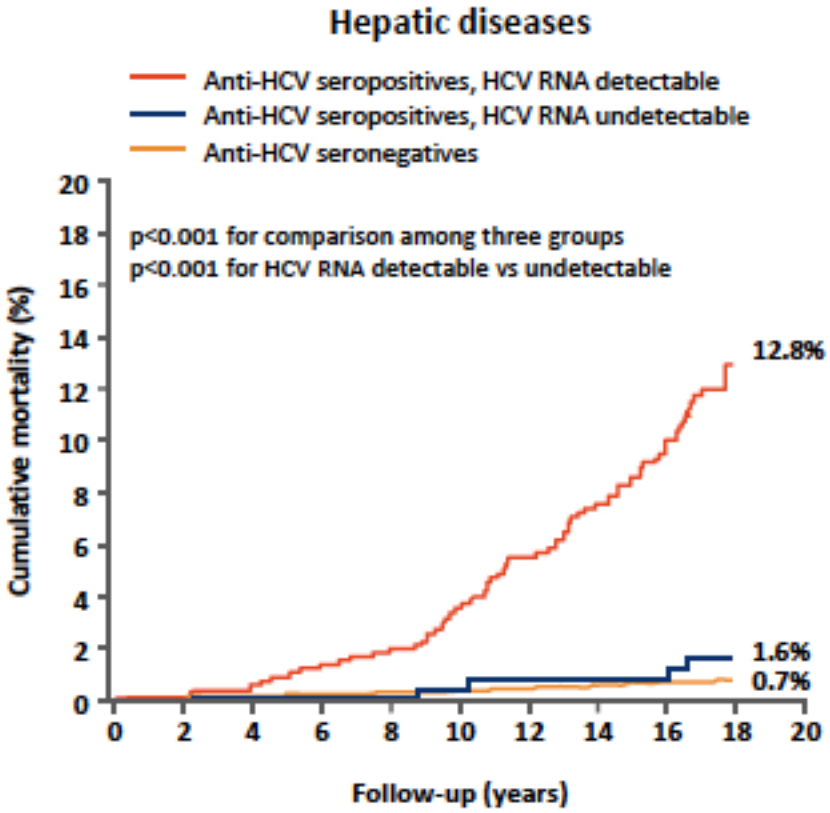
In the modern cART era ,after adjusting for HIV disease and treatment, mortality was significantly increased among HIV/HBV, HIV/HCV and HIV/HBV/HCV co-infected patients when compared to HIV monoinfected.

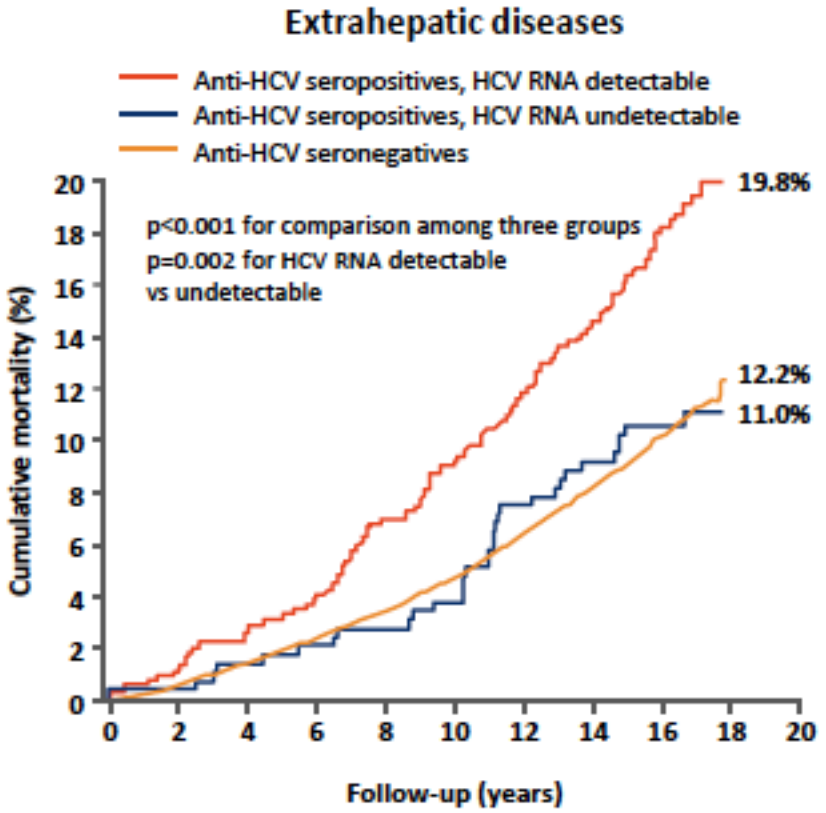
Wansom T et al CROI 2014 poster# 686

Chronic HCV increases mortality from hepatic and non-hepatic diseases

The REVEAL HCV Cohort Study

- 23 820 adults in Taiwan prospectively followed since 1991/2
- 1095 were anti-HCV positive; 69.4% had detectable HCV RNA

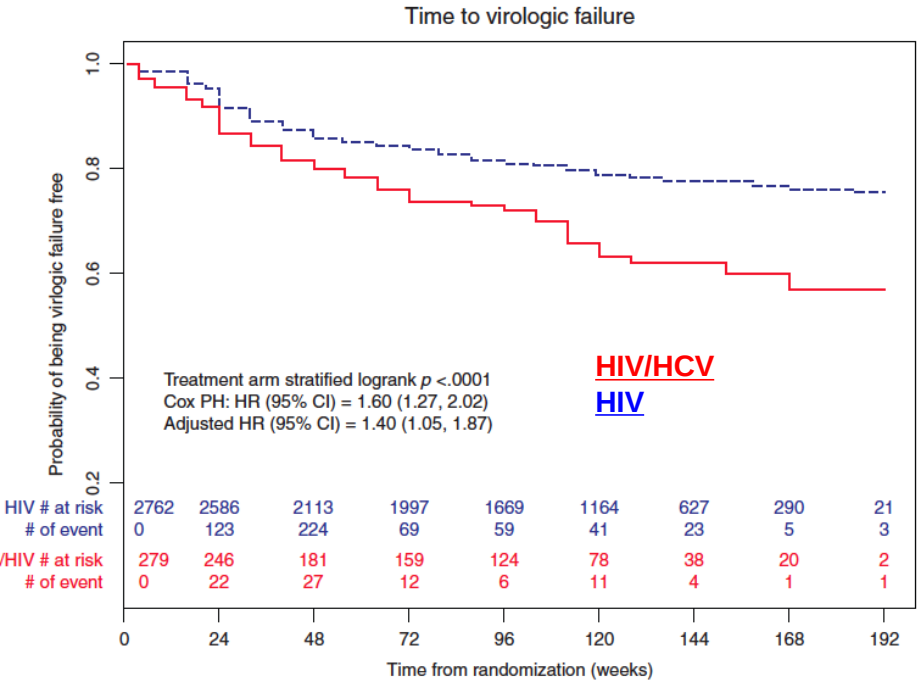


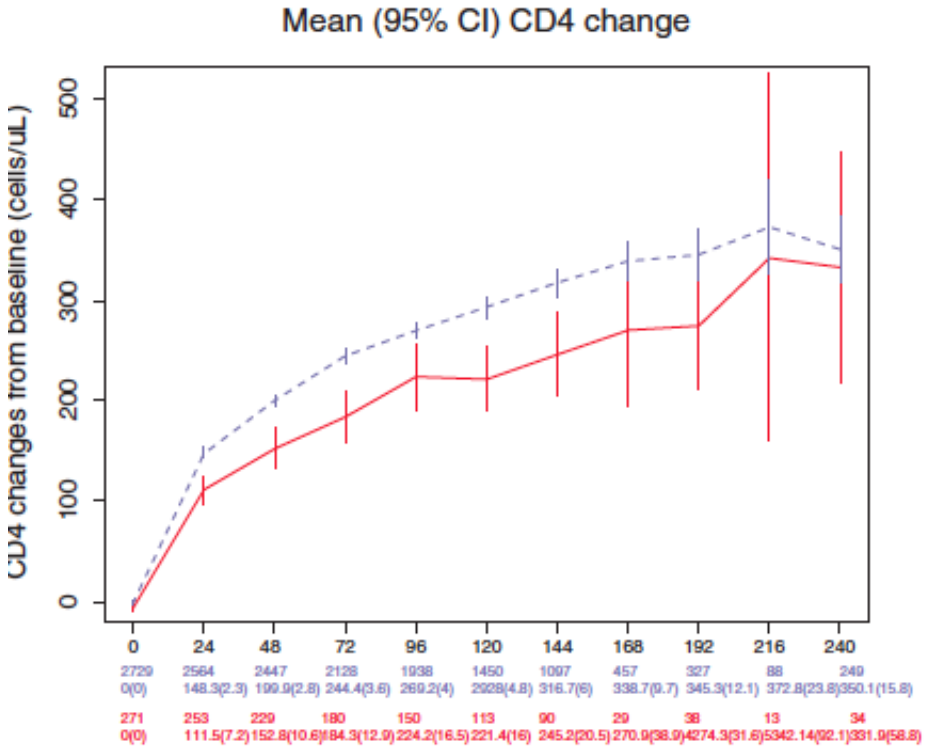


LEE et al, *J Infect Dis* 2012;206:469–477

Hepatitis C virus/HIV coinfection and responses to initial antiretroviral treatment

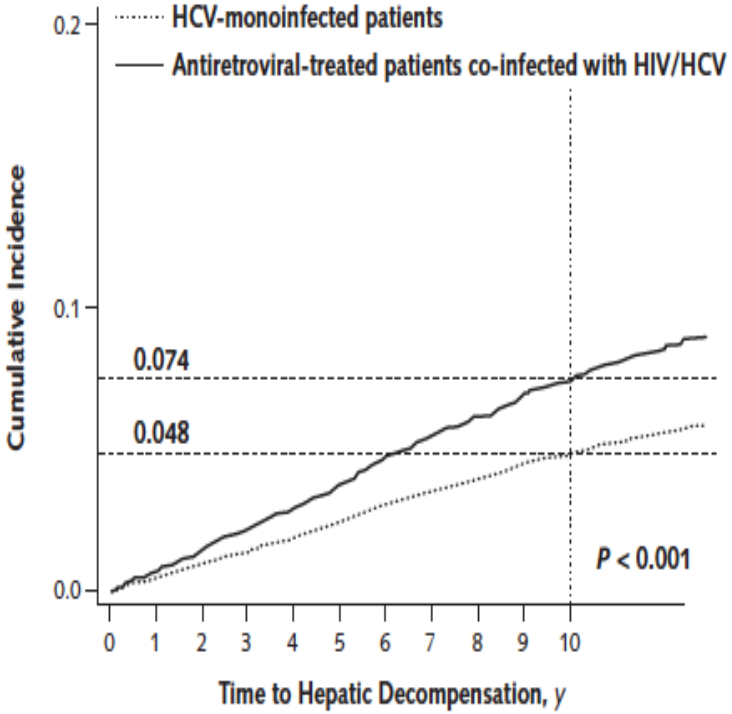
- Four ACTG anti HIV Tx studies including 3041 pts including 279 HCV+ subjects were combined to compare initial ART responses between HIV vs HCV/HIV :
  - virologic failure,
  - CD4 cell measures,
  - occurrence of AIDS/death
  - grade 3/4 safety events

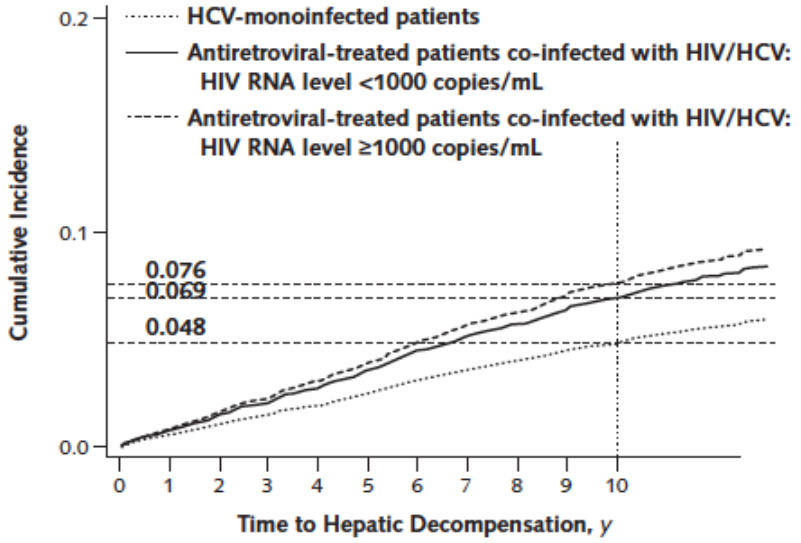


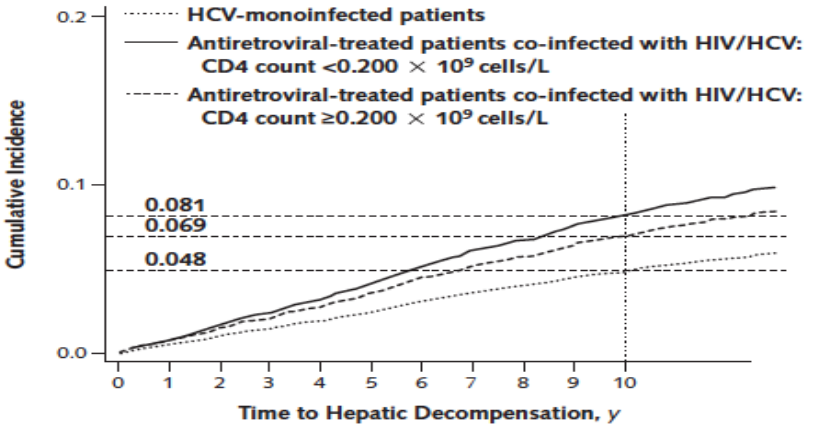


Hua L. et al. AIDS 2013, 27:000–000

ART and hepatic de-compensation in HCV/HIV vs. HCV alone







Sustained Virological Response to Interferon Plus Ribavirin ReducesOverall, Liver Related and Non–Liver-Related Mortality in 1599 Patients Coinfected With HIV and Hepatitis C Virus

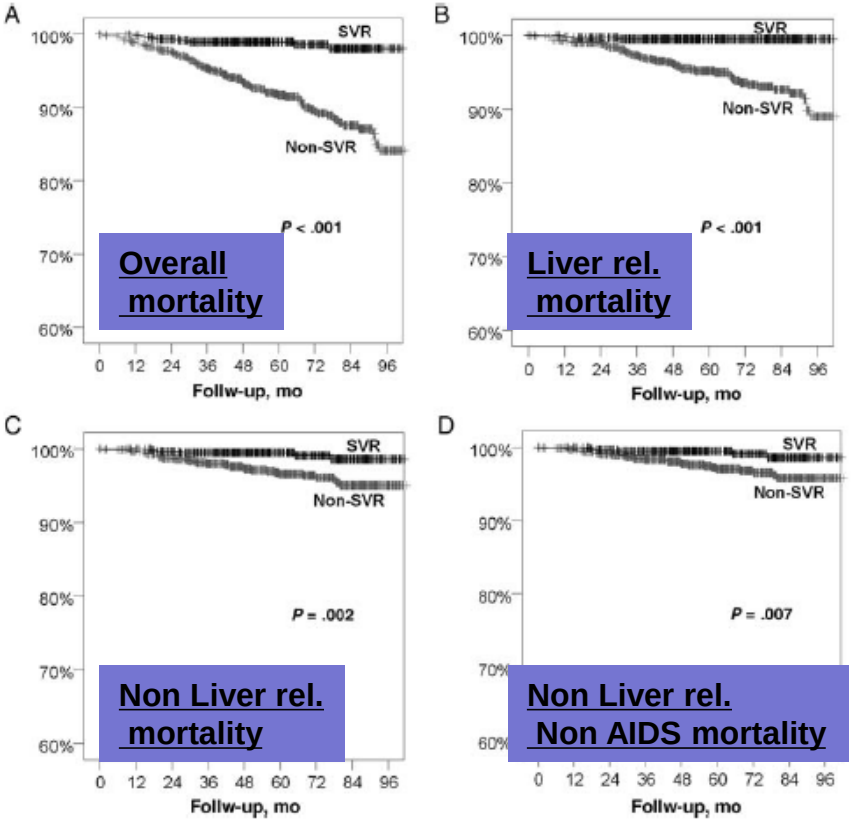


Figure 1. Kaplan-Meier curves showing the occurrence of overall deaths (*A*), liver-related deaths (*B*), non–liver related deaths (*C*), and non–liver-related, non–AIDS-related deaths (*D*) in 1599 patients coinfected with human immunodeficiency virus and hepatitis C virus, with or without sustained virological response after therapy with interferon plus ribavirin. Abbreviation: SVR, sustained virological response.

Table 4. Crude and Adjusted Hazard Ratios for Non–Liver-Related Events During Follow-up for Nonresponders to Interferon Plus Ribavirin Compared With Responders (Cox Regression Analysis)

Event	Crude HR (95% CI)	*P*	Adjusted[a] HR (95% CI)	*P*
New AIDS-defining conditions	2.86 (1.39–5.9)	.004	1.90 (.89–4.1)	.095
Non–liver-related deaths	4.08 (1.59–10.5)	.003	3.19 (1.21–8.4)	.019
Non–liver-related, non–AIDS-related deaths	3.42 (1.32–8.9)	.012	2.85 (1.07–7.6)	.036

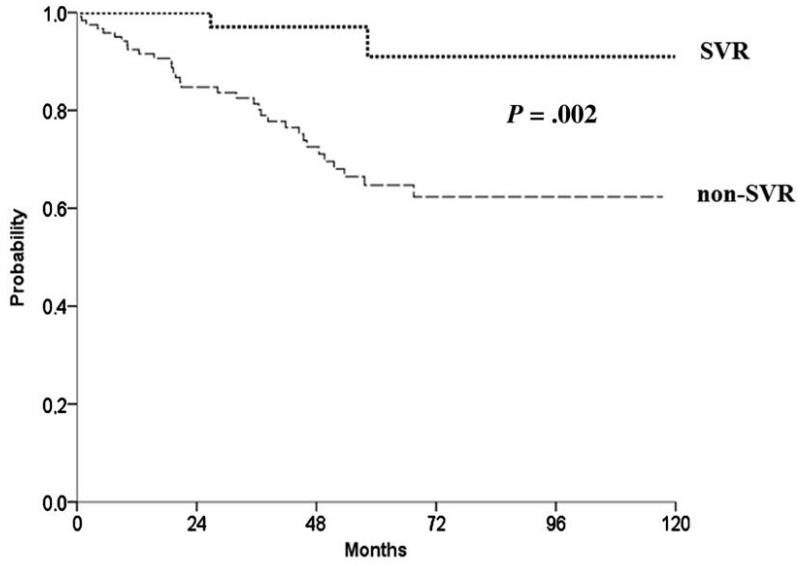
Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Adjusted for age, sex, human immunodeficiency virus (HIV) transmission category (injection drug users vs non–injection drug users), CD4+ T-cell nadir, advanced fibrosis (F3–F4 at biopsy or aspartate aminotransferase–to–platelet ratio >2), baseline HIV RNA levels <50 copies/mL, and combination antiretroviral therapy.

Berenguer Clin Inf Dis 2012; 55: 728-36

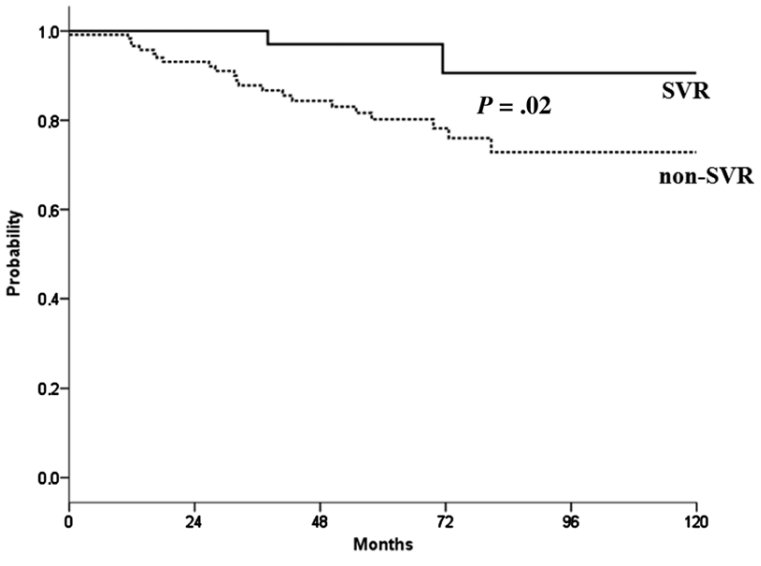
Benefits From Sustained Virologic Response to Pegylated Interferon Plus Ribavirin in 166 HIV/HCV Coinfected Patients With Compensated Cirrhosis

Incidence of decompensation



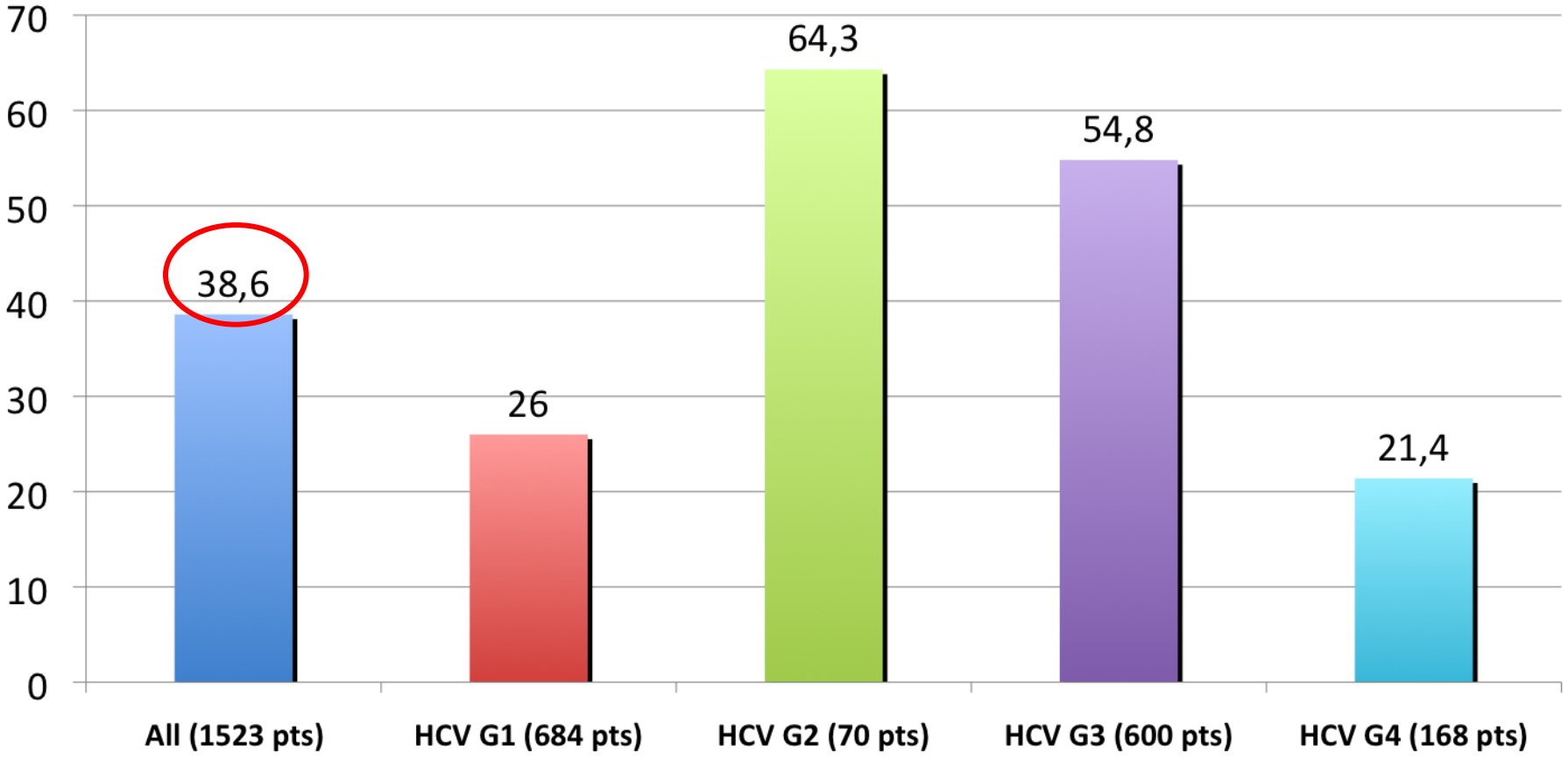
Patients at risk:						
SVR	43	33	25	14	8	1
non-SVR	123	95	61	29	8	1

Overall mortality

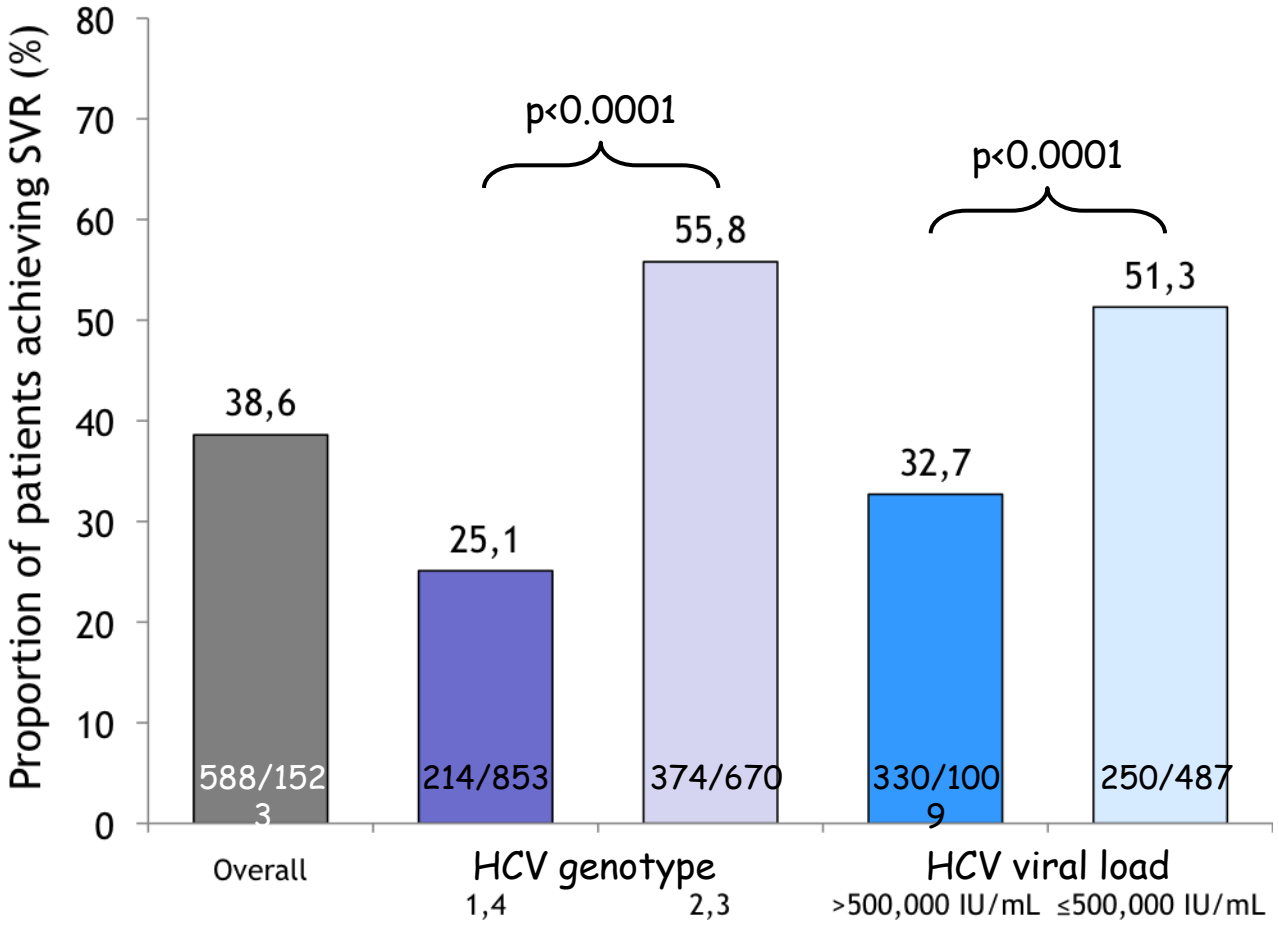


Patients at risk:						
SVR	43	33	25	14	8	1
non-SVR	123	99	65	36	10	1

Percentage of SVR in 1523 HIV/HCV coinfected pts included in the database OPERA and treated with PEGIFN + RBV



Opera study: Sustained virological response by baseline characteristics



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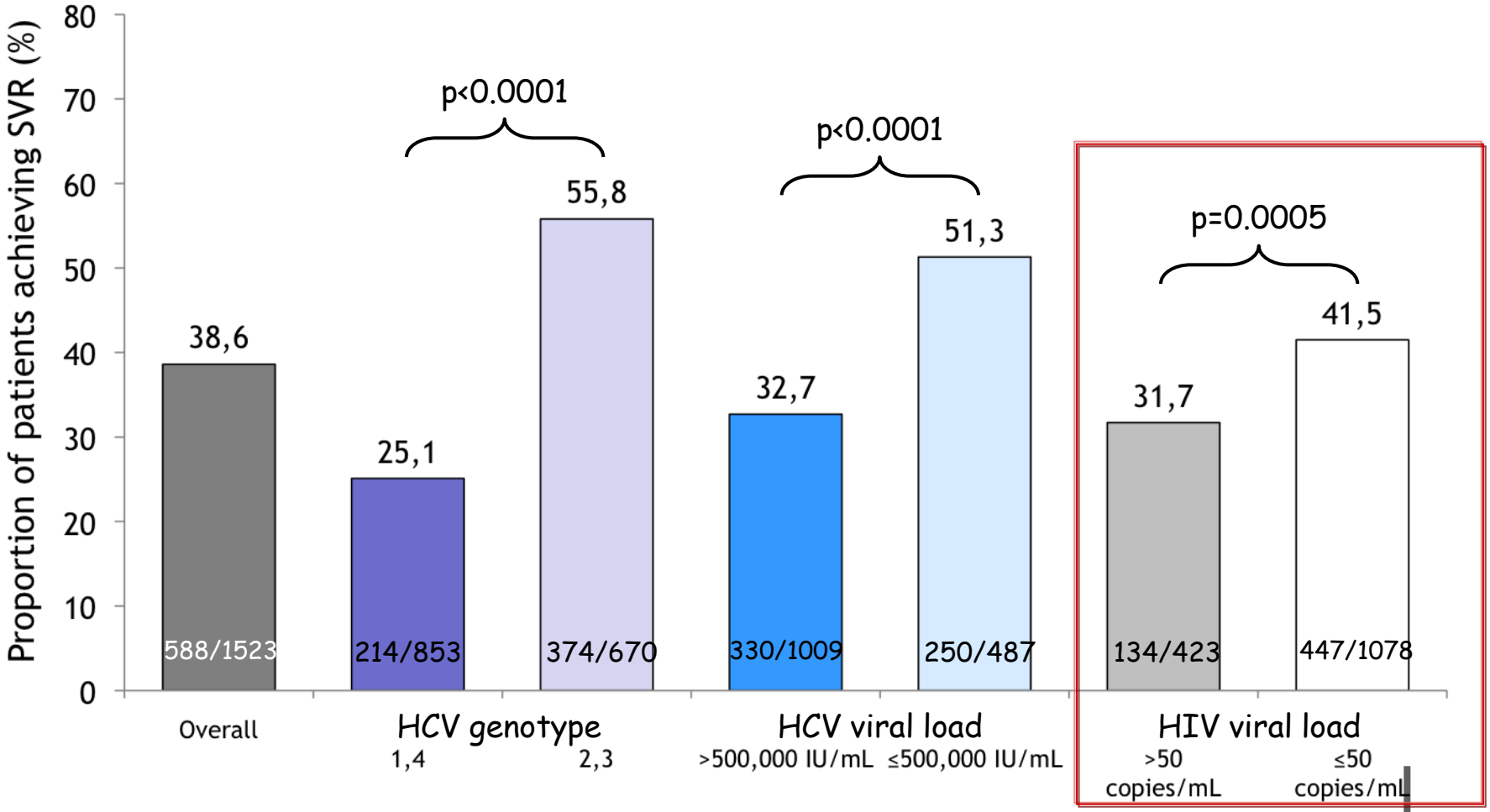
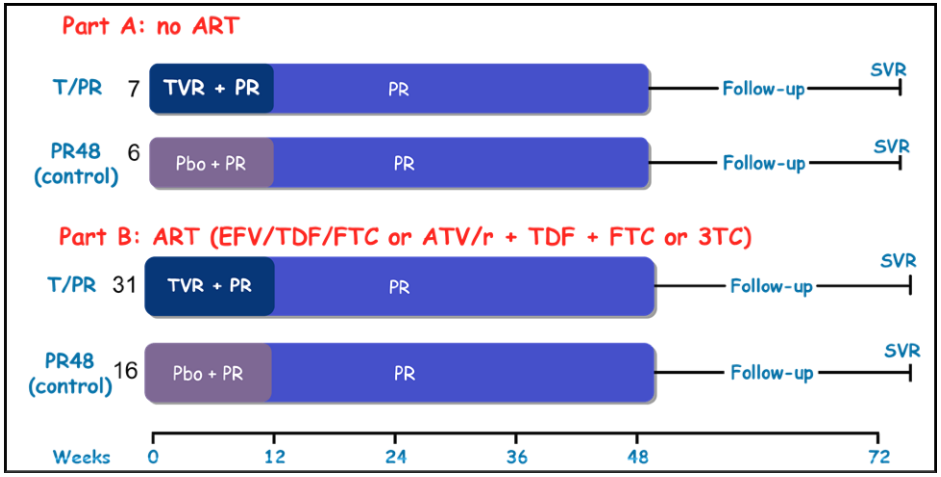
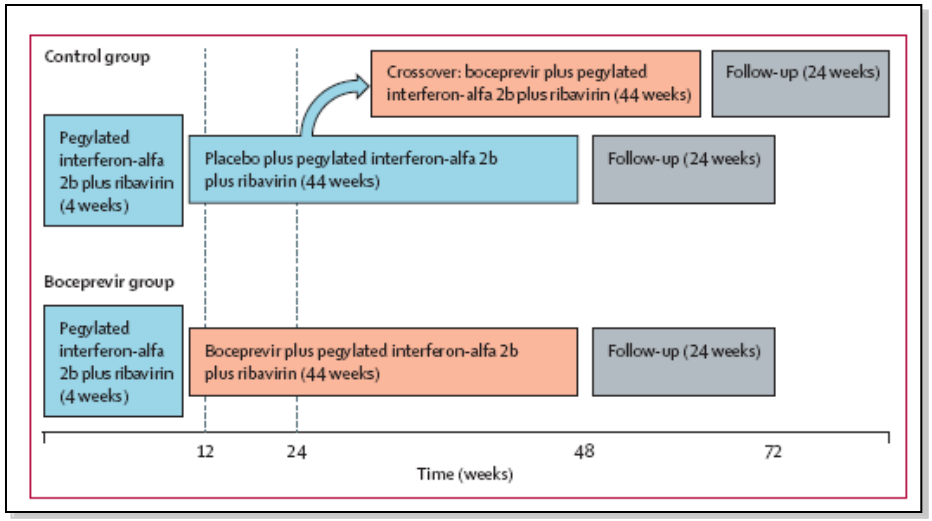


Telaprevir and Boceprevir Phase II trials in G1 HCV/HIV1 co-infected treatment naïves



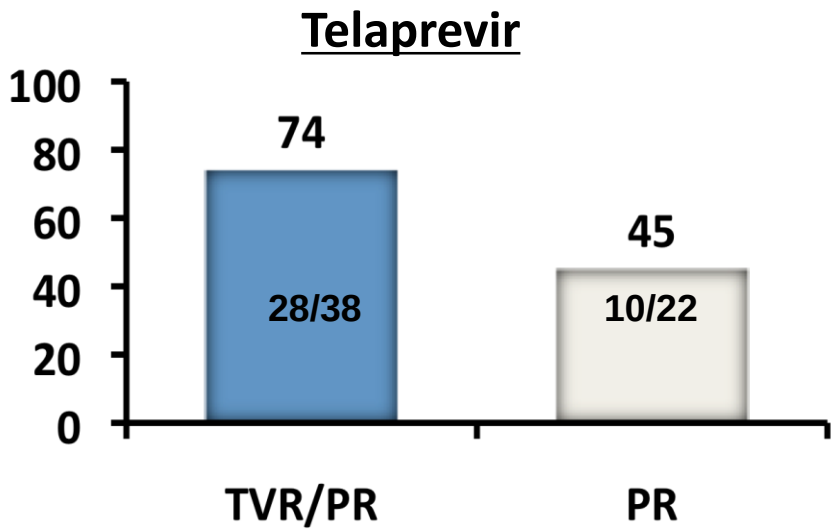


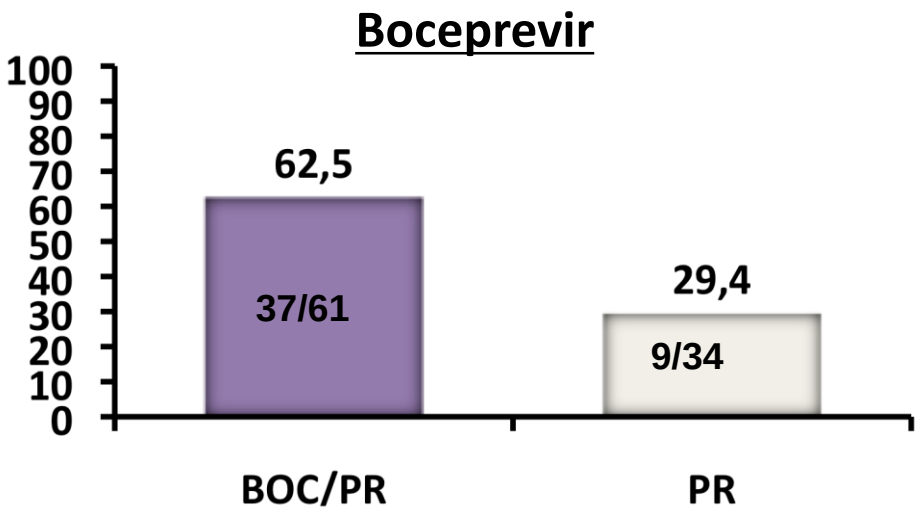
Sulkowski MS, et al Ann.Internal.Medicine 2013

Sulkowski M et al lancet Infect Dis 2013

Telaprevir and Boceprevir Phase II trials in G1 HCV/HIV1 co-infected treatment naïves

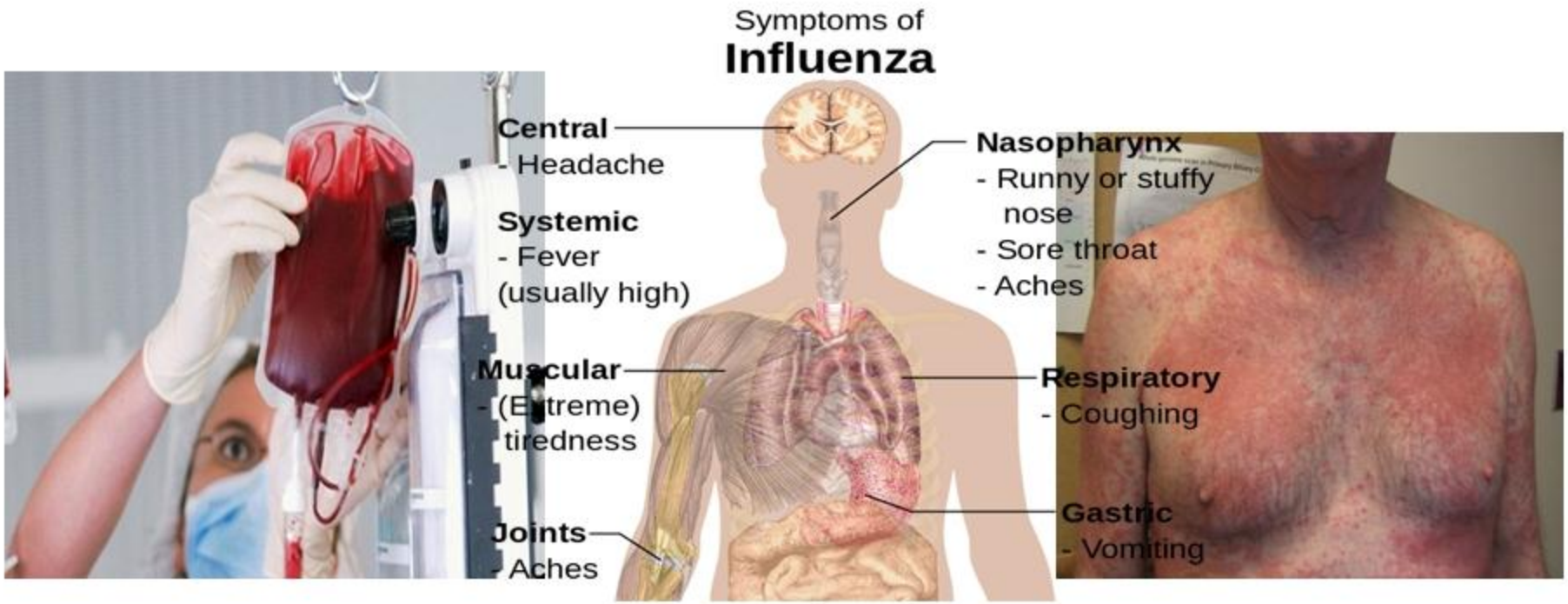
Variable	Telaprevir Study	Boceprevir Study
Not on cART	7	0
CD4 & HIVRNA	≥500 & HIVRNA≤1000.000 ≥ 300 & HIVRNA ≤ 50 c/mL	≥200 & HIVRNA ≤50 c/mL





No new safety signal compared to mono-infected patients

Significant side-effects



Treatment is effective but difficult

TVR in HIV/HCV co-infection: SAEs and premature discontinuations due to AEs

AEs	TVR Treatment Phase (Weeks 1–12) TVR/PR (n=38)	PR (n=22)	Difference (95% CI)	Overall Treatment Phase (Weeks 1–48) TVR/PR (n=38)	PR (n=22)	Difference (95%CI)
Overall						
Any AE	37 (97)	21 (95)	2 (–8, 12)	38 (100)	22 (100)	-
~~AEs leading to death~~	~~0 (0)~~	~~0 (0)~~		~~0 (0)~~	~~0 (0)~~	
Serious AEs	**2** (5)	0 (0)	5 (–2, 12)	**7** (18)	2 (9)	9 (–8, 26)
AEs leading to treatment discontinuation	**2** (5)	0 (0)	5 (–2, 12)	**3** (8)	0 (0)	8 (–1, 16)
Special interest						
Pruritus‡	13 (34)	1 (5)	30 (12, 47)	15 (39)	2 (9)	30 (11, 50)
Rash	11 (29)	4 (18)	11 (–11, 32)	13 (34)	5 (23)	11 (–12, 35)
Anemia	5 (13)	4 (18)	–5 (–24, 14)	7 (18)	4 (18)	0.2 (–20, 20)
Anorectal discomfort	5 (13)	1 (5)	9 (–5, 22)	5 (13)	2 (9)	4 (–12, 20)

Discontinuation of TVR only due to AE, n = 1 (due to jaundice)[2]
Discontinuation of all study drugs due to AE (overall treatment phase), n = 3 (due to cholelithiasis and hemolytic anemia and vomiting)[2]

1. Sulkowski MS, et al. Ann Intern Med 2013;159:86–96
2. Sherman KE, et al. Hepatology 2011;54(Suppl. S1): Abstract LB-8

BOC+PR for the treatment of HIV/HCV co-infected patients: Patient disposition

n (%)	BOC+PR (n=64)	PR (n=34)
Treated	64 (100)	34 (100)
Discontinued during treatment phase	24 (38)	19 (56)
AE	13 (20)	3 (9)
Treatment failure	6 (9)	15 (44)
Lost to FU	1 (2)	0
Did not wish to continue	3 (5)	1 (3)
Non-compliance with protocol	1 (2)	0
Completed treatment phase	40 (63)	11 (32)
Ongoing	0	0
Entered crossover	–	4 (12)

Sulkowski M, et al. Lancet Infect Dis 2013; 13:597–605

Antiretroviral therapy in candidates for PEG IFN + RBV + TPV/BOC/SMV/FDV/SOF.

CLASS		TELAPREVIR	BOCEPREVIR
NRTI	AZT, ddI, d4T: NO WITH PR	🟥	🟥
	ABC:	🟩	🟩
	TDF; ° AUC increased 30%	🟩°	🟩
	FTC, LAM	🟩	🟩
PI	ATZ/R; ^ Cthrough incresaed 30%	🟩^	🟧
	DRV/R	🟧	🟥
	LPV/R ,, FPV/R,	🟥	🟥
NNRTI	EFV	🟩	🟥
	NVP	🟥	🟥
	RPV	🟩	🟩
	ETV; #Etravirine AUC - 23%	🟩	🟩#
INI	RAL/DOL	🟩	🟩
	Elvitegravir/cobicistat	🟩	No data
CCR5 I	MAR:150 mg bid withTEL	🟩	No data

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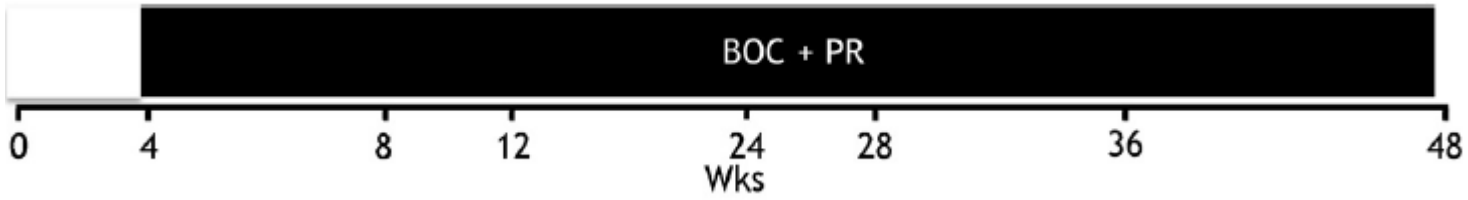
Triple anti-HCV Stopping Rules

Time Point	Criterion	Stopping Rule
Wk 4 or 12	HCV RNA > 1000 IU/mL (> 100 if Telaprevir started after lead in with PR)	Discontinue all therapy
Wk 24	Detectable HCV RNA	Discontinue PR
Any	Discontinuation of PR for any reason	Discontinue TEL

*



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Time Point	Criterion	Stopping Rule
Wk 12	HCV RNA ≥ 100 IU/mL	Discontinue all therapy
Wk 24	Detectable HCV RNA	Discontinue all therapy
Any	Discontinuation of PR for any reason	Discontinue BOC

* SPC Telaprevir

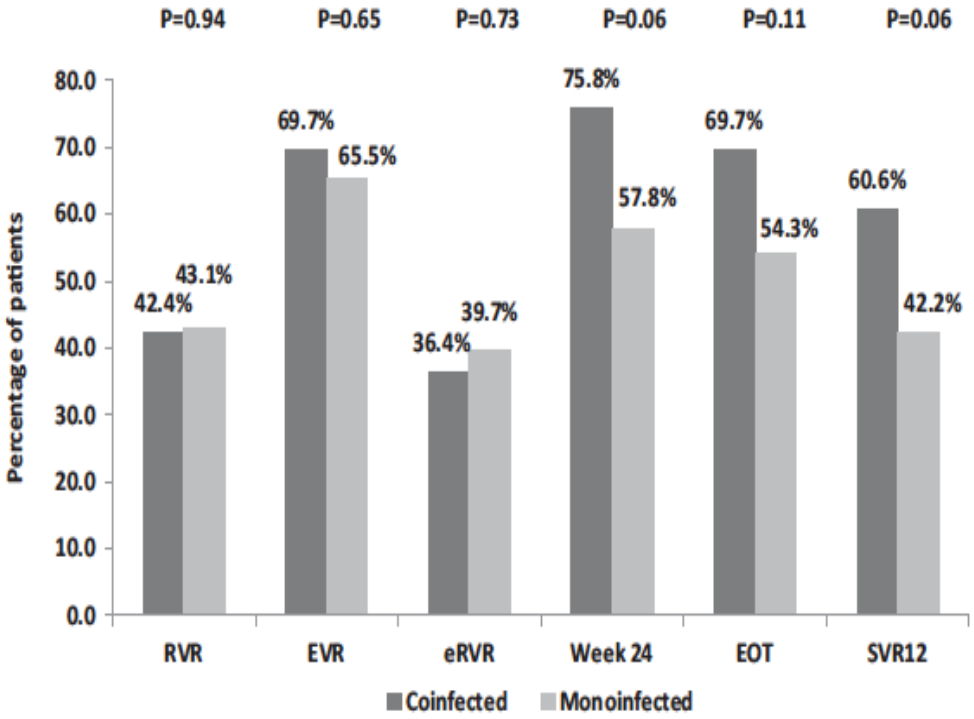
** SPC Boceprevir

Puoti M. et al.: Optimizing Treatment in HIV/HCV coinfection - Digestive and Liver Disease 45S (2013) S355–S362

Virological response rates for telaprevir-based hepatitis C triple therapy in patients with and without HIV coinfection

Variable	HIV/HCV (33)	HCV mono (116)	p
Age (years) [median (IQR)]	57 (52–59)	56 (51–61)	0.78*
African American [n (% of total)]	14 (42.4)	19 (16.4)	< 0.01
Previous response: Naive + Rel [n (% of total)]	8 (24.3)	58 (50.0)	< 0.01
Advanced fibrosis/cirrhosis [n (% of total)]	16 (48.5)	40/112(35.7)	0.18
CD4 T-cell count (cells/**µL) [median (IQR)]**	478 (362–763)		
HIVRNA Undetectable/< 20 copies/mL [n			
ART regimen switch before triple therapy total)]			

Predictors of SVR12 Variable	Adjusted OR (95%CI)
HIV-infected	3.55 (1.44–8.75)
Race, African American	0.37 (0.15–0.92)
Response, NR/intolerant	0.46 (0.23–0.93)



Martel-Laferrière V, et al. HIV Medicine (2013)

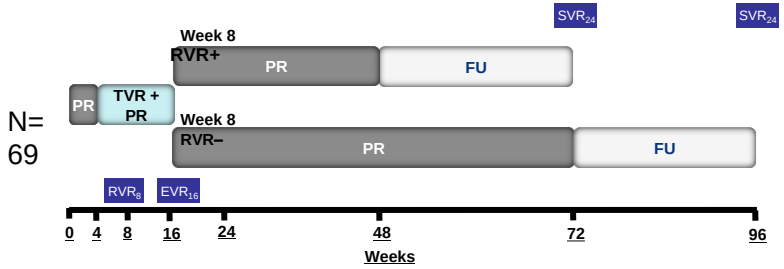
Tolerability of triple therapy with TEL in HIV coinfected vs HIV uninfected patients with HCV G1

Reference	Parameter	HIV+	HIV-
Laferriere V	Treatment discontinuation for SAE	6/33 [18.2%]	15/107 [13.7%]
	Severe anemia	11/33 [33 %]	40/107 [37.6%]
	Rash	5/33 [15%]*	36/107 [34%]
	Perianal discomfort	4/33 [12%] §	47/107 [44%]

* p=0.05 vs HIV-; § =0.01 vs. HIV-

Co-infected treatment-experienced patients

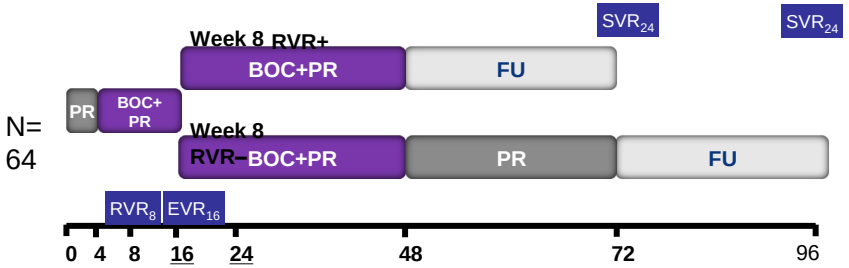
ANRS HC26 TelapreVIH



CD4 ≥200/mm3 and ≥15%, plasma HIV-RNA levels <50 copies/mL
Patients were also administered ART
Authorised drugs: ATV, ATV/r, EFV, RAL, TDF, FTC, 3TC

(partial RVR8: 15 IU/mL <HCV-RNA <1,000 IU/mL)

ANRS HC27 BocepreVIH



CD4 ≥200/mm3 and ≥15%, plasma HIV-RNA levels <50 copies/mL
Patients were also administered ART
Authorised drugs: ATV, ATV/r, RAL, TDF, ABC, FTC, 3TC

HCV RNA > 100 IU/mL

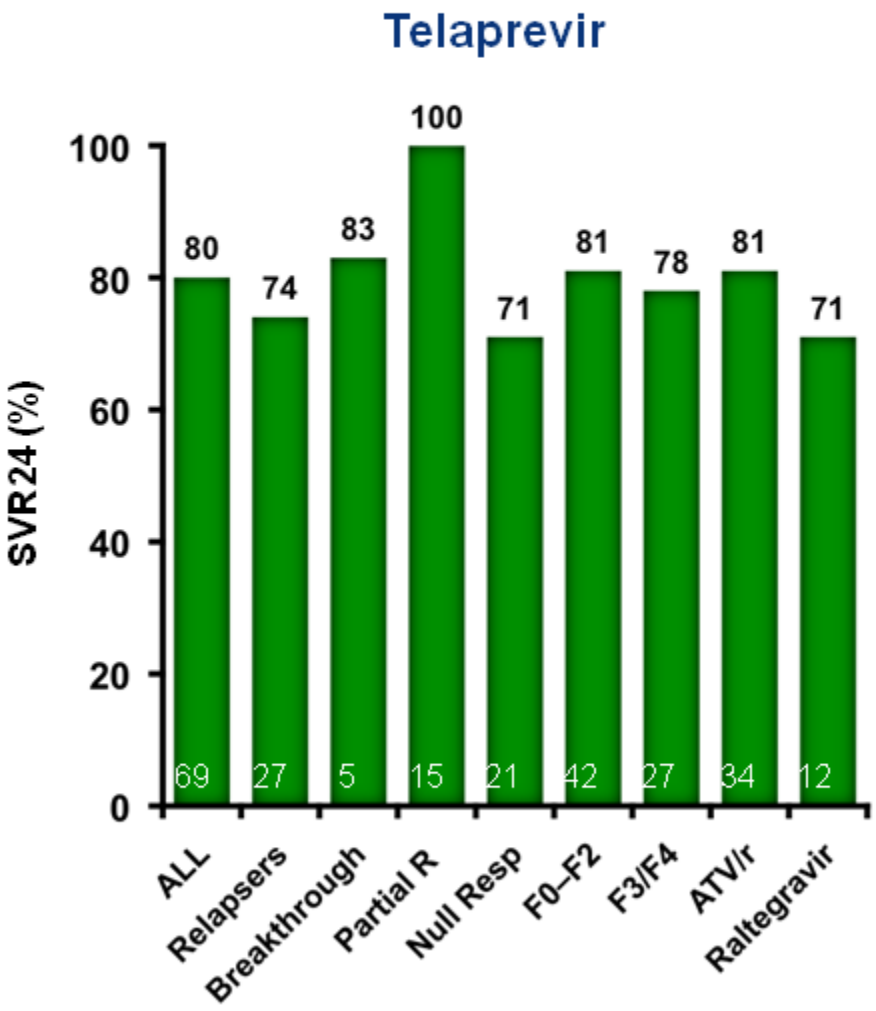
partial RVR8 (HCV RNA >15 IU/mL and <1000 IU/mL at Week 8)

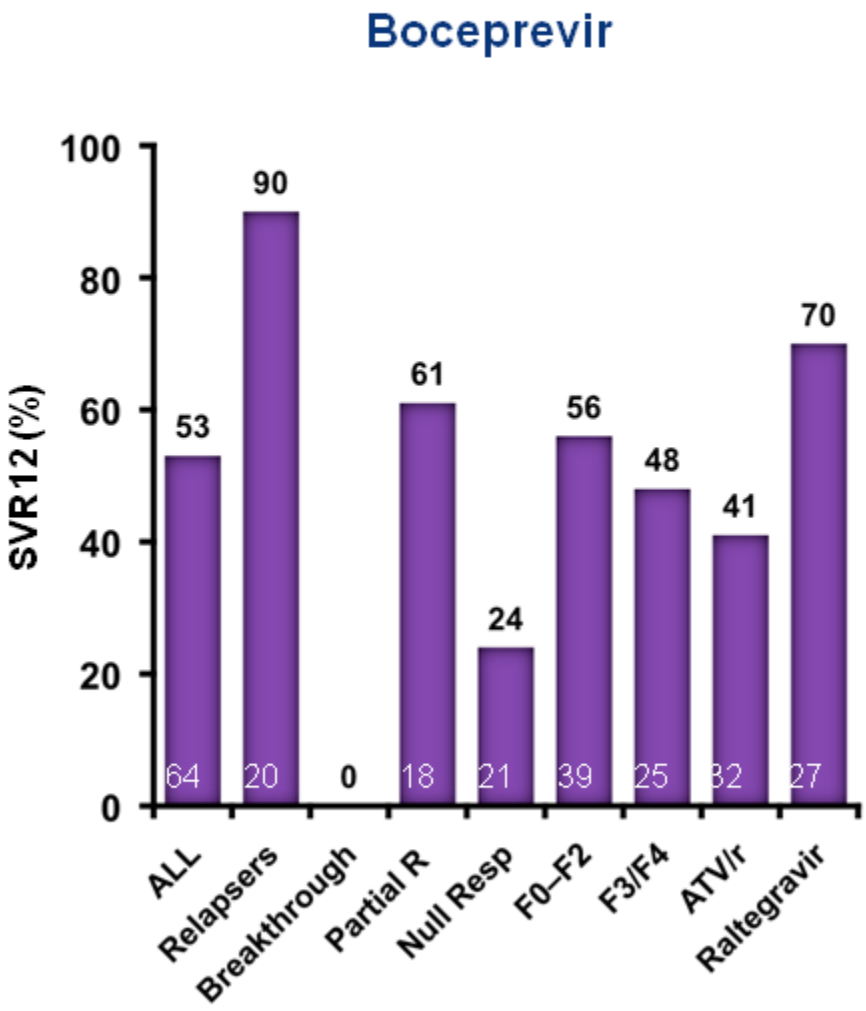
Poizot-Martin I, et al. CROI 2014 Cotte L, et al. CROI 2014

:Baseline disease characteristics and demographics of patients

ANRS HC26 TelapreVIH	T12/PR (N=69)	BOC+PR (N=64)
Median age, years (IQR)	50 (47–52)	49(46-52)
Male, n (%)	55 (80)	48(75)
Non-black, n (%)	59 (85)	
PWID, n (%)	38 (55)	47(73)
CDC stage C, n (%)	13 (19)	14(22)
CD4 cell count, cells/mm^3 (range)	630 (459–736)	728(527-923)
HIV RNA <50 copies/mL, n (%)	68 (99)	61(95)
ART regimen, n (%)		
TDF/FTC/ATVr	34 (49)	32(50)
TDF/FTC/RAL	12 (17)	27(42)
Other	13 (19)	5(8)
HCV genotype 1a, n (%)	48 (70)	50(78)
Severe fibrosis (F3) / cirrhosis (F4), n (%)	11 (16) / 16 (23)	14(22)/11(17)
Previous response to treatment, n (%)		
Relapse	27 (39)	20(31)
HCV breakthrough	6 (9)	5(8)
Partial response	15 (22)	18(28)
Null response	21 (30)	21(33)

ANRS studies TelapreVIH (HC26) and BocepreVIH (HC 27) SVR in HIV HCV treatment experienced patients





SVR24 in HIV/HCV PR experienced treated with PR + TVR (69) or BOC (62); 4 weeks lead in + 44 weeks standard + 24 additional weeks if HCV RNA at Week 8 >15 UI/mL

Cotte L et al. CROI 2014; Poizot Martin I. et al CROI 2014

ANRS HC26 TelapreVIH: Safety

Incidence, n (%)	T12/PR (N=69)
Grade 4 AEs	14 (20)
Hematological	**11 (16)**
Cutaneous	0 (0)
Grade 4 anemia (< 65 g/L)	4 (6)
EPO use	45 (65)
RBC transfusion	16 (23)
Grade 4 neutropenia (< 0.50 giga/L)	3 (4)
G-CSF Use	4 (6)
Grade 4 thrombocytopenia (< 50 giga/L)	1 (1.4)
TPO-R agonist use	1 (1.4)
Platelet transfusionn	1 (1.4)
Treatment interruption due to AE	**14 (20)**
Telaprevir dose reduction	4 (6)
Peg IFN dose reduction	15 (22)
RBV dose reduction	30 **(43)**

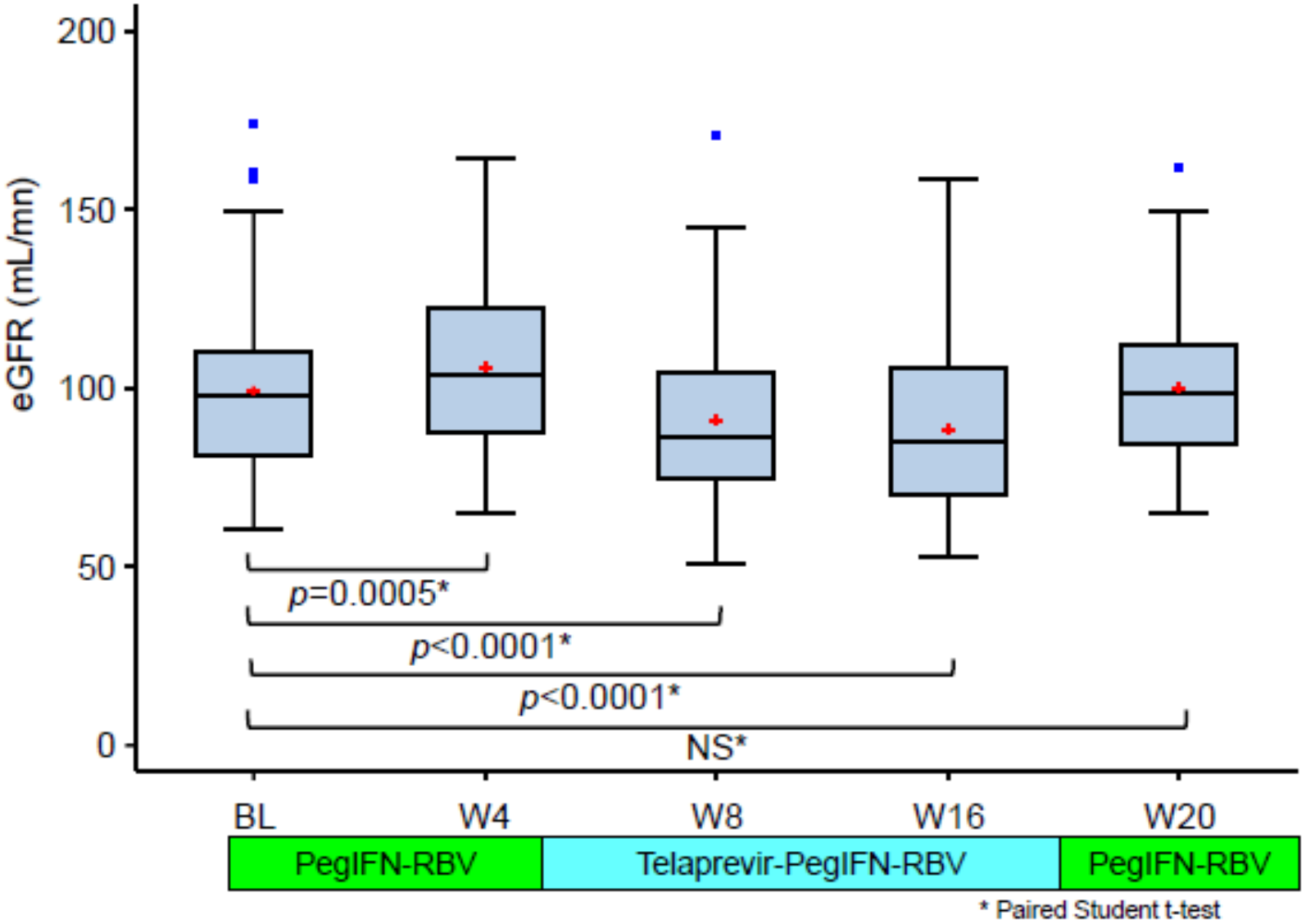
Cotte L, et al. CROI 2014

ANRS HC27 BocepreVIH:Safety

Adverse Events	Any AE N	Patients N (%)
Blood and lymphatic system	**204**	**63 (98%)**
Investigations	192	62 (97%)
General disorders	**86**	**54 (84%)**
Gastrointestinal	78	38 (59%)
Metabolism and nutrition	66	43 (67%)
Skin	54	33 (52%)
Infections	44	29 (45%)
Psychiatric	34	27 (42%)
Musculoskeletal	34	26 (41%)
Respiratory	24	20 (31%)
Kidney	20	16 (25%)
Nervous system	17	15 (23%)
Cardiac	12	11 (17%)
Eye	10	10 (16%)
Vascular disorders	6	6 (9%)

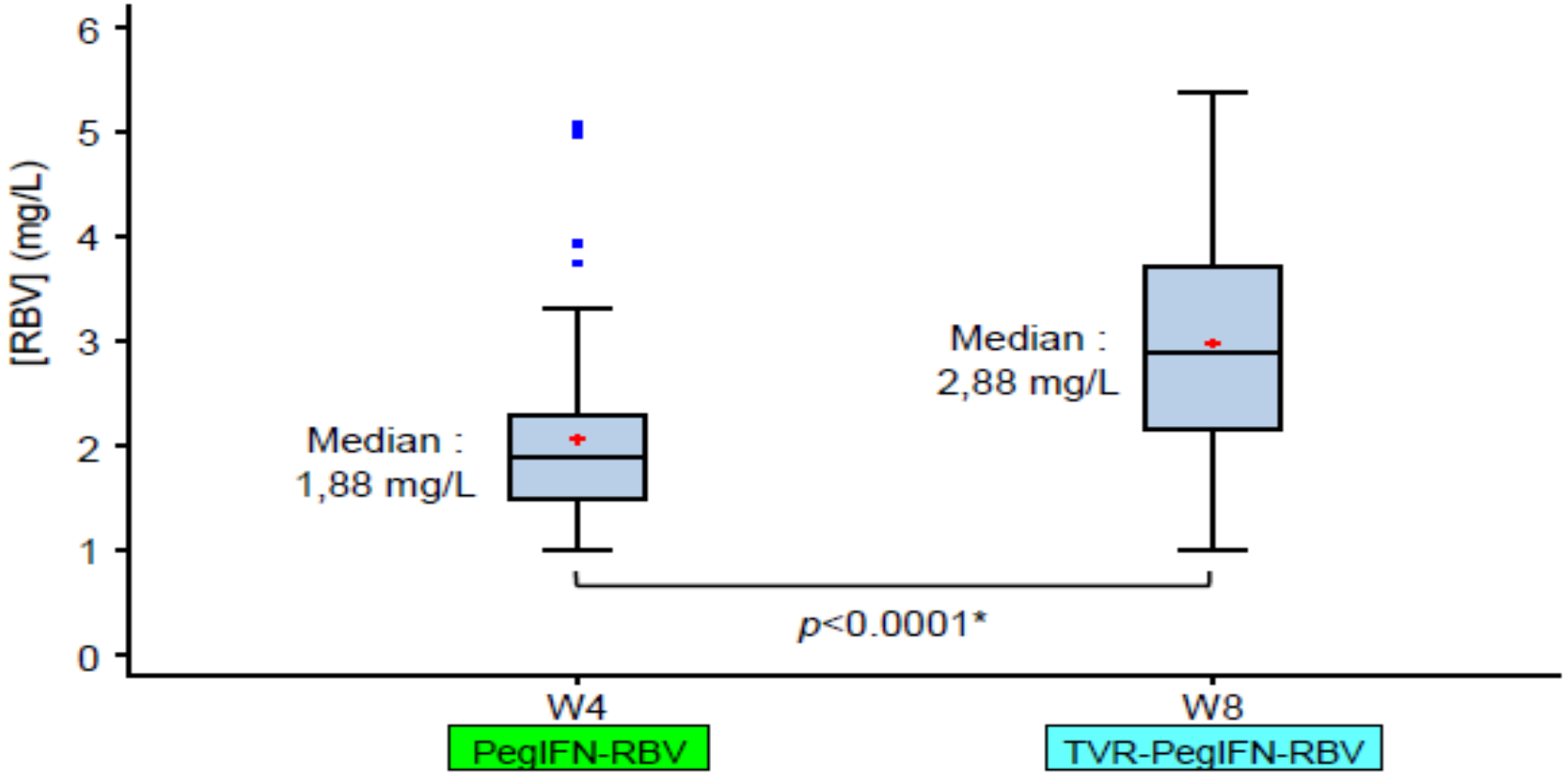
Clinical and Biological AEs reported in at least 7% of patients.

Evolution of eGFR



Cotte et al., CROI 2014 Poster 664SB

RBV trough concentrations



* Paired Student t-test

[RBV]	W4 (n=67)	W8 (n=62)	p*
< 3 mg/L	59 (88%)	34 (55%)	<0.0001
≥ 3 mg/L	8 (12%)	**28 (45%)**	

* McNemar's test

Cotte et al., CROI 2014 Poster 664LB

Boceprevir/Telaprevir-Based Therapy in HIV-Infection: Interim Analysis of a Multicenter Cohort

Karin Neukam, Daniela Munteanu, Antonio Rivero, Annette Haberl, Manuel M.Marquez, Patrick Ingiliz, Ignacio de los Santos-Gil, Thomas Lutz, Juergen K.Rockstroh, Juan A. Pineda

- Multi-center retrospective German-Spanish cohort in 2012-2013
- Data collection in all HIV-HCV co-infections patients treated with TVR or BOC + Peg-IFN+ Ribavirin
  - 12 German centers and 8 Spanish centers
- Treatment efficacy and safety data were collected at TW 4,TW12 and 8, 16 week after treatment

Neukam K CROI 2014 Ab 660

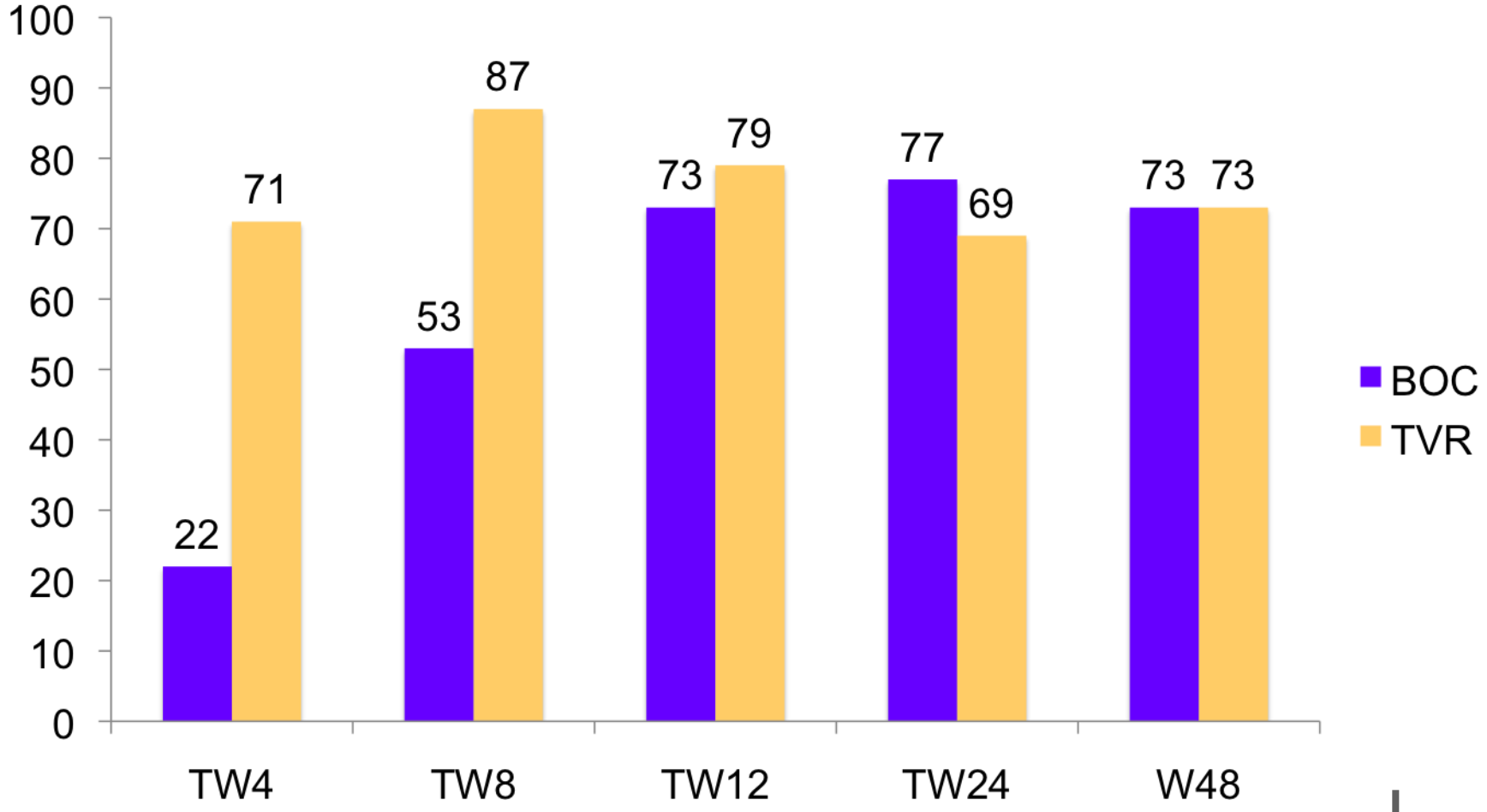
Baseline characteristics

Population n=183	BOC(32)	TVR(151)
Age (median (IQR)	46(43-51)	48 (45-51)
Male	81	85
IL28B rs12979860 genotype CT/TT	68	72
F4 (>14.6kPa)	75	53
Genotype 1a	58	69
HCV-RNA level > 600000UI/ml	84	78
TDF/FTC	69	63
ATV/r	9.4	42
RAL	66	41

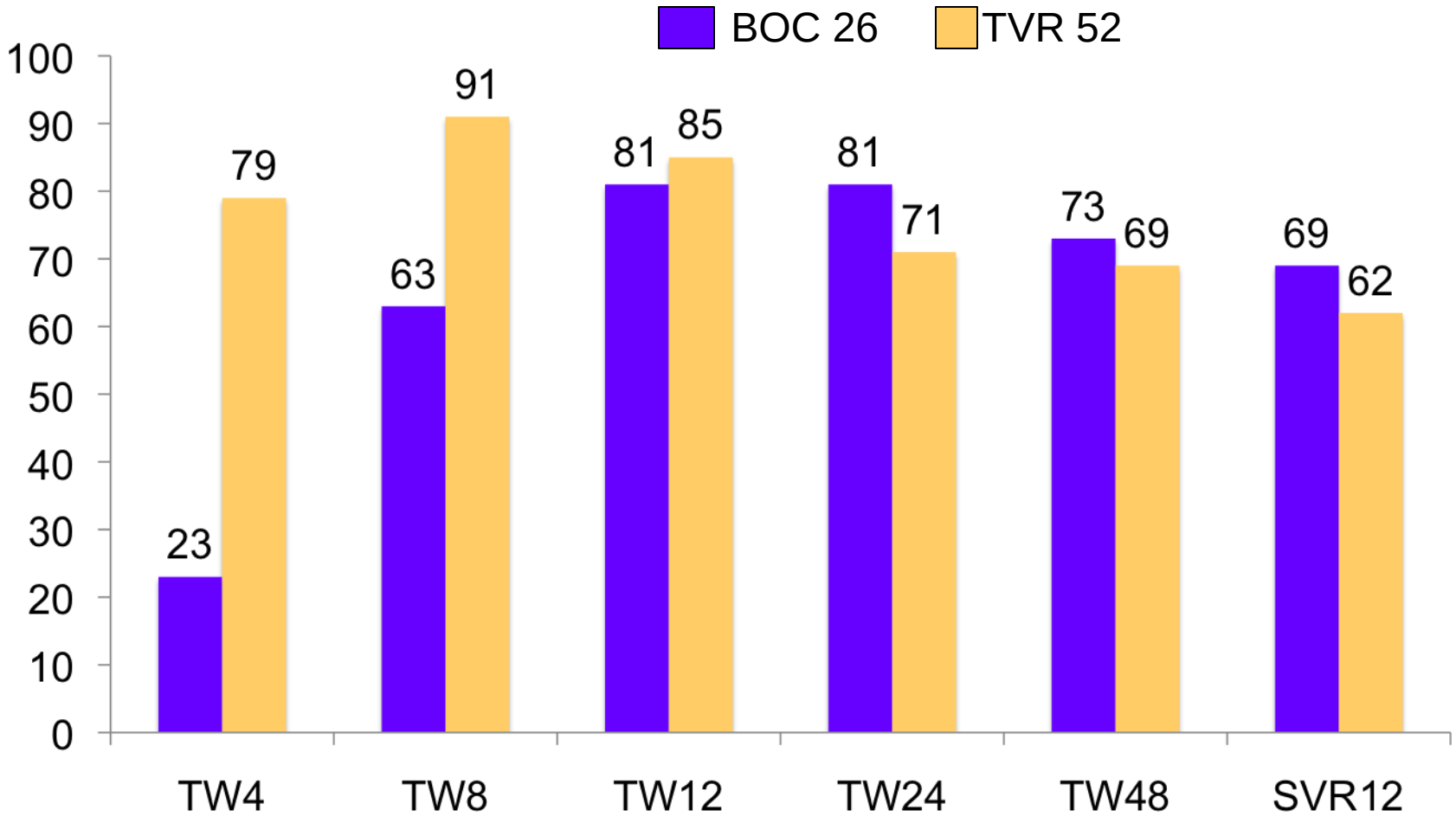
	BOC 32	TVR 151
Previous response to anti- HCV therapy		
Naives	14	44
Relapsers	7	25
Partial responders	0	21
Null Responders	5	45
Other	6	16

Neukam K CROI 2014 Ab 660

HCV virologic response (W48)



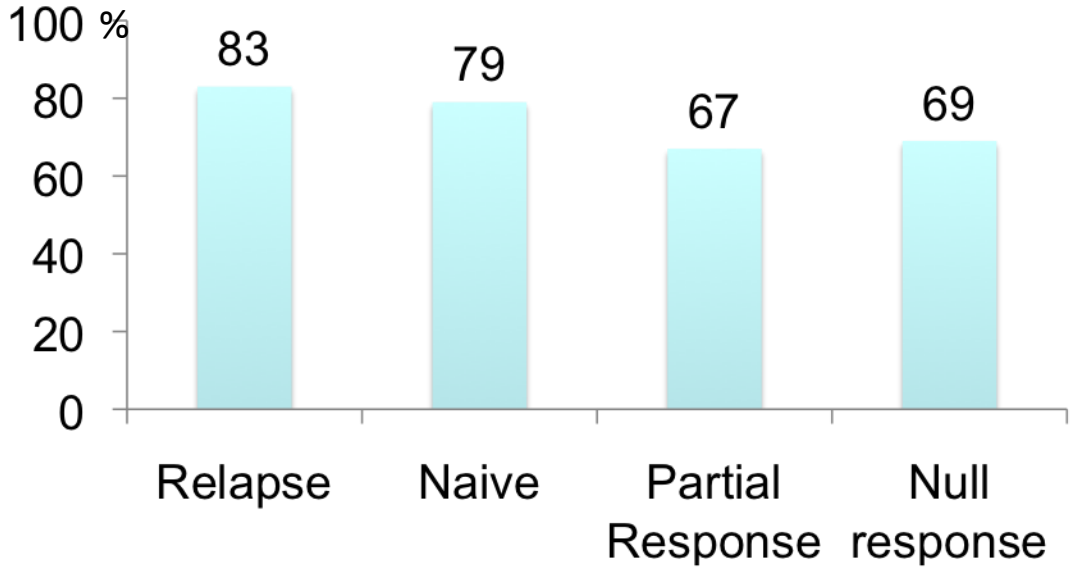
HCV virologic response (ITT-SVR 12)

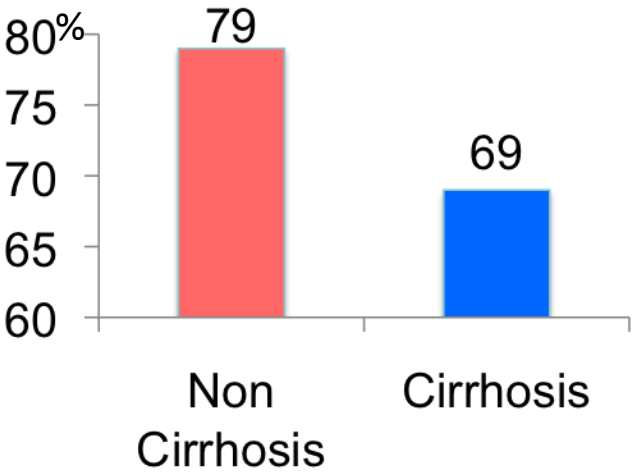


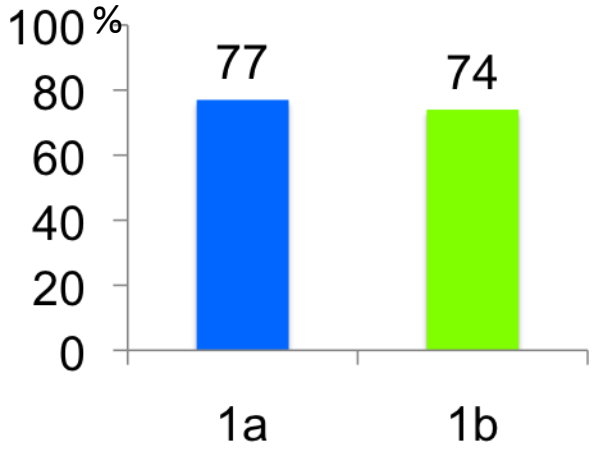
Neukam K CROI 2014 Ab 660

OVERALL SVR 12: 50/78 (64.1%)

HCV virologic response (ITT-SVR 12)







Neukam K CROI 2014 Ab 660

Main safety events observed among patients receiving BOC or TVR-based triple therapy

Population n=183	BOC(32) %	TVR(151)
Discontinuation adverse events	6.3	11.3
Hepatic decompensations	9.4	3.3
Rash (grade II-IV)	0	10.6
Anemia (<10mg/dL)	37.5	29.8
Neutropenia (<1000cells/mL)	47	32
Trombocitopenia (<50000cells/mL)	18.8	21.9
Blood Transfusion	12.5	7.3
EPO	18.8	12.6

Neukam K CROI 2014 Ab 660

Telaprevir Treatment of HIV/HCV Genotype 1 Patients with Severe Fibrosis: Efficacy Results to Week 16

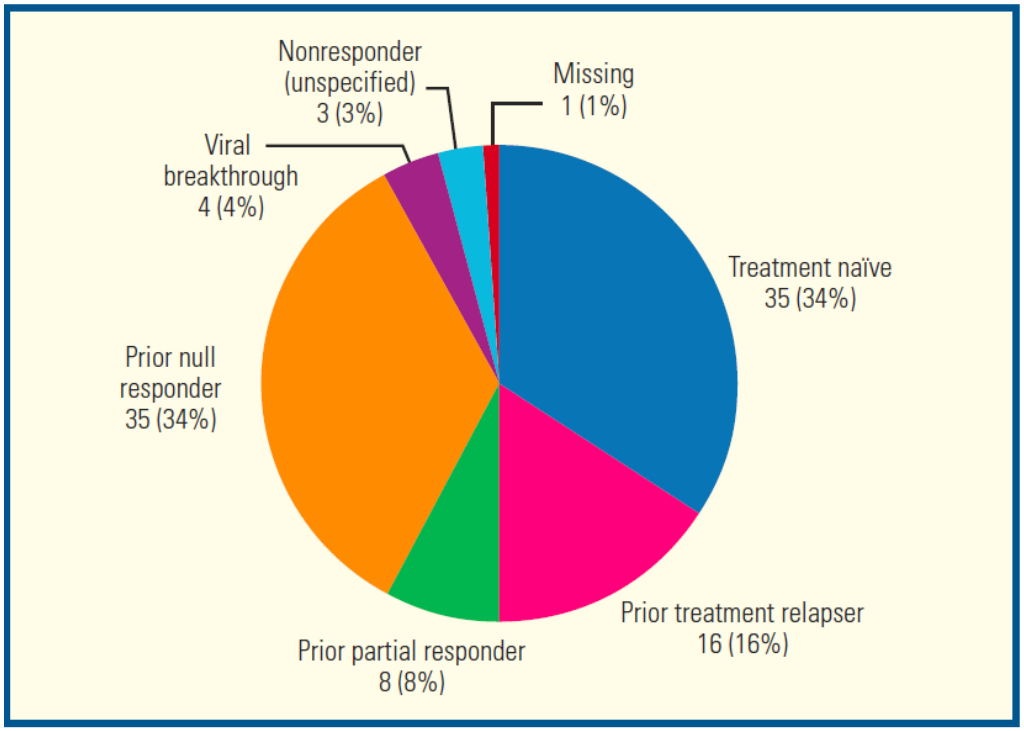
A. Cori,[1] M. Doroana,[2] O. Chernova,[3] J. Rockstroh,[4] D. Bánhegyi,[5] C. Bergin,[6] G. Verucchi,[7] A. Hill,[8] B. Hadacek,[9] M. Nelson[10]

[1]San Gerardo Hospital, Division of Infectious Diseases, Monza, Italy; [2]Hospital de Santa Maria, Servico de Doenças Infecciosas, Lisbon, Portugal; [3]State Healthcare Institution, Tolyatti, Russian Federation; [4]University Hospital Bonn, Department of Internal Medicine, Bonn, Germany; [5]Szent László Hospital, Budapest, Hungary; [6]St James's Hospital, Department of Gastrointestinal Medicine and Infectious Diseases, Dublin, Ireland; [7]University of Bologna, Division of Infectious Diseases, Bologna, Italy; [8]Janssen Research & Development, High Wycombe, UK; [9]Janssen Pharmaceuticals, Paris, France; [10]Chelsea and Westminster Hospital, London, UK

Patients 102

Mean age 44 years
HCV-RNA levels > 800000UI/mL 67%
F3/F4 59% / 41%

HIV-RNA<50copie/ml 96%
CD4 Mean 644/mmc



Gori A CROI 2014

HCV RNA <25 IU/mL at Week 4 and 12

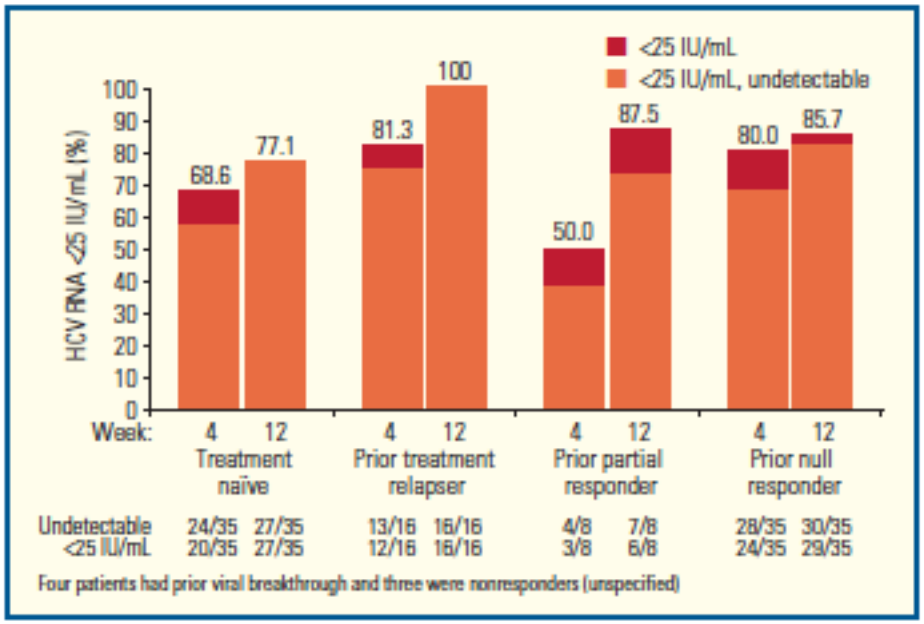


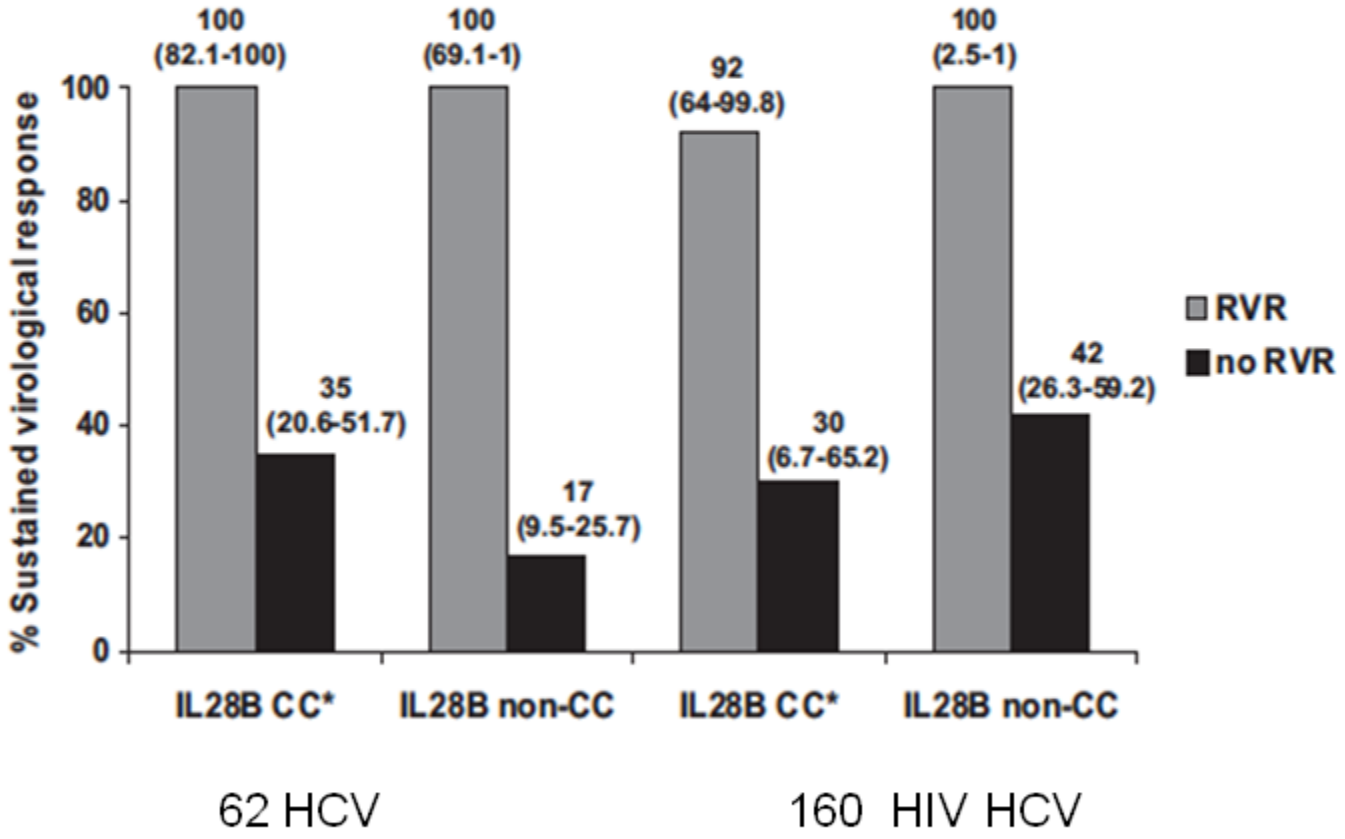
Table 5. Grade 2–4 Adverse Events Reported by at Least 2% of Patients (Telaprevir Related).

Adverse event, n (%)	All (N=102)
Patients with one or more Grade 2–4 AE	**37 (36)**
Anemia SSC	12 (12)
Thrombocytopenia SSC	8 (8)
Asthenia	7 (7)
Rash SSC	6 (6)
Nausea	6 (6)
Neutropenia SSC	4 (4)
Fatigue	4 (4)
Hyperbilirubinemia	3 (3)
ECG/QT SSC	2 (2)
Pruritus SSC	2 (2)
Hypophosphatemia	2 (2)
Headache	2 (2)

SSC = special search category
ECG = electrocardiogram

Gori A CROI 2014

High levels of SVR to PR in HCV with RVR independently from IL28 SNP and HIV co-infection



Neukam K et al. Journal of Infection 2013

Prevalence and Predictive value of RVR (HCVRNA undetectable at the 4th week of triple therapy) with anti HCV PI in HCV+/HIV-

Setting	Treatment	%RVR	SVR in pts with RVR
HCVG1 Naïve Relapser & NR F0-F2[1]	PR + BOC	889 /1511 55%	766/889 86%
HCVG1 Naïve Relapser & NR F3-F4[1]	PR + BOC	120/278 43%	106/120 89%
HCV G1 Naive[2]	PR + TEL	422/583 72%	365/420 87%
HCV G1 Relapsers[3]	PR + TEL	201/251 80%	183/201 91%
HCV G1 PR[3]	PR + TEL	56/84 67%	38/56 68%
HCVG1 NR[3]	PR + TEL	42/130 32%	28/42 68%

1 Vierling JM et al. EASL 2013; 2 Sarrazin et al HepDART 2013; 3Berg T, et al. Hepatology 2011;54(Suppl. S1):375A

PR + Second generation DAAs in co-infected patients

C212[1]

106pts

- HCV treatment-naïve
- Prior PR relapsers

→ SMV + PR (RGT) → PR → Follow-up

- Partial response
- Null response
- Cirrhotic patients (F4)

→ SMV + PR → PR → Follow-up

STARTVerso4[2]

308pts

FDV with Darunavir/ritonavir FDV AUC >130%
FDV with Efavirenz <FDV AUC < 35%

FDV 240 mg + PR → PR or follow up (RGT)

FDV 240 mg + PR → PR

FDV 120 mg + PR → PR or follow up (RGT)

SOF + PR[3]

23pts naive 15 G 1a, 4 G1b, 1 G2b, 2 G3a, 1 G4a/b/c

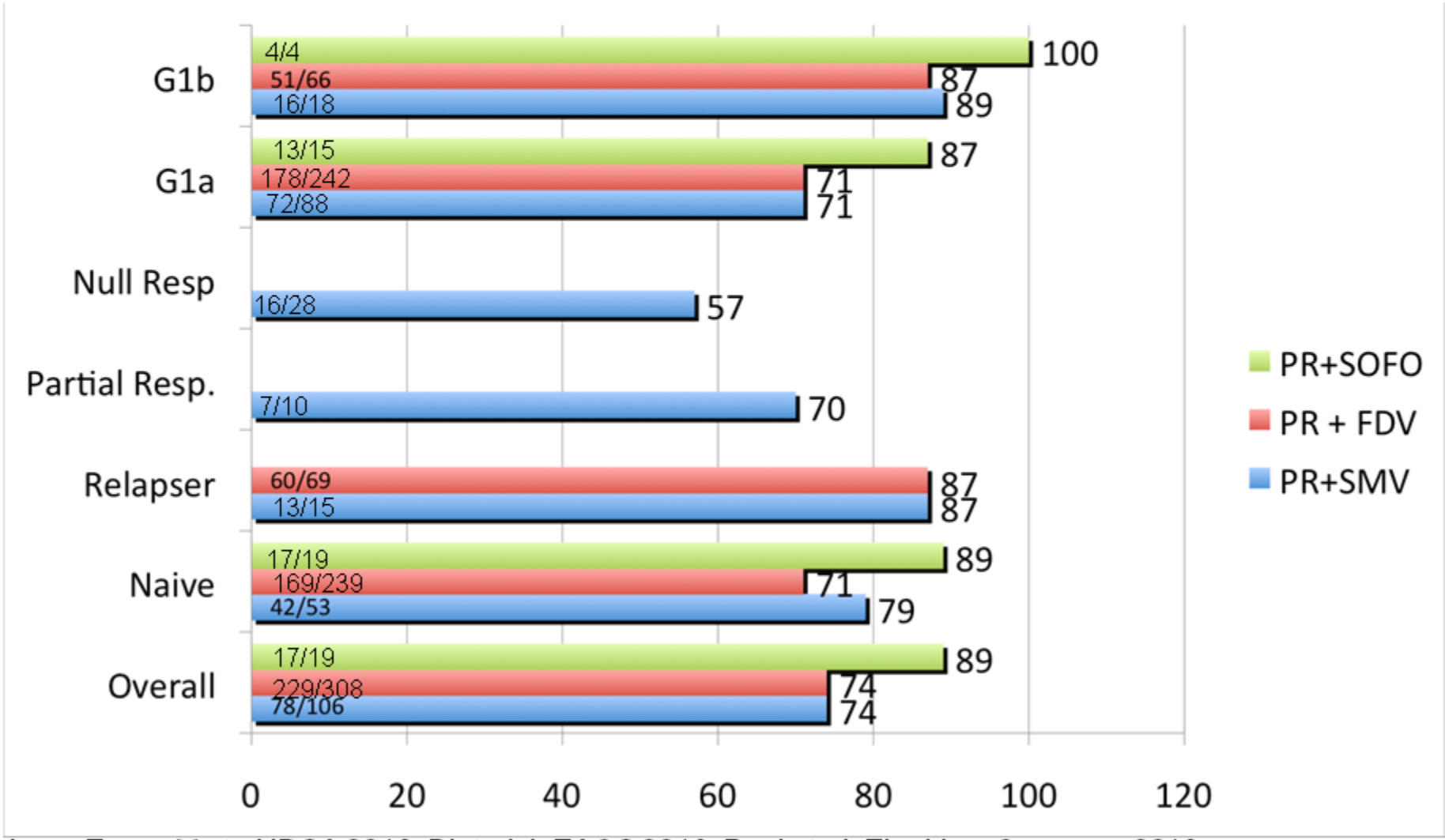
GT 1 – 4: SOF + PR → Follow-up

SVR4 SVR12 SVR24

Week 12 24 36 48 60 72

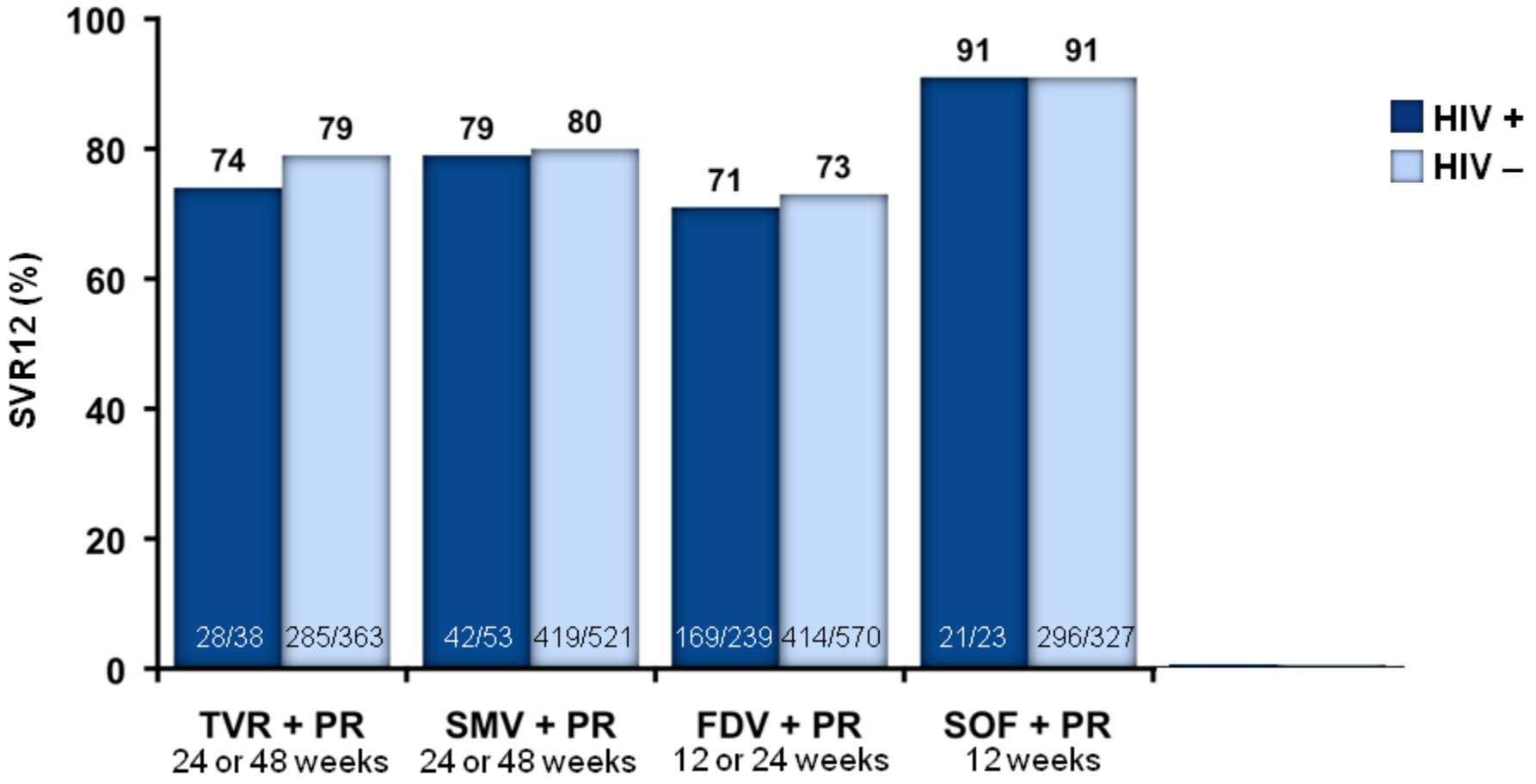
1. Dietrich D et al. EACS 2013; 2. Rockstroh J et al EACS 2013 & AASLD 2013
3. Rodriguez-Torres M et al IDSA week; 4. Sulkowski M et al AASLD 2013

SVR 4 in HIV/HCV G1 treated with PR + SOFOSBUVIR or SIMEPREVIR or FALDAPREVIR



Rodriguez Torres M et al IDSA 2013; Dieterich EACS 2013; Rockstroh The Liver Congress 2013

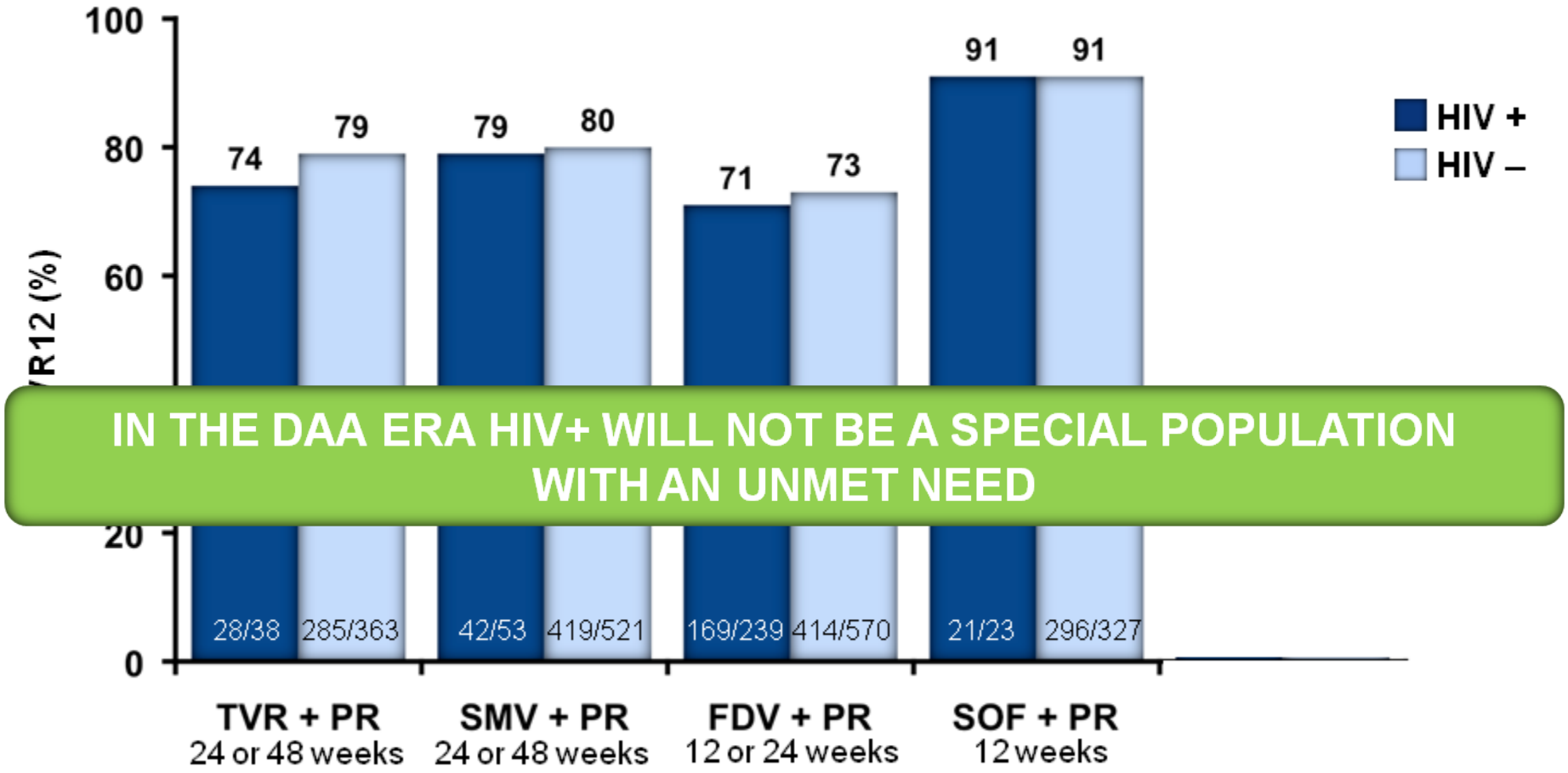
SVR12 after treatment with PR + TVR, SMV, FDV and SOF in HCV G1 treatment-naïve patients: HIV + vs HIV –



Cirrhosis	**10%**	**13%**	**11%**	**Excluded**

Sulkowski M, AASLD 2012; TVR EU SmPC; Dieterich CROI 2014; Rockstroh J et al EACS 2013 & AASLD 2013; Rodriguez Torres M et al IDSA 2013; Naggie CROI 2014; SOF EU SmPC

SVR12 after treatment with PR + TVR, SMV, FDV and SOF in HCV G1 treatment-naïve patients: HIV + vs HIV –



IN THE DAA ERA HIV+ WILL NOT BE A SPECIAL POPULATION WITH AN UNMET NEED

Cirrhosis	**10%**	**13%**	**11%**	**Excluded**

Sulkowski M, AASLD 2012; TVR EU SmPC; Dieterich CROI 2014; Rockstroh J et al EACS 2013 & AASLD 2013; Rodriguez Torres M et al IDSA 2013; Naggie CROI 2014; SOF EU SmPC

Antiretroviral therapy in candidates for PEG IFN + RBV + TPV/BOC/SMV/FDV/SOF.

CLASS		SIMEPREVIR	FALDAPREVIR *120/ § 240 mg	SOFOSBUVIR
NRTI	AZT, ddI, d4T: no with PR orR	■	■	■/■
	ABC:	■	■	■
	TDF; ° AUC increased 30%	■°	■°	■
	FTC, LAM	■	■	■
PI	ATZ/R; ^ Cthrough incresaed 30%	■	■ §	■
	DRV/R	■	■ §	■
	LPV/R ,, FPV/R,	■	■	■
NNRTI	EFV	■	■*	■
	NVP	■	■	■
	RPV	■	■	■
	ETV; #Etravirine AUC - 23%	■	■	■
INI	RAL/DOL	■	■	■
	Elvitegravir/cobicistat	No data	No data	■
CCR5 I	MAR:150 mg bid with FDV	No data	■	■

Adverse events in combination with Ribavirin (no head to head studies)

Drug	BOC	TVR	SMV	FDV	SOFO
Tx Duration	28-48	24-48	**24-48**	**24-48**	**12**
N pills/n of doses	12/3	6/2-3	**1/1**	**1/1**	**1/1**
Food effect	Yes Light snack	Yes Fatty meal	**Yes Breakfast**	**Minimal**	**Yes Breakfast**
Anemia	++	++			
Fatigue	++				**(+/-)**
Dysgeusia	++				
Nausea Vomiting	+	+	**(+)**	**(+)**	
Diarrhea	-	+	**-**	**(+)**	**-**
Anorectal signs	-	++	**-**	**-**	**-**
Pruritus		+	**+**		
Rash Photosensitivity	(+)	++	**+**	**+**	

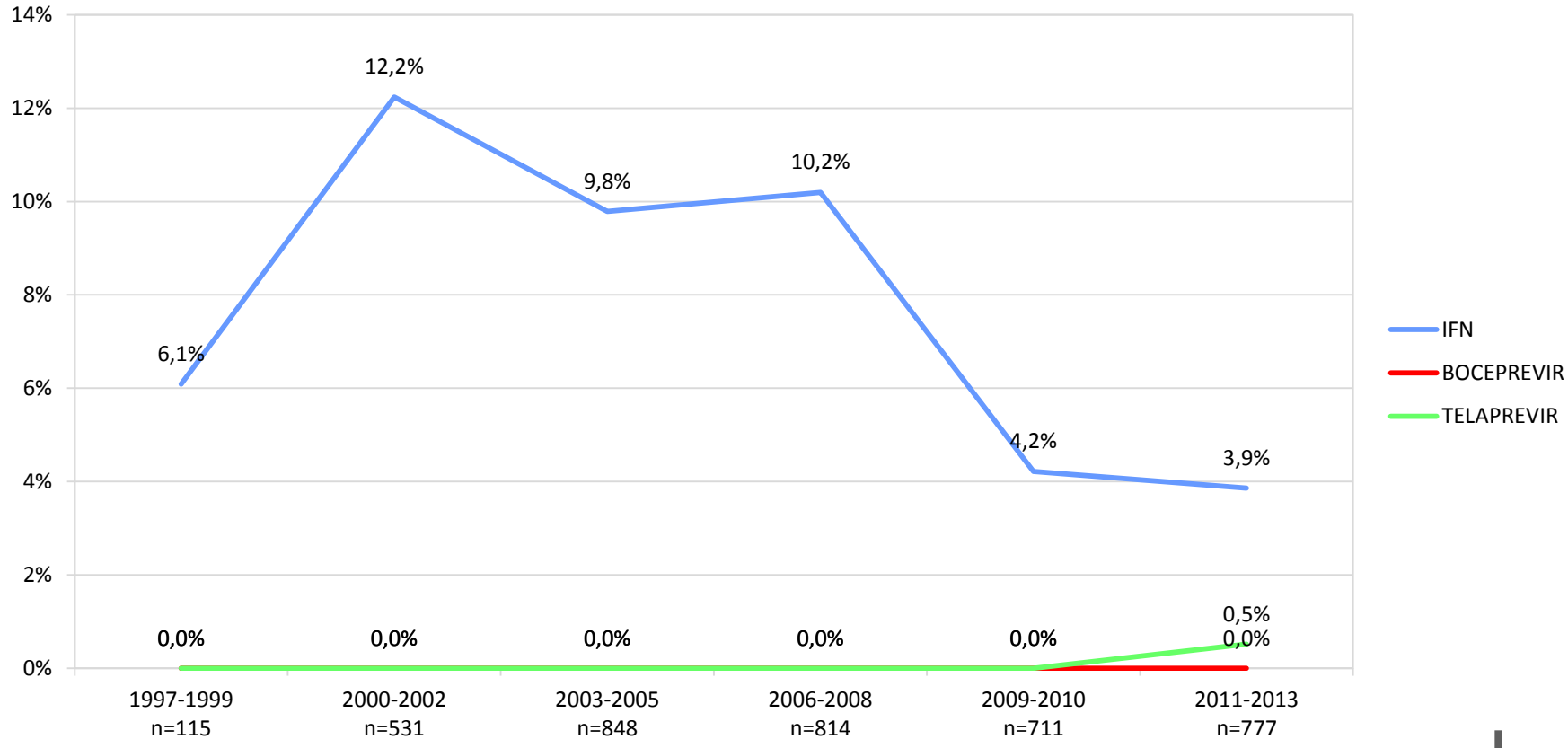
Victrelis EU SmPC; Incivo EU SmPC; Mauss et al Hepatology 2014; Simeprevir FDA Advisory Committee meeting briefing materials; Janssen data on file; Boehringer Ingelheim data on file; Sulkowsky et al Hepatology 2013; Sovaldi EPAR product information

Laboratory abnormalities in combination with PEGIFN + Ribavirin (no Head to Head studies)

Drug	BOC	TVR	SMV	FDV	SOFO
Neutrophils	↓	=	=	=	=
Lympho	=	↓	=	=	=
Hb	↓↓	↓↓	=	=	=
PLT	(↓)	(↓)	=	=	=
Bilirubine	=	(↑)	↑ Direct & indir.	↑ Direct	=
Creatinine	↓	↓	=	=	=
Uric Acid	↑	↑	=	=	=
Triglycerides	↑	=	=	=	=
Cholesterol	↑	↑			

Victrelis EU SmPC; Incivo EU SmPC; Mauss et al Hepatology 2014; Simeprevir FDA Advisory Committee meeting briefing materials; Janssen data on file; Boehringer Ingelheim data on file; Sulkowsky et al Hepatology 2013; Sovaldi EPAR product information

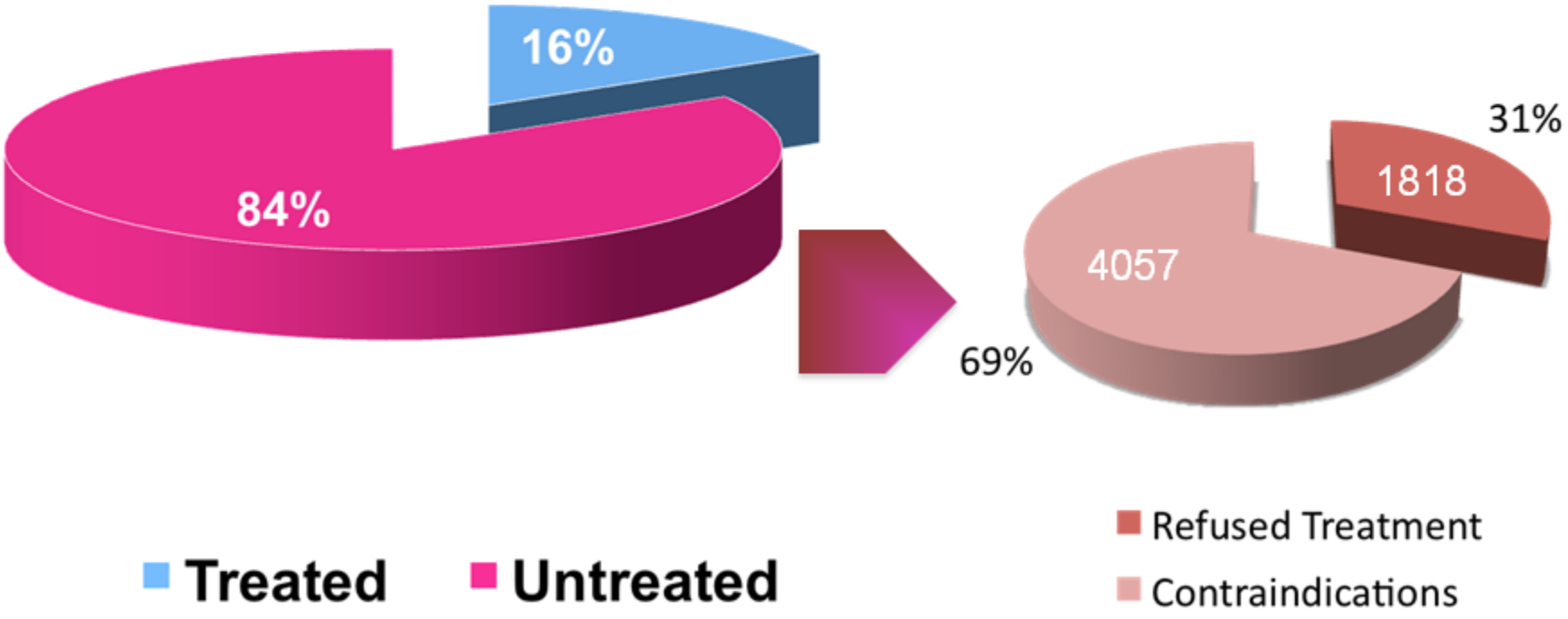
Prportion of HCVAb+/HCV-RNA+ patients starting any anti-HCV Tx for the first time, according to drug compound and period of starting



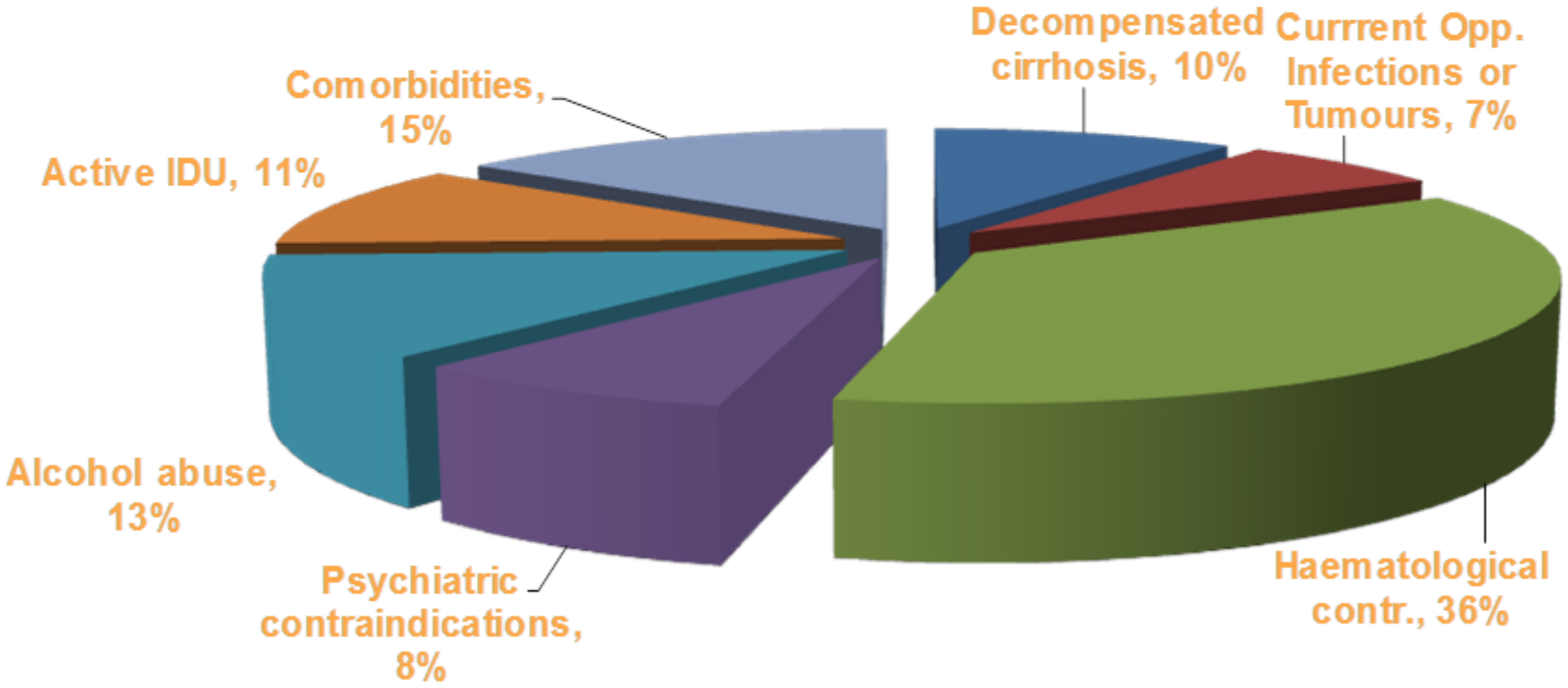
for 2013, 10 months

Survey Italian database Opera

- Questionnaire sent to 31 Italian HIV outpatients clinic
- Population of HCV coinfected
  - 7017 pts (33% of all HIV+)



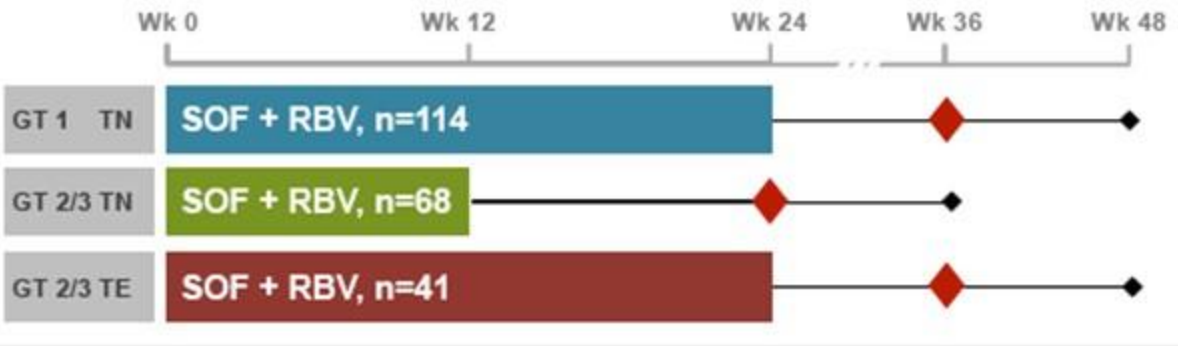
Italian Database Opera Survey
Why 84% HCV coinfected patients were not treated?
1818 pts refused treatment 4057 had contraindications
Prevalence of contraindications in 4057 Italian HIV HCV+



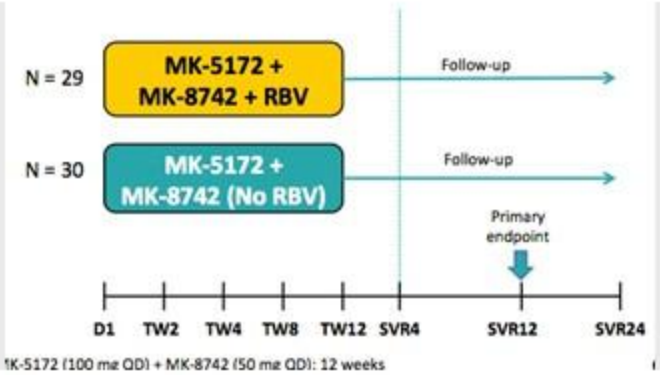
WHAT ABOUT AN INTERFERON FREE REGIMEN ?

IFN Free DAAs regimens in co-infected patients

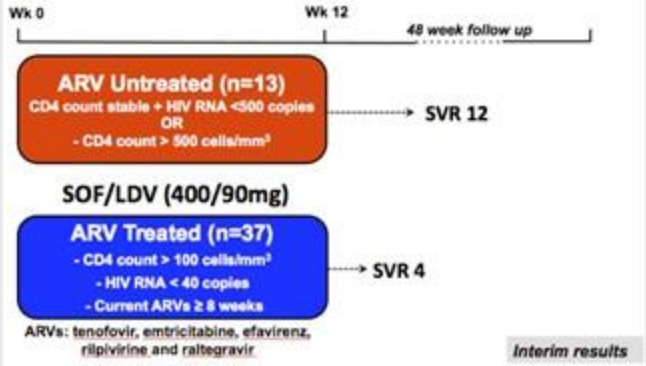
Photon 1 Study
Dieterich D et al.
APASL 2014



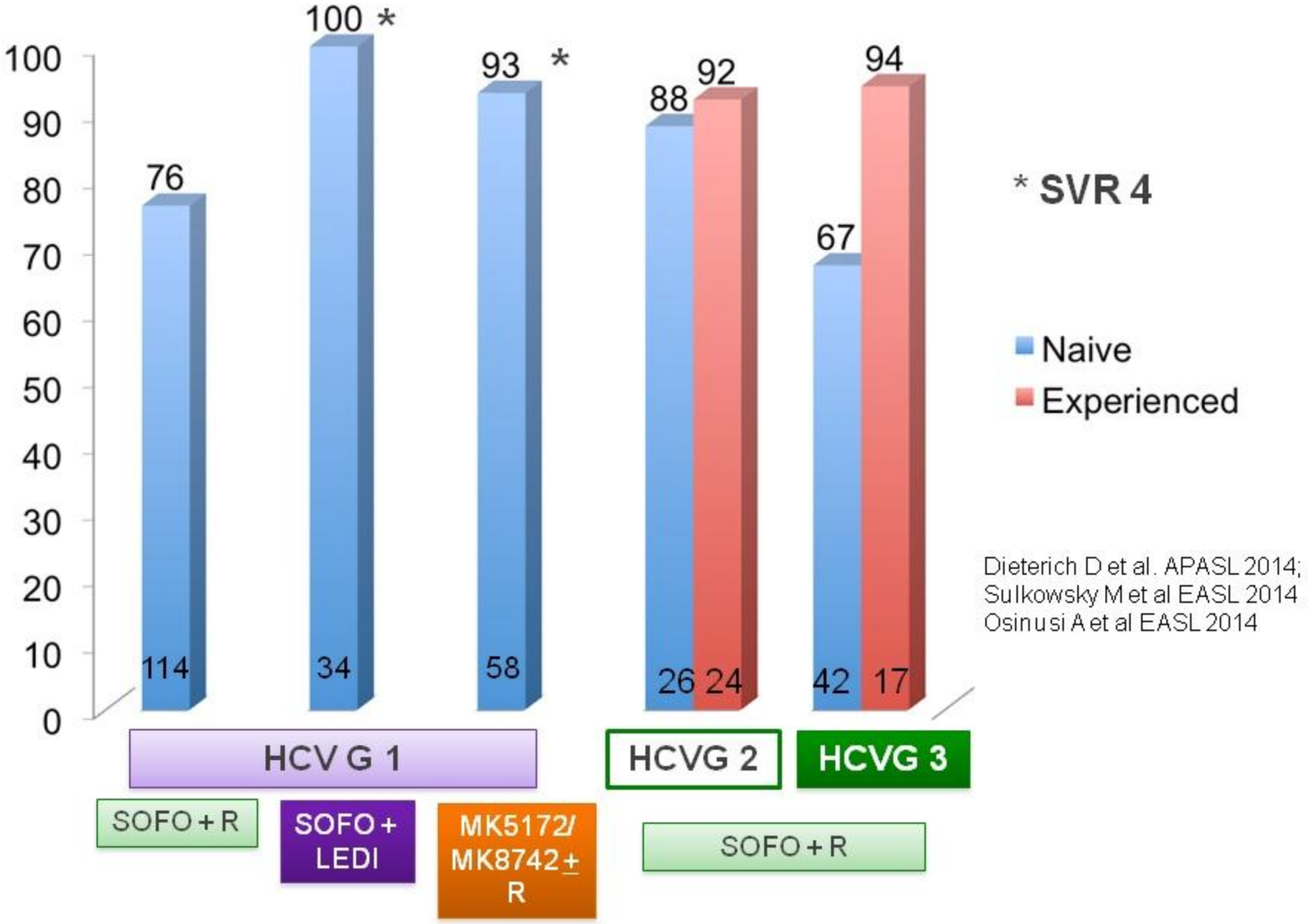
C-Worthy Study
Sukowsky M. et al.
EASL 2014



SOFOSBUVIR/LEDIPASVIR FDC study
Osinusi A. et al.
EASL 2014



SVR with IFN Free DAAs regimens in HIV/HCV co-infected patients



Dieterich D et al. APASL 2014;
Sulkowsky M et al EASL 2014
Osinusi A et al EASL 2014

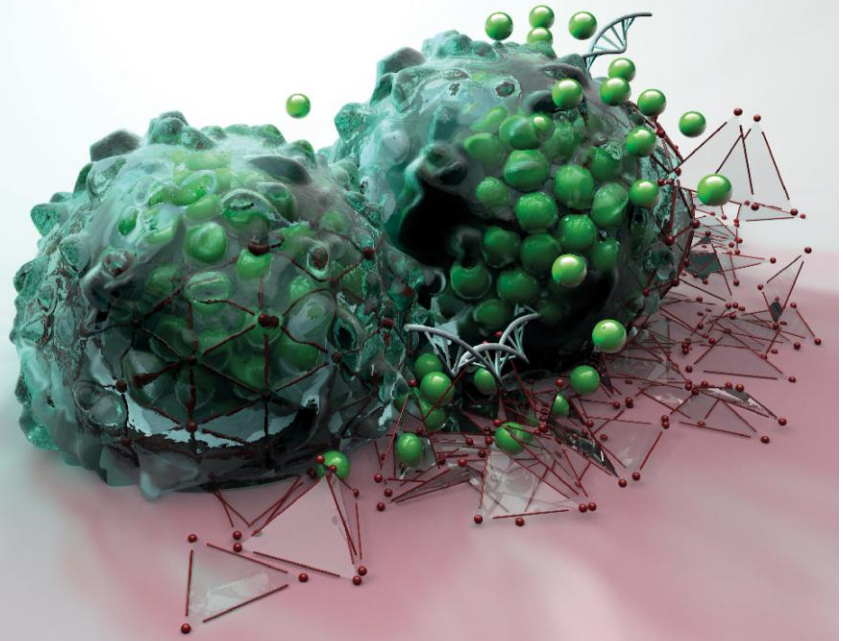
Antiretroviral therapy allowed in studies including Ledipasvir or MK5172/MK 8742

CLASS		Ledipasvir	MK 5172/MK 8742
MK 8742NRTI	AZT, ddI, d4T: no with PR orR	🟥	🟥
	ABC:	🟥	🟩
	TDF;	🟩	🟩
	FTC, LAM	🟩	🟩
PI	ATZ/R;	🟥	🟥
	DRV/R	🟥	🟥
	LPV/R ,, FPV/R,	🟥	🟥
NNRTI	EFV	🟩	🟥
	NVP	🟥	🟥
	RPV	🟩	🟥
	ETV	🟥	🟥
INI	RALTEGRAVIR	🟩	🟩
	Elvitegravir/cobicistat	🟥	🟥
CCR5I	MARAVIROC	🟥	🟥

APRIL **2014**

EASL Recommendations on Treatment of Hepatitis C

2014



EASL

European Association for the Study of the Liver

Coordinator: Jean-Michel Pawlotsky
Panel members: Alessio Aghemo (EASL Governing Board)
Geoffrey Dusheiko
Xavier Forns
Massimo Puoti
Christophe Sarrazin

EASL RECOMMENDATIONS ON TREATMENT OF HEPATITIS C APRIL 2014

- Indications for HCV treatment in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection (A1).

- The same treatment regimens can be used in HIV-co-infected patients as in patients without HIV infection, as the virological results of therapy are identical (A1).

EASL RECOMMENDATIONS ON TREATMENT OF HEPATITIS C APRIL 2014

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EASL RECOMMENDATIONS ON TREATMENT OF HEPATITIS C APRIL 2014

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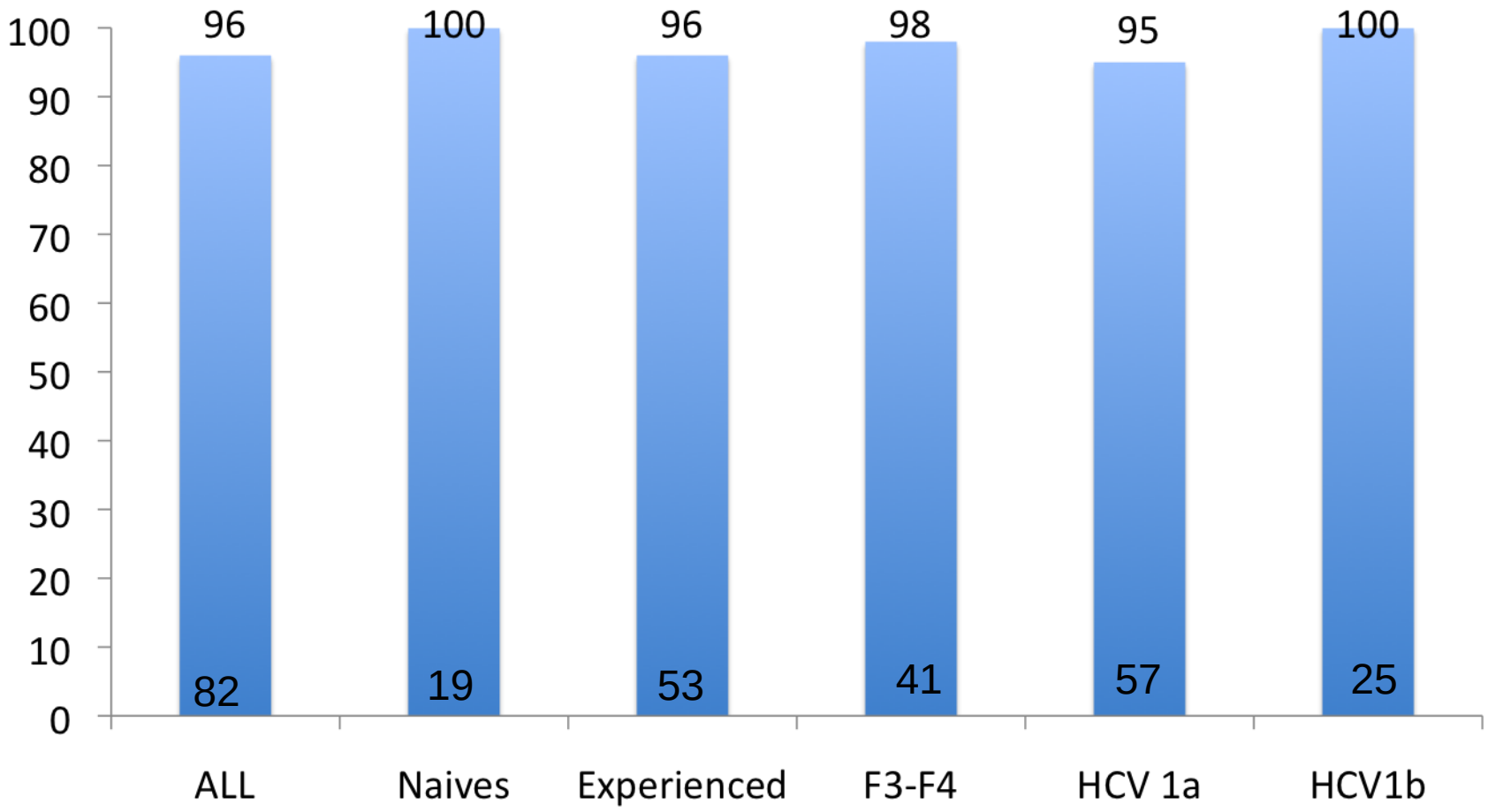
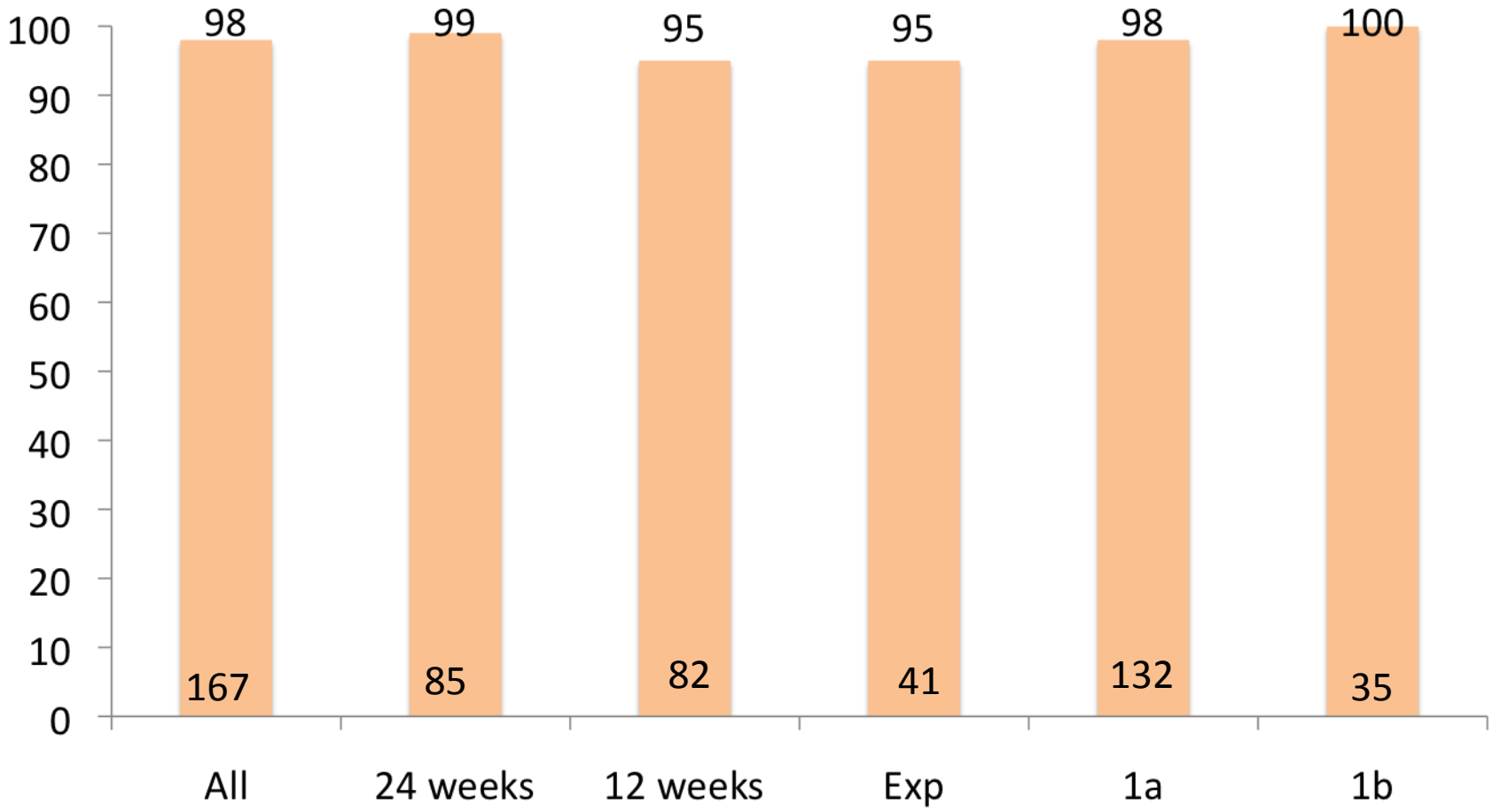
Sofosbuvir + Simeprevir ± RBV for 12 weeks



Jacobson IM, et al. AASLD 2013, Washington DC. #LB-3

Sofosbuvir + Daclatasvir ± Ribavirin for 12-24 weeks in 167 HCV G1 (32 F4)



Sulkowski M et al NEJM 2014

Treat now or wait? Considerations

What is the likelihood of SVR and tolerability with currently approved therapies?

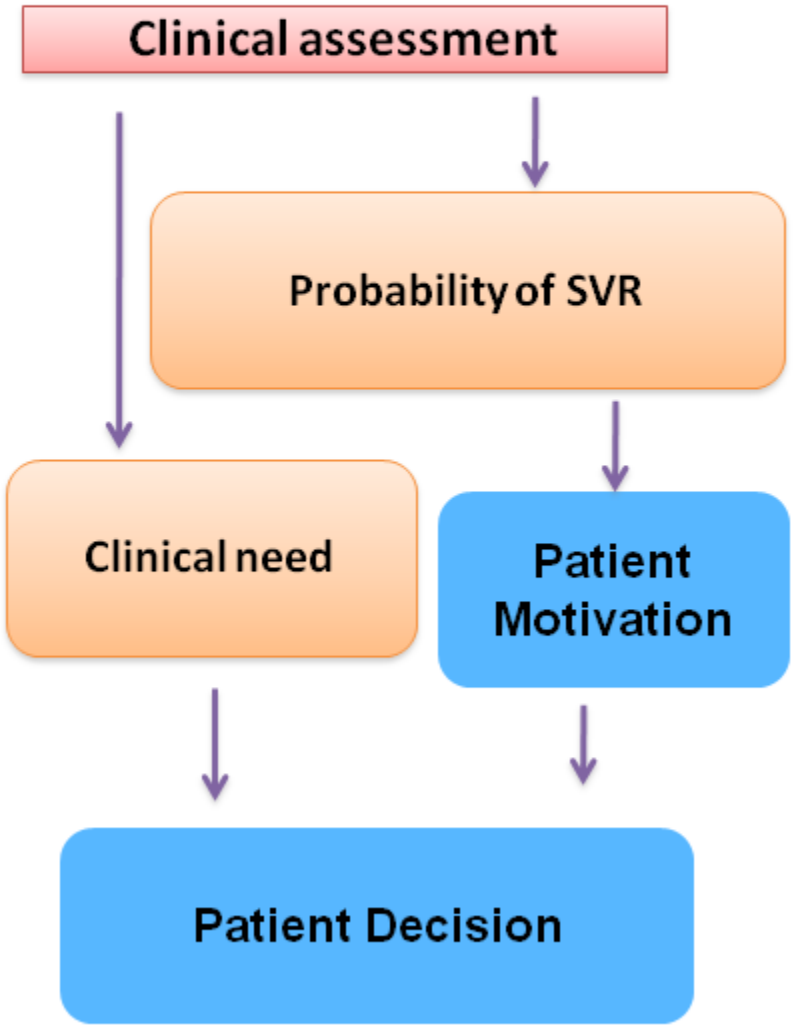
What are the morbidity/mortality risks of deferring treatment to a later date?

What are the potential benefits (efficacy, safety and convenience) of future therapies?

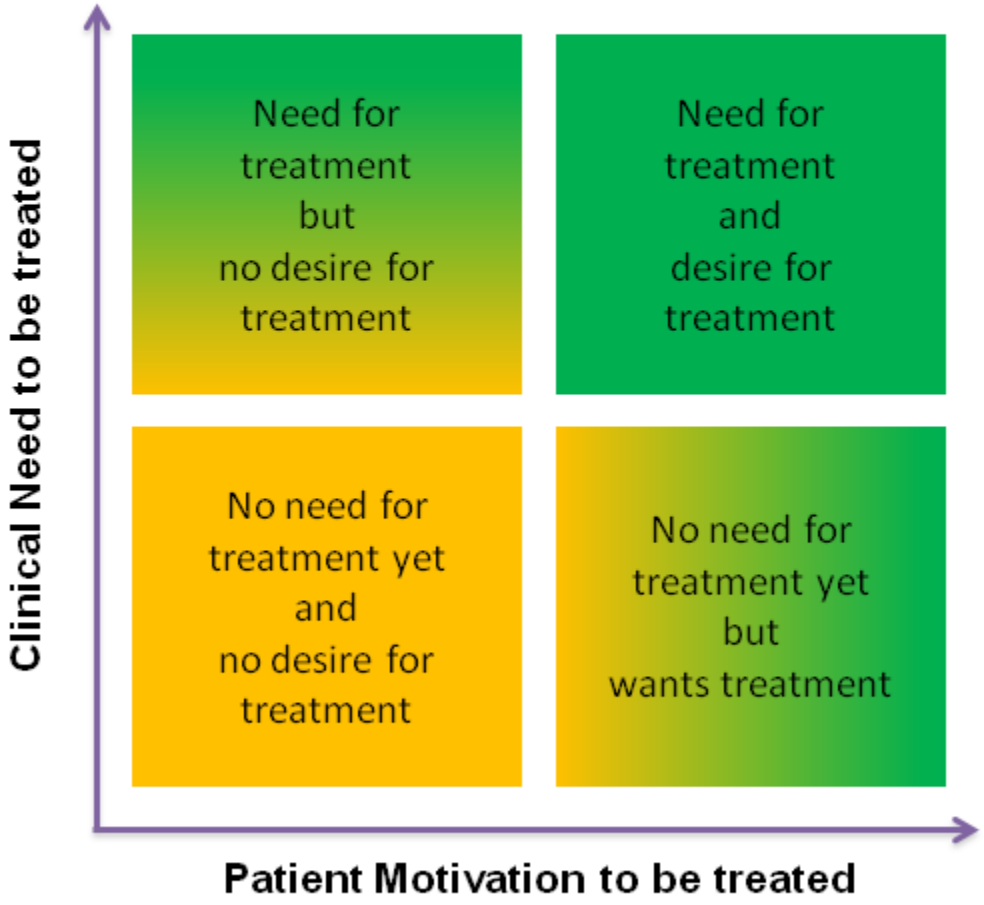
What is the motivation for the patient to undergo therapy?

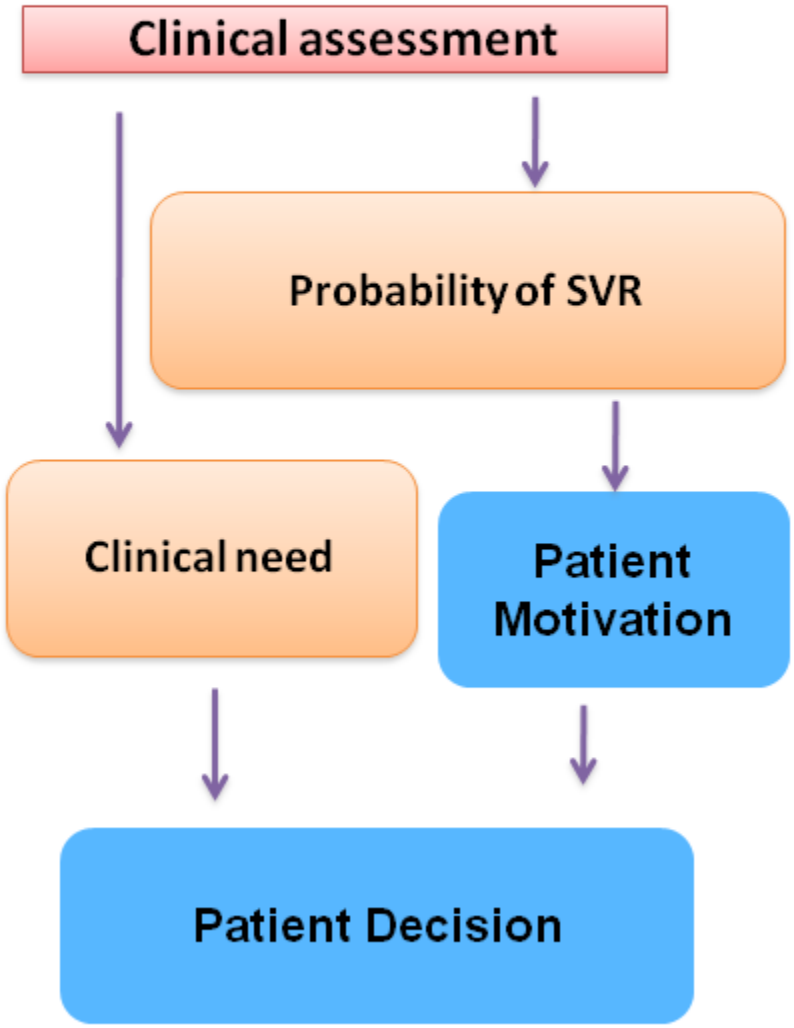
SVR = CURE

Treat now or wait?



Treat now or wait?





2014-2015 Where Do We Set The Bar of current options when new treatments are on the way?

EASL GUIDELINES 2014 + RECOMMENDATIONS 2014

F3-F4 Prioritized for treatment ; F2 treatment is justified; F0-F1 individualized treatment

Available drugs	Naïve or Relapser	Eligible to IFN	HCV G1	HCV G2	HCV G3	HCV G4
PR+ TEL, BOC	Yes	Yes	PR + BOC/TEL (efficacy > 85% in RVR)	PR response guided therapy (efficacy > 85% in RVR)		
	No			Informed deferral		
	Any	No	Informed deferral			
+ SOFO, SMV, DCV	Yes	Yes	PR + SOFO/SMV / DCV	SOFO+R 12-20w	PR+SOFO	PR + SOFO /SMV/DCV
	Yes	No	SOFO + SMV /DCV ± RBV SOFO + RBV (2*)		SOFO+R 24w SOFO + DCV 12-24w	SOFO+R 24w SOFO+SMV SOFO+DCV
	No	Yes/No				

Grade of Evidence: High quality Moderate Low or Very Low