Trattamento coinfezione HIV/HCV

Nicola Coppola

Dipartimento di Salute Mentale, Fisica e Medicina Preventiva

Seconda Università di Napoli

nicola.coppola@unina2.it

S.G. 56 anni

- HIV noto da 21 anni
- CDC-93: B1
- In terapia anti-HIV con Abacavir/lamivudina/darunavir-r
- CD4: 360cells/ml
- HIV RNA : negativo
- Anti-HCV noto da 21 anni
- HCV genotipo 1a
- IL28B-CC
- Trattamento con Peg-IFN plus Riba con relapse
- Eco addome: margini irregolari

D.R. 41 anni

- HIV noto da 3 anni
- CDC-93: A1
- In terapia anti-HIV con tenofovir/emtricitabina/rilpivirina
- CD4: 710cells/ml
- HIV RNA: negativo
- Anti-HCV noto da 3 anni
- HCV genotipo 3
- IL28B-TT
- Naive al trattamento anti-HCV
- Biopsia epatica: fibrosi 2 secondo Ishak

Coinfezione HIV-HCV

-Terapia anti-HCV-

- Perché?
- Come?
  - Duplice terapia (Peg-IFN+Riba)
  - Triplice terapia (Peg-IFN+Riba+DAA)
  - Regimi IFN-free

Coinfezione HIV-HCV

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Coinfezione HIV-HCV

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- **Perché?**
  - **Impatto dell'epatopatia cronica nella mortalità dei soggetti HIV positivi**
- Come?
  - Duplice terapia (Peg-IFN+Riba)
  - Triplice terapia (Peg-IFN+Riba+DAA)
  - Regimi IFN-free

Disclosure

Finanziamento di Gilead Sciences S.r.l. “L’infezione da HBV nelle popolazioni speciali (donne in gravidanza, popolazioni immigrate, popolazioni in età pediatrica): progetti di awareness ed accesso alla diagnosi”, Fellowship Program 2011 e 2013

Finanziamento di Hoffmann-La Roche Ldt “L’infezione da HBV in una popolazione di immigrati irregolari”

HIV and HCV infections: serious world health concerns

HIV infection

- 34 million people worldwide have HIV[1]
- The global incidence of HIV is 2.7 million/year[1]
- 1.8 million deaths in 2010[1]

HCV infection

- 170 million people worldwide have HCV[2]
- Incidence of HCV is ~150 000/year in US/W. Europe[2]
- 5–7% of HCV patients die from the disease[2]

HIV-HCV co-infection

- Around a quarter of patients with HIV in Europe are co-infected with HCV[3]
- 10% of patients with HCV are HIV co-infected[4]
- HIV-HCV co-infection may result in multi-systemic disorders[5]
- HCV co-infection results in a 50% increase in mortality in AIDS patients[6]

1. World Health Organization. Global Summary of the HIV.AIDS Epidemic. Available from: http://www.who.int/hiv/data/en/; 2. World Health Organization. Hepatitis C. Available from: http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index.html; 3. Soriano V, et al. J Infect Dis 2008;198:1337–44
4. Maier I, Wu GY. World J Gastroenterol 2002;8:577–9; 5. Operskalski EA & Kovacs A. Curr HIV/AIDS Rep 2011;8:12–22
6. Branch A, et al. Clin Infect Dis 2012;55:137–44

Liver-Related Deaths in Persons Infected With the Human Immunodeficiency Virus

The D:A:D Study

*The Data Collection on Adverse Events of Anti-HIV Drugs Study Group**

Arch Intern Med. 2006;166:1632-1641

Studio di coorte (11 coorti) che ha arruolato 23.441 pz anti-HIV positivi presso 188 centri tra Europa, Stati Uniti ed Australia e li ha monitorati per una media di 3.5 anni al fine di valutarne la mortalità AIDS e non AIDS-correlata.

Table 1. Death Rates per 100 Person-Years of Follow-up, Stratified by the Latest CD4 Cell Count*

CD4 Cell Count, /μL	Follow-up, Person-Years	AIDS-Related Deaths		Liver-Related Deaths	
		No.	Rate (95% CI)	No.	Rate (95% CI)
<50	1657	202	12.19 (10.51-13.87)	22	1.33 (0.77-1.88)
50-99	1711	50	2.92 (2.11-3.73)	21	1.23 (0.70-1.75)
100-199	6044	69	1.14 (0.87-1.41)	44	0.73 (0.51-0.94)
200-349	15 421	32	0.21 (0.14-0.28)	52	0.34 (0.25-0.43)
350-499	17 578	20	0.11 (0.07-0.18)	21	0.12 (0.07-0.17)
≥500	34 370	11	0.03 (0.02-0.06)	21	0.06 (0.04-0.09)
<200	9412	321	3.41 (3.04-3.78)	87	0.92 (0.73-1.12)
≥200	67 369	63	0.09 (0.07-0.12)	94	0.14 (0.11-0.17)
Total	76 781	384	0.50 (0.45-0.55)	181	0.24 (0.20-0.27)

Table 2. Characteristics of Patients Who Died of AIDS-Related Causes, Liver-Related Causes, and Other Causes

Characteristic	Cause of Death		
	AIDS Related (n = 388)	Liver Related (n = 181)	Other (n = 677)
Male, %	78.4	73.8	82.6
Age at death, median (range), y	42 (23-82)	43 (29-82)	45 (22-84)
Mode of infection, %			
Homosexual contact	45.4	19.1	42.4
Intravenous drug use	20.4	59.6	29.8
Heterosexual contact	17.0	11.5	16.5
Other/not known	17.3	9.8	11.2
Hepatitis virus coinfections, %			
HCV serologic tests positive*	23.7	66.1	33.4
HBV serologic tests positive, inactive infection†	17.8	20.2	23.3
HBV seropositive, active infection†	8.5	16.9	10.0
HBV vaccinated‡	1.5	4.4	2.4
HCV seropositive and active HBV infection	8.0	7.1	2.7
HCV and HBV serologic tests both negative	38.9	3.8	24.8

Liver-Related Deaths in Persons Infected With the Human Immunodeficiency Virus

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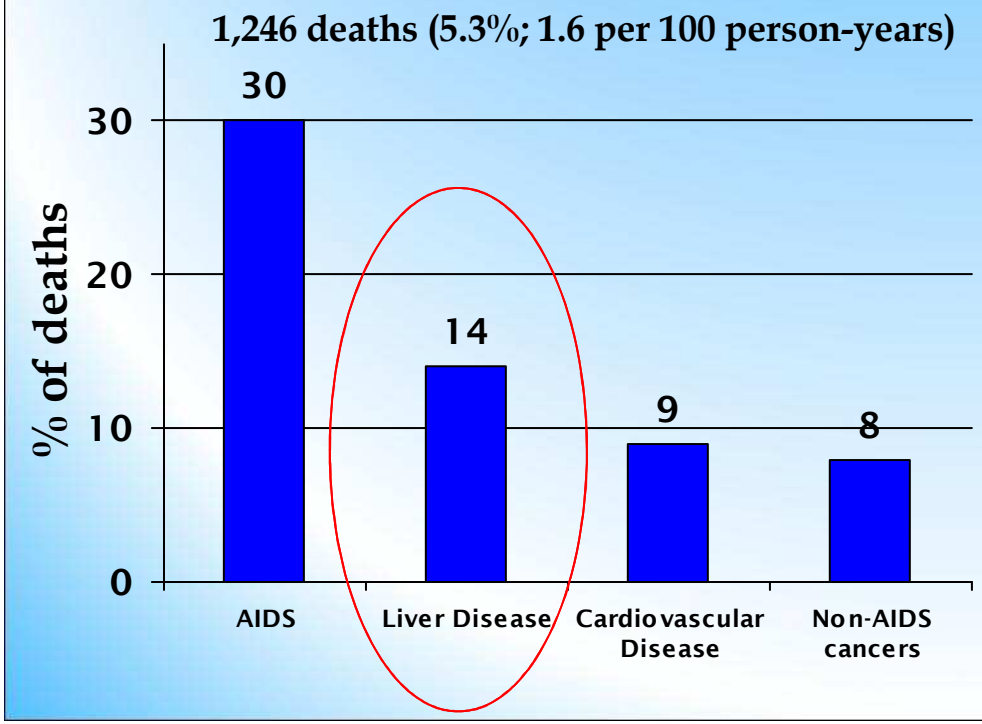

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Liver disease remains 2nd leading cause of death in later HAART era in HIV-infected persons in D:A:D

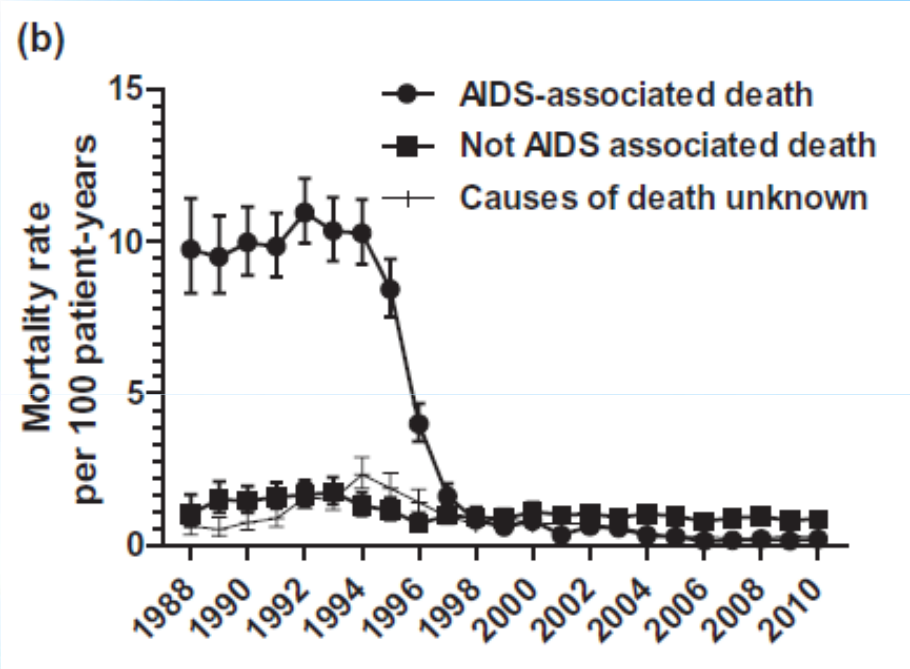
- 33,308 participants from 1999-2008
  - 15.3% with HCV (Ab or RNA+)
  - 11.5% HBV (prior/active)
- 2482 deaths
  - 29.9% AIDS-related
  - **13.7% liver-related**
  - 11.6% CVD-related
- **Liver-related deaths declined over time**
  - **2.67/1000 PYs (99-00) to 1.45/1000 PYs (07-08)**
- Rates highest in CD4<100 cells/mm^3

Factor	Adjusted RR	95% CI
Age, per 5 years older	1.16	1.09-1.24
IDU (MSM reference)	5.02	3.56-7.08
HTN	2.34	1.83-2.99
Diabetes	2.37	1.68-3.35
HCV	1.67	1.21-2.31
HBV	2.37	1.74-3.22
CD4 count per 50 cell/uL increase	0.82	0.79-0.85
HIV RNA >5 log cp/ml	1.68	1.01-2.80

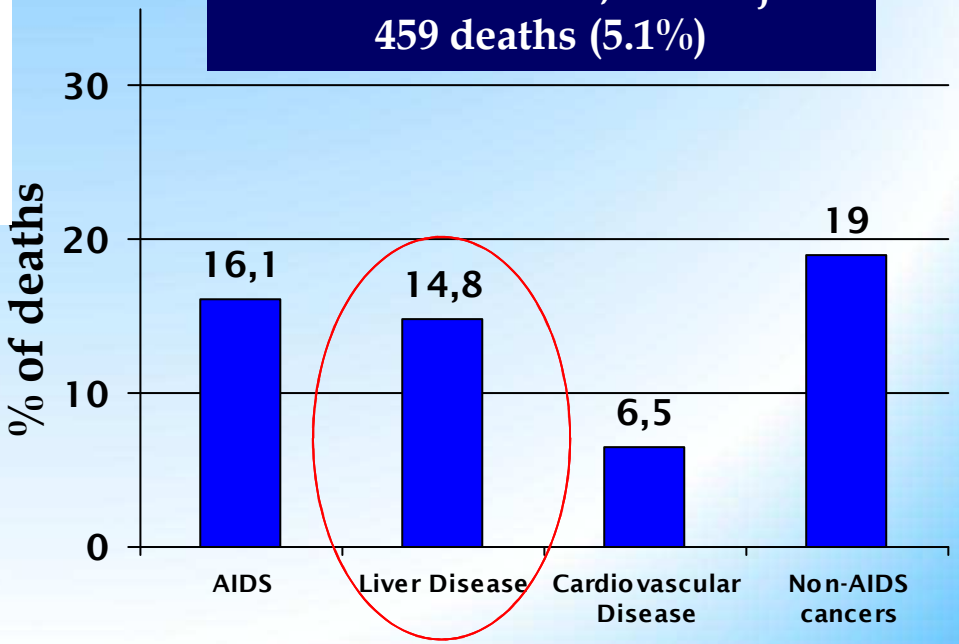
D:A:D study, *AIDS* Jun 2010 24 (10)

Decreasing mortality and changing patterns of causes of death in the Swiss HIV Cohort Study*

R Weber,[1†] M Ruppik,[1†] M Rickenbach,[2] A Spoerri,[3] H Furrer,[4] M Battegay,[5] M Cavassini,[6] A Calmy,[7] E Bernasconi,[8] P Schmid,[9] M Flepp,[10] J Kowalska,[11] B Ledergerber[1] and the Swiss HIV Cohort Study (SHCS)[‡]



From 2005 to 2009 9,053 subjects: 459 deaths (5.1%)



HIV Medicine, 2013

Coinfezione HIV-HCV

-Terapia anti-HCV-

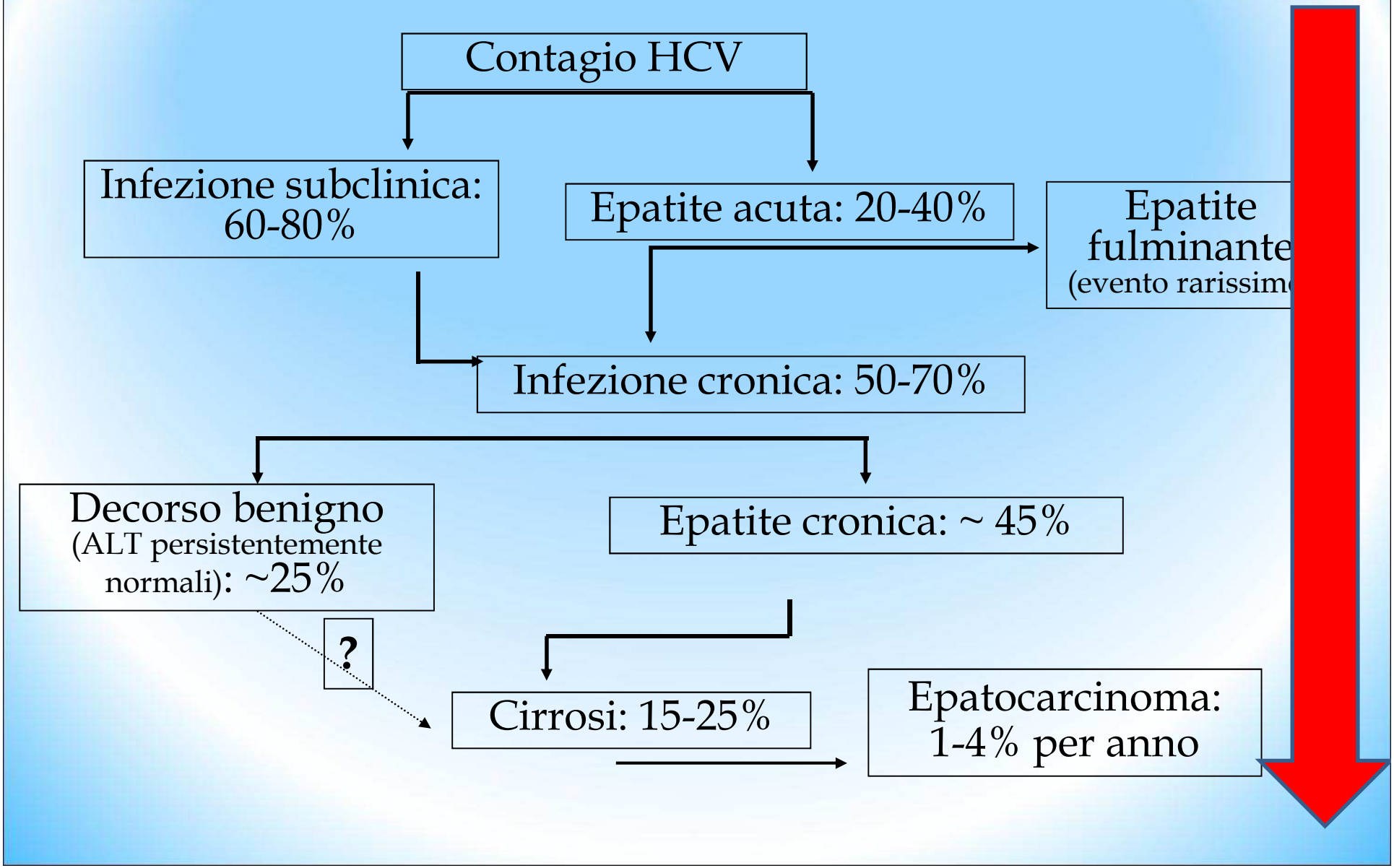
- Perché?
- Come?
  - Duplice terapia (Peg-IFN+Riba)
  - Triplice terapia (Peg-IFN+Riba+DAA)
- Problematiche
  - Interazioni
  - Effetti collaterali
  - Resistenze

Coinfezione HIV-HCV

-Terapia anti-HCV-

- **Perché?**
  - Impatto dell'epatopatia cronica nella mortalità dei soggetti HIV positivi
  - **Progressione rapida della fibrosi**
- Come?
  - Duplice terapia (Peg-IFN+Riba)
  - Triplice terapia (Peg-IFN+Riba+DAA)
  - Regimi IFN-free

Storia naturale dell'infezione da HCV nei soggetti HIV

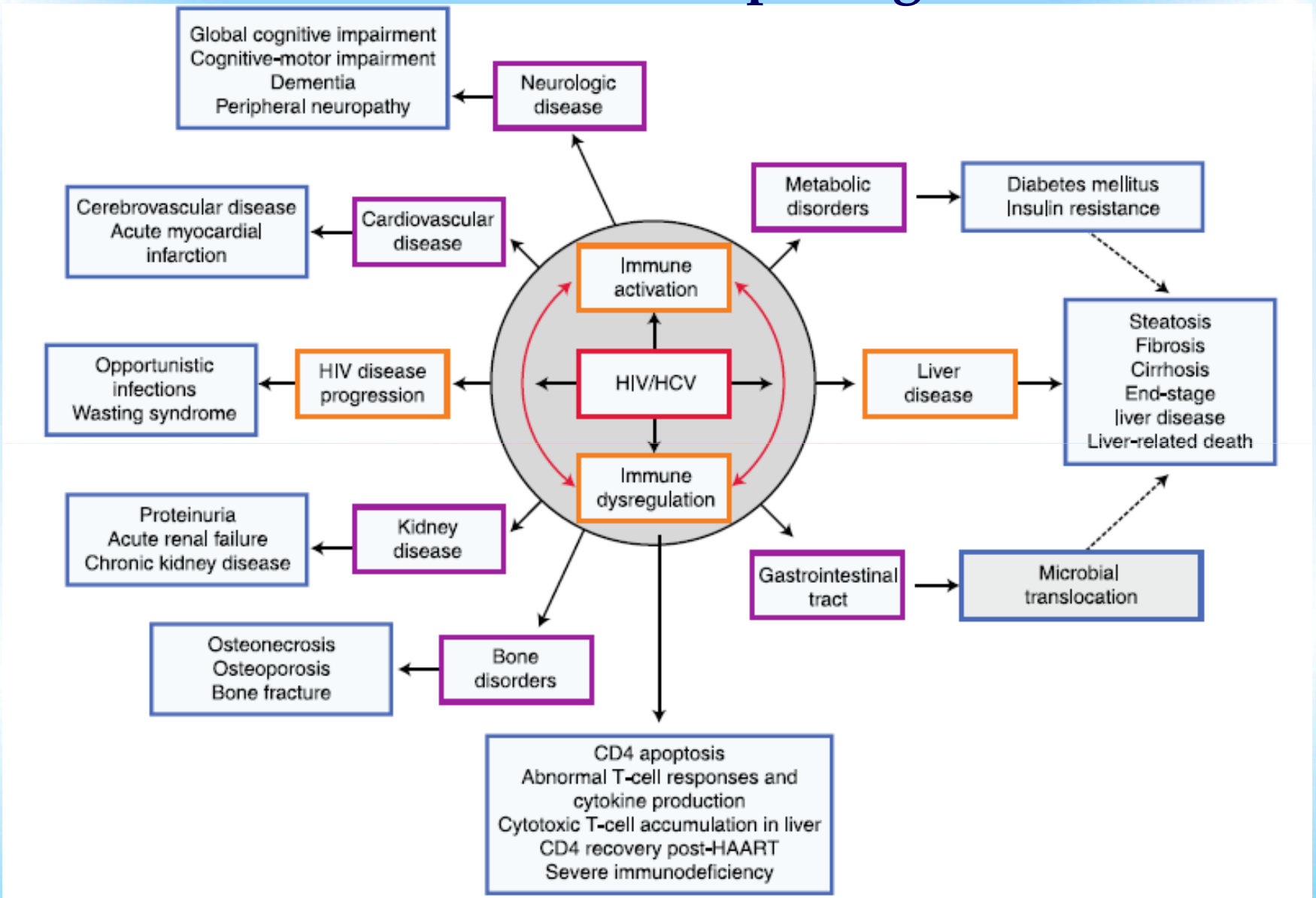


Coinfezione HIV-HCV

- evoluzione della fibrosi -

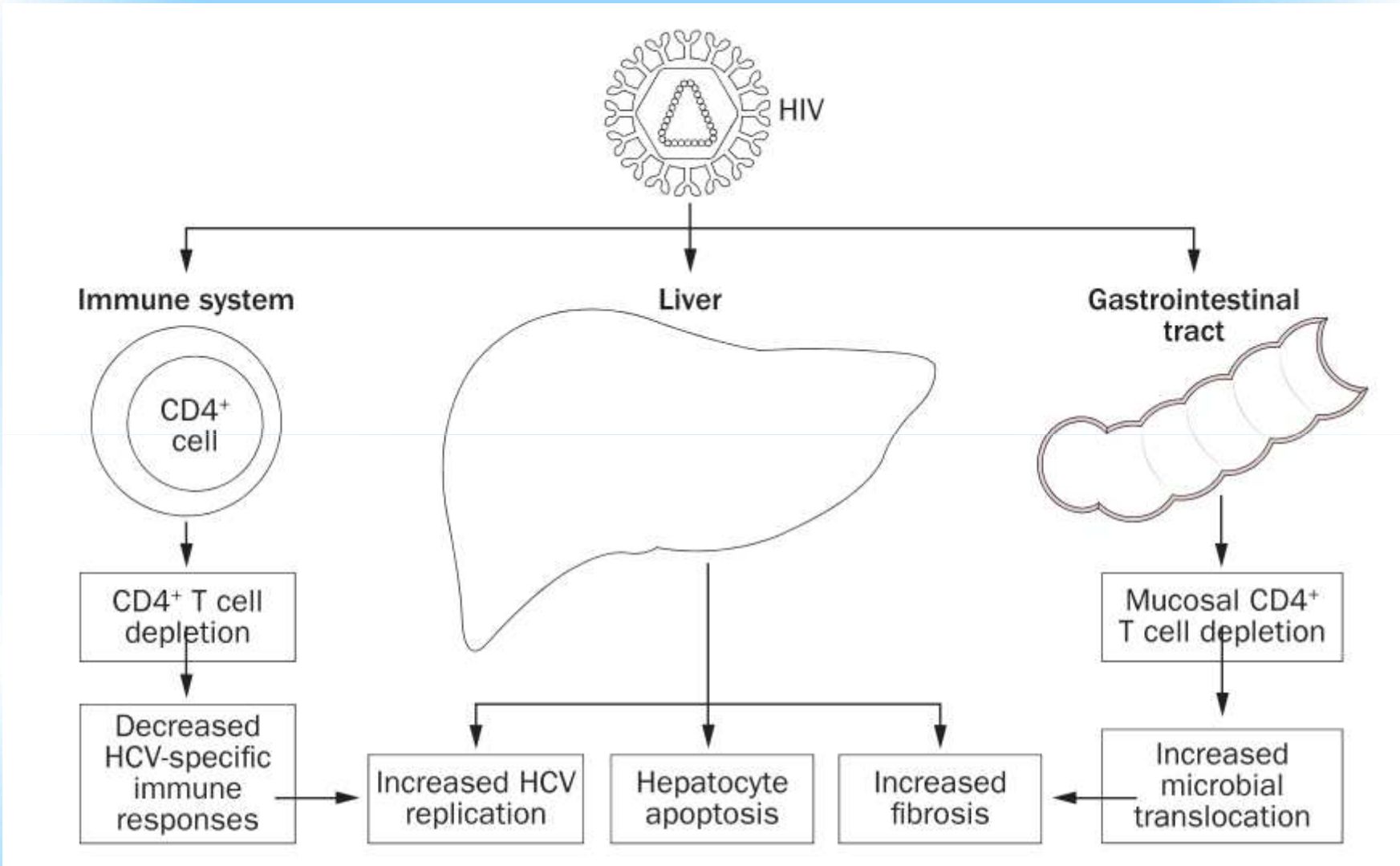
- **Evoluzione della fibrosi**
  - **Basi molecolari**
  - **evidenze cliniche**
- **Conseguenze:**
  - **sviluppo di cirrosi**
  - **sviluppo di HCC**
  - **scompenso epatico**
  - **aumentata mortalità**

HIV-HCV coinfection: pathogenesis



Curr HIV/AIDS Rep. 2011; 8: 12–22.

HIV-HCV coinfection: liver diseases progression



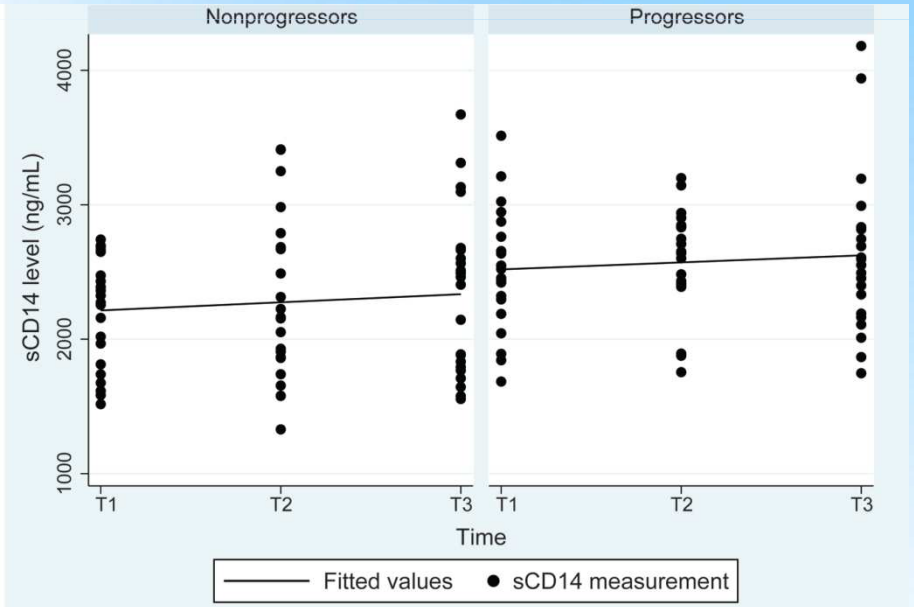
Chen YC, Nat Rev Gastroenterol Hepatol 2014

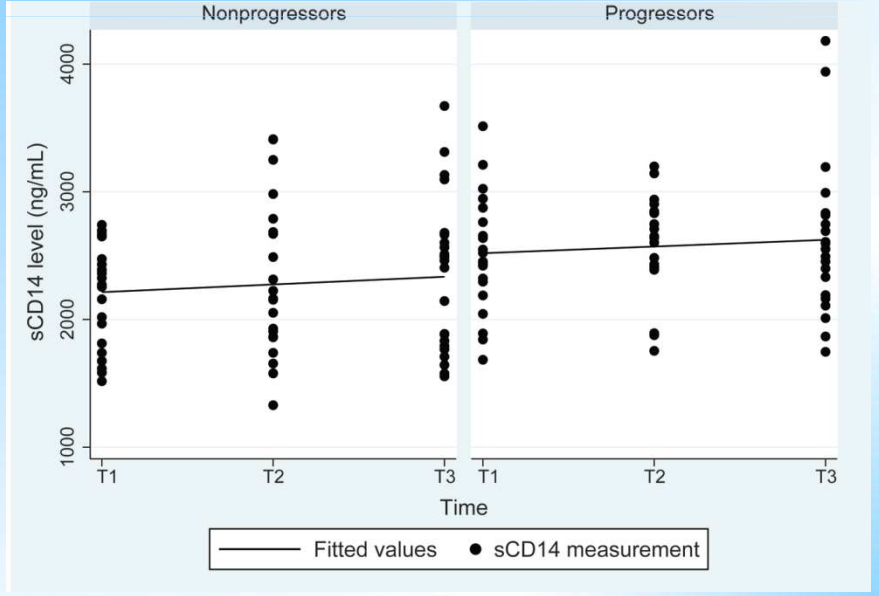
Microbial Translocation and Liver Disease Progression in Women Coinfected With HIV and Hepatitis C Virus

Audrey L. French,[1,2] Charlesnika T. Evans,[4,5] Denis M. Agniel,[1] Mardge H. Cohen,[1,2] Marion Peters,[6] Alan L. Landay,[3] and Seema N. Desai[3]

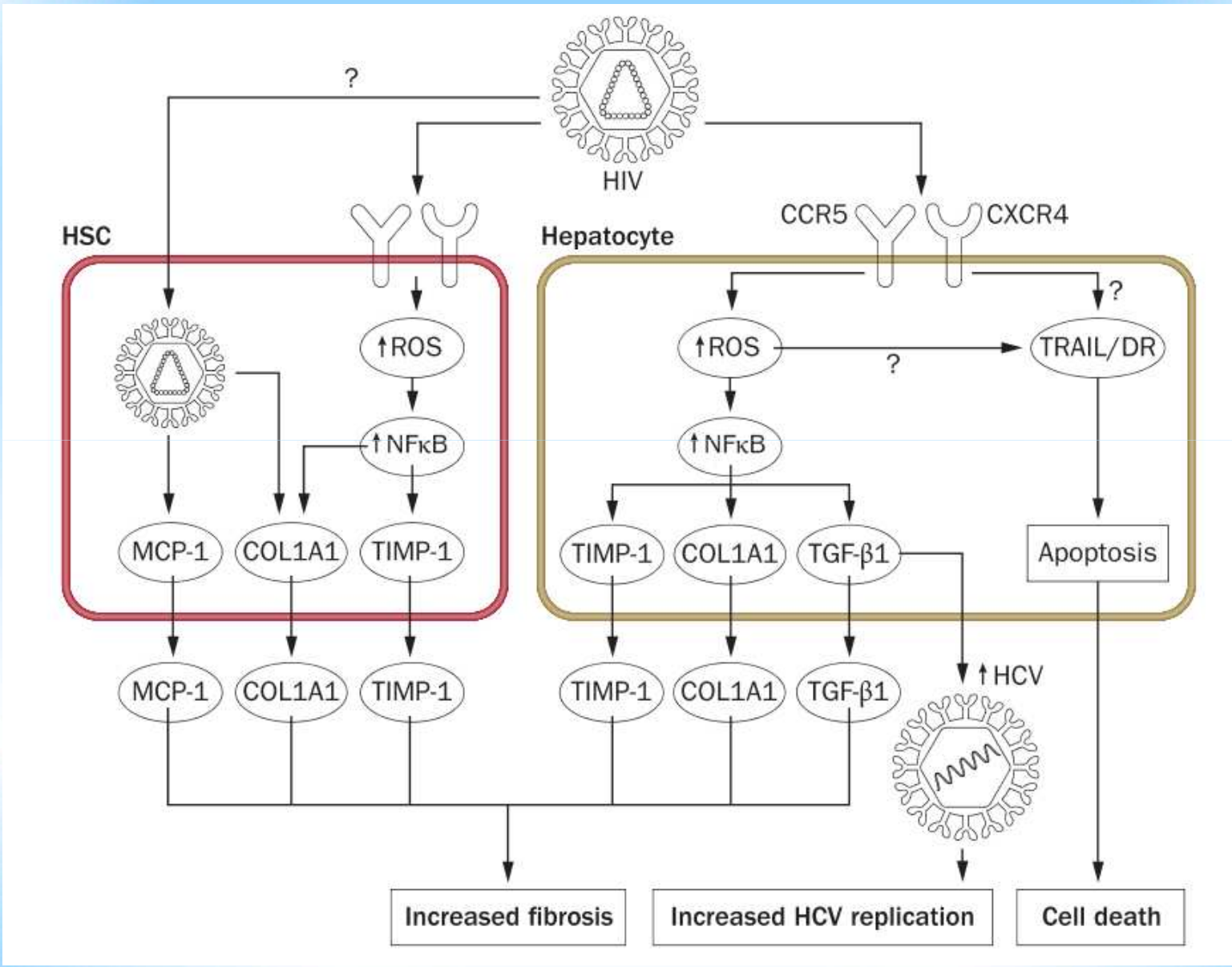
J Infect Dis 2013

Serial plasma lipopolysaccharide (LPS), endotoxin core antibody, intestinal fatty acid–binding protein (I-FABP), soluble CD14 (sCD14), interleukin 6 (IL-6), interleukin 10, and tumor necrosis factor α (TNF-α) levels over a 5-year period in 44 HIV/HCV-coinfected women, 21 of whom experienced liver disease progression and 23 were nonprogressors.





HIV-HCV coinfection: liver diseases progression

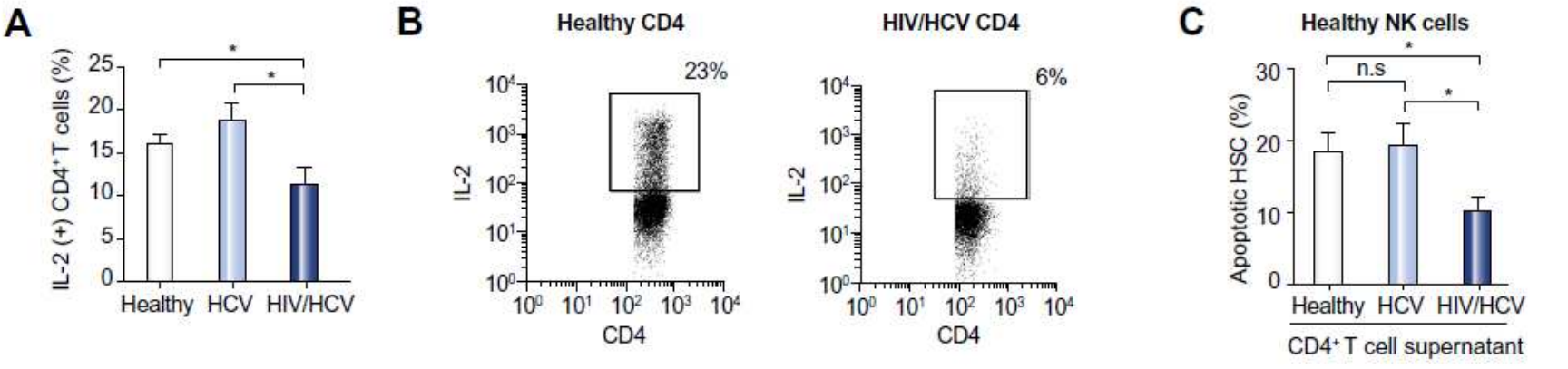


Chen YC, Nat Rev Gastroenterol Hepatol 2014

Impaired CD4$^+$ T cell stimulation of NK cell anti-fibrotic activity may contribute to accelerated liver fibrosis progression in HIV/HCV patients

Andreas Glässner, Marianne Eisenhardt, Pavlos Kokordelis, Benjamin Krämer, Franziska Wolter, Hans Dieter Nischalke, Christoph Boesecke, Tilman Sauerbruch, Jürgen K. Rockstroh, Ulrich Spengler, Jacob Nattermann*

NK cells from HCV (n = 35), HIV/HCV (n = 28), HIV (n = 8) patients and healthy controls (n = 30).
NK cells were cultured in the presence or absence of supernatants from CD3/CD28-stimulated CD4+ cells.
Then, NK cells were co-incubated with activated HSC and studied for degranulation, IFN-γ secretion, and induction of HSC apoptosis.



J Hepatol 2013

Coinfezione HIV-HCV

- evoluzione della fibrosi -

- **Evoluzione della fibrosi**
  - **Basi molecolari**
  - **evidenze cliniche**
- **Conseguenze:**
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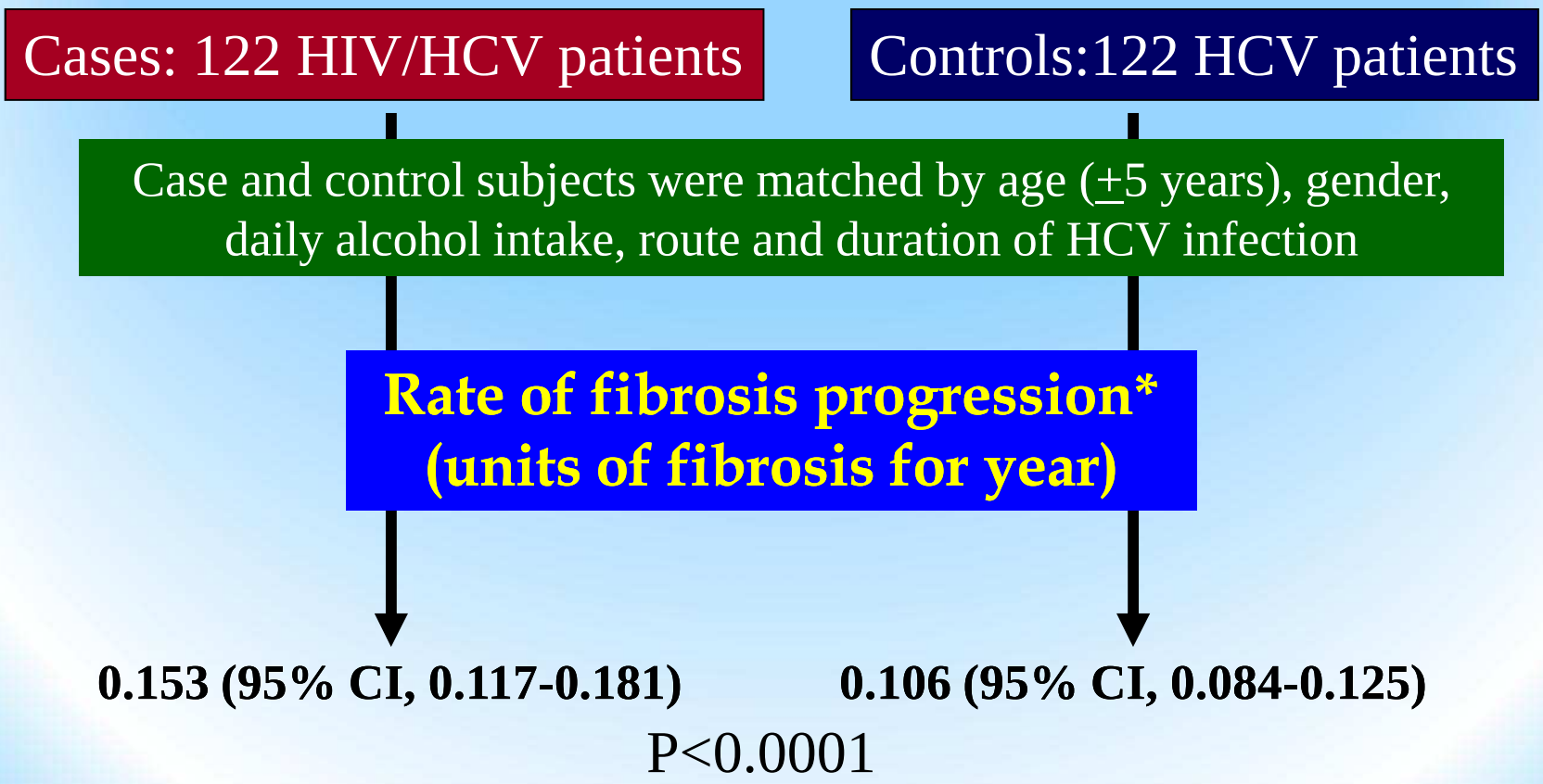
  - **sviluppo di HCC**
  - **scompenso epatico**
  - **aumentata mortalità**

Fibrosis progression and HIV coinfection



*** Ratio between fibrosis stage (METAVIR scoring system) and the HCV duration**

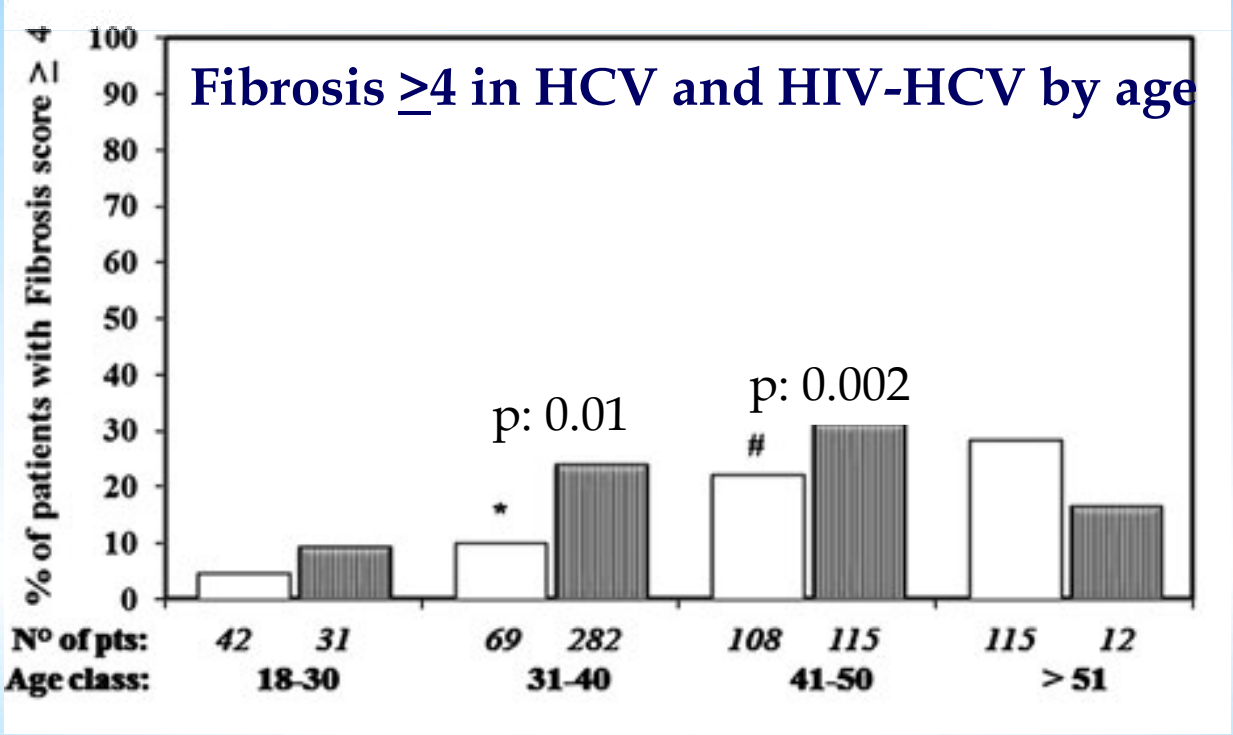
Benhamou et al. Hepatology, 1999

Factors influencing liver fibrosis and necroinflammation in HIV/HCV coinfection and HCV monoinfection

C. Sagnelli · C. Uberti-Foppa · G. Pasquale · S. De Pascalis · N. Coppola · L. Albarello · C. Doglioni · A. Lazzarin · E. Sagnelli

Infection 2013

Liver biopsies (LBs) from 440 consecutive HIV/HCV-coinfected patients (Group HIV/HCV) and 374 consecutive HCV-monoinfected patients (Group HCV) were evaluated for necroinflammation and fibrosis (Ishak)



Impact of HIV on HCV Fibrosis Progression Rates

Rapid fibrosis progression among 174 HIV/HCV-co-infected non cirrhotic adults between 2 liver biopsies (median time interval 2.9 years)

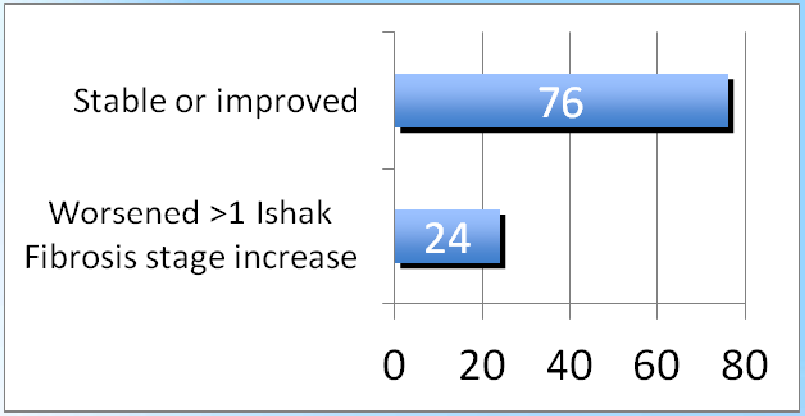


Table 2. Ishak fibrosis stage at first and second liver biopsy among 174 HIV/hepatitis C virus-co-infected adults.[a]

First biopsy fibrosis stage	Second biopsy fibrosis stage							
	0	1	2	3	4	5	6	
0	45	20	12	2	2	3	1	85
1	8	20	12	7	2	0	2	51
2	1	2	11	2	0	0	1	17
3	0	0	1	8	3	5	2	19
4	0	0	0	0	0	0	2	2
	54	42	36	19	7	8	8	174

[a]Shaded regions represents subjects in whom the fibrosis stage observed at second biopsy was at least two Ishak units greater than observed at first biopsy (two-stage progression).

Sulkowski M AIDS 2007; 21: 2209-2216

Anti-hepatitis C virus treatment may prevent the progression of liver fibrosis in non-responder human immunodeficiency virus/hepatitis C virus coinfected patients

Caterina Sagnelli[a,b], Caterina Uberti-Foppa[a], Laura Galli[a], Giuseppe Pasquale[c], Nicola Coppola[c], Luca Albarello[d], Carlo Doglioni[d], Adriano Lazzarin[a], Evangelista Sagnelli[c,]*

49 patients with two sequential liver biopsies:
-18 non-responders to IFN+ Ribavirine treatment (Group HCV Rx)
- 31 patients who remained untreated for HCVdisease (Group HCVuntreated)

Table 3 – Histological changes between the 1st and 2nd liver biopsy (LB) in Group HCV Rx and Group HCV untreated, expressed as Improvement Progression Unit (IPU) or Deterioration Progression Unit (DPU) for liver fibrosis, necro-inflammation (HAI) and steatosis.

	Fibrosis		HAI		Steatosis	
	Group HCV Rx 18 cases *n* (%)	Group HCV untreated 31 cases *n* (%)	Group HCV Rx 18 cases *n* (%)	Group HCV untreated 31 cases *n* (%)	Group HCV Rx 18 cases *n* (%)	Group HCV untreated 31 cases *n* (%)
Marked improvement (>6 IPU)	–	–	2 (11.2)	4 (12.9)	–	–
Moderate improvement (2–6 IPU)	–	–	1 (5.6)	5 (16.2)	2 (11.2)	2 (6.4)
Unchanged (<2 IPU to <2 DPU)	16 (88.9)	24 (77.4)	12 (66.7)	14 (45.2)	14 (77.8)	28 (90.3)
Moderate deterioration (2–6 DPU)	2 (11.2)	2 (6.5)	3 (16.7)	7 (22.5)	2 (11.2)	1 (3.3)
Marked deterioration (>6 DPU)	–	5 (16.1)	–	1 (3.2)	–	–

Br J Infect Dis 2014

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  - **sviluppo di HCC**
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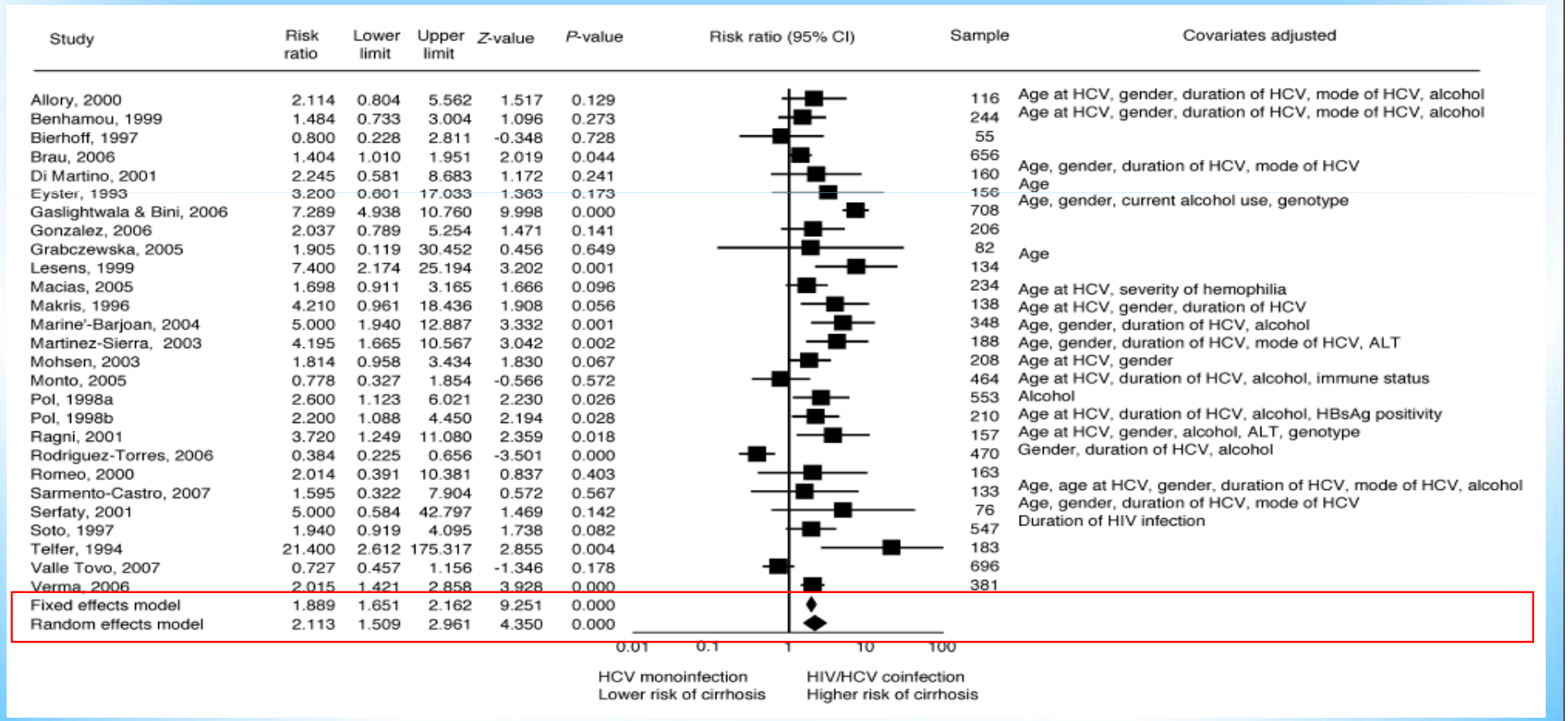
  - **aumentata mortalità**

Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis

AIDS 2008, 22:1979–1991

Hla-Hla Thein[a,b], Qilong Yi[c], Gregory J. Dore[d] and Murray D. Krahn[a,b,e]

Metanalisi includente 27 studi pubblicati entro settembre 2007 che hanno confrontato il rischio di evoluzione in cirrosi tra soggetti con monoinfezione da HCV e coinfetti.



Study	Risk ratio	Lower limit	Upper limit	*Z*-value	*P*-value	Sample	Covariates adjusted
Allory, 2000	2.114	0.804	5.562	1.517	0.129	116	Age at HCV, gender, duration of HCV, mode of HCV, alcohol
Benhamou, 1999	1.484	0.733	3.004	1.096	0.273	244	Age at HCV, gender, duration of HCV, mode of HCV, alcohol
Bierhoff, 1997	0.800	0.228	2.811	-0.348	0.728	55	
Brau, 2006	1.404	1.010	1.951	2.019	0.044	656	
Di Martino, 2001	2.245	0.581	8.683	1.172	0.241	160	Age, gender, duration of HCV, mode of HCV
Eyster, 1993	3.200	0.601	17.033	1.363	0.173	156	Age
Gaslightwala & Bini, 2006	7.289	4.938	10.760	9.998	0.000	708	Age, gender, current alcohol use, genotype
Gonzalez, 2006	2.037	0.789	5.254	1.471	0.141	206	
Grabczewska, 2005	1.905	0.119	30.452	0.456	0.649	82	Age
Lesens, 1999	7.400	2.174	25.194	3.202	0.001	134	
Macias, 2005	1.698	0.911	3.165	1.666	0.096	234	Age at HCV, severity of hemophilia
Makris, 1996	4.210	0.961	18.436	1.908	0.056	138	Age at HCV, gender, duration of HCV
Marine'-Barjoan, 2004	5.000	1.940	12.887	3.332	0.001	348	Age, gender, duration of HCV, alcohol
Martinez-Sierra, 2003	4.195	1.665	10.567	3.042	0.002	188	Age, gender, duration of HCV, mode of HCV, ALT
Mohsen, 2003	1.814	0.958	3.434	1.830	0.067	208	Age at HCV, gender
Monto, 2005	0.778	0.327	1.854	-0.566	0.572	464	Age at HCV, duration of HCV, alcohol, immune status
Pol, 1998a	2.600	1.123	6.021	2.230	0.026	553	Alcohol
Pol, 1998b	2.200	1.088	4.450	2.194	0.028	210	Age at HCV, duration of HCV, alcohol, HBsAg positivity
Ragni, 2001	3.720	1.249	11.080	2.359	0.018	157	Age at HCV, gender, alcohol, ALT, genotype
Rodriguez-Torres, 2006	0.384	0.225	0.656	-3.501	0.000	470	Gender, duration of HCV, alcohol
Romeo, 2000	2.014	0.391	10.381	0.837	0.403	163	
Sarmento-Castro, 2007	1.595	0.322	7.904	0.572	0.567	133	Age, age at HCV, gender, duration of HCV, mode of HCV, alcohol
Serfaty, 2001	5.000	0.584	42.797	1.469	0.142	76	Age, gender, duration of HCV, mode of HCV
Soto, 1997	1.940	0.919	4.095	1.738	0.082	547	Duration of HIV infection
Telfer, 1994	21.400	2.612	175.317	2.855	0.004	183	
Valle Tovo, 2007	0.727	0.457	1.156	-1.346	0.178	696	
Verma, 2006	2.015	1.421	2.858	3.928	0.000	381	
Fixed effects model	1.889	1.651	2.162	9.251	0.000		
Random effects model	2.113	1.509	2.961	4.350	0.000		

Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome

Massimo Puoti, Raffaele Bruno[a], Vincent Soriano[b], Francesco Donato[c], Giovanni Battista Gaeta[d], Gian Paolo Quinzan[e], Davide Precone[f], Umberto Gelatti[c], Victor Asensi[f] and Emanuela Vaccher[g] for the HIV

AIDS 2004

All 41 HIV-infected subjects with a diagnosis of HCC included in three cancer registry databases (as cases) and 1,085 HCC cases that occurred in the province of Brescia, North Italy, in the period 1995–1998 and all cases reported at the CLIP were enrolled as controls

Table 3. Multivariate analysis of clinical, biochemical and pathologic variables significantly associated with survival in 425 patients with hepatocellular carcinoma (41 HIV-infected patients and 384 HIV-uninfected patients from the Brescia HCC Study Group database).

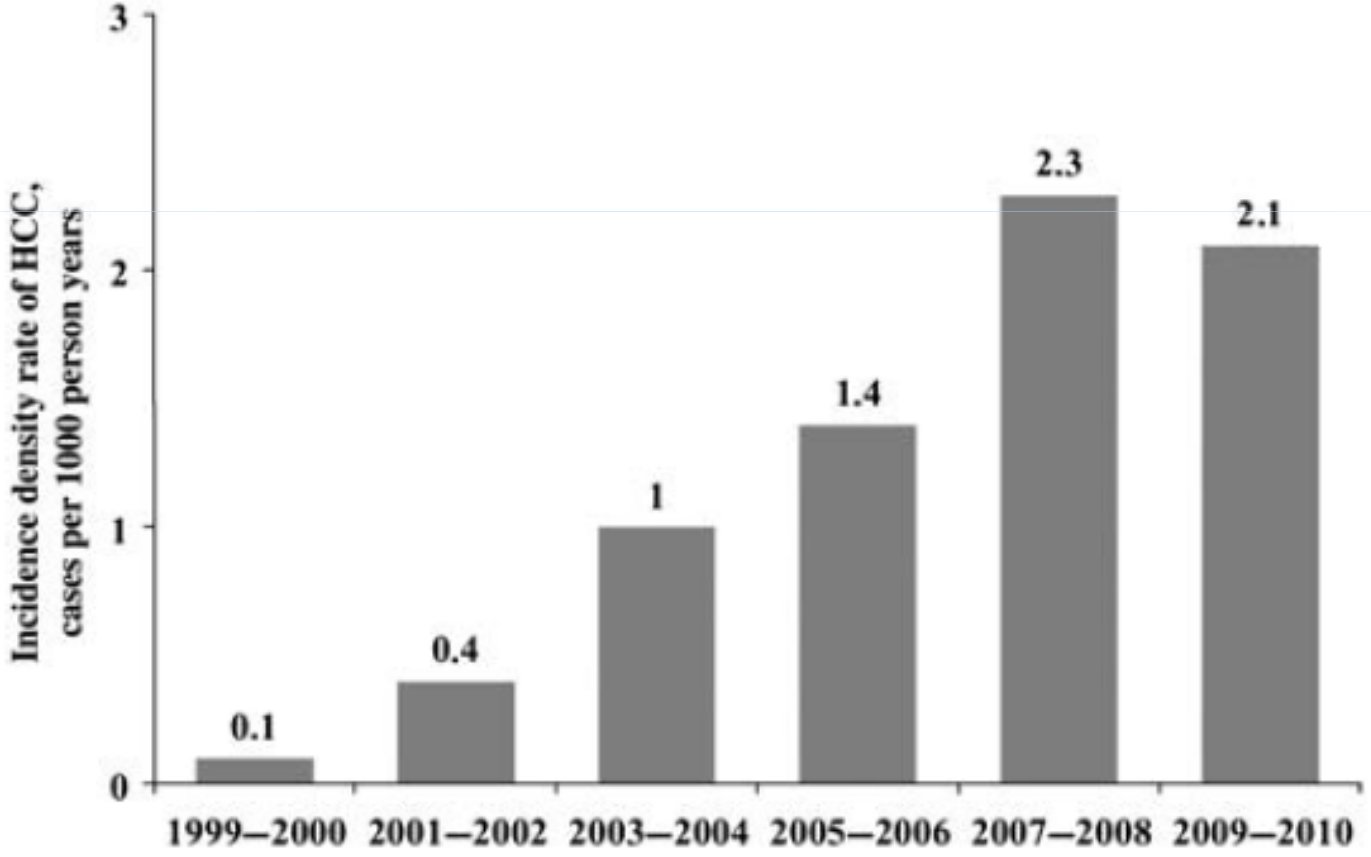
Variables and categories	Hazard ratio	95% confidence interval	*P*
Liver function status			
Child–Pugh class A	1.0		
Child–Pugh class B	1.68	1.25–2.26	< 0.001
Child–Pugh class C	2.09	1.49–2.94	< 0.001
Portal Vein invasion			
No	1.0		0.05
Yes	1.43	1.01–2.04	
Lesion morphology [diameter (cm)]			
< 5 cm	1.0		0.015
> 5 cm	1.49	1.08–2.07	
Serum alfafetoprotein (ng/dL)			
< 400	1.0		0.012
⩾ 400	1.49	1.01–2.04	
Treatment:			
Any type	1.0		< 0.001
None or medical treatment	3.27	1.37–4.51	
Anti HIV reactivity			
Negative	1.0		0.015
Positive	1.63	1.10–2.40	

Increasing Incidence of Hepatocellular Carcinoma in HIV-Infected Patients in Spain

CID 2013

Nicolás Merchante,[1,a] Esperanza Merino,[3] José López-Aldeguer,[7] Francisco Jover,[4] Marcial Delgado-Fernández,[10,a] Maria José Galindo,[8] Enrique Ortega,[9] Antonio Rivero,[12,a] Carlos Mínguez,[13] Alberto Romero-Palacios,[14,a] Sergio Padilla,[5] Manuel Márquez-Solero,[11,a] Concepción Amador,[6] Maria José Ríos-Villegas,[2,a] Francisco Téllez,[15,a] Joaquín Portilla,[3] and Juan A. Pineda[1,a]

All 82 HIV-infected patients diagnosed of HCC in 18 hospitals in Spain before 31 December 2010 were included.



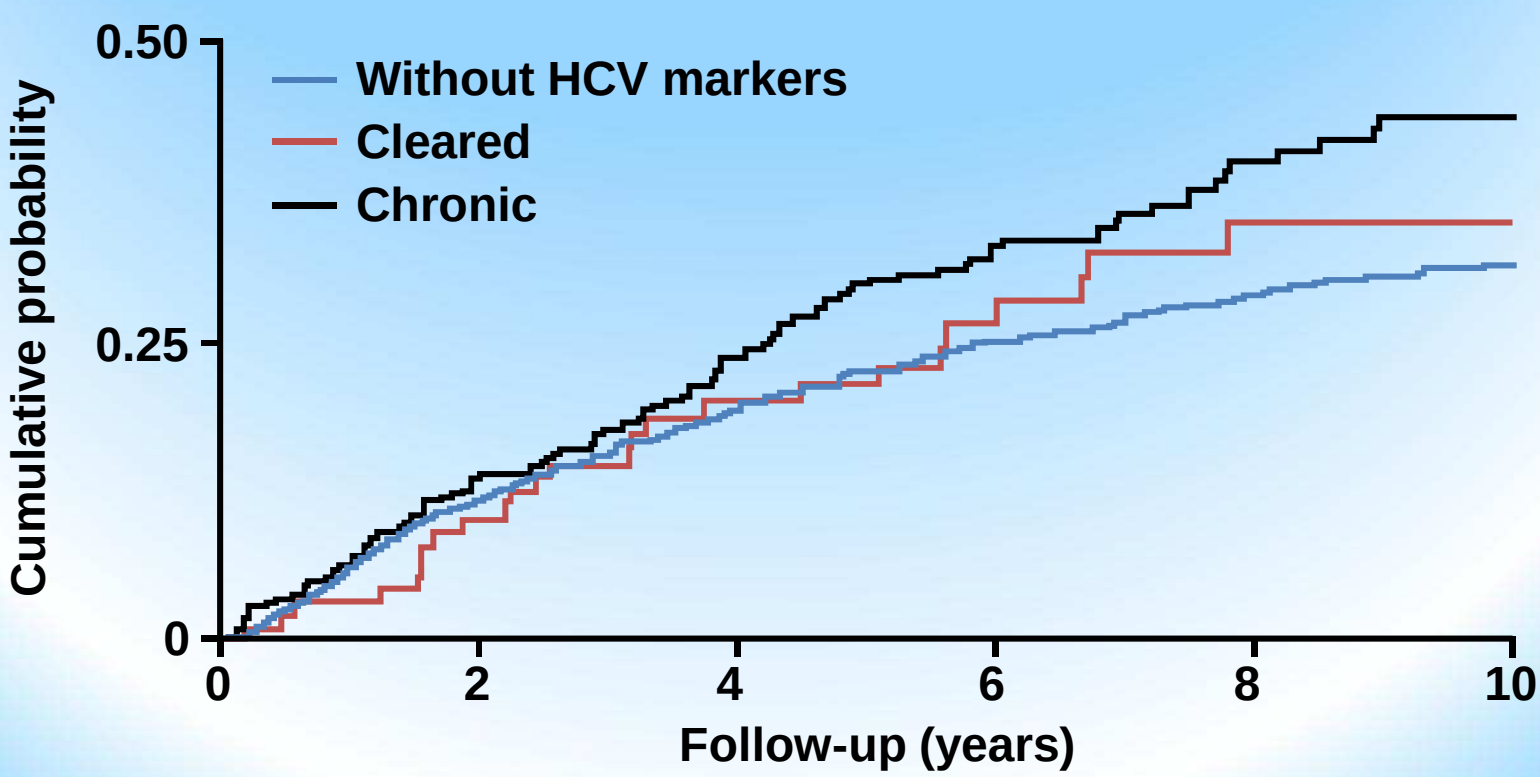
Coinfezione HIV-HCV

- evoluzione della fibrosi -

- **Evoluzione della fibrosi**
  - **Basi molecolari**
  - **evidenze cliniche**
- **Conseguenze:**
  - **sviluppo di cirrosi**
  - **sviluppo di HCC**
  - **scompenso epatico**
  - **aumentata mortalità**

Mortality in HCV-infected patients with HIV

Chronic HCV infection is independently associated with a 50% increase in mortality among patients with a diagnosis of AIDS

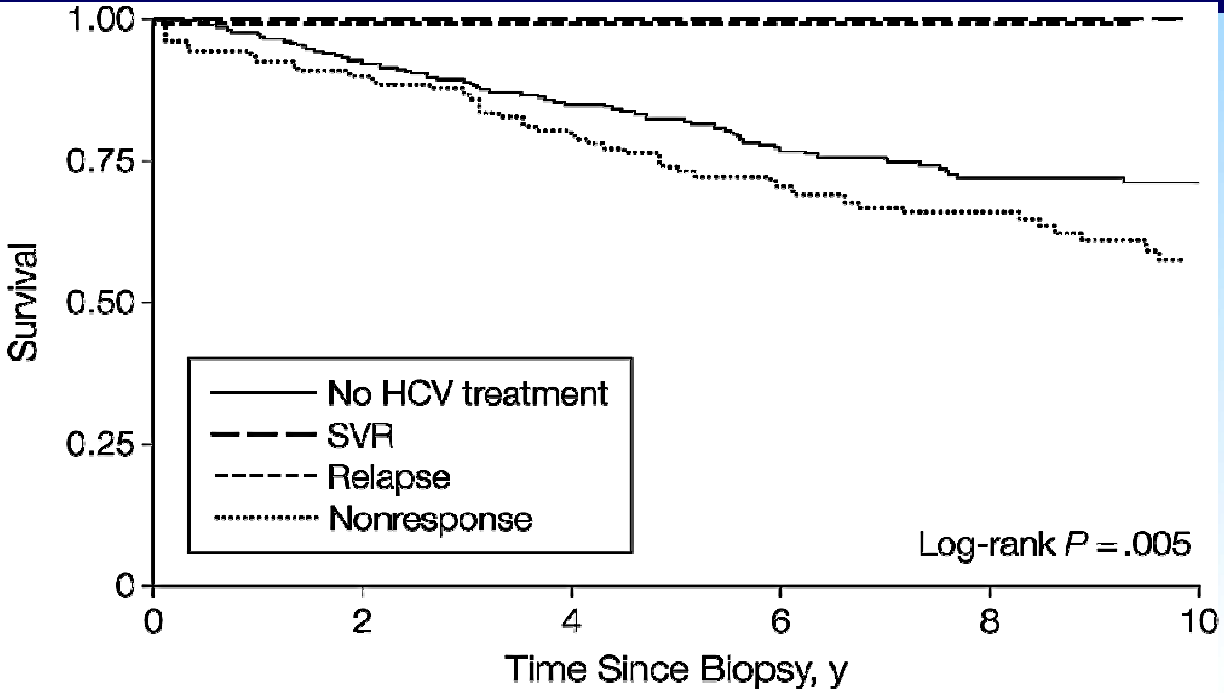


Branch A, et al. Clin Infect Dis 2012;55:137–44

Relationship of Liver Disease Stage and Antiviral Therapy With Liver-Related Events and Death in Adults Coinfected With HIV/HCV

Limketkai BN et al. JAMA 2012;308:370-8

Studio di coorte che ha arruolato 638 pazienti coinfetti senza evidenza clinica di cirrosi. I pz sono stati sottoposti a biopsia epatica e monitorati per un periodo mediano di 5.82 anni.



No. at risk						
No HCV treatment	610	397	302	196	118	45
SVR	0	19	24	15	9	7
Relapse	2	15	11	6	5	2
Nonresponse	17	109	100	81	59	26

Sustained Virological Response to Interferon Plus Ribavirin Reduces Liver-Related Complications and Mortality in Patients Coinfected with Human Immunodeficiency Virus and Hepatitis C Virus

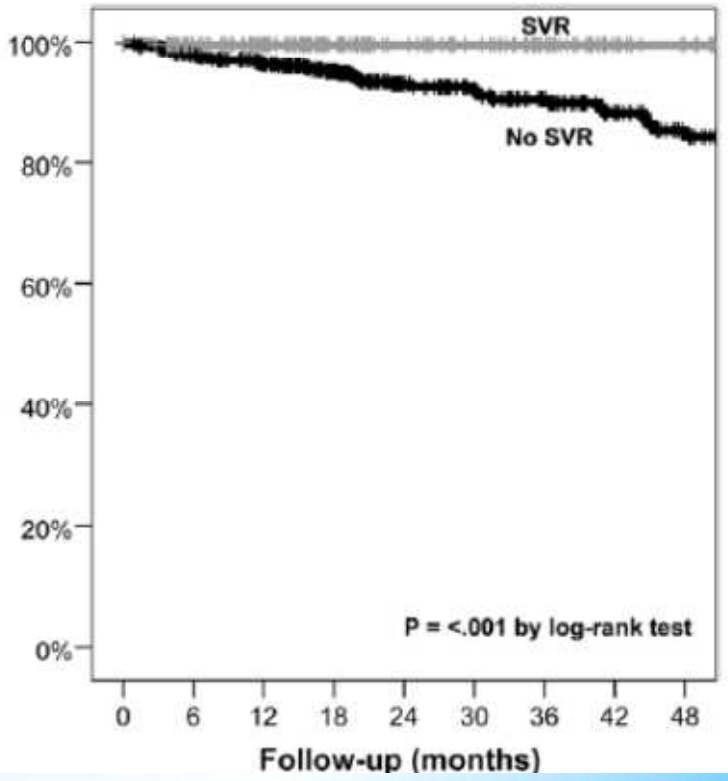
Juan Berenguer,[1]* Julio Álvarez-Pellicer,[2] Pilar Miralles Martín,[1] José López-Aldeguer,[3] Miguel Angel Von-Wichmann,[4] Carmen Quereda,[5] Josep Mallolas,[6] José Sanz,[7] Cristina Tural,[8] José María Bellón,[1] Juan González-García,[2]* and The GESIDA3603/5607 Study Group

HEPATOLOGY 2009;50:407-413

Studio di coorte che ha arruolato 711 pazienti HIV/HCV+ che hanno iniziato IFN e RBV tra il 2000 ed il 2005 in 11 unità spagnole e li ha monitorati per un periodo medio di 20.8 mesi.

Occurrence of liver-related events

Event	Non-SVR (N = 493)	SVR (N = 218)	P
Follow-up-months, median (IQR)	22.1 (12.7-39.1)	18.7 (11.3-36.9)	0.071
Lost to follow-up-n (%)	25 (5)	13 (6)	0.955
Deaths-n (%)	34 (6.9)	2 (0.9)*	0.001
Liver-related-n (%)	18 (3.7)	1 (0.5)*	0.029
AIDS-related-n (%)	2 (0.4)	0 (0)	0.826
Other causes-n (%)	14 (2.8)	1 (0.5)	0.079
Liver decompensation-n (%)†	45 (9.1)	1 (0.5)*	<0.001
Hepatocarcinoma-n (%)	9 (1.8)	0 (0)	0.100
Liver transplantation-n (%)	11 (2.2)	0 (0)	0.058

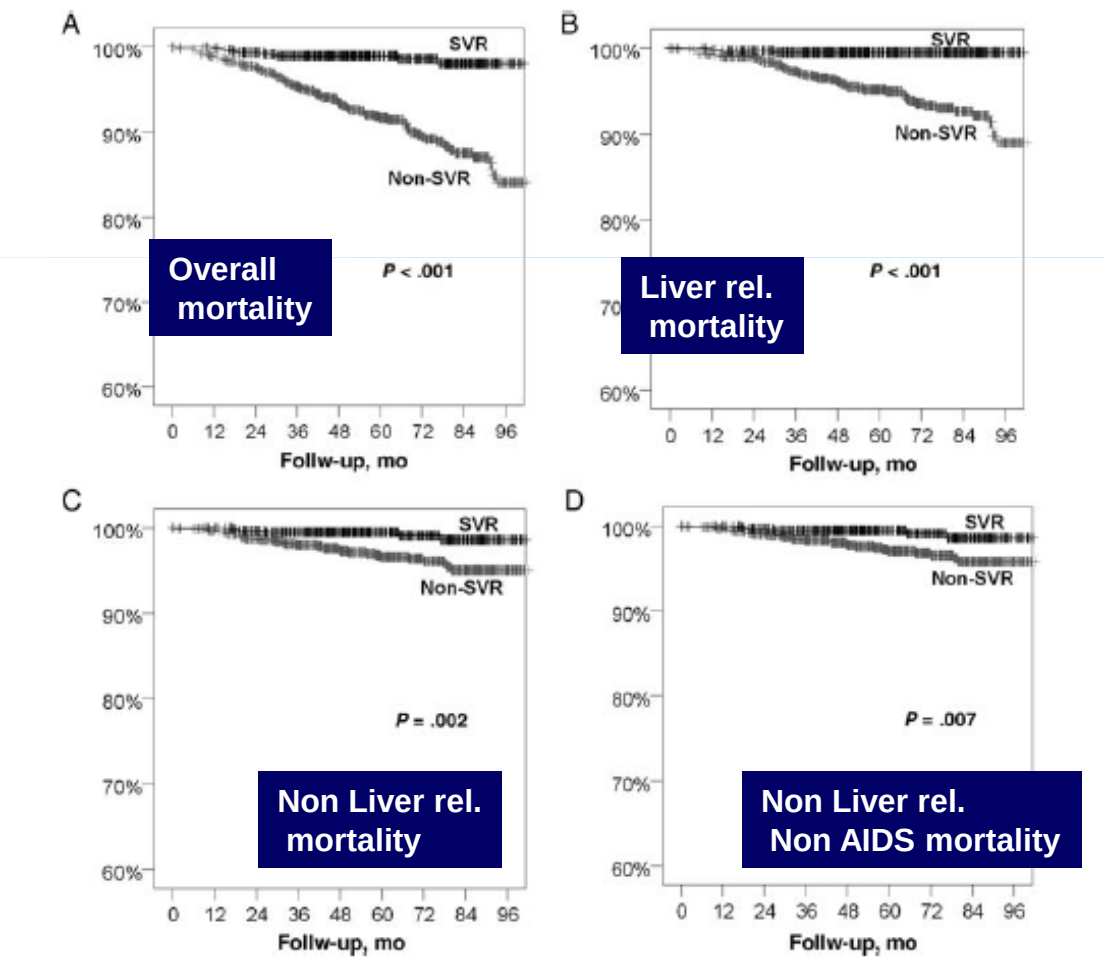


Sustained Virological Response to Interferon Plus Ribavirin Reduces Non–Liver-Related Mortality in Patients Coinfected With HIV and Hepatitis C Virus

Berenguer J, et al

Clinical Infectious Diseases 2012;55(5):728–36

Studio di coorte che ha arruolato 1599 pazienti HIV/HCV+ trattati con IFN e RBV tra il 2000 ed il 2008 in 19 unità spagnole e li ha monitorati per 5 anni (mediana)



Coinfezione HIV-HCV

-Terapia anti-HCV-

- **Perché?**
  - **L'efficacia della ART riduce la mortalità AIDS correlata e magnifica la mortalità non AIDS correlata**
  - **La progressione di HCV nei soggetti anti- HIV è rapida**
  - **LA SVR migliora la sopravvivenza**
- Come?
  - Duplice terapia (Peg-IFN+Riba)
  - Triplice terapia (Peg-IFN+Riba+DAA)
  - Regimi IFN-free

Coinfezione HIV-HCV

-Terapia anti-HCV-

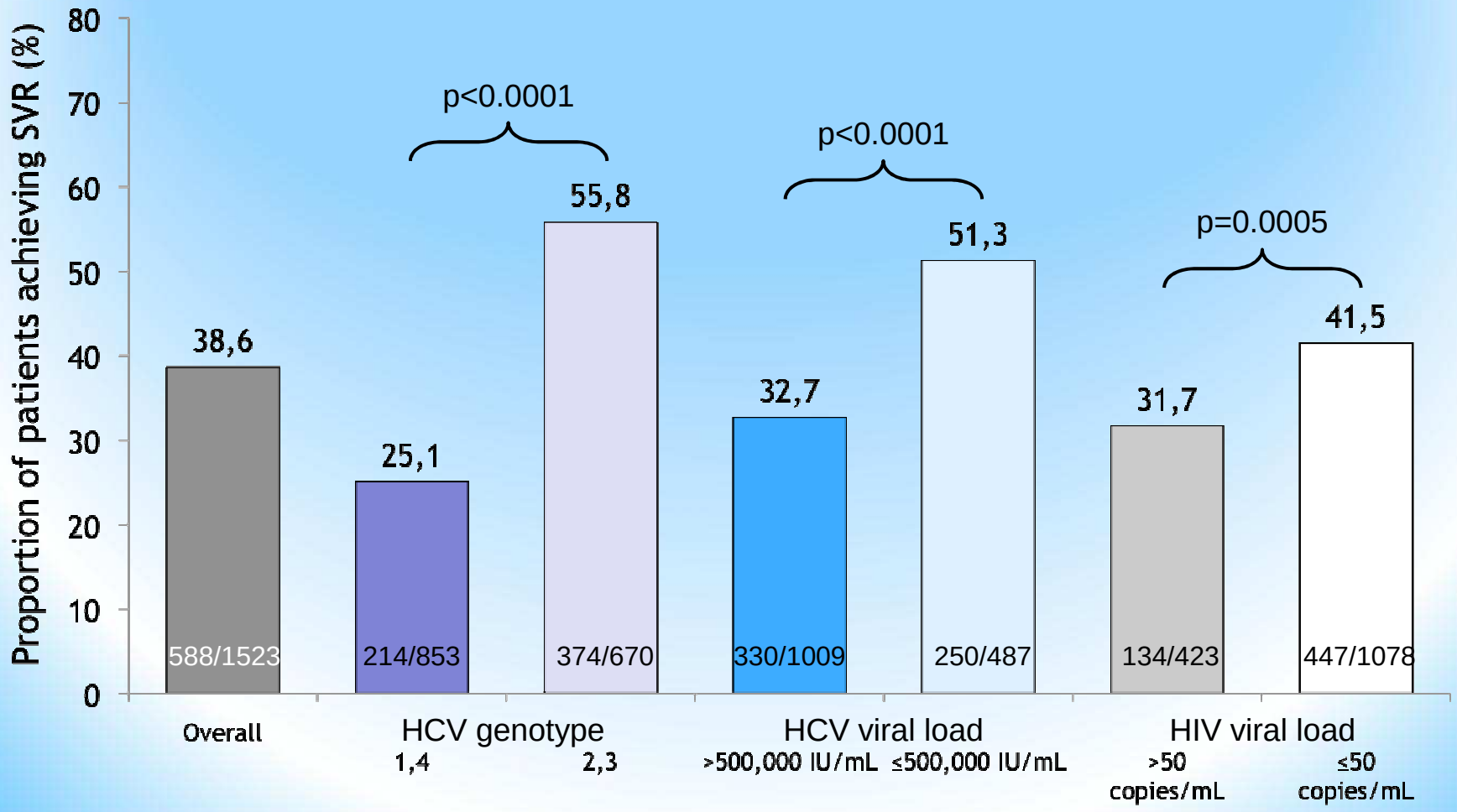
- Perché?
- **Come?**
  - **Duplice terapia (Peg-IFN+Riba)**
  - **Triplice terapia (Peg-IFN+Riba+DAA)**
  - **Regimi IFN-free**
- Fattori predittivi

Summary of Results from Coinfection Trials

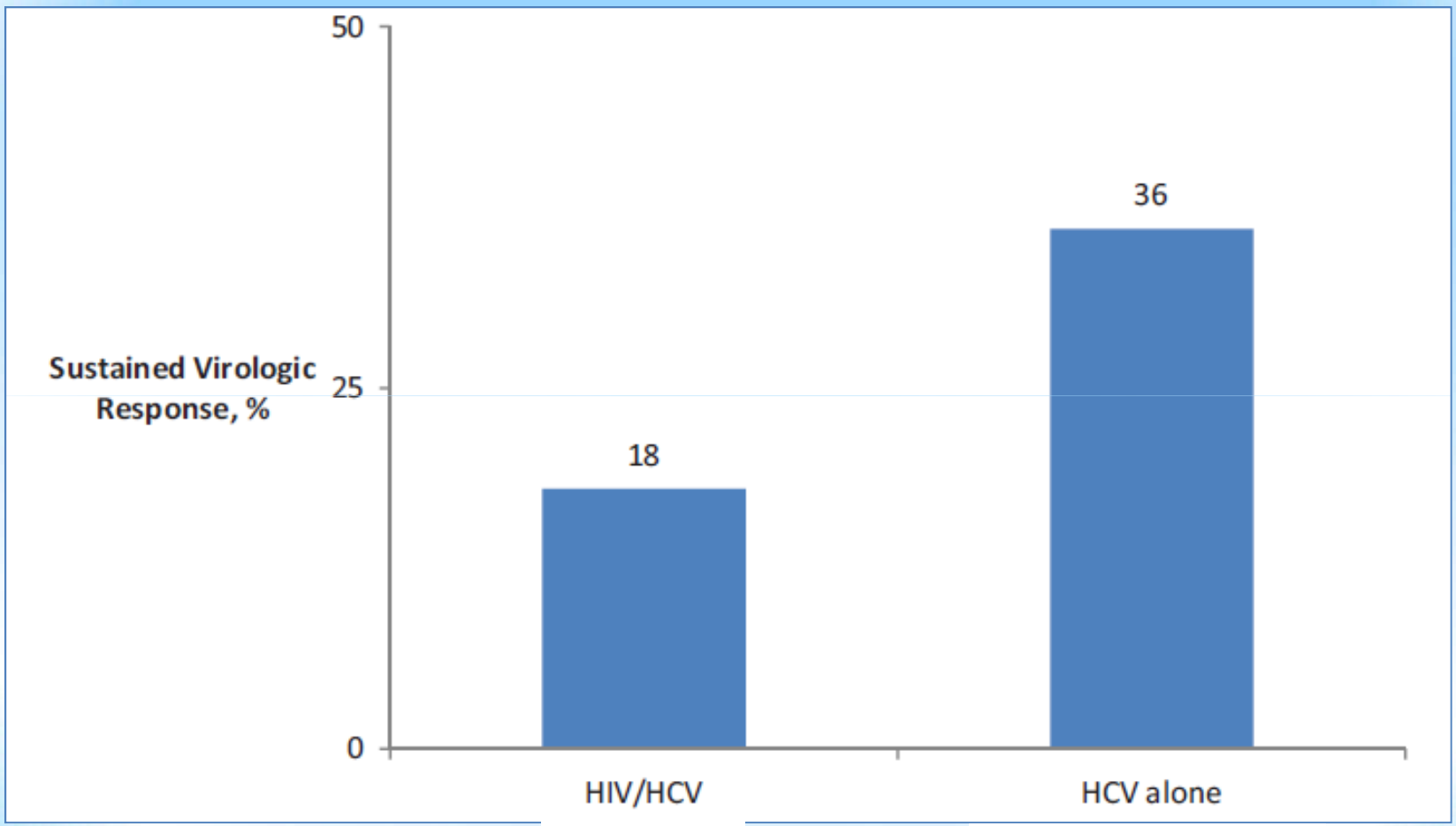
Study	N	Treatment	SVR (%)		
			All	GT 1	GT non-1
RIBAVIC	412	PEG IFN α-2b + RBV 800	27	17*	44
		IFN α-2b + RBV 800	20	6	43
ACTG	133	PEG IFN α 2a + RBV 600	27	14	73
		IFN α -2a + RBV 600	12	6	33
APRICOT	860	PEG IFN α 2a + RBV 800	40	29	62
		IFN α -2a + RBV 800	12	7	20
LAGUNO	93	PEG IFN α-2b + W/B RBV	44	38	53
		IFN α-2b + W/B RBV	21	7	47
PRESCO	389	PEG IFN α-2a + W/B RBV	50	36	72
		G1 48 w 31 72w 52			
		G2 24 w 67 48w 82			

Opera study: Sustained virological response by baseline characteristics

SVR was achieved by 588/1523 patients (38.6%)



SVR rate with Peg-IFN+RIBA in HIV/HCV and HCV patients by genotype 1 and high HCV load (>800,000copies/ml)



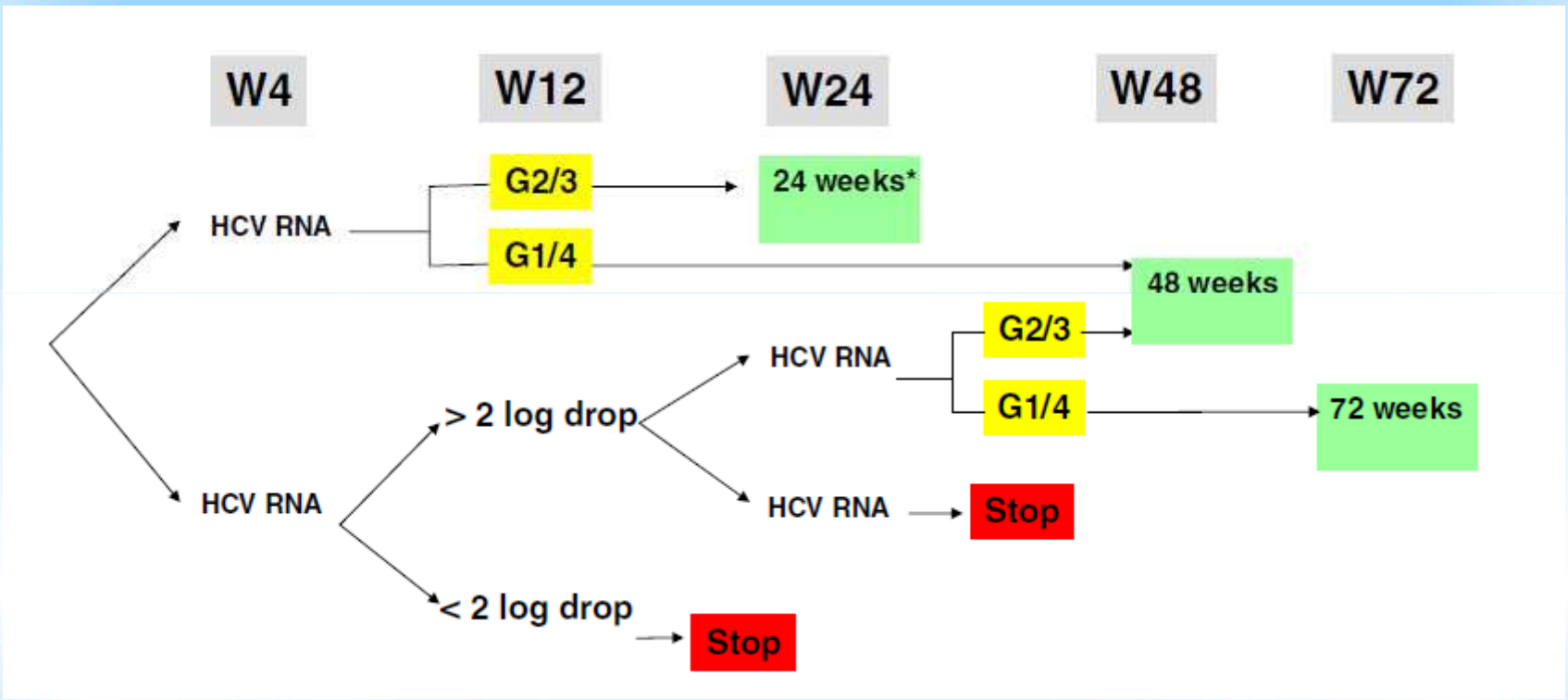
Torriani FJ
NEJM 2004

Hadziyannis SJ
Ann Intern Med 2004

Sulkowski MS, Sem Liv Dis 2014

European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults

JK Rockstroh,[1] S Bhagani,[2] Y Benhamou,[3] R Bruno,[4] S Mauss,[5] L Peters,[6] M Puoti,[7] V Soriano,[8] C Tural[9] and the EACS Executive Committee



HIV Medicine 2009

Coinfezione HIV-HCV

-Terapia anti-HCV-

- Perché?
- Come?
  - Duplice terapia (Peg-IFN+Riba)
  - Triplice terapia (Peg-IFN+Riba+DAA)
- **Fattori predittivi**

Fattori predittivi di risposta alla duplice nei soggetti coinfetti

- IL 28-B
- Numero di CD4
- Tipo di ART
- Insulino-resistenza
- Nuovi fattori predittivi

Fattori predittivi di risposta alla duplice nei soggetti coinfetti

Anche nei coinfetti il polimorfismo rs12979860 del gene codificante per il recettore dell'IL28B si è rivelato un importante predittore di risposta all'IFN, particolarmente nei genotipi 1 e 4.

Pineda JA et al. Clin Infect Dis 2010;51:788-95
Rallon NI et al. AIDS 2011;25:1025-33

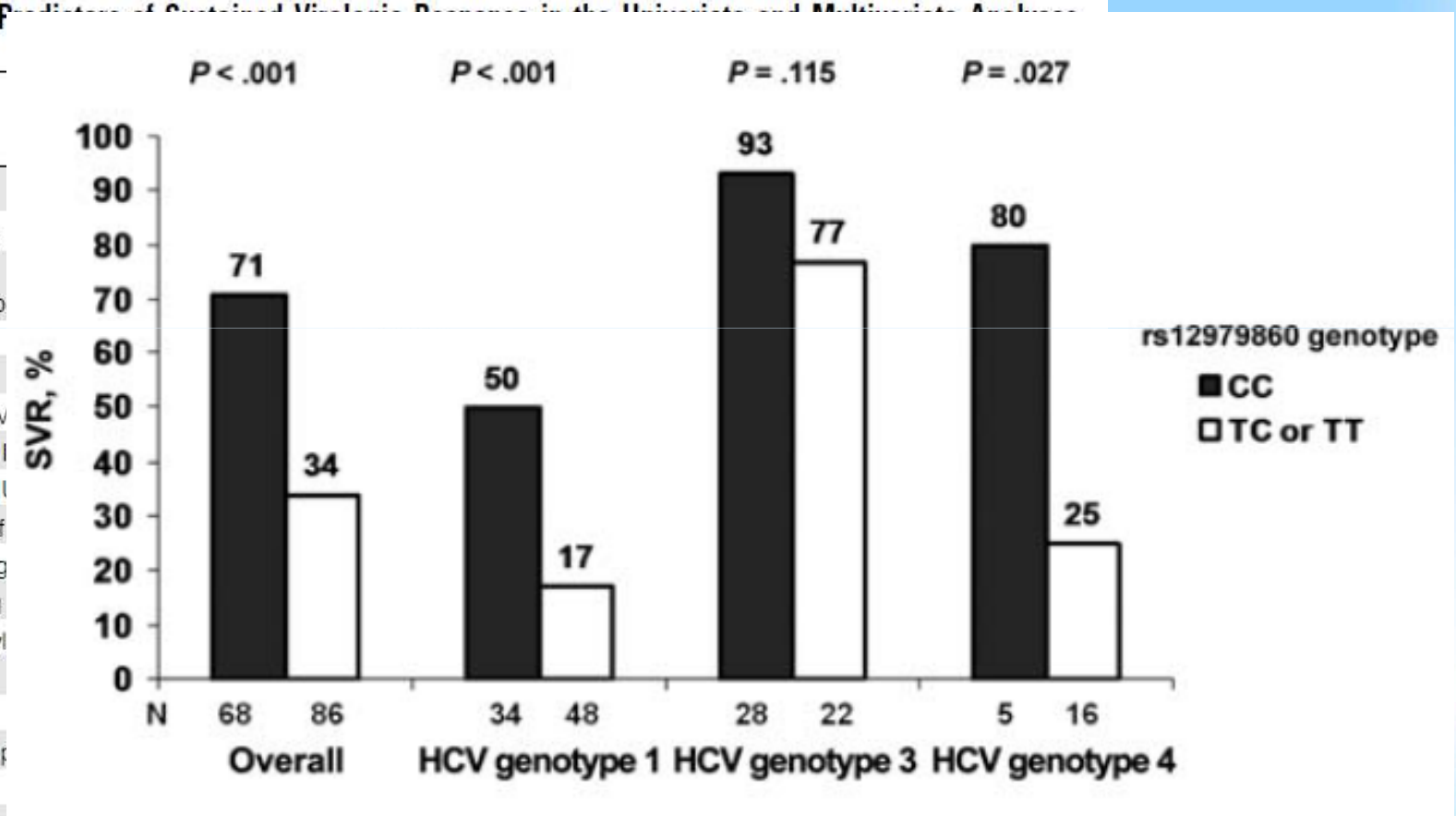
Prediction of Response to Pegylated Interferon plus Ribavirin by *IL28B* Gene Variation in Patients Coinfected with HIV and Hepatitis C Virus

Clinical Infectious Diseases 2010;51(7):788–795

Juan A. Pineda,[1] Antonio Caruz,[3] Antonio Rivero,[4] Karin Neukam,[1] Irene Salas,[3] Angela Camacho, José C. Palomares,[2] José A. Mira,[1] Antonio Martínez,[5] Carmen Roldán,[1] Julián de la Torre,[4] and Juan Macías[1]

Studio prospettico su 154 pz HIV/HCV trattati con peg-IFN e RBV tra il 2001 ed il 2008

Table 3. P



Variable				
Age				
≤42 years				
>42 years				
HCV genotyp				
1–4				
2–3				
Baseline HCV				
≥600,000 I				
<600,000 I				
Daily dose of				
≤15 mg/kg				
>15 mg/kg				
Type of pegyl				
Alfa-2a				
Alfa-2b				
Exposure to p				
<80%				
≥80%		75 (52)	.050	4.78 (0.77–30.30)	.094
rs12979860 genotype				
TC/TT		29 (34)			
CC		48 (71)	<.001	5.05 (2.04–12.5)	<.001

Fattori predittivi di risposta alla duplice nei soggetti coinfetti

- La conta basale dei CD4 ha mostrato importanza solo nei soggetti con genotipo 1

Opravil M et al. J Acquir Immune Def Syndr 2008;47:36-49
Valerio L et al. J Acquir Immune Def Syndr 2008;47:50-55

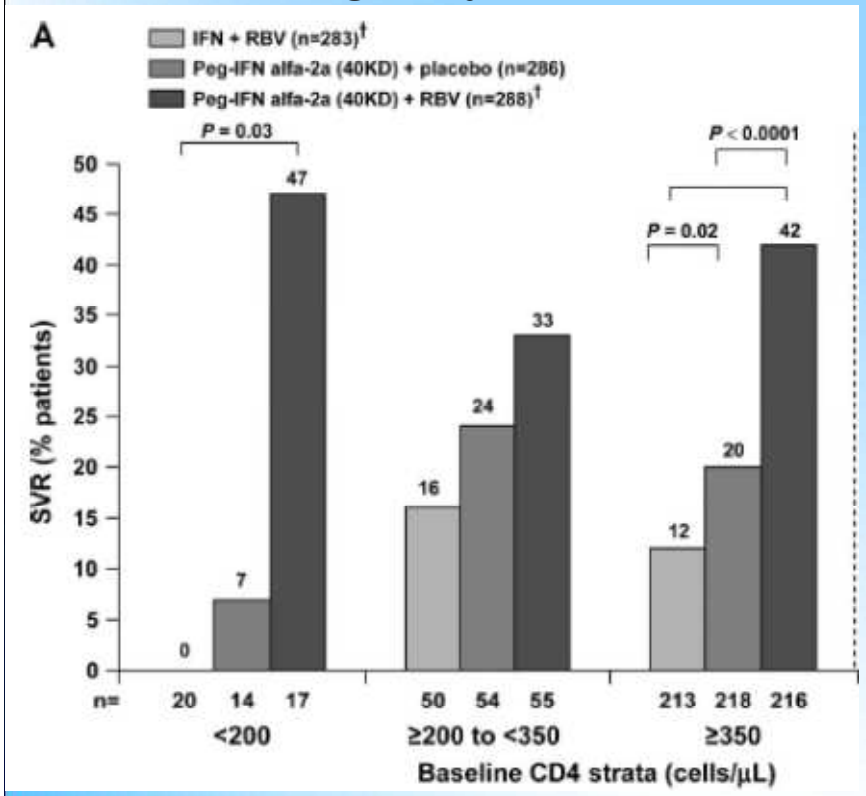
Effect of Baseline CD4 Cell Count on the Efficacy and Safety of Peginterferon Alfa-2a (40KD) Plus Ribavirin in Patients With HIV/Hepatitis C Virus Coinfection

Milos Opravil, MD, Joe Sasadeusz, MD,† David A. Cooper, MD,‡ Jürgen K. Rockstroh, MD,§ Nathan Clumeck, MD,‖ Bonaventura Clotet, MD,¶ Julio Montaner, MD,# Francesca J. Torriani, MD,** Jean DePamphilis, PhD,†† and Douglas T. Dieterich, MD‡‡*

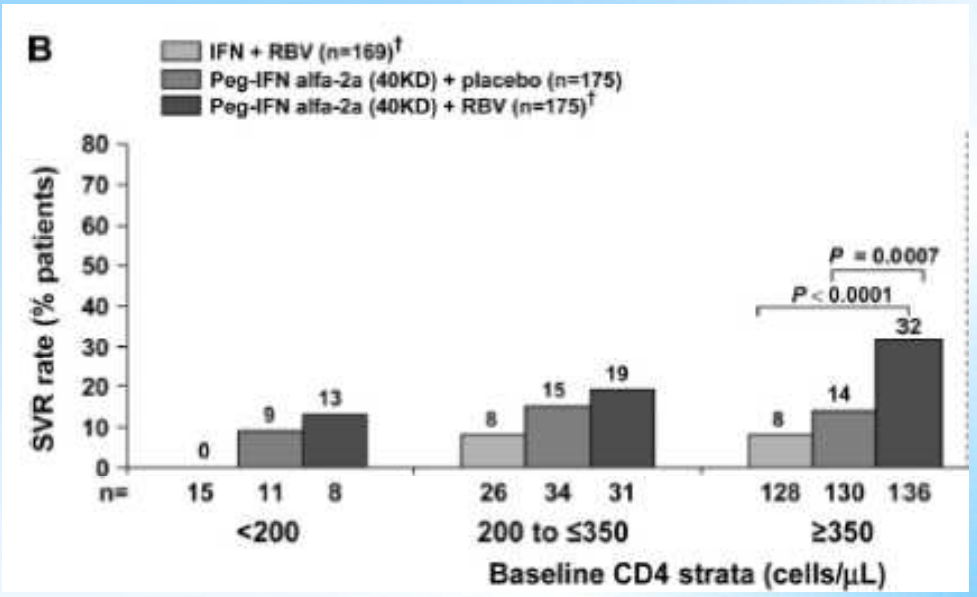
J Acquir Immune Defic Syndr 2008;47:36–49

RCT includente 857 pazienti coinfetti assegnati ad uno di tre bracci (IFNα-2a 3MU x3/wk+RBV, pegIFN α-2a 180µg/wk+placebo, pegIFN α-2a 180µg/wk+RBV). I tassi di SVR nei tre bracci sono stati posti in correlazione alla conta basale dei CD4.

All genotypes



HCV genotype 1



Fattori predittivi di risposta alla duplice nei soggetti coinfetti

- È controverso il significato dell'insulino-resistenza quale predittore negativo di risposta all'IFN nei coinfetti.

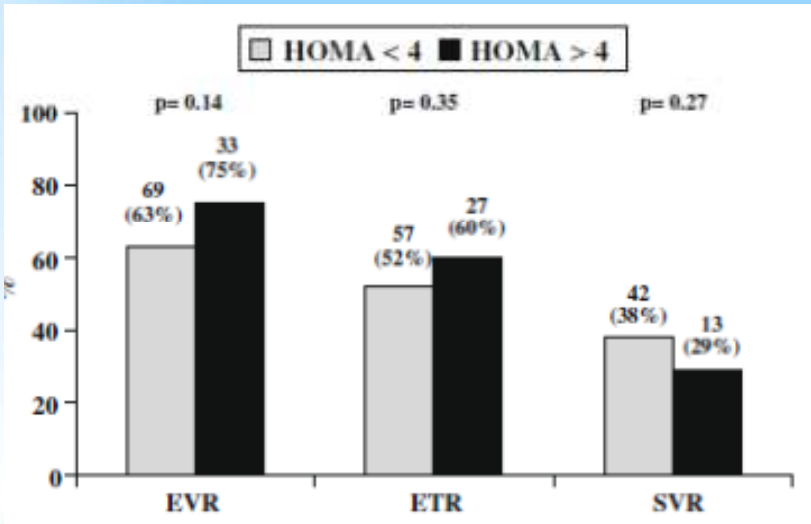
Ryan P et al. J Acquir Immune Def Syndr 2010;55:176-81
Merchante N et al. J Hepatol 2009;50:684-92

Insulin resistance is not a relevant predictor of sustained virological response to pegylated interferon plus ribavirin in HIV/HCV co-infected patients☆

Nicolás Merchante[1,†], Ignacio de los Santos-Gil[2], Dolores Merino[3,†],

Journal of Hepatology 50 (2009) 684–692

Studio prospettico includente 155 pazienti coinfetti trattati con pegIFN e RBV tra il 2001 ed il 2006. La SVR è stata posta in relazione all'insulino resistenza valutata tramite HOMA.



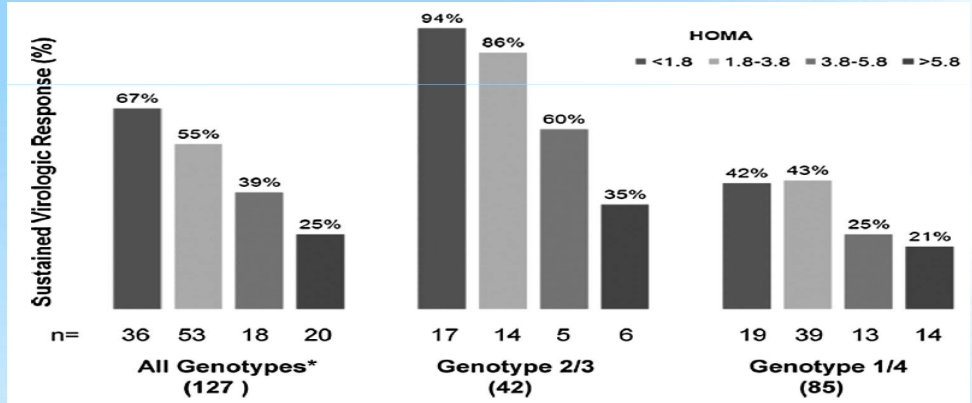
Genotype	*n*	SVR no. (%)	*p* (bivariate)
1–4			
HOMA <4	71	19 (27)	0.8
HOMA ⩾4	29	7 (24)	
HOMA <2.8	45	12 (27)	0.9
HOMA ⩾2.8	55	14 (25)	
3			
HOMA <4	39	23 (59)	0.14
HOMA ⩾4	16	6 (37)	
HOMA <2.8	30	18 (60)	0.23
HOMA ⩾2.8	25	11 (44)	

Insulin Resistance Impairs Response to Interferon Plus Ribavirin in Patients Coinfected With HIV and Hepatitis C Virus

Pablo Ryan, MD,† Salvador Resino, PhD,‡ Pilar Miralles, MD,* Jaime Cosín, MD,* Juan Carlos López, MD, PhD,* Silvia Moreno, BS,‡ Pilar Catalán, MS,* Margarita Ramírez, RN,* Isabel Gutiérrez, RN,* and Juan Berenguer, MD, PhD**

J Acquir Immune Defic Syndr 2010;55:176–181

Studio retrospettivo comprendente 218 pazienti coinfetti trattati con IFN e RBV tra il 2000 ed il 2007. La SVR è stata posta in relazione all'insulino resistenza, valutata tramite HOMA.



	All Patients (%)	Patients With Genotype 1/4 (%)	Patients With Genotype 2/3 (%)
All patients	67/134 (50.0)	32/85 (37.6)	33/42 (78.6)
Patients without IR	54/93 (58.1)*	25/58 (43.1)†	28/31 (90.3)‡
Patients with IR	13/41 (31.7)*	7/27 (25.9)†	5/11 (45.5)‡

HCV genotype was not available in 7 patients.
*$P = 0.005$; †$P = 0.099$; ‡$P = 0.005$ (Fisher exact test).

Fattori predittivi di risposta alla duplice nei soggetti coinfetti

- Il livello sierico di 25OH-D_3 è da poco emerso quale predittore di risposta all'IFN nei pazienti HIV/HCV+.

Mandorfer M et al. AIDS 2013,27:227-32

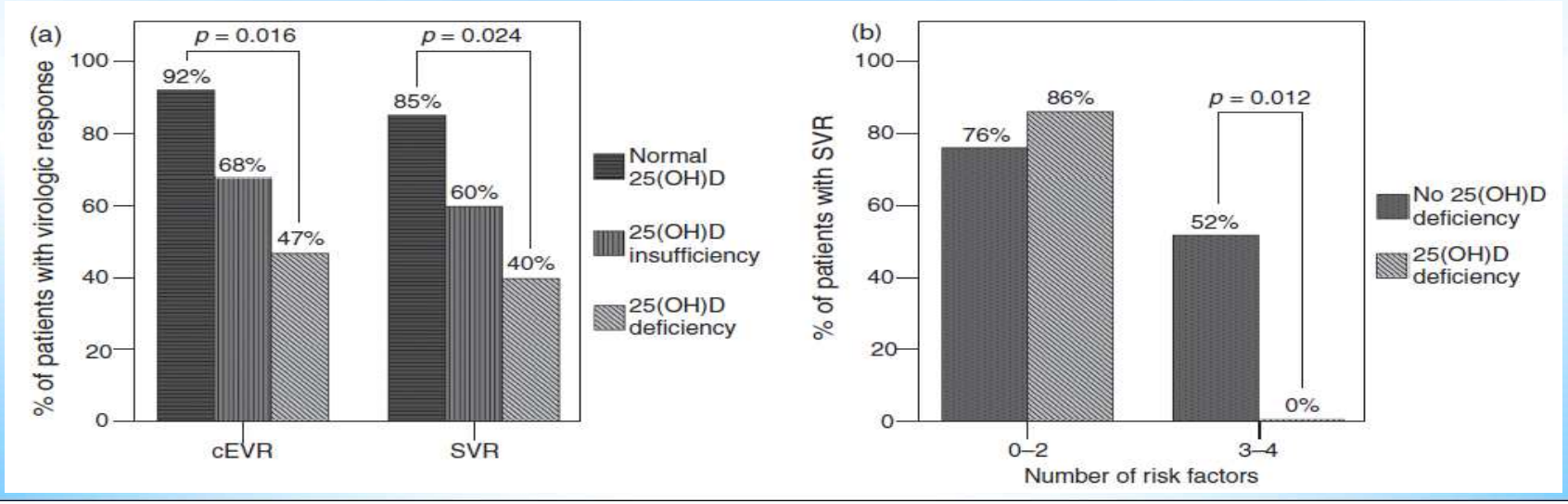
Low vitamin D levels are associated with impaired virologic response to PEGIFN + RBV therapy in HIV–hepatitis C virus coinfected patients

Mattias Mandorfer[a], Thomas Reiberger[a], Berit A. Payer[a], Arnulf Ferlitsch[a], Florian Breitenecker[a], Maximilian C. Aichelburg[b], Barbara Obermayer-Pietsch[c], Armin Rieger[b], Michael Trauner[a], Markus Peck-Radosavljevic[a], the Vienna HIV & Liver Study Group

AIDS 2013, **27**:227–232

Studio prospettico includente 65 pazienti HIV/HCV+ trattati con peg-IFN e RBV. I tassi di SVR sono stati posti in relazione ai livelli di 25OH-D pretrattamento. Genotipi 1/4, alta viremia, fibrosi avanzata ed IL28 non C/C sono stati considerati come fattori predittivi negativi di risposta al trattamento.

Patient characteristics	All patients $n=65$	Normal 25(OH)D $n=13$ (20%)	25(OH)D insufficiency $n=37$ (57%)	25(OH)D deficiency $n=15$ (23%)	*P*
Virologic response					
RVR	28 (43%)	7 (54%)	15 (41%)	6 (40%)	0.406
cEVR	44 (68%)	12 (92%)	25 (68%)	7 (47%)	0.008
SVR	39 (60%)	11 (85%)	22 (60%)	6 (40%)	0.029



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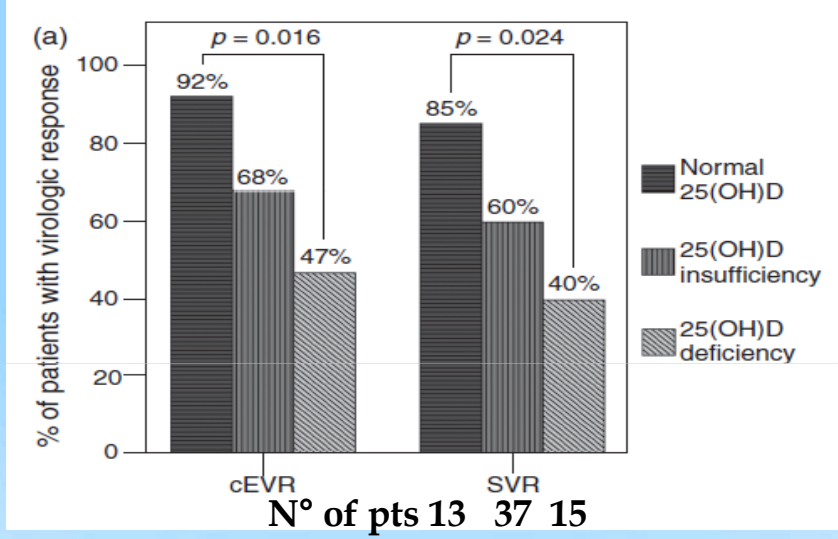
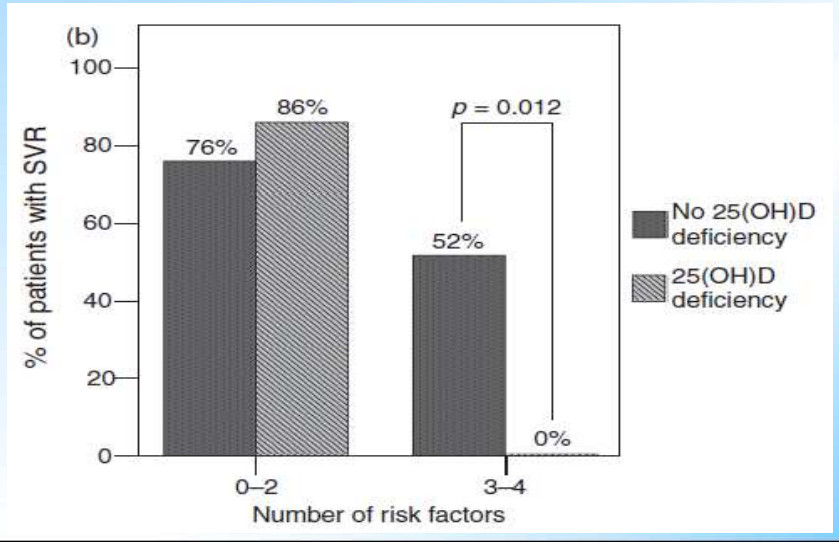


N° of pts 13 37 15

Genotipi 1/4, alta viremia, fibrosi avanzata ed IL28 non C/C sono stati considerati come fattori predittivi negativi di risposta al trattamento.



AIDS 2013, **27**:227–232

Coinfezione HIV-HCV

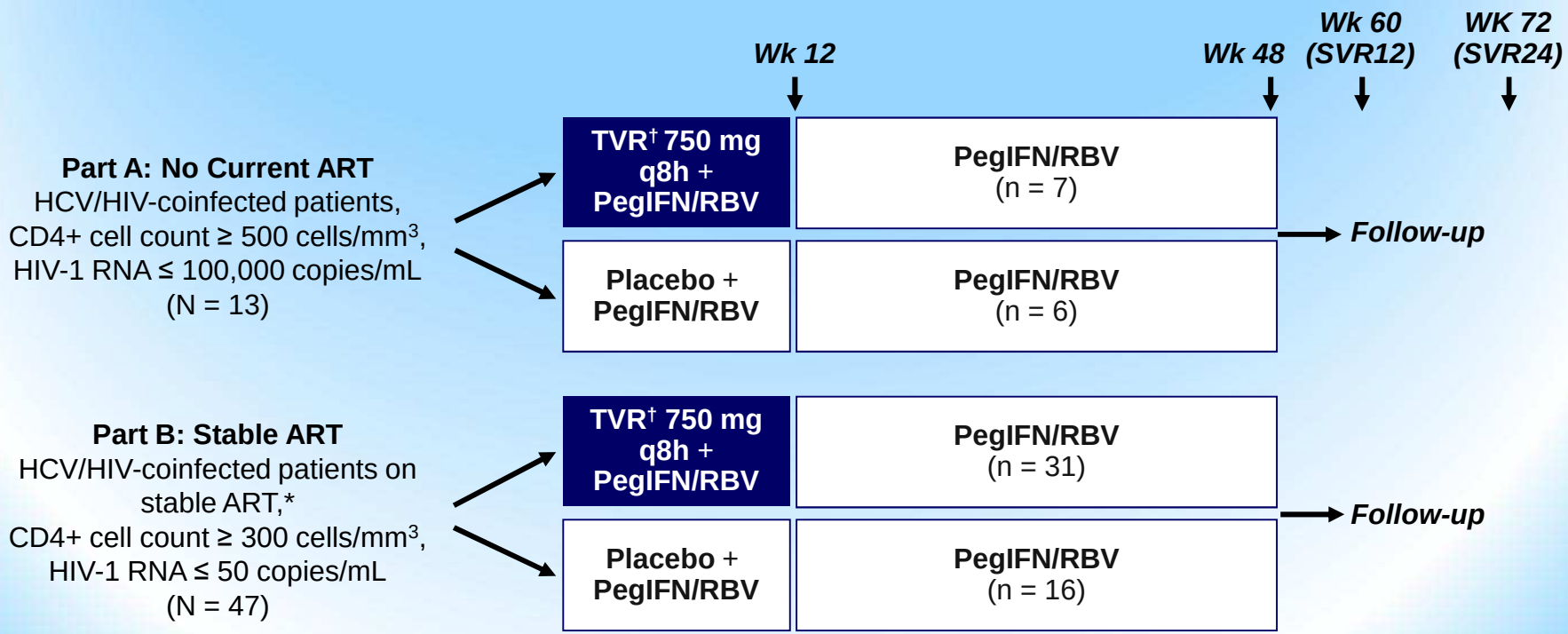
-Terapia anti-HCV-

- Perché?
- Come?
  - Duplice terapia (Peg-IFN+Riba)
  - **Triplice terapia (Peg-IFN+Riba+DAA)**
  - IFN-free regimens
- Fattori predittivi

HIV patients

Study 110: Telaprevir + PegIFN/RBV in GT1 HCV Tx-Naive HCV/HIV Coinfection

Multicenter, randomized, double-blind, placebo-controlled phase II trial

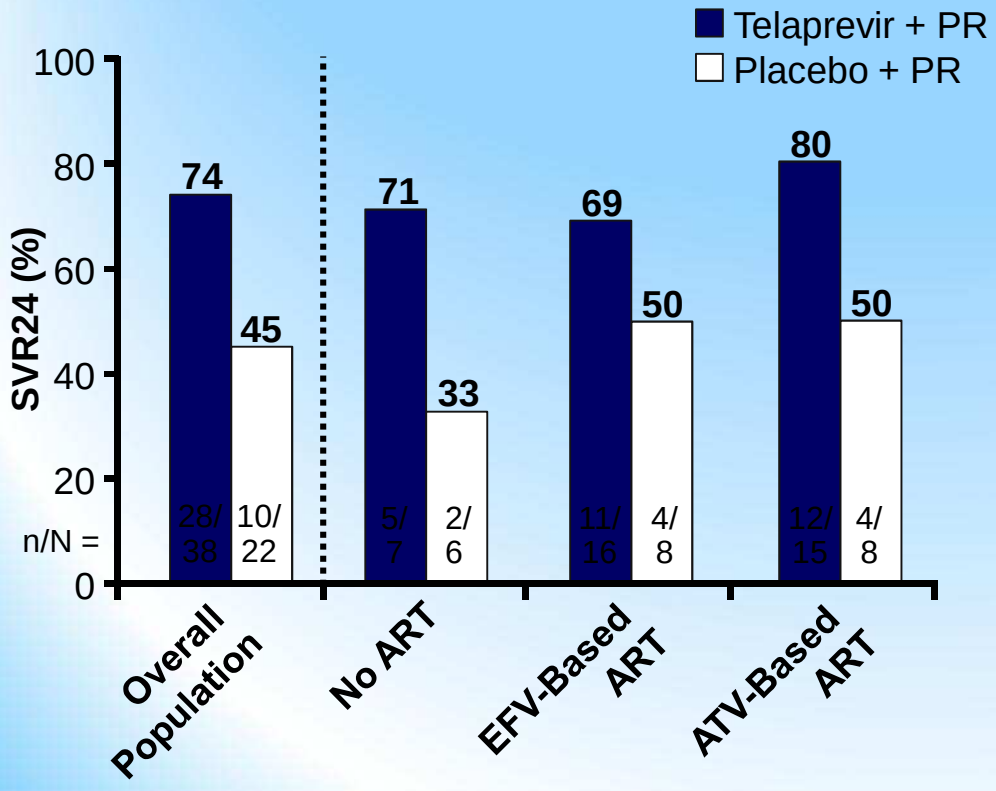


*Either EFV/TDF/FTC or ATV/RTV + TDF + (FTC or 3TC).
†TVR dose increased to 1125 mg q8h with EFV.

Sulkowski MS, et al. AASLD 2012. Abstract 54.

Study 110: SVR24 With TVR + PegIFN/RBV in HCV GT1/HIV-Coinfected Patients

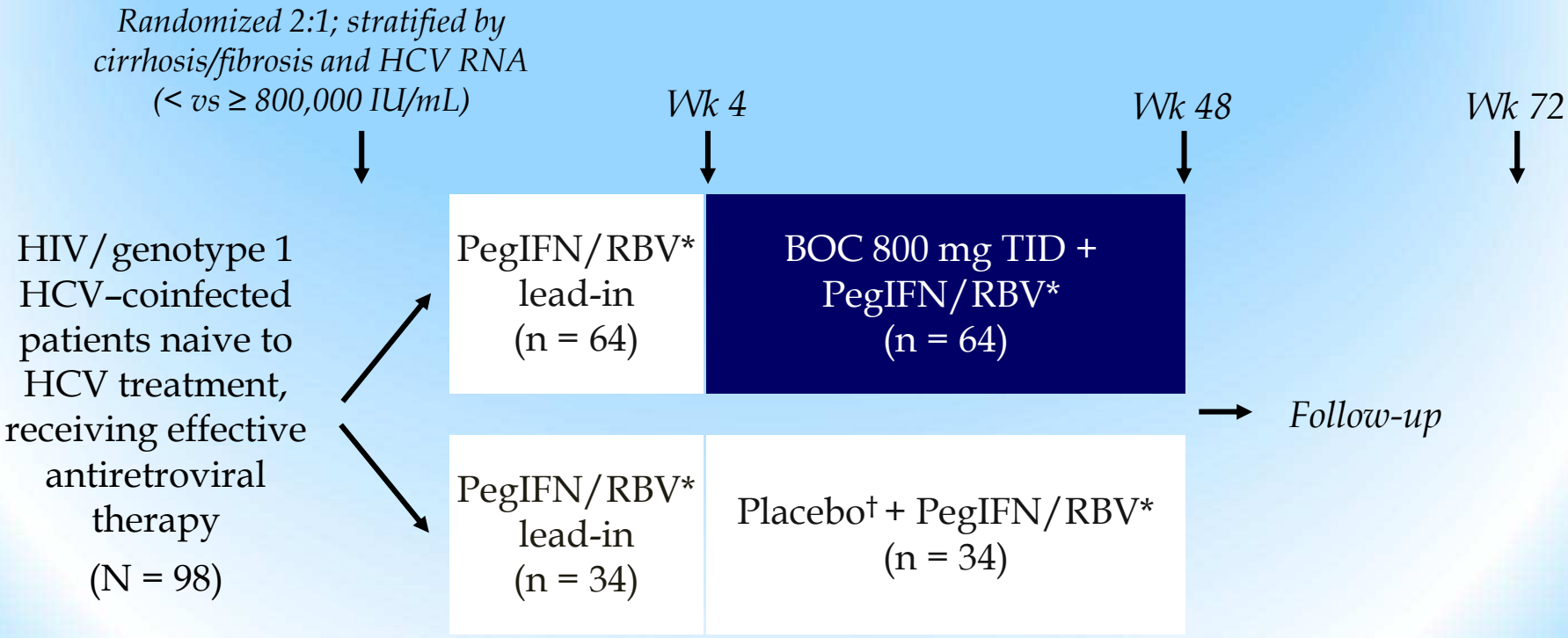
- Higher SVR24 rate with TVR-based therapy



- No significant drug–drug interactions with TVR and ART
  - TVR plasma levels similar in patients with or without ART
  - EFV and ATV/RTV plasma levels similar in patients with or without TVR
- No HIV breakthroughs in patients using ART during HCV treatment
- Safety and tolerability similar to treatment in patients with HCV monoinfection

Sulkowski MS, et al. AASLD 2012. Abstract 54.

Boceprevir + PegIFN/RBV in GT1 HCV Therapy–Naive HIV/HCV Coinfection

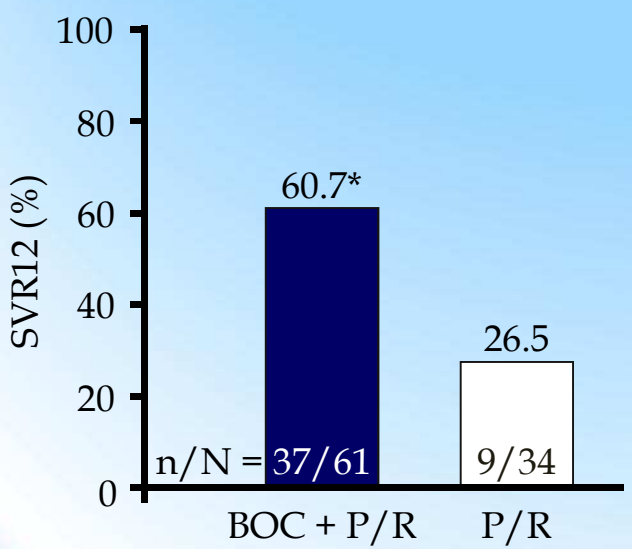


*PegIFN 1.5 µg/kg/wk; RBV 600-1400 mg/day, according to weight, in divided BID dose.
†Patients in placebo arm with HCV RNA ≥ lower limit of quantification at Wk 24 eligible to receive open-label BOC plus pegIFN/RBV.

Mallolas J, et al. EASL 2012. Abstract 50.

Higher SVR12 Rates With BOC + P/R vs P/R Alone in HIV/HCV Coinfection

- Interim efficacy analysis
  - 3 BOC pts had not yet reached SVR12 time point



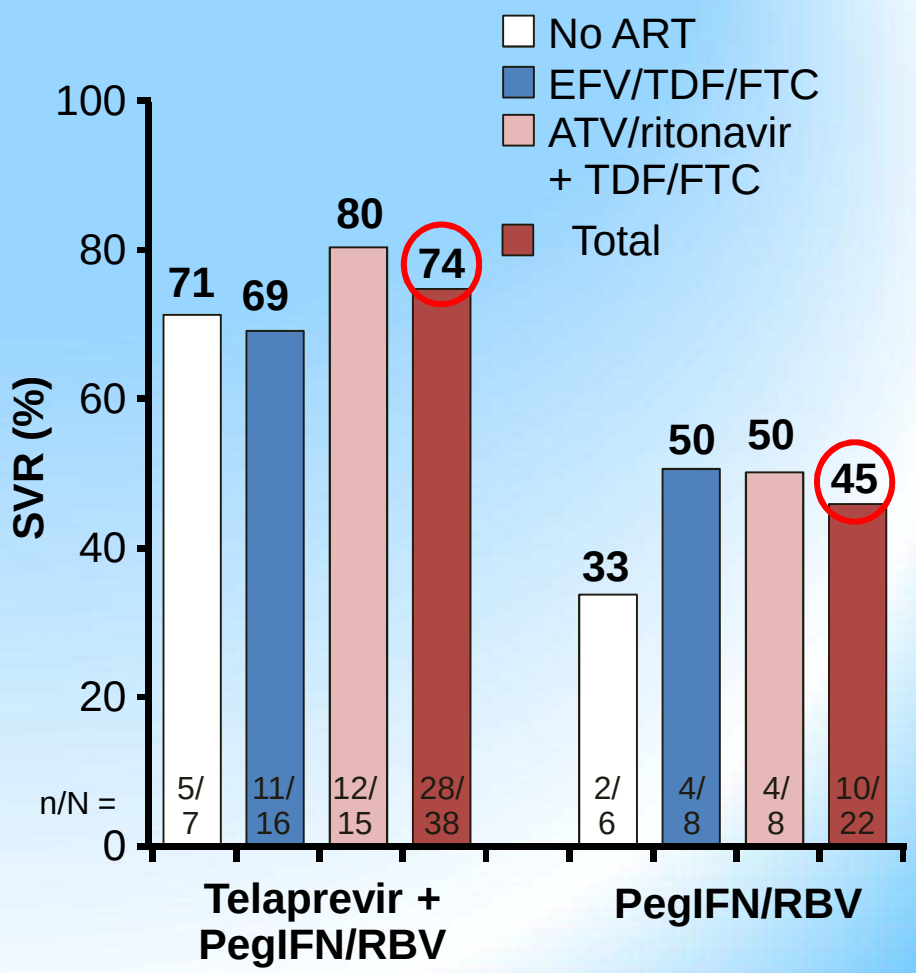
*Reflects presented data; speaker noted verbally that remaining 3 pts have now reached and achieved SVR12

- HIV-1 RNA breakthrough observed in 7 pts
  - BOC + P/R: n = 3/64
  - Placebo + P/R: n = 4/34
- Tolerability similar to that seen in HCV monoinfection
  - Similar rates of total and serious adverse events in BOC and placebo groups
  - Higher rates of discontinuation due to toxicity with BOC (20%) vs placebo (9%)
- Caution needed with drug-drug interactions

Mallolas J, et al. EASL 2012. Abstract 50.

Study 110: Telaprevir + PegIFN/RBV in GT1 HCV/HIV Coinfection

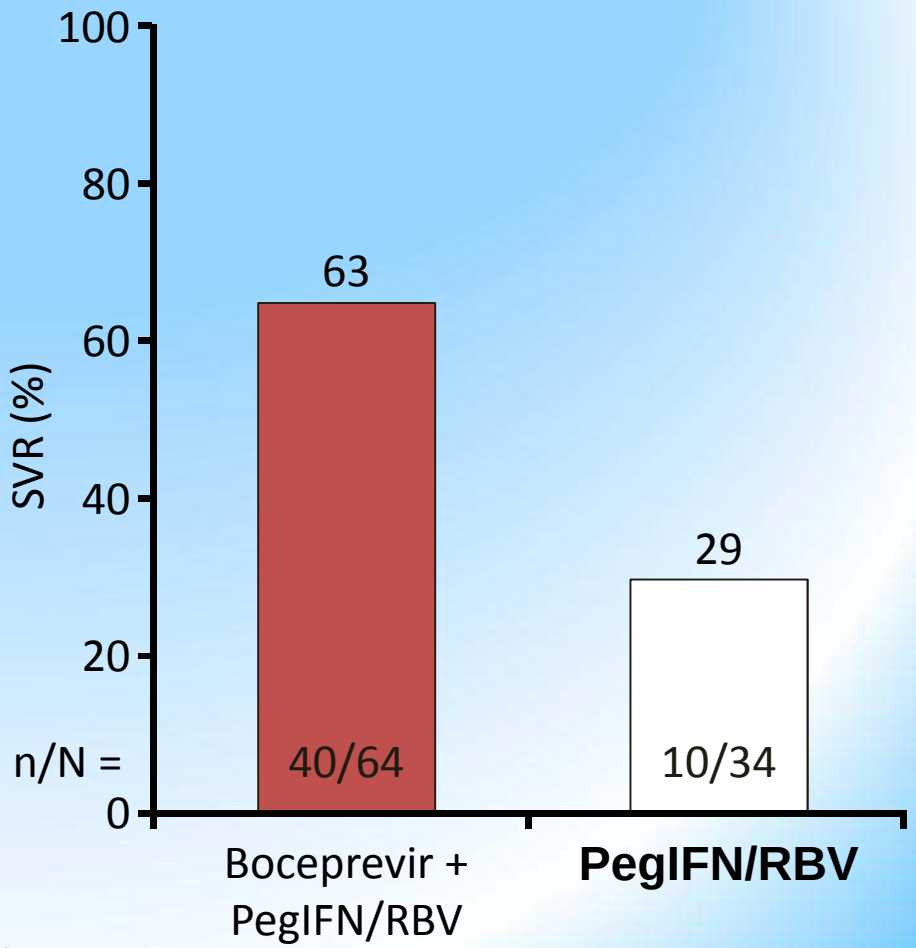
- Phase II randomized controlled trial[34]
  - Telaprevir TID + pegIFN/RBV vs pegIFN/RBV alone for 48 weeks
- HCV treatment-naive HIV+ patients (N = 60)
- No HIV breakthrough
- Safety and tolerability
  - Increased pruritus, headache, nausea, rash, and dizziness with telaprevir-based therapy
  - Anemia: 18% in both groups
- SVR comparable to GT1 HCV-monoinfected patients (75%)[35]



Sulkowski MS, et al. Ann Intern Med. 2013;159:86-96.

Study P05411: Boceprevir + PegIFN/RBV in GT1 HCV/HIV Coinfection

- Phase II randomized controlled trial[36]
  - PegIFN/RBV lead-in 4 weeks then boceprevir + pegIFN/RBV for 44 weeks vs pegIFN/RBV alone for 48 weeks
- HCV treatment-naive HIV+ patients (N = 98)
  - All with HIV-1 RNA < 50 cells/mL on antiretroviral therapy
- No difference in HIV breakthrough
- Safety and tolerability
  - Increased anemia, pyrexia, and decreased appetite with boceprevir-based therapy
- SVR comparable to GT1 HCV-monoinfected patients (68%)



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

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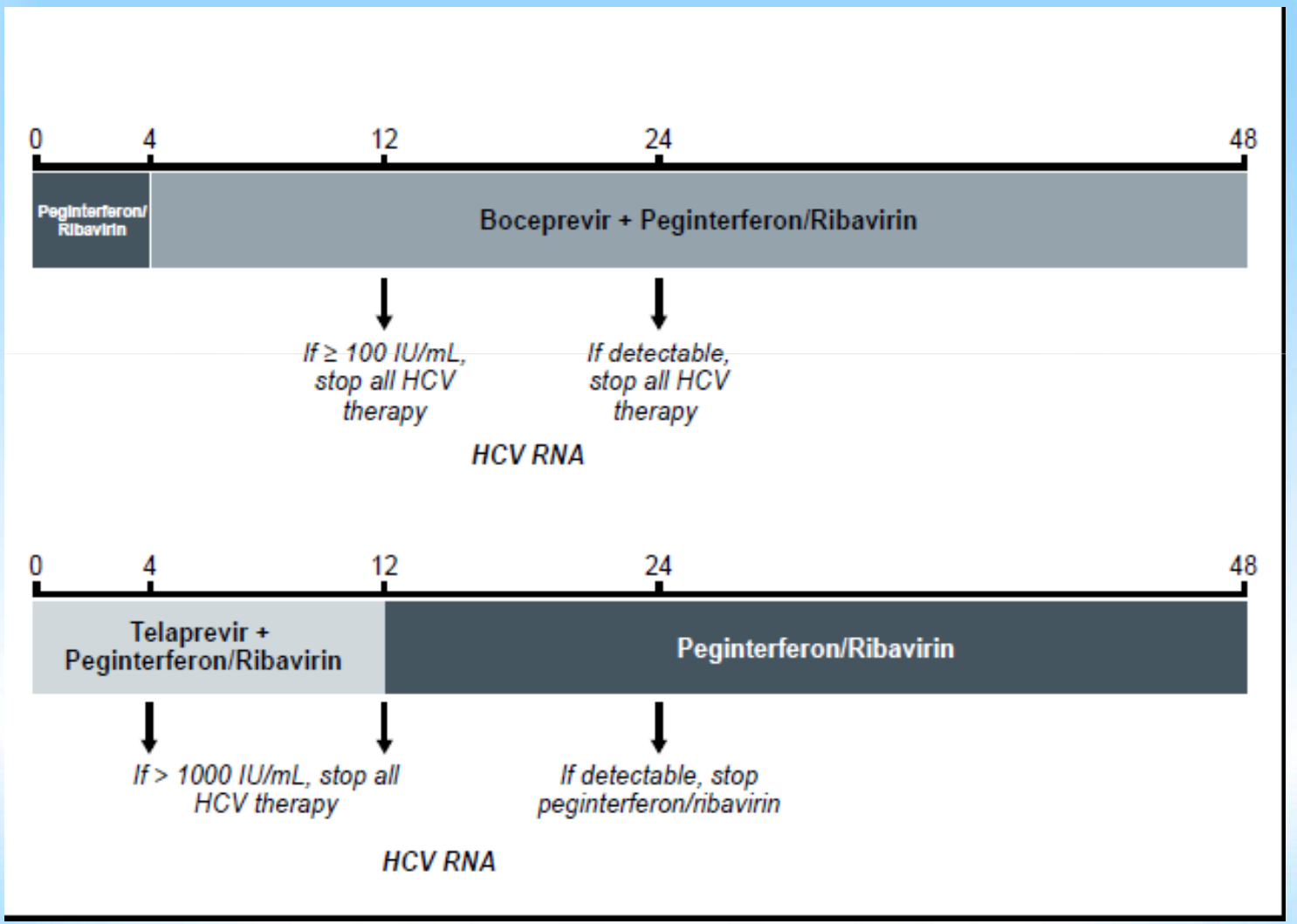
Treatment Paradigm With HCV PIs in the HCV/HIV-Coinfection Setting



Both BOC and TVR Have Potential for Many Drug–Drug Interactions

- BOC
  - Strong inhibitor of CYP3A4/5
  - Partly metabolized by CYP3A4/5
  - Potential inhibitor of and substrate for P-gp
- TVR
  - Substrate of CYP3A
  - Inhibitor of CYP3A
  - Substrate and inhibitor of P-gp

Most drug–drug interactions can be overcome by careful survey of the patient's medications and judicious substitutions during HCV therapy (or just during the period of PI-based triple therapy)

Drugs Contraindicated with Boceprevir and Telaprevir

Drug Class*	Contraindicated With BOC[1]	Contraindicated With TVR[2]
Alpha 1-adrenoreceptor antagonist	Alfuzosin	Alfuzosin
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin	N/A
Antimycobacterials	Rifampin	Rifampin
Antiretrovirals	EFV, all RTV-boosted PIs	DRV/RTV, FPV/RTV, LPV/RTV
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agents	Cisapride	Cisapride
Herbal products	*Hypericum perforatum* (St John's wort)	*Hypericum perforatum*
HMG CoA reductase inhibitors	Lovastatin, simvastatin	Lovastatin, simvastatin
Oral contraceptives	Drospirenone	N/A
Neuroleptic	Pimozide	Pimozide
PDE5 inhibitor	Sildenafil or tadalafil when used for treatment of pulmonary arterial HTN	Sildenafil or tadalafil when used for treatment of pulmonary arterial HTN
Sedatives/hypnotics	Triazolam; orally administered midazolam	Orally administered midazolam, triazolam

*Studies of drug–drug interactions incomplete.

1. Boceprevir [package insert]. July 2012. 2. Telaprevir [package insert]. October 2012.

Recommendations for Coadministration of TVR and BOC With Select Antiretroviral Agents

Antiretroviral Agent	Telaprevir		Boceprevir	
	Europe[38-40]	US[41]	Europe[38-40]	US[41]
Atazanavir/ritonavir	Monitor for hyperbilirubinemia	Standard dose	Case-by-case consideration	Do not use
Darunavir/ritonavir; fosamprenavir/ritonavir; lopinavir/ritonavir	Not recommended	Not recommended	Not recommended	Not recommended
Raltegravir	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
Efavirenz	Increase dose (1125 mg q8h)	Increase dose (1125 mg q8h)	Not recommended	Do not use
Rilpivirine	No dose adjustment	No guidance	No dose adjustment	No dose adjustment[44]

Note: Telaprevir and boceprevir interact with CYP3A4/5 and p-glycoprotein. Simeprevir should not be coadministered with any boosted or unboosted PI or any NNRTI except rilpivirine.[42] Sofosbuvir has no reported DDIs with HIV drugs except tipranavir/ritonavir.[43]

38. Telaprevir [EU package insert]. 39. Boceprevir [EU package insert]. 40. Kakuda TN, et al. IWCPHT 2012. Abstract O-18. 41. DHHS Antiretroviral Guidelines for Adults and Adolescents. February 2013. 42. Simeprevir [package insert]. 43. Sofosbuvir [package insert]. 44. Boceprevir [package insert].

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Review - Entecavir

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Drug Interactions - Warning with boceprevir and certain boosted HIV PIs.

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In response to feedback about commonly prescribed comedications, ~40 new drugs

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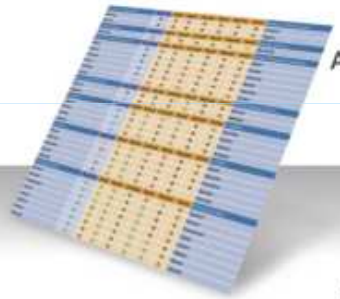

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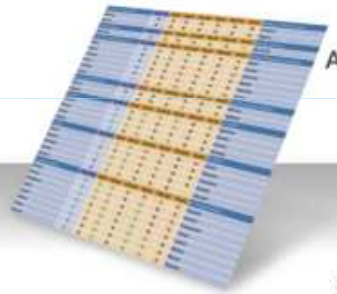

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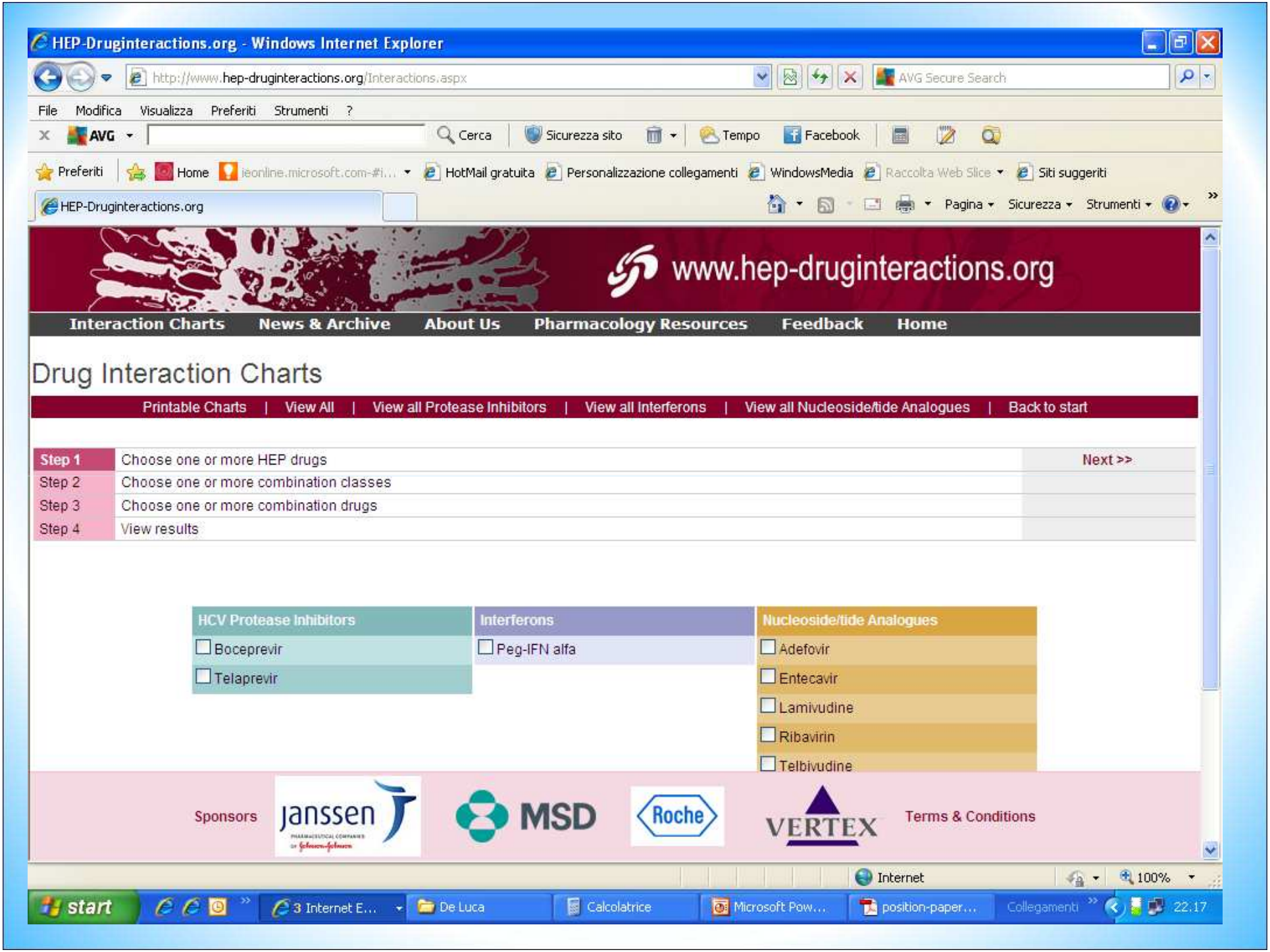
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Boceprevir
Telaprevir
Interferons
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Nucleoside/tide Analogues
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Antiretroviral therapy in candidates for PEG IFN + RBV + TPV/BOC

CLASS	Antiretrovirals	TELAPREVIR	BOCEPREVIR
NRTI	AZT, ddI, d4T	Avoid coadministration	Avoid Coadministration
	ABC:	Combine with caution. No data. Potential interaction with UDP-glucuronyl tranferase Impact of Abacavir on RBV metabolism at lower RBV doses ?	
	TDF	Can be combined Without efavirenz 30% increase TDF AUC	Can be combined
	FTC, LAM	Can be combined. No Data but no potential interactions	
PI	LPV/R , DRV/R, FPV/R,	Avoid coadministration	Avoid Coadministration
	ATZ/R	Can be combined	
NNRTI	EFV	TPV 1125 mg tid 50% increase of the dose	
	NVP	Avoid coadministration	
	RPV	Can be Combined + 79% AUC RPV → additional toxicity if combined with other drugs increasing QT? → check QT	
	ETV	Can be combined	Combine with caution AUC – 23% in pts with MDR HIV
II	RAL	Can be combined	Can be combined

Boceprevir in HCV/HIV co-infection: Summary of Safety

n (%)	PR	BOC/PR
Treated	34 (100)	64 (100)
Any AE	34(100)	63 (98)
Serious AE	7 (21)	11 (17)
Death	0	0
Treatment related side effects	34 (100)	61 (95)
Study discontinuation due to an AE	3 (9)	13 (20)
Any drug modification due to an AE	8 (24)	18 (28)

*Four subjects in the BOC/PR group discontinued treatment for reasons unrelated to AE or treatment failure;
AE: adverse event

Sulkowski M, et al CROI 2012

Telaprevir in HCV/HIV co-infection: SAEs and premature discontinuations

	Part A		Part B			
	No ART		EFV+TDF+FTC		ATV/r+TDF+FTC	
n	PR (n=6)	T/PR (n=7)	PR (n=8)	T/PR (n=16)	PR (n=8)	T/PR (n=15)
SAEs*	0	1	0	1	1	5
Reason for discontinuation						
Discontinuation due to HCV futility rule, n	2	0	1	1	1	1
Discontinuation of TVR only due to AE, n (due to jaundice)‡	0	0	0	0	0	1
Discontinuation of all study drugs due to AE (overall treatment phase), n	0	0	0	0	0	2
Due to cholelithiasis	0	0	0	0	0	1
Due to hemolytic anemia§	0	0	0	0	0	1

*One additional patient had an SAE of pneumococcal pneumonia reported after the Week 4 safety follow-up visit
‡ Reported as severe AE, occurred at Week 3; §Patient had Grade 3 hemoglobin, also experienced Grade 4 hemoglobin (SAE of hemolytic anemia); AE: adverse event; SAE: serious AE

Sherman KE, et al. Hepatology 2011;54(Suppl. S1): Abstract LB-8

Fattori predittivi di reazione avversa

- I polimorfismi rs1127354 e rs7270101 del gene dell'Inosina Trifosfatasi (ITPA) hanno confermato anche nei coinfetti la loro associazione con l'anemia emolitica da RBV

Naggie S et al. J Infect Dis 2012;205:376-83
Domingo P et al. Antimicrob Agents Chemother 2012;56:2987-93

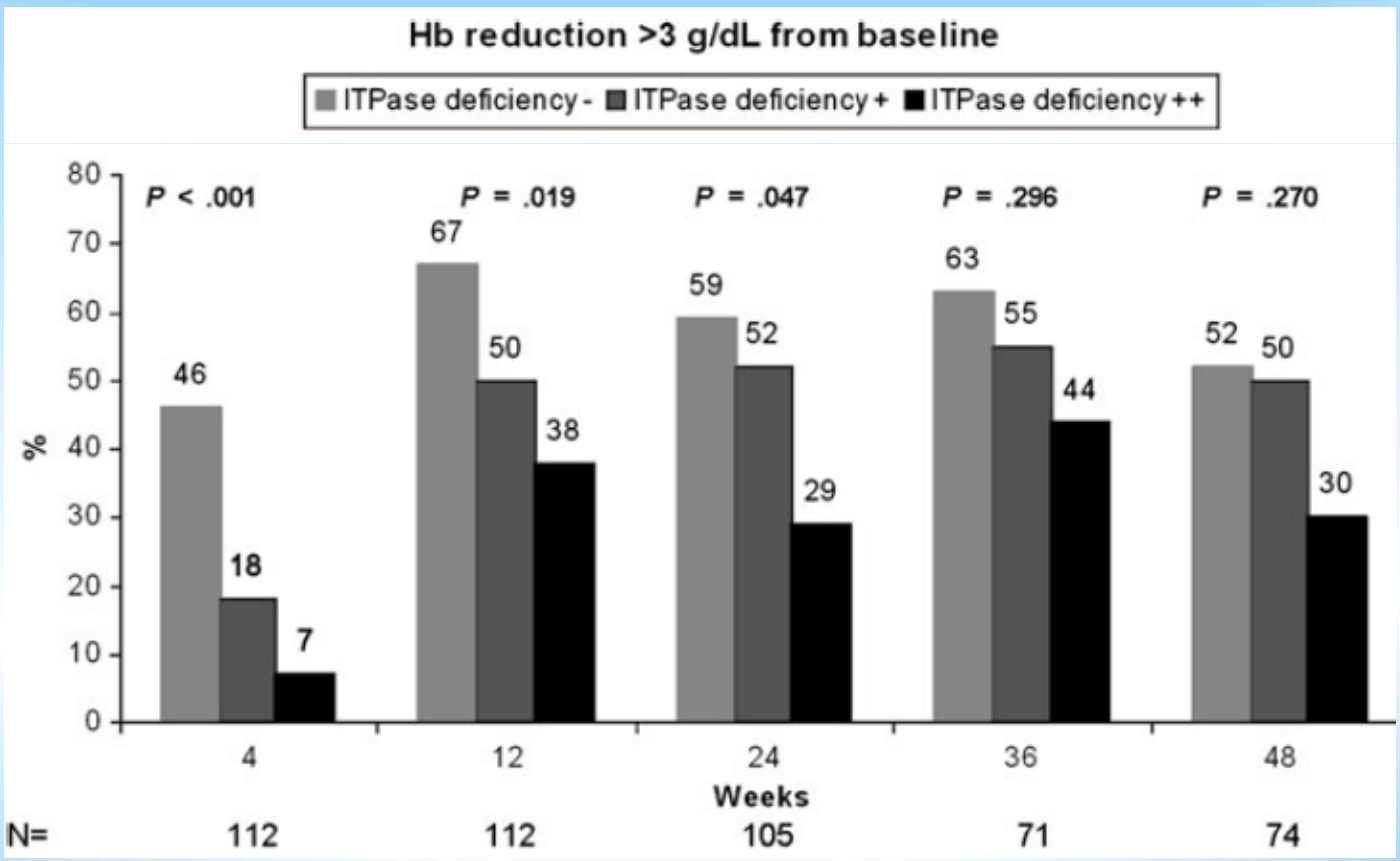
Variants in the ITPA Gene Protect Against Ribavirin-Induced Hemolytic Anemia in HIV/HCV-Coinfected Patients With All HCV Genotypes

The Journal of Infectious Diseases 2012;205:376–83

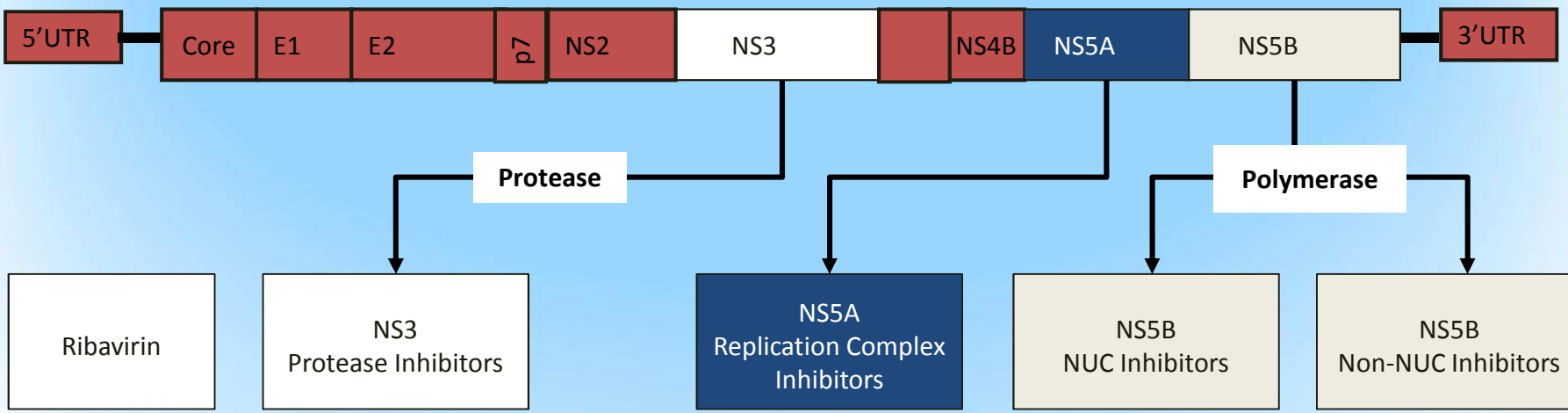
Susanna Naggie,[1] Norma I. Rallon,[2] José M. Benito,[2] Judith Morello,[2] Sonia Rodriguez-Novoa,[2] Paul J. Clark,[1] Alexander J. Thompson,[1] Kevin V. Shianna,[3] Eugenia Vispo,[2] John G. McHutchison,[1] David B. Goldstein,[3] and Vincent Soriano[2]

rs1127354	rs7270101	Predicted ITPase Activity, %	Predicted ITPase Deficiency
Wild type (C/C)	Wild type (A/A)	100	–
Wild type (C/C)	Heterozygosity (A/C)	60	+
Heterozygosity (C/A)	Wild type (A/A)	30	++

Studio includente 161 pazienti coinfetti, precedentemente trattati con pegIFN e RBV tra il 2002 ed il 2008. È stata indagata la correlazione tra i polimorfismi rs1127354 e rs7270101 del gene dell'ITPA e la riduzione dell'Hb alla quarta settimana di trattamento.



Multiple Classes of Direct-Acting Antiviral Agents



Telaprevir
Boceprevir
Simeprevir
Asunaprevir
ABT-450
Grazoprevir (MK-5172)
Faldaprevir
Sovaprevir
ACH-2684

Daclatasvir
Ledipasvir
Ombitasvir
Elbasvir (MK-8742)
GS-5885
GS-5816
ACH-3102
PPI-668
GSK2336805
Samatasvir

Sofosbuvir
VX-135
IDX21437
ACH-3422

Dasabuvir
BMS-791325
PPI-383
GS-9669
TMC647055

*Representative list; may not be fully inclusive.

Interferon-Containing and Interferon-Free HCV Therapy for HIV-Infected Patients

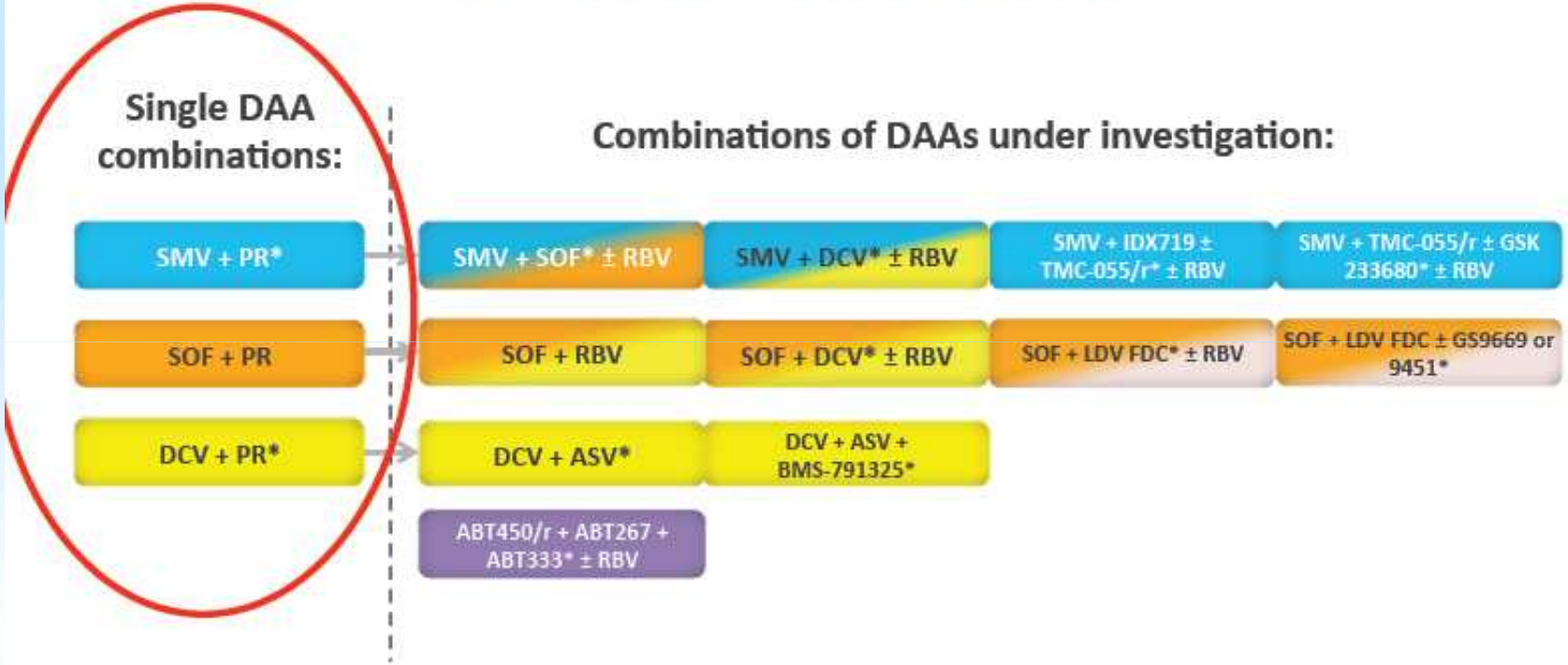
Mark S. Sulkowski, MD[1]

Table 1 Sustained virological response for oral direct-acting antiviral regimens for the treatment of HCV genotype 1 infection in HIV-infected adults

Direct acting anti-viral agent (Oral)	Peginterferon (Subcutaneous injection)	Ribavirin (Oral)	Regimen duration	Sustained virological response (%, *n* of *N*)
Telaprevir 750 mg every 8 h[36]	Alfa-2a 180 μg/wk	1000 or 1200 mg/d	48 wks (telaprevir for the initial 12 wks only)	74% (28 of 38)
Boceprevir 800 mg every 8 h[35]	Alfa-2b 1.5 μg/kg/wk	Ribavirin 600–1400 mg/d	48 wks (48 wks for peginterferon and ribavirin; 44 wks for boceprevir)	63% (40 of 64)
Simeprevir 150 mg once daily[37]	Alfa-2a 180 μg/wk	1000 or 1200 mg/d	24 or 48 wks based on HCV RNA response at treatment week 4 (simeprevir for the initial 12 wks only)	79% (42 of 53)
Sofosbuvir 400 mg once daily[40]	Alfa-2a 180 μg/wk	1000 or 1200 mg/d	12 wks (all drugs)	89% (17 of 19)
Sofosbuvir 400 mg once daily[41]	None	1000 or 1200 mg/d	24 wks (all drugs)	76% (87 of 114)

Sem Liv Dis 2014

Treatment of HCV: development of new regimens

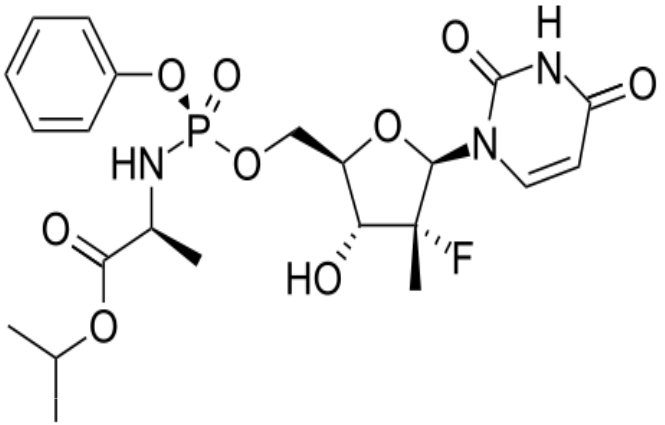


*Not yet approved in Europe. PR, pegylated interferon and ribavirn; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; DCV, daclatasvir;

Clinicaltrials.gov (Accessed July 2014)

SOFOSBUVIR

- Nucleotide analog Pol inhibitor
- High genetic barrier
- Pan-genotypic
- One daily dose (400 mg)
- No food effect
- Low potential for DDI
  - No hepatic CYP450 metabolism
- Renally cleared
- Generally safe and well-tolerated
  in clinical studies to date (>3,000 patients)
  - With pegIFN/RBV: fatigue, headache, nausea, insomnia, anemia
  - With RBV: fatigue, headache



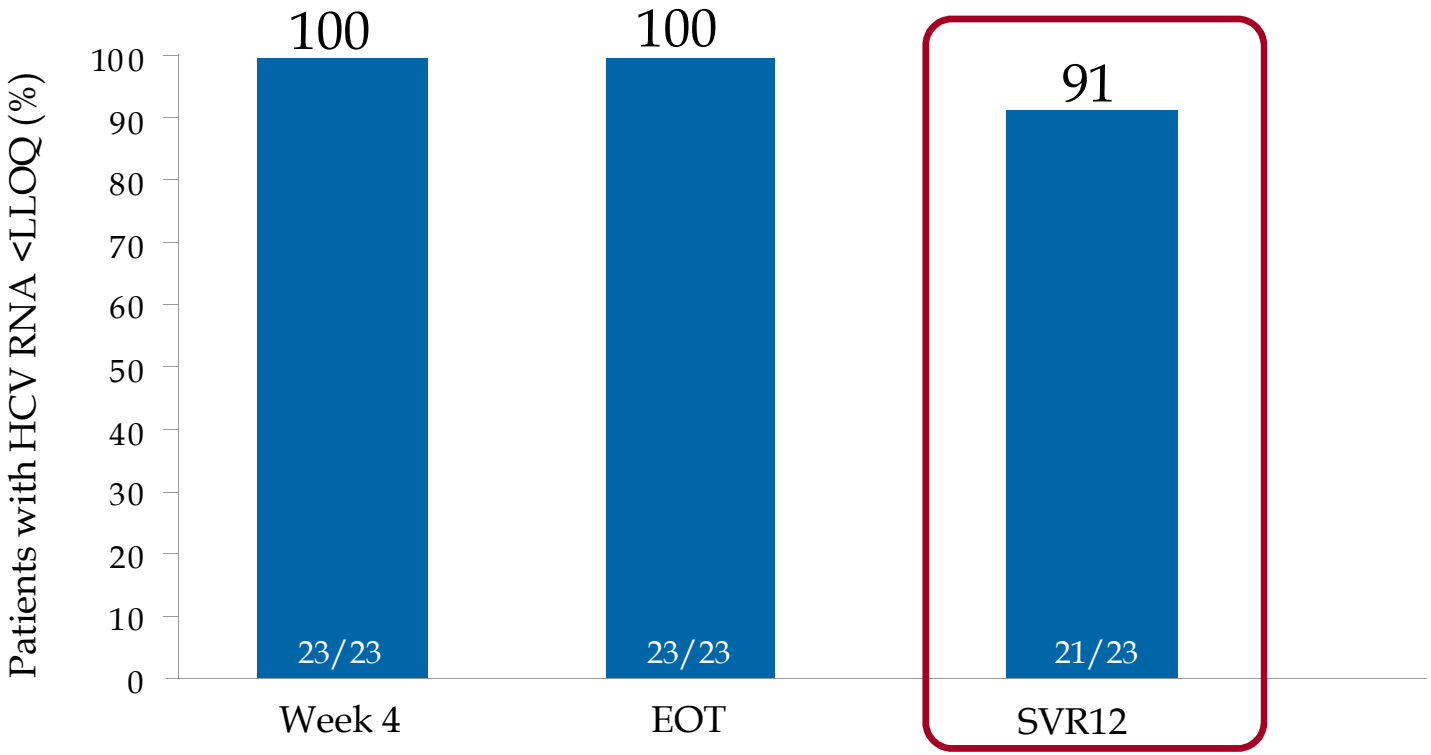
Sofosbuvir: Dosing and Administration

Characteristic	Sofosbuvir
Dose	400 mg/day PO*
Formulation	400-mg tablet
Dose reductions	Never
Pills per day	1
With food	No food restrictions
PegIFN	Either pegIFN acceptable, use according to package instructions
RBV	Weight-based dosing according to package instructions; dose reduction required in patients with renal impairment
Most common AEs	▪ With pegIFN/RBV: fatigue, headache, nausea, insomnia, anemia ▪ With RBV: fatigue, headache
Drug class	NS5B nucleotide inhibitor

*Used in combination with RBV ± pegIFN, depending on HCV genotype and other patient characteristics, in registrational trials.

7. Sofosbuvir [package insert].

Treatment-Naïve HCV/HIV Co-infected Patients
SOF + PegIFN + RBV x 12 weeks



- SVR12 was similar by HCV GT and by HIV ARV regimen
- There was no on-treatment HCV or HIV virologic breakthrough
- Relapse occurred in 1 patient and accounted for all virologic failures
- Two patients discontinued treatment early due to adverse events
  - one patient discontinued at week 6 and was lost to follow-up
  - one patient achieved SVR12 after 8 weeks of SOF + RBV therapy

Rodriguez-Torres M, et al. IDWeek 2013; San Francisco, CA. Poster #714

Safety Summary
Treatment-Naïve HCV/HIV Co-infected Patients

Adverse event, n (%)	SOF + PegIFN + RBV (N=23)
Any AE	16 (70)
Serious AE	0
Grade 3 AE	7 (30)
Grade 4 AE	0
Discontinuation due to AE*	2 (9)
Common AEs in > 10% of patients	
Anemia	12 (52)
Fatigue	8 (35)
Hyperbilirubinemia	4 (17)
Neutropenia	4 (17)
Myalgia	4 (17)
Abdominal pain	3 (13)

*Anemia at Week 6 (n=1) and altered mood at Week 8 (n=1).
Hyperbilirubinemia occurred only among patients receiving atazanavir + ritonavir

- No significant changes in CD4 T-cell count from baseline to follow-up Week 12

Rodriguez-Torres M, et al. IDWeek 2013; San Francisco, CA. Poster #714

Simeprevir: Dosing and Administration

Characteristic	Simeprevir
Dose	150 mg/day PO*
Formulation	150-mg capsule
Dose reductions	Never
Pills per day	1
With food	Take with food
PegIFN	Either pegIFN acceptable; use according to package instructions
RBV	Weight-based dosing according to peginterferon used
Most common AEs	With pegIFN/RBV: rash, pruritus, nausea
Drug class	PI
Additional considerations	Strongly consider Q80K testing in patients with genotype 1a infection; if present, consider alternative therapies

*Used in combination with both pegIFN and RBV in registrational trials.

3. Simeprevir [package insert].

SIMEPREVIR

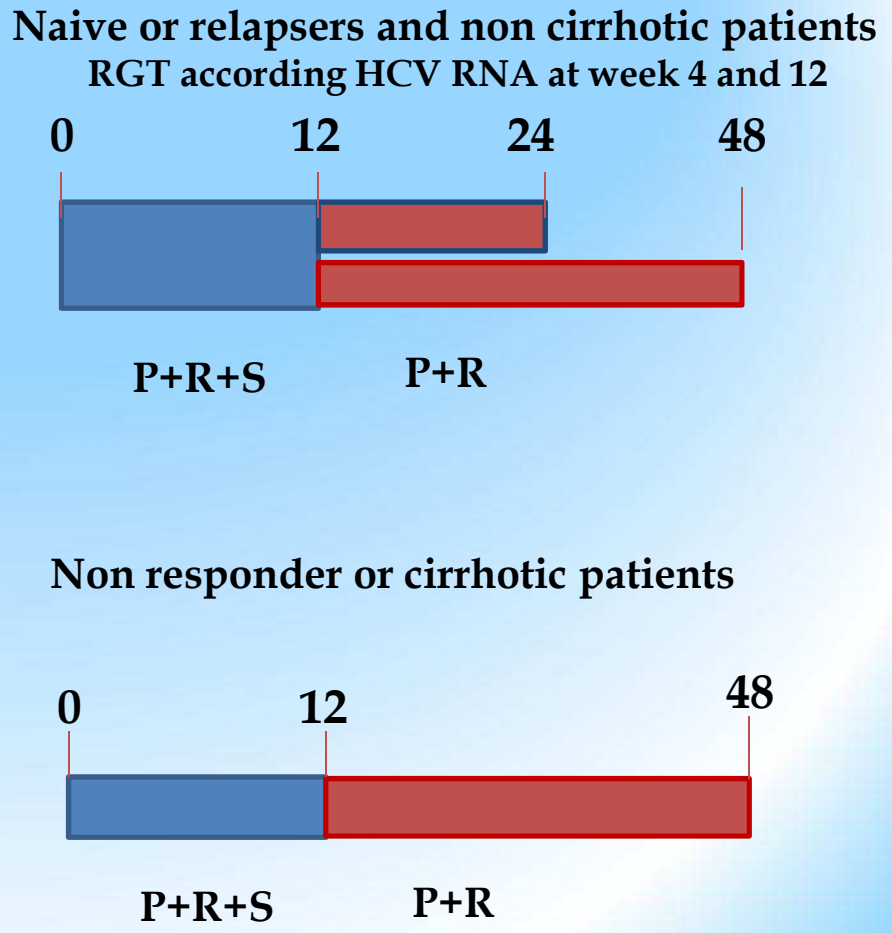
- HCV NS3/4A protease inhibitor
  - Competitive reversible macrocyclic non-convalent inhibitor of NS3/4A protease

- One 150 mg capsule, once-daily dosing with food
  - Exposure increased by ~60% with any type of food
  - Targeted to the liver, substrate of transporter OATP
  - Excretion primarily via feces, minimal in urine (<1%)
  - Metabolism primarily via CYP3A

OATP = organic anion transporter protein; CYP3A = cytochrome P450 3A

C212 Study: Simeprevir + PegIFN/RBV in GT1 HCV/HIV Coinfection

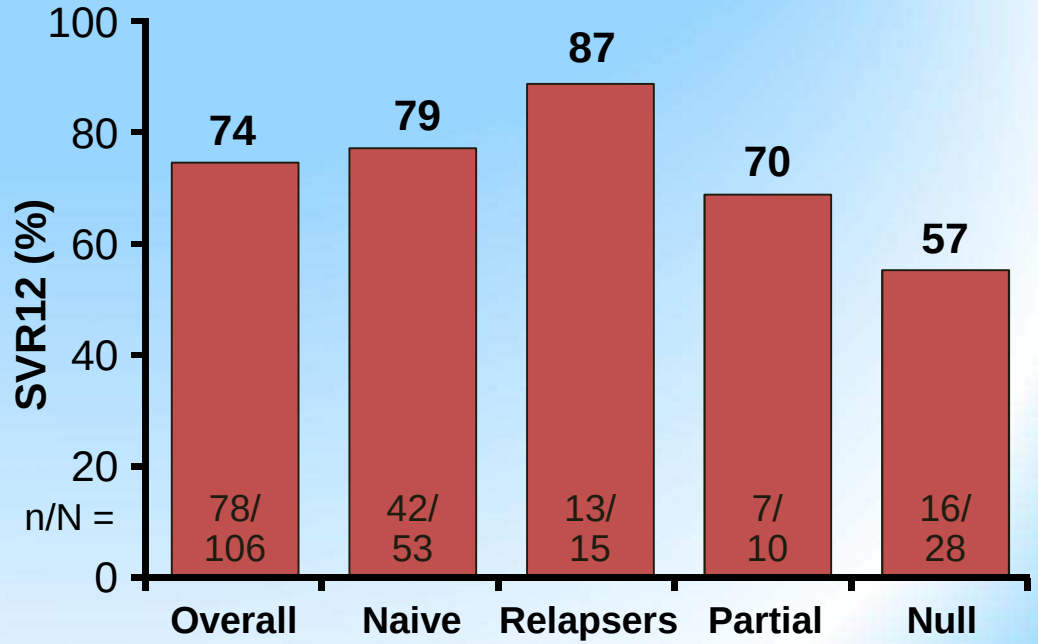
- Phase III randomized controlled trial[45]
  - 24- or 48-week regimens: SPV + pegIFN/RBV for 12 weeks, then pegIFN/RBV alone
- HCV treatment-naive or -experienced HIV+ patients (N = 106)
  - 88% on ART (VL < 50 cells/mL)
  - Excluded: boosted PIs, NNRTIs other than RPV



Dieterich D, et al. CID 29 September 2014

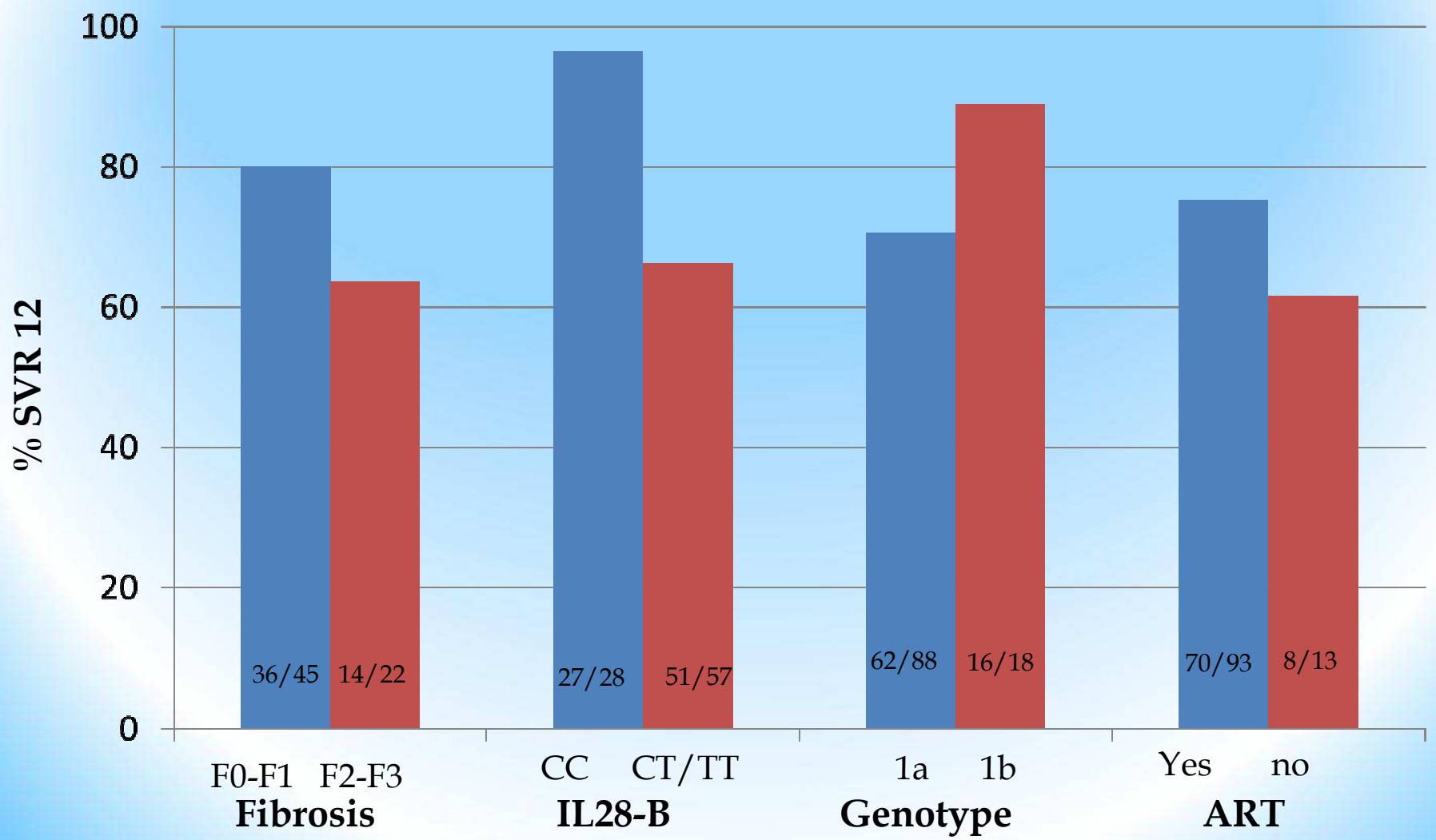
C212 Study: Simeprevir + PegIFN/RBV in GT1 HCV/HIV Coinfection

- All, but one, patients with SVR 12 had SVR 24 (a HCV reinfection)



Dieterich D, et al. CID 29 September 2014

C212 Study: Simeprevir + PegIFN/RBV in GT1 HCV/HIV Coinfection



Dieterich D, et al. CID 29 September 2014

C212 Study: Simeprevir + PegIFN/RBV in GT1 HCV/HIV Coinfection

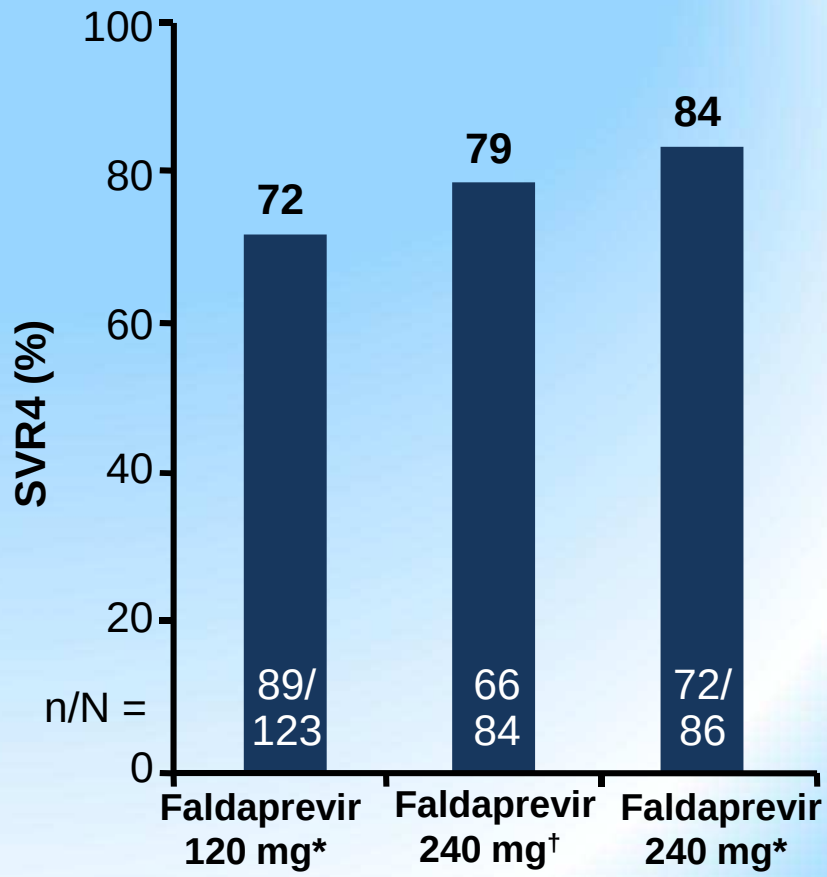
Table 4. AEs during the first 12 weeks of treatment (simeprevir plus PR treatment phase)

	No. of patients (%) N=106
Any AE	102 (96.2)
Worst Grade 1 or 2 AE	67 (63.2)
Worst Grade 3 AE	29 (27.4)
Worst Grade 4 AE	6 (5.7)
Serious AE	6 (5.7)
AE with fatal outcome	0 (0)
AE leading to permanent discontinuation	
Of at least one study drug	5 (4.7)
Simeprevir and PR	3 (2.8)
Simeprevir only	1 (0.9)
Most common AEs (>25% in simeprevir group)	
Fatigue	43 (40.6)
Headache	30 (28.3)
Nausea	27 (25.5)
AEs of clinical or special interest	
Neutropenia	30 (28.3)
Anemia	22 (20.8)
Pruritus	21 (19.8)
Rash	17 (16.0)
Sunburn	3 (2.8)
Photosensitivity	2 (1.9)
Increased bilirubin	5 (4.7)

Dieterich D, et al. CID 29 September 2014

STARTVerso4: Faldaprevir + PegIFN/RBV in GT1 HCV/HIV Coinfection

- Phase III open-label study
  - 24- or 48-week regimens: faldaprevir + pegIFN/RBV for 12 or 24 weeks, then pegIFN/RBV alone
- HCV treatment-naive or previous relapser HIV+ patients (N = 308)
  - 96% on ART (VL < 50 cells/mL)
- Safety profile similar to monoinfected pts
  - Most frequent AEs: nausea, fatigue, diarrhea, headache
  - Decrease in hemoglobin consistent with pegIFN/RBV historical data
- 1 patient had HIV rebound requiring new ART regimen

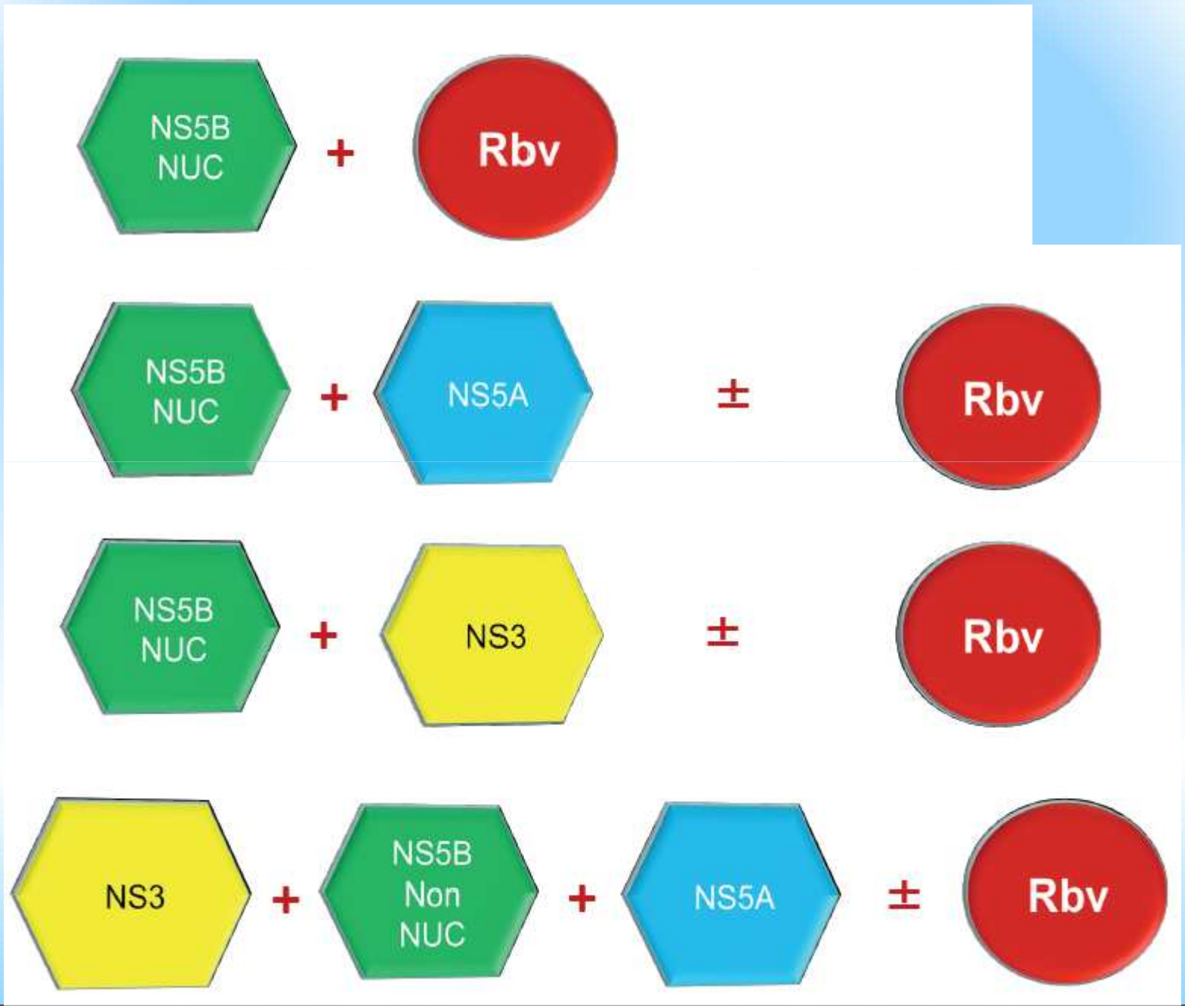


*24 wks of therapy; †12 wks of therapy

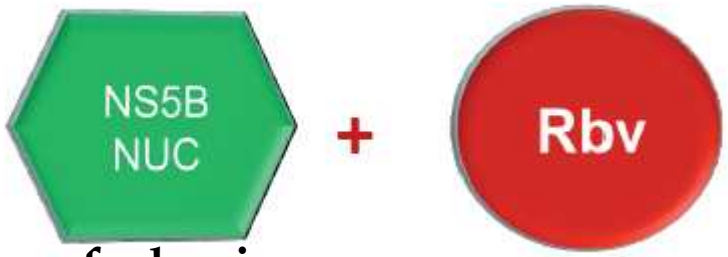
Rockstroh JK, et al. AASLD 2013. Abstract 1099.

IFN-free regimens

IFN-free regimens



IFN-free regimens



sofosbuvir

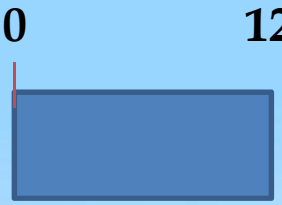
Sofosbuvir and Ribavirin for Hepatitis C in Patients With HIV Coinfection

JAMA 2014

Mark S. Sulkowski, MD; Susanna Naggie, MD; Jacob Lalezari, MD; Walford Jeffrey Fessel, MD; Karam Mounzer, MD; Margaret Shuhart, MD; Anne F. Luetkemeyer, MD; David Asmuth, MD; Anuj Gaggar, MD, PhD; Liyun Ni, PhD; Evguenia Svarovskaia, PhD; Diana M. Brainard, MD; William T. Symonds, PharmD; G. Mani Subramanian, MD, PhD; John G. McHutchison, MD; Maribel Rodriguez-Torres, MD; Douglas Dieterich, MD; for the PHOTON-1 Investigators

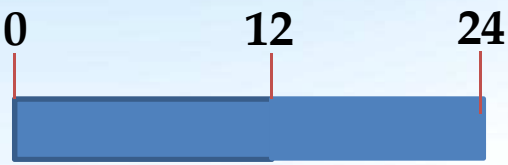
- Phase III open-label study
  - 12- (GT2/3 treatment-naive) or 24-week regimens (GT1 treatment-naive, GT2/3 treatment experienced): sofosbuvir + RBV
- HCV treatment-naive or -experienced HIV+ patients (N = 223)
  - Approx 76% on ART (VL < 50 cells/mL), various standard regimens

Naive HCV 2 or 3 patients



Rib+Sob

Naive HCV 1 or non responder HCV 2 or 3 patients



Rib+Sob

Sofosbuvir and Ribavirin for Hepatitis C in Patients With HIV Coinfection

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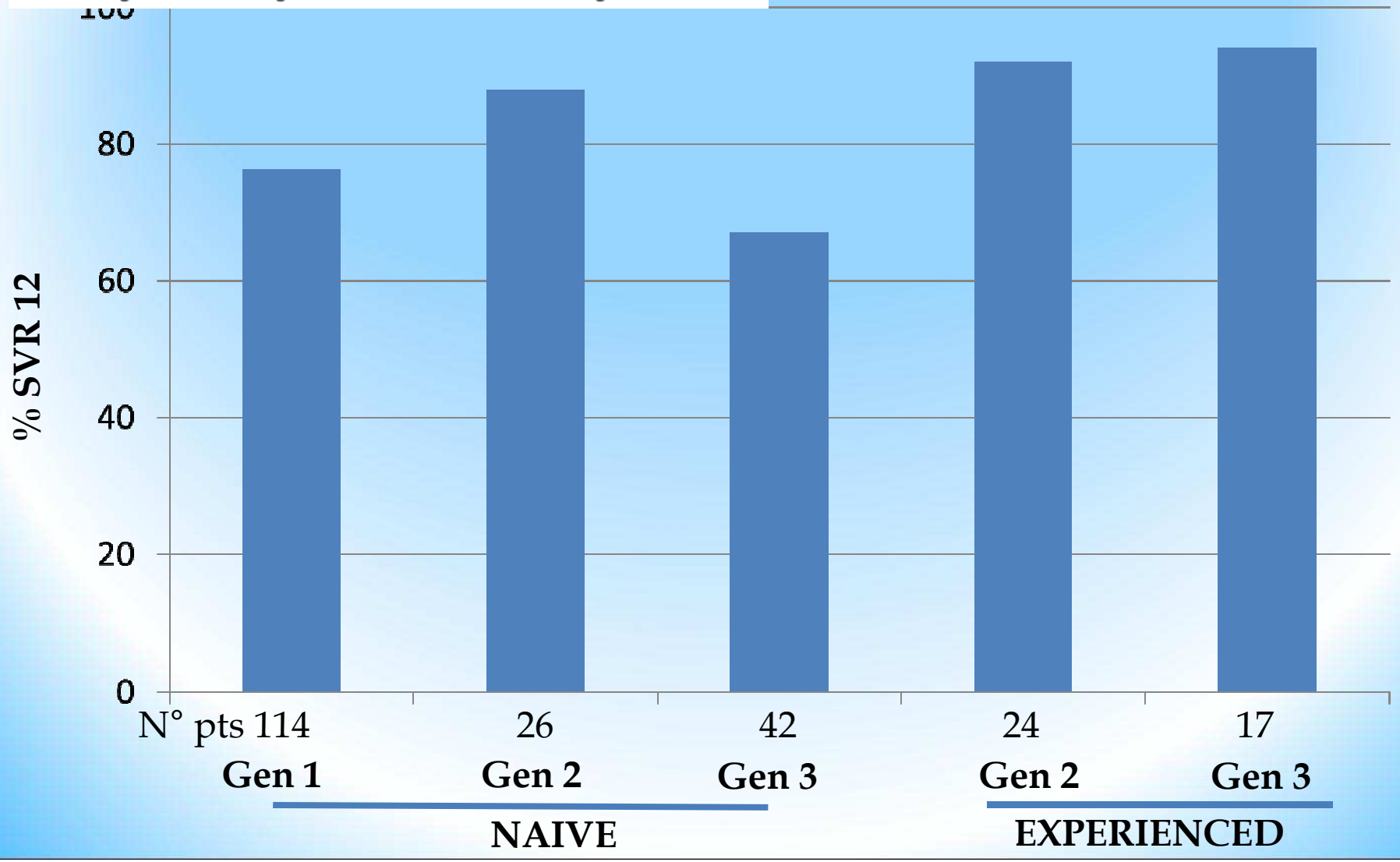

Sofosbuvir and Ribavirin for Hepatitis C in Patients With HIV Coinfection

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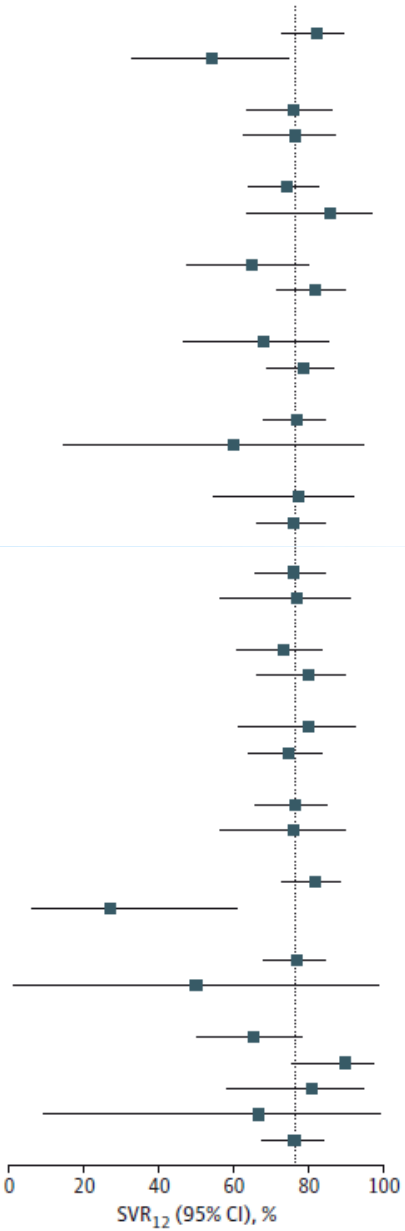
JAMA 2014

Figure 2. Rates of 12-Week Sustained Virologic Response by Subgroup in Treatment-Naive Patients With Hepatitis C Virus Genotype 1 Receiving 24 Weeks of Sofosbuvir and Ribavirin

	No. of Patients With SVR	Total No. of Patients
Genotype		
1a	74	90
1b	13	24
Age, y		
<50	48	63
≥50	39	51
Sex		
Men	69	93
Women	18	21
Race		
Black	24	37
Nonblack	63	77
Ethnicity		
Hispanic/Latino	17	25
Non-Hispanic/Latino	70	89
Cirrhosis		
No	84	109
Yes	3	5
HCV RNA level, $\log_{10}$ IU/mL		
<6	17	22
≥6	70	92
Body mass index		
<30	67	88
≥30	20	26
Baseline ALT		
≤1.5 × ULN	47	64
>1.5 × ULN	40	50
IL28B		
CC	24	30
Non-CC	62	83
Interferon classification		
Eligible	65	85
Ineligible	22	29
Study drug completion status		
Completed	84	103
Prematurely discontinued	3	11
ARV at enrollment		
Yes	86	112
No	1	2
ARV Class		
NNRTI	32	49
PI	35	39
Integrase inhibitor	17	21
Other	2	3
Overall	87	114



Sofosbuvir and Ribavirin for Hepatitis C in Patients With HIV Coinfection

Mark S. Sulkowski, MD; Susanna Naggie, MD; Jacob Lalezari, MD; Walford Jeffrey Fessel, MD; Karam Mounzer, MD; Margaret Shuhart, MD; Anne F. Luetkemeyer, MD; David Asmuth, MD; Anuj Gaggar, MD, PhD; Liyun Ni, PhD; Evguenia Svarovskaia, PhD; Diana M. Brainard, MD; William T. Symonds, PharmD; G. Mani Subramanian, MD, PhD; John G. McHutchison, MD; Maribel Rodriguez-Torres, MD; Douglas Dieterich, MD; for the PHOTON-1 Investigators

JAMA 2014

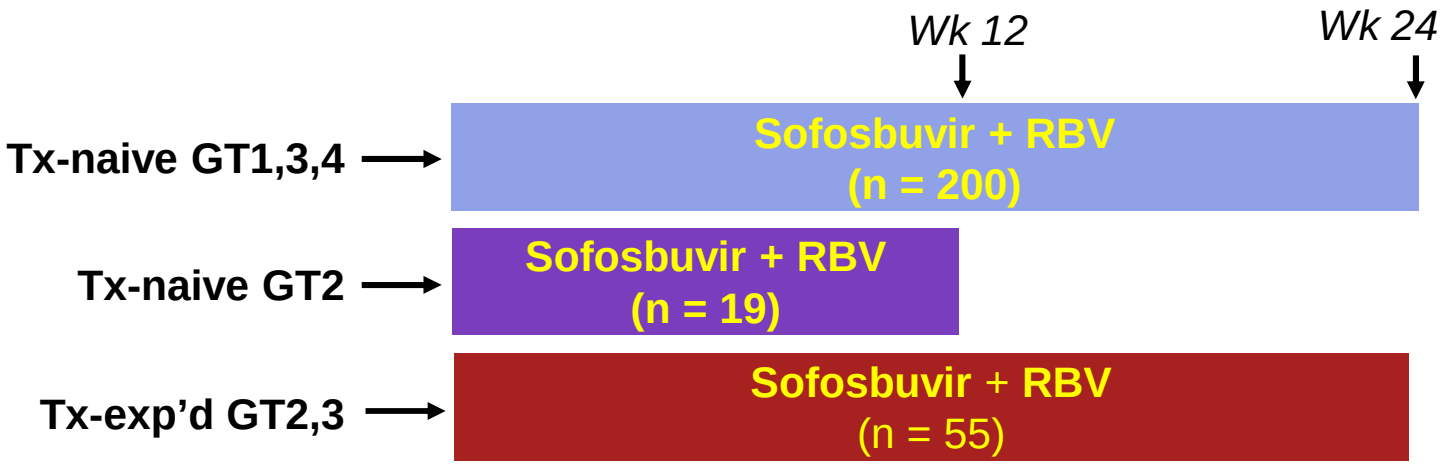
- Safety profile similar to monoinfected patients; consistent with RBV
  - Most frequent AEs: fatigue, insomnia, headache, nausea, diarrhea
- 2 patients had transient HIV rebound due to nonadherence

Table 3. Discontinuations, Adverse Events, and Hematologic Abnormalities

Parameter	No (%) of Patients With Hepatitis C Virus (HCV)		
	Treatment Naive		Treatment Experienced
	Genotype 1 (n = 114)	Genotype 2 and 3 (n = 68)	Genotype 2 and 3 (n = 41)
Duration of treatment, mean (SD), wk	23.0 (4.04)	11.7 (1.52)	23.8 (2.44)
Discontinuation due to adverse events	3 (2.6)	3 (4.4)	1 (2.4)
Death	0	1 (1.5)	0
Serious adverse events[a]	8 (7.0)	5 (7.4)	1 (2.4)
Common adverse events[b]			
Fatigue	41 (36.0)	24 (35.3)	19 (46.3)
Insomnia	15 (13.2)	14 (20.6)	8 (19.5)
Nausea	18 (15.8)	12 (17.6)	6 (14.6)
Headache	16 (14.0)	9 (13.2)	5 (12.2)
Irritability	14 (12.3)	7 (10.3)	2 (4.9)
Cough	14 (12.3)	4 (5.9)	4 (9.8)
Upper respiratory tract infection	13 (11.4)	8 (11.8)	5 (12.2)
Diarrhea	12 (10.5)	6 (8.8)	5 (12.2)
Dizziness	7 (6.1)	1 (1.5)	5 (12.2)
Anemia	13 (11.4)	6 (8.8)	3 (7.3)
Laboratory events			
Decreased hemoglobin concentration, g/dL			
<10	22 (19.3)	7 (10.3)	5 (12.2)
<8.5	2 (1.8)	1 (1.5)	0
Total bilirubin			
3 to ≤6 mg/dL	13 (11.4)	3 (4.4)	4 (9.8)
Taking atazanavir	12 (92.3)	3 (100)	4 (100)
Not taking atazanavir	1 (7.7)	0	0
>6 mg/dL	9 (7.9)	1 (1.5)	2 (4.9)
Taking atazanavir	8 (88.9)	1 (100)	2 (100)
Not taking atazanavir	1 (11.1)	0	0

PHOTON-2: Sofosbuvir + RBV in GT1-4 HCV Patients Coinfected With HIV

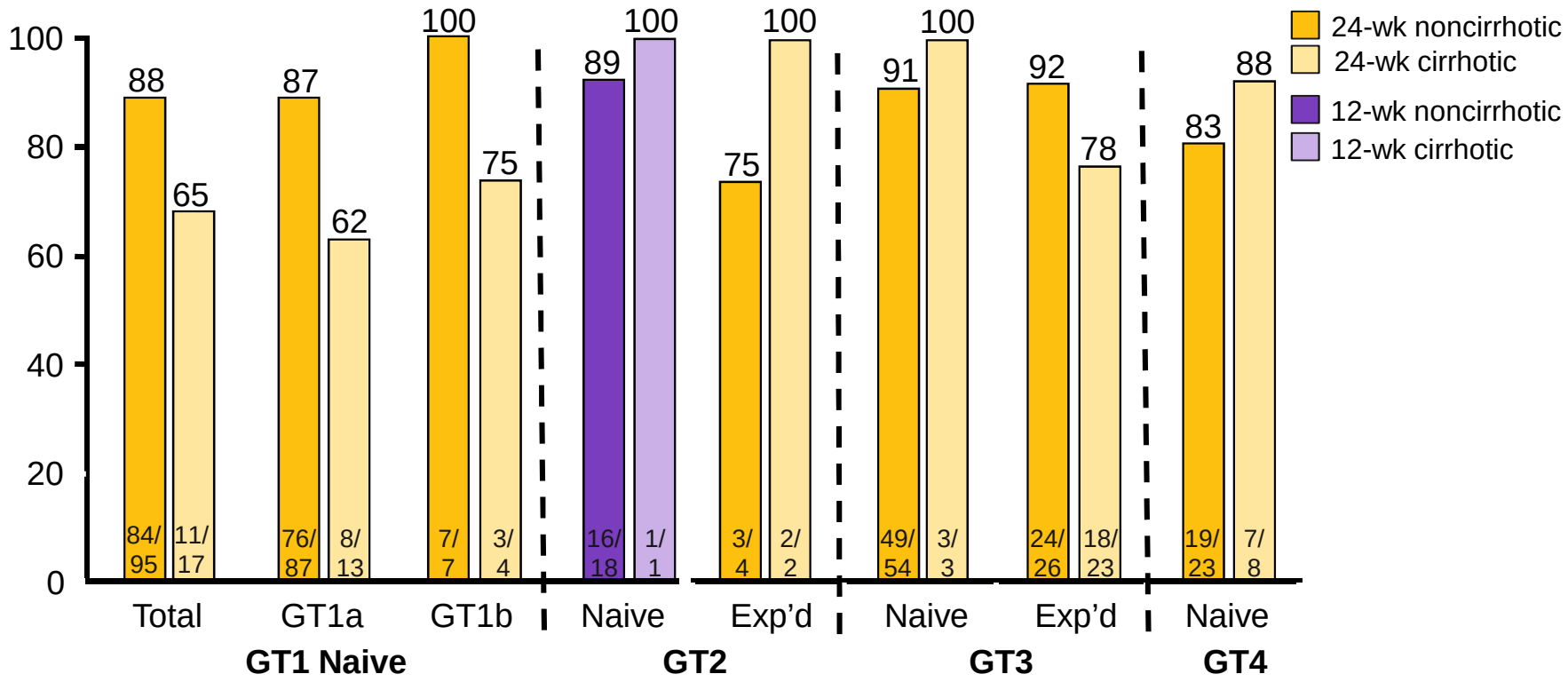
- Nonrandomized, open-label phase III study; primary endpoint: SVR12
- Stable ART (HIV-1 RNA < 50 copies/mL for ≥ 8 wks before enrollment)
  - 97% on ART: TDF/FTC, 100%; EFV, 25%; ATV/RTV, 17%; DRV/RTV, 21%; RAL; 23%; RPV, 5%
- **Cirrhosis at baseline: All pts, 20%;** tx-naive patients, 13%; tx-exp'd patients, 45%



Sofosbuvir 400 mg QD; weight-based RBV 1000 or 1200 mg/day

Molina JM, et al. AIDS 2014. Abstract MOAB0105LB.

PHOTON-2: SVR12 by Genotype and Cirrhosis



- Absolute CD4+ count—but not CD4%—decreased, consistent with effect of RBV on lymphocytes

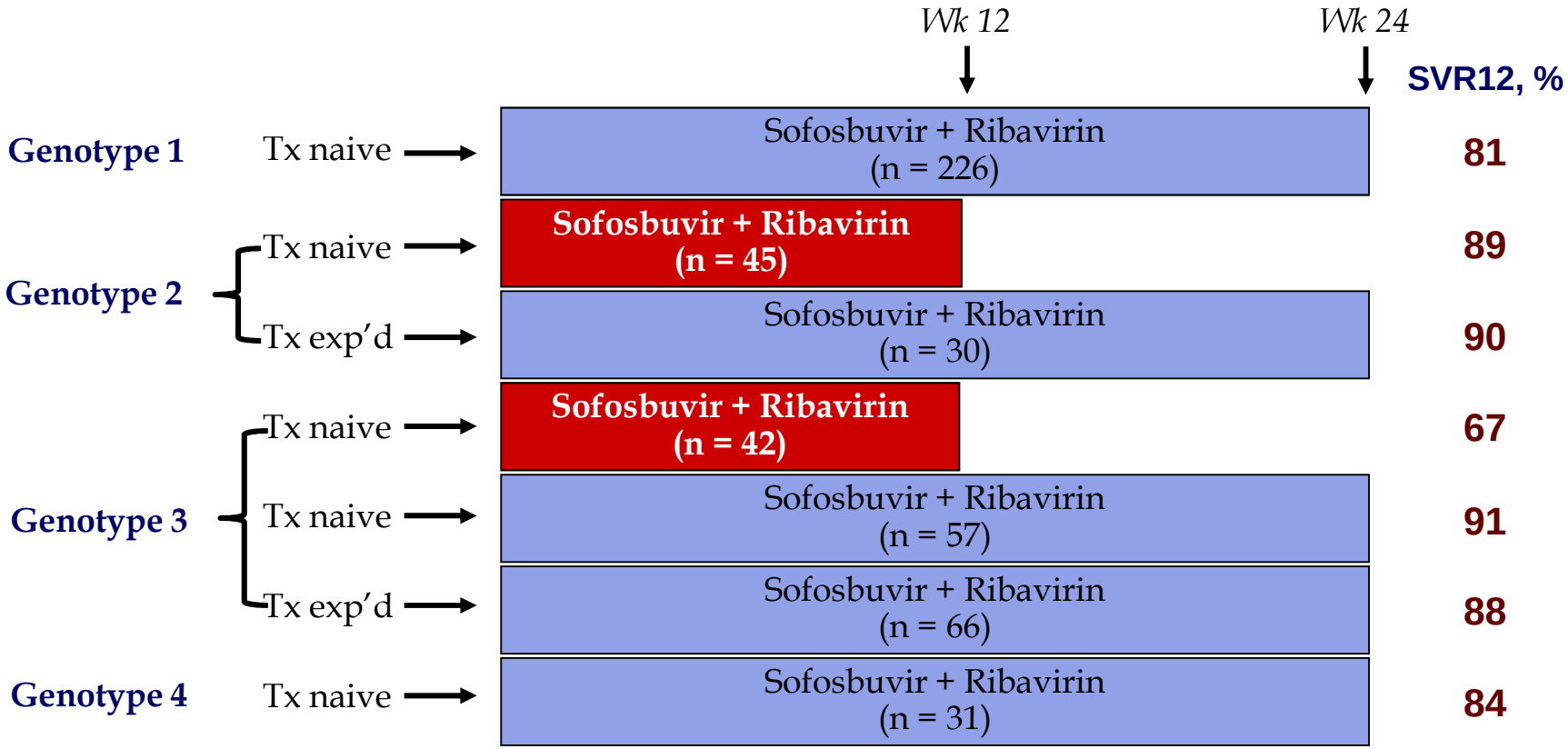
Molina JM, et al. AIDS 2014. Abstract MOAB0105LB.

PHOTON-1 and -2: Sofosbuvir + Ribavirin in GT1-4 HCV Pts Coinfected With HIV

- Pooled analysis from nonrandomized, open-label phase III studies
- Stable ART (HIV-1 RNA < 50 copies/mL for > 8 wks before enrollment)
  - 96% on ART (100% on TDF/FTC, 30% on EFV, 17% on ATV/RTV, 19% on DRV/RTV, 20% on RAL, 5% on RPV)
- 15% of pts with cirrhosis

Rockstroh, JK et al. AASLD 2014. Abstract 195.

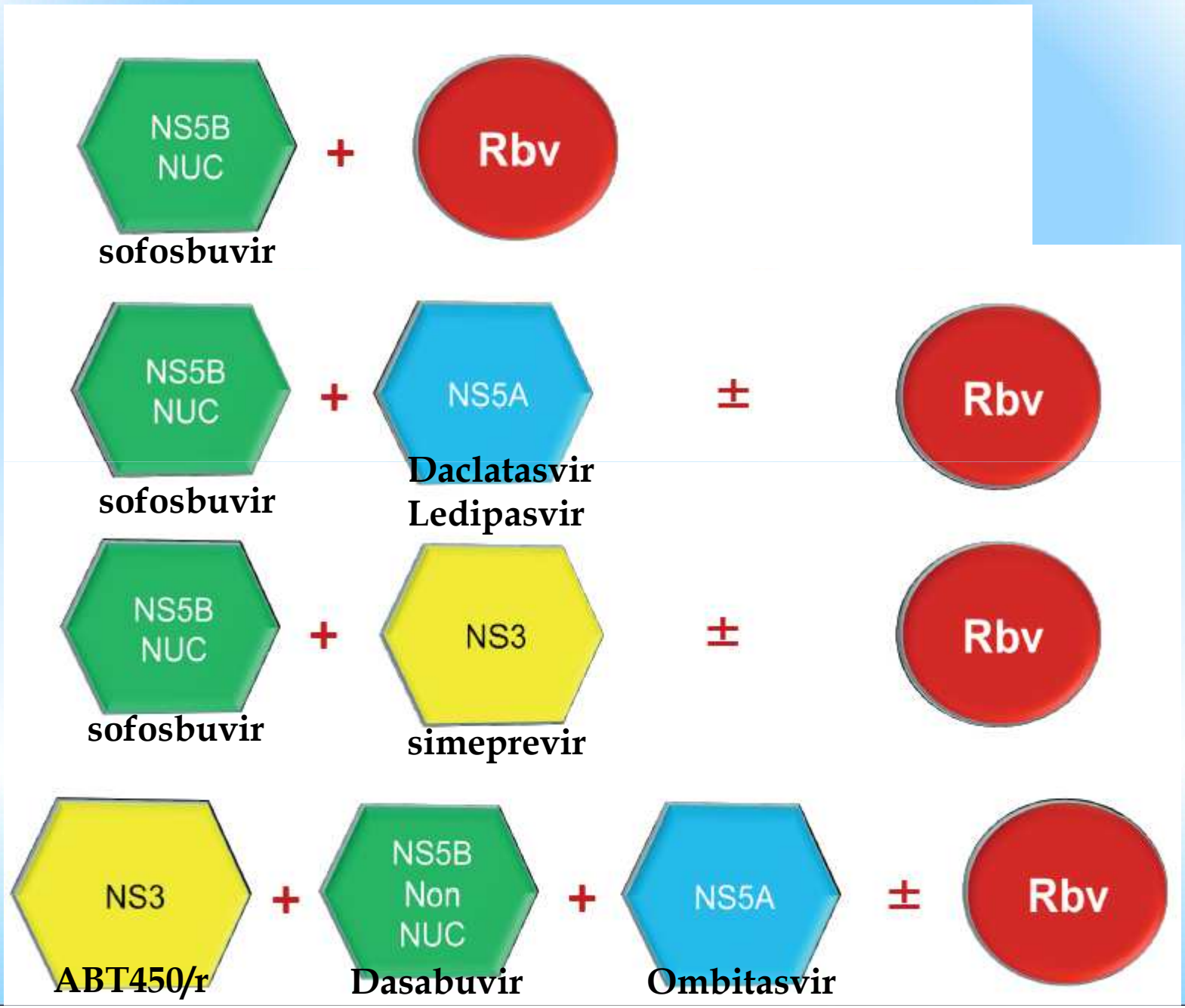
PHOTON-1 and -2: Sofosbuvir + Ribavirin in GT1-4 HCV Pts Coinfected With HIV



Sofosbuvir 400 mg QD; weight-based ribavirin 1000 or 1200 mg/day

Rockstroh, JK et al. AASLD 2014. Abstract 195

IFN-free regimens



Interferon-Containing and Interferon-Free HCV Therapy for HIV-Infected Patients

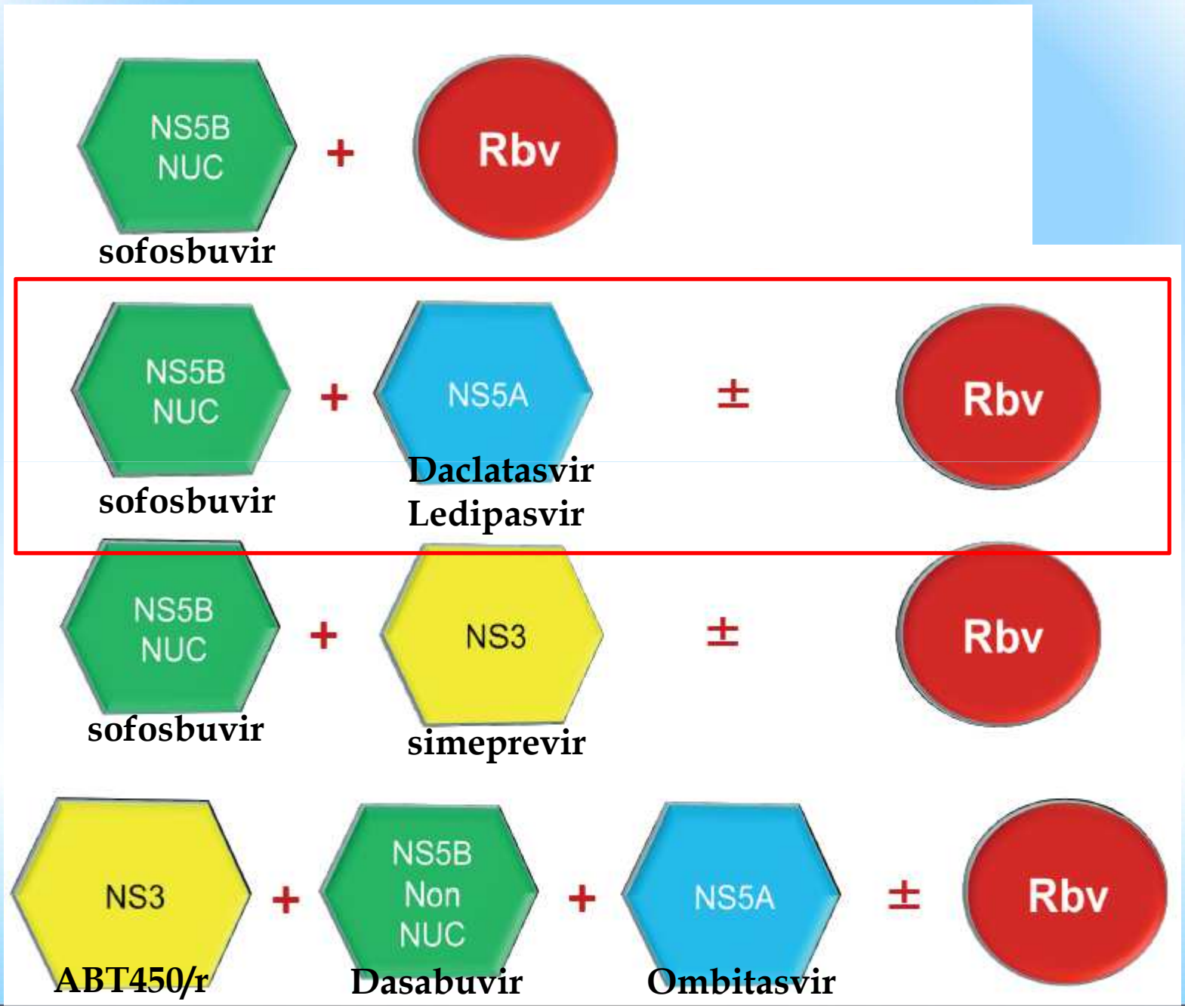
Mark S. Sulkowski, MD[1]

Table 2 Clinical trials of Interferon-free, oral direct-acting antiviral regimens for the treatment of HCV infection in HIV-infected adults

HCV treatment regimen					ClinicalTrials.gov identifier
NS3/4A protease inhibitor	NS5A inhibitor	NS5B nucleotide analogue polymerase inhibitor	NS5B non-nucleoside analogue polymerase inhibitor	Ribavirin	
None	Ledipasvir	Sofosbuvir	None	None	NCT01878799
None	Daclatasvir	Sofosbuvir	None	None	NCT02032888
ABT450/ ritonavir	ABT267	None	ABT333	1000 or 1200 mg/d	NCT01939197
MK-5172	MK-8742	None	None	1000 or 1200 mg/d	NCT01717326

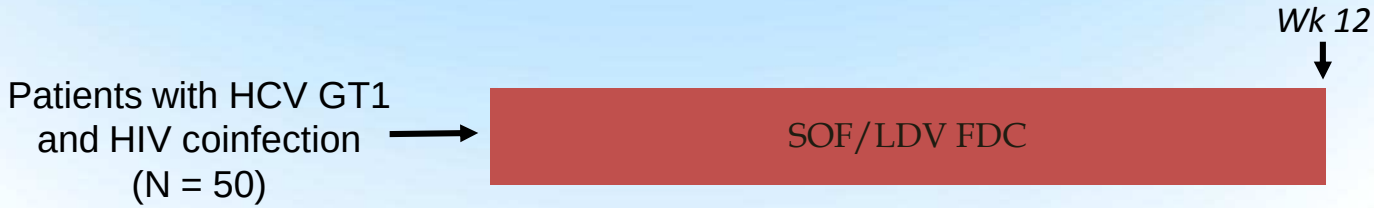
Sem Liv Dis 2014

IFN-free regimens



ERADICATE: SOF/LDV in ARV-Treated and Untreated HCV/HIV-Coinfected Patients

- Single-arm phase II trial
- ARV use in 37 ARV-treated patients: efavirenz (41%), raltegravir (27%), rilpivirine (21%), rilpivirine and raltegravir (8%), efavirenz and raltegravir (3%)
- Median baseline CD4+ count: ARV treated 576 cells/mm^3 (range: 113-1612), ARV untreated 687 cells/mm^3 (range: 319-1287)
- SVR12 in ARV-treated patients: 100%; not yet available in ARV-untreated patients
- No clinically significant changes in HIV-1 RNA or CD4+ cell count
- SOF/LDV well tolerated, no discontinuations or grade 4 AEs



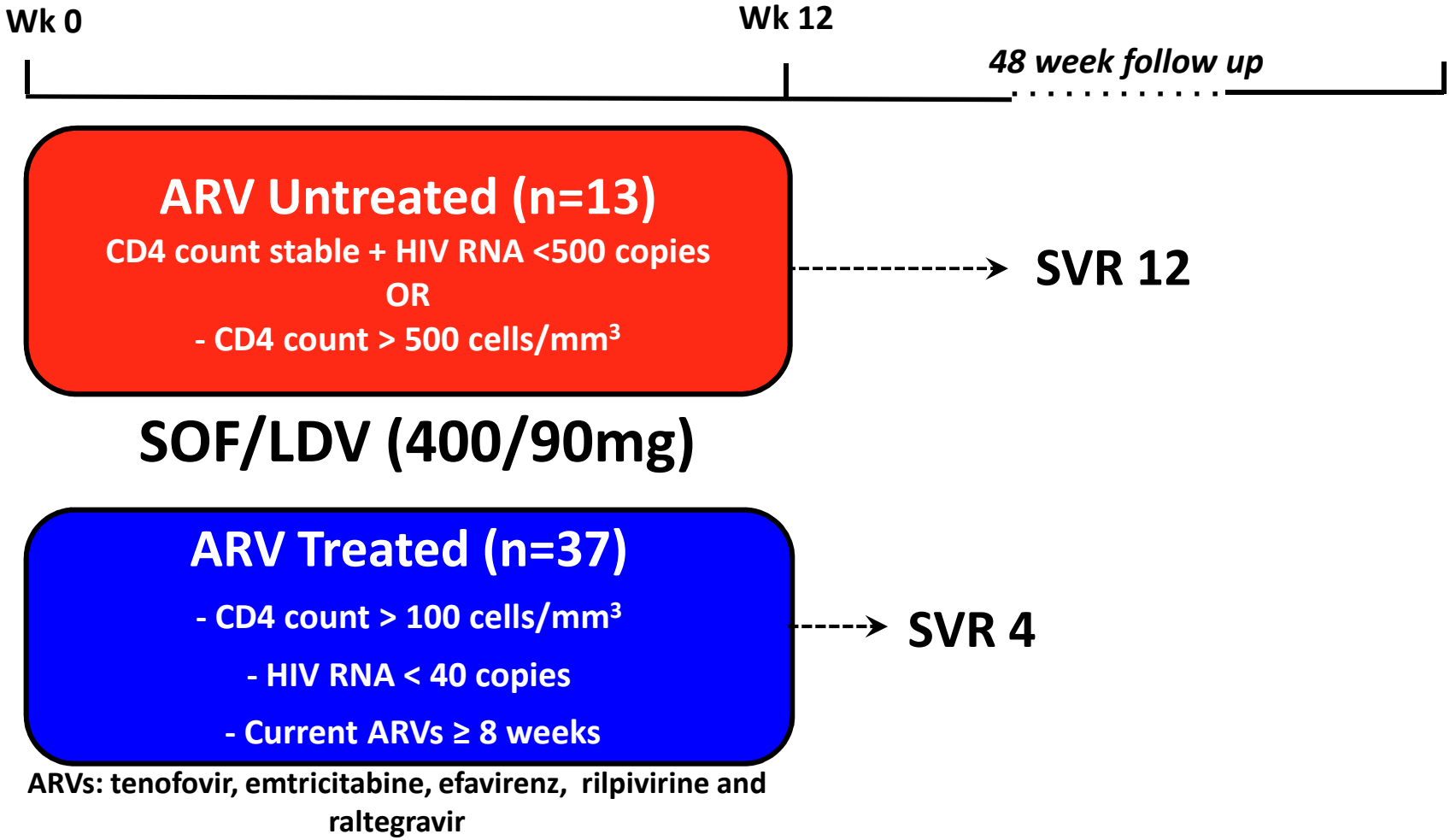
Sofosbuvir/ledipasvir 400/90 mg FDC tablet once daily.

Osinusi A, et al. EASL 2014. Abstract O14.

SOF/Ledipasvir for HIV/HCV-coinfection

ERADICATE

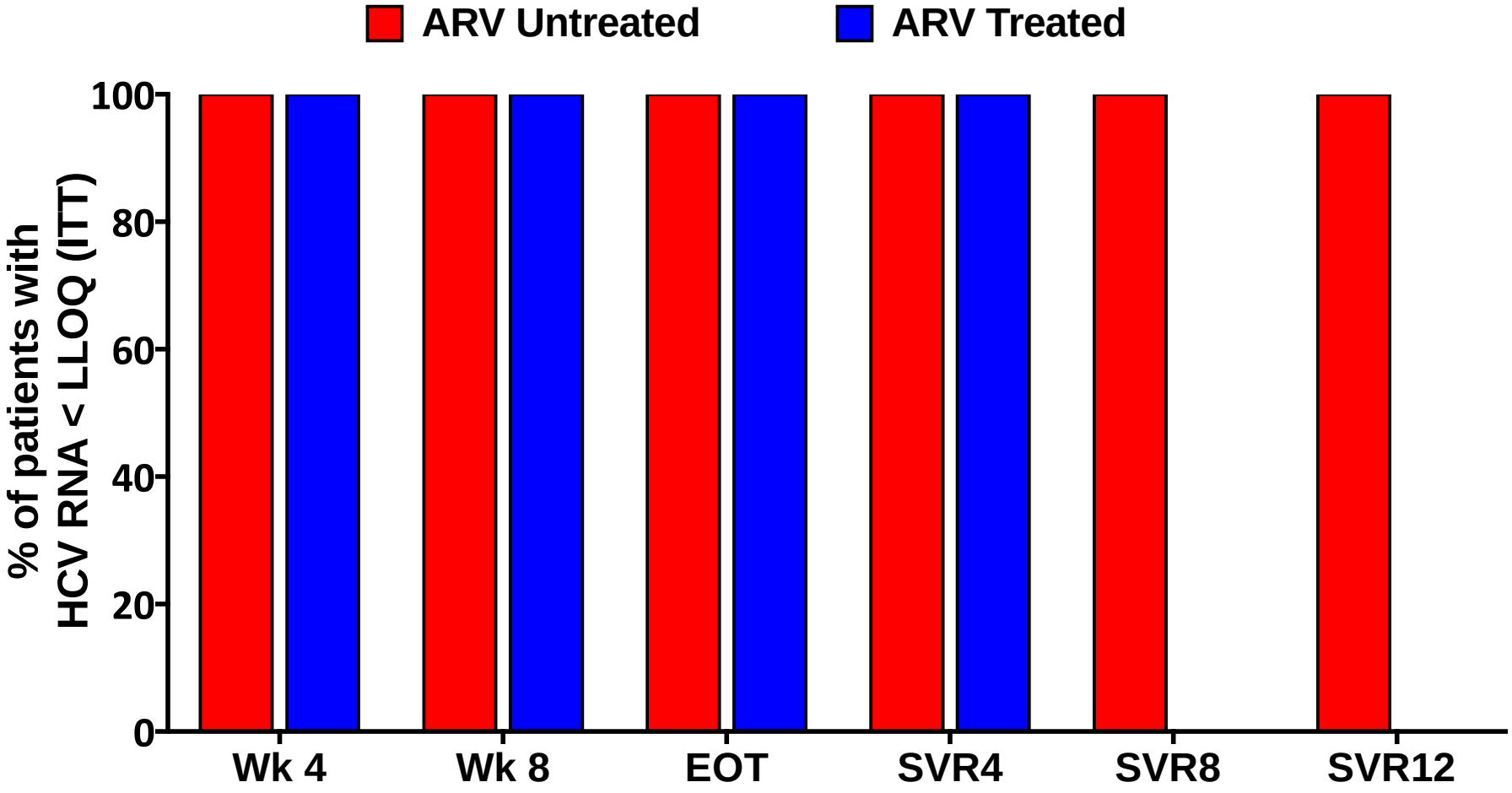
- Fifty HIV/HCV genotype 1, treatment-naive subjects
- HAI fibrosis stage 0 – 3



Osinusi A, EASL, 2014, O14

SOF/Ledipasvir for HIV/HCV-coinfection

ERADICATE

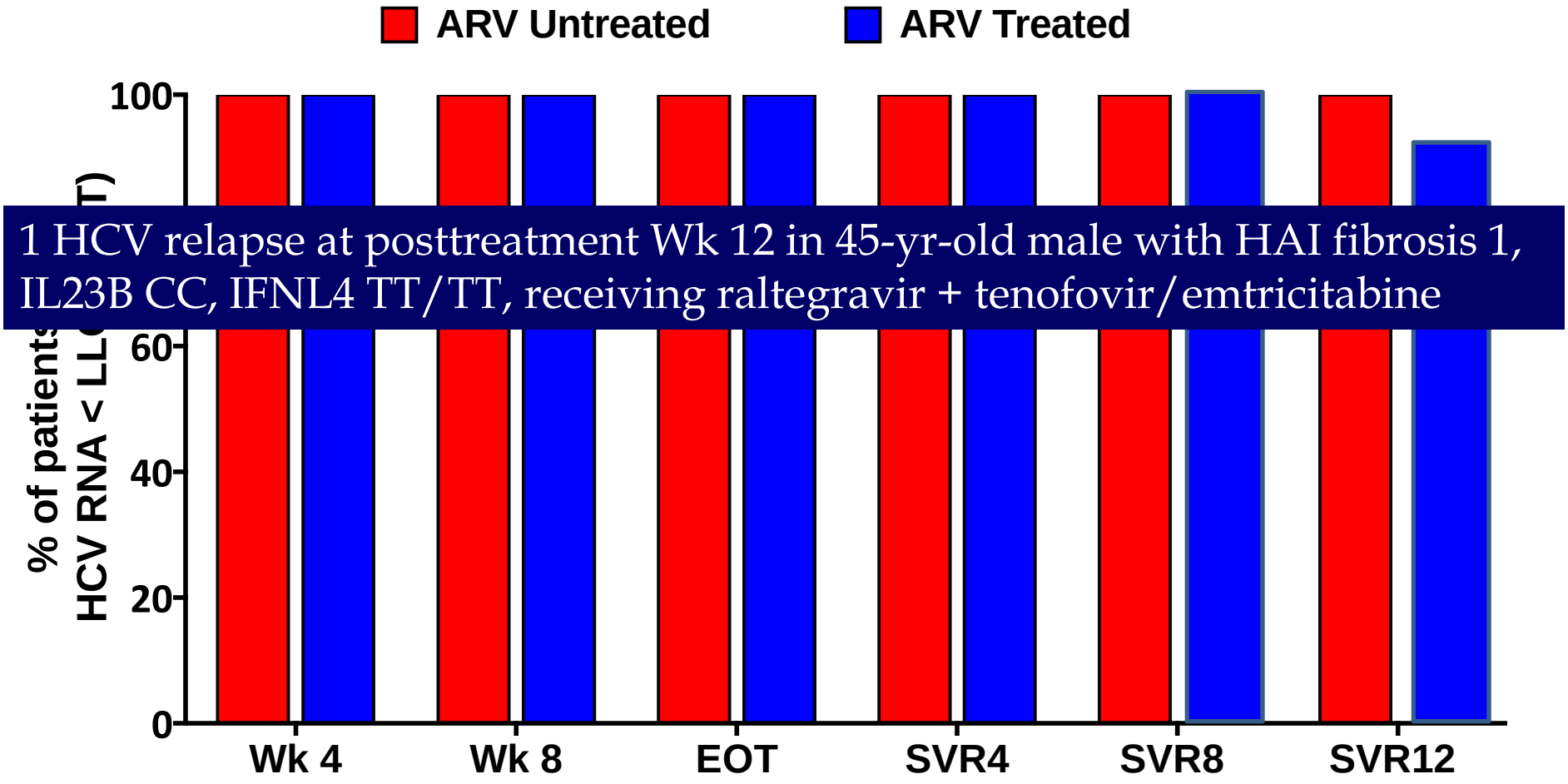


ARV -	13/ 13	13/13	13/ 13	12/12	10/10	10/10
ARV +	37/37	37/37	30/30	22/22	/	/

Osinusi A, EASL, 2014, O14

SOF/Ledipasvir for HIV/HCV-coinfection

ERADICATE

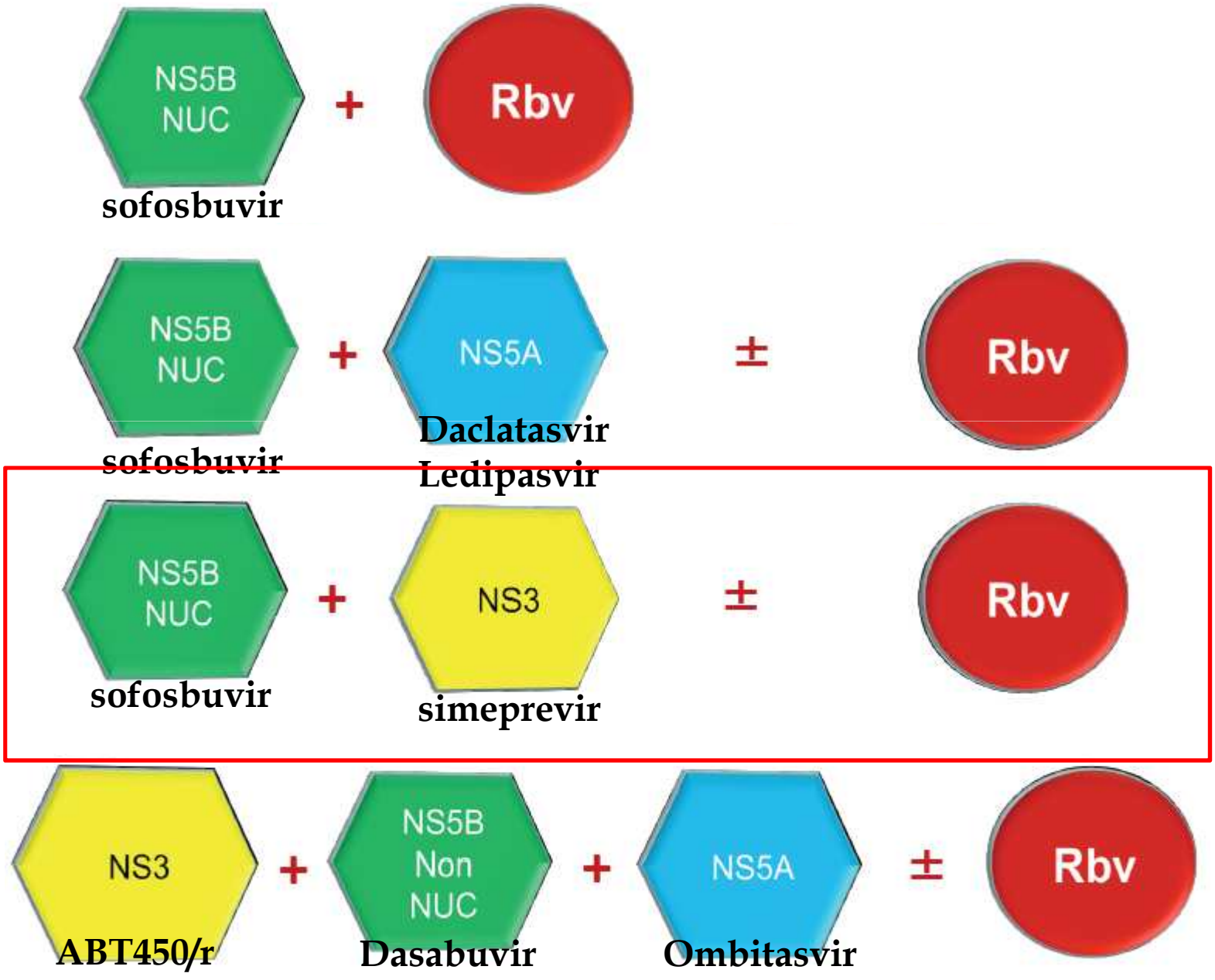


1 HCV relapse at posttreatment Wk 12 in 45-yr-old male with HAI fibrosis 1, IL23B CC, IFNL4 TT/TT, receiving raltegravir + tenofovir/emtricitabine

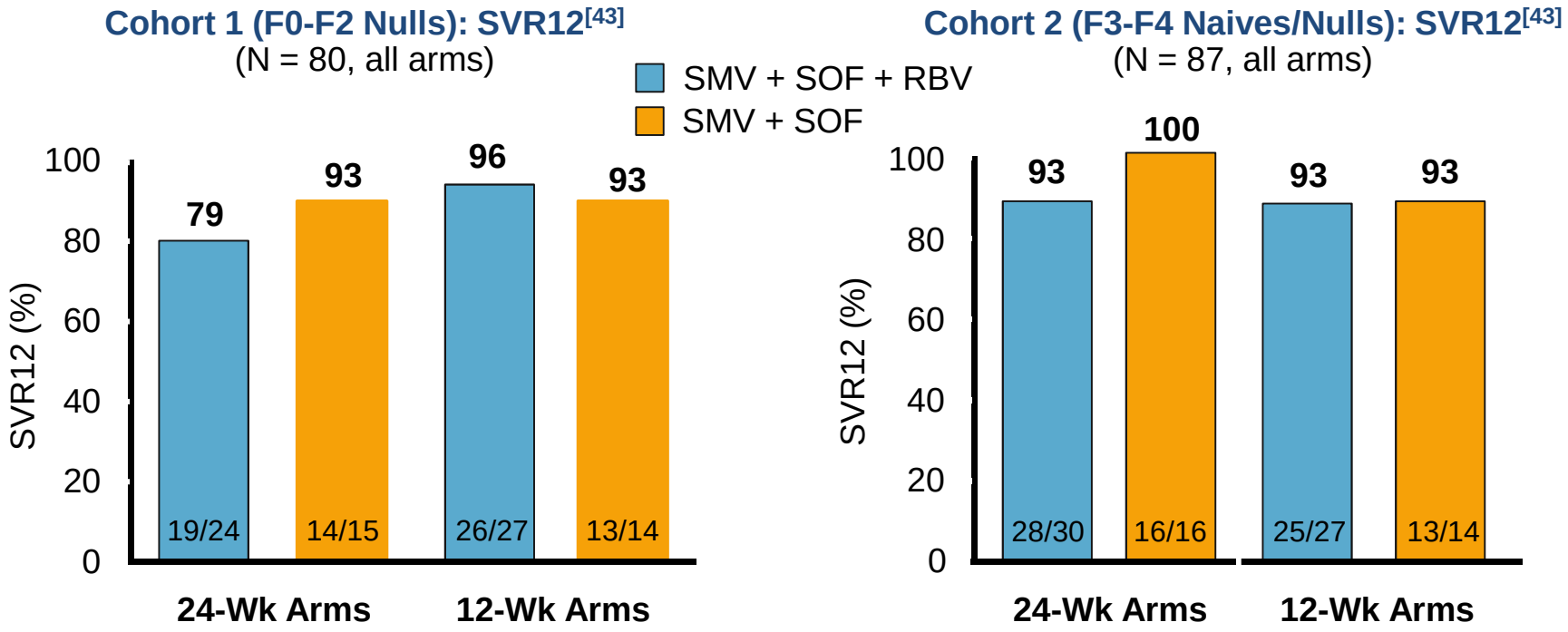
ARV -	13/ 13	13/13	13/ 13	12/12	12/12	12/12
ARV +	37/37	37/37	30/30	22/22	37/37	36/37

Townsend KS, et al. AASLD 2014. Abstract 84.

IFN-free regimens



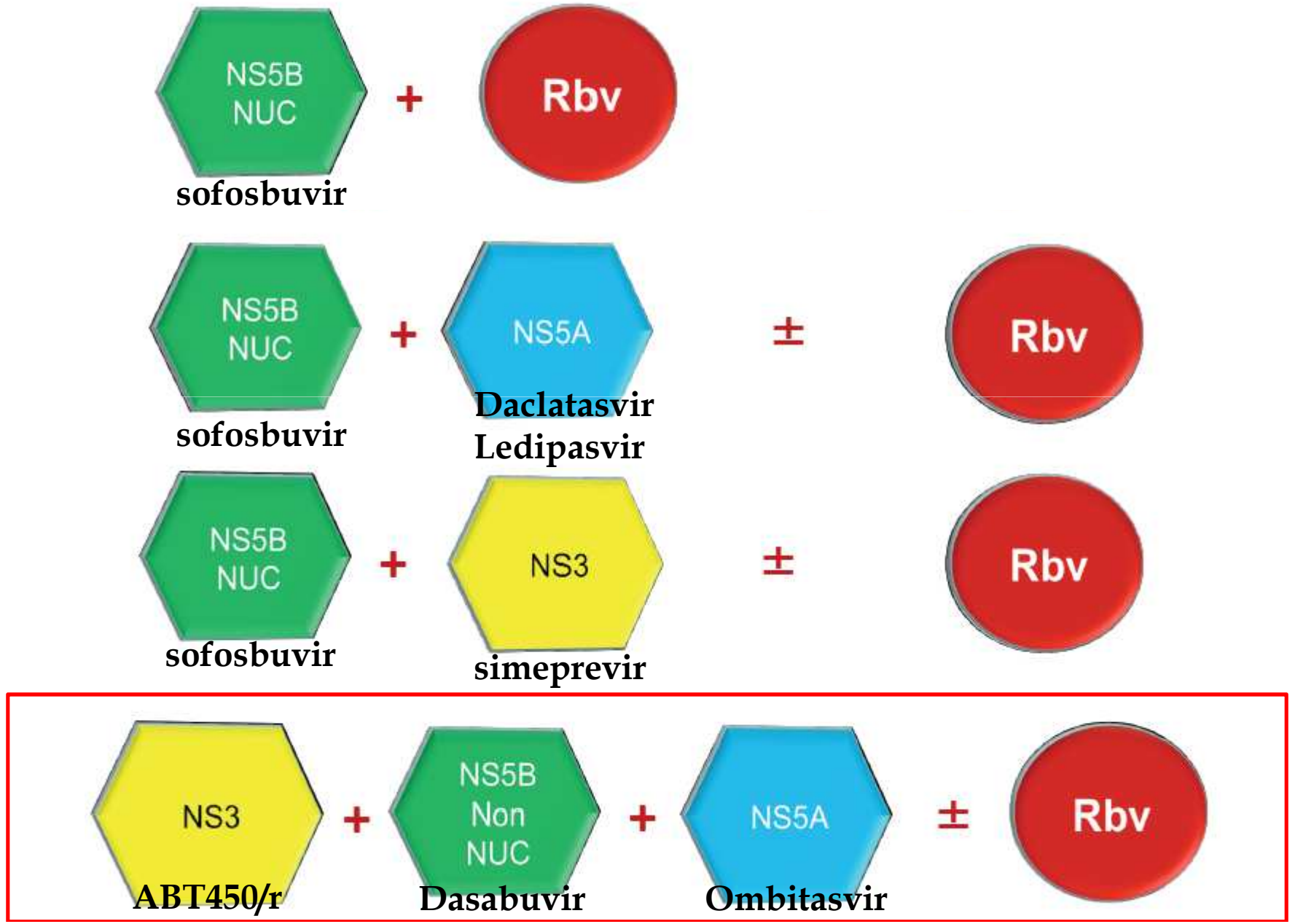
COSMOS: Sofosbuvir + Simeprevir ± RBV in GT1 HCV Monoinfection



- SVR in pts with Q80K mutation = 83% to 100%
- Study investigating SOF + SMV in HCV/HIV-coinfected patients planned[2]

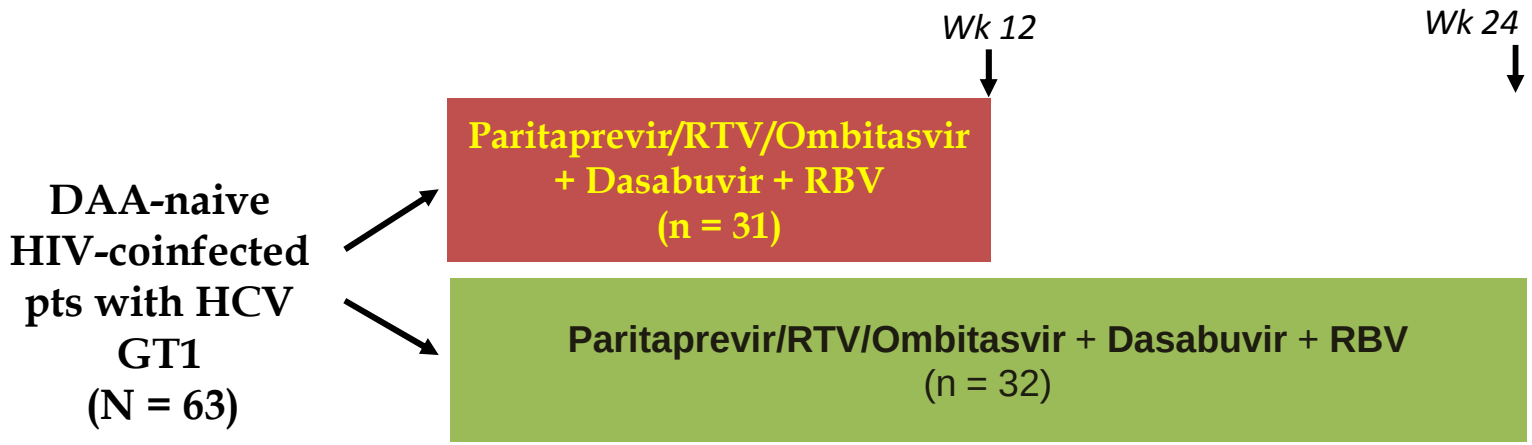
43. Lawitz E, et al. Lancet. 2014;[Epub ahead of print]. 49. ClinicalTrials.gov. NCT02206932.

IFN-free regimens



TURQUOISE I: Paritaprevir/RTV/Ombitasvir + Dasabuvir + RBV in GT1 HCV/HIV Pts

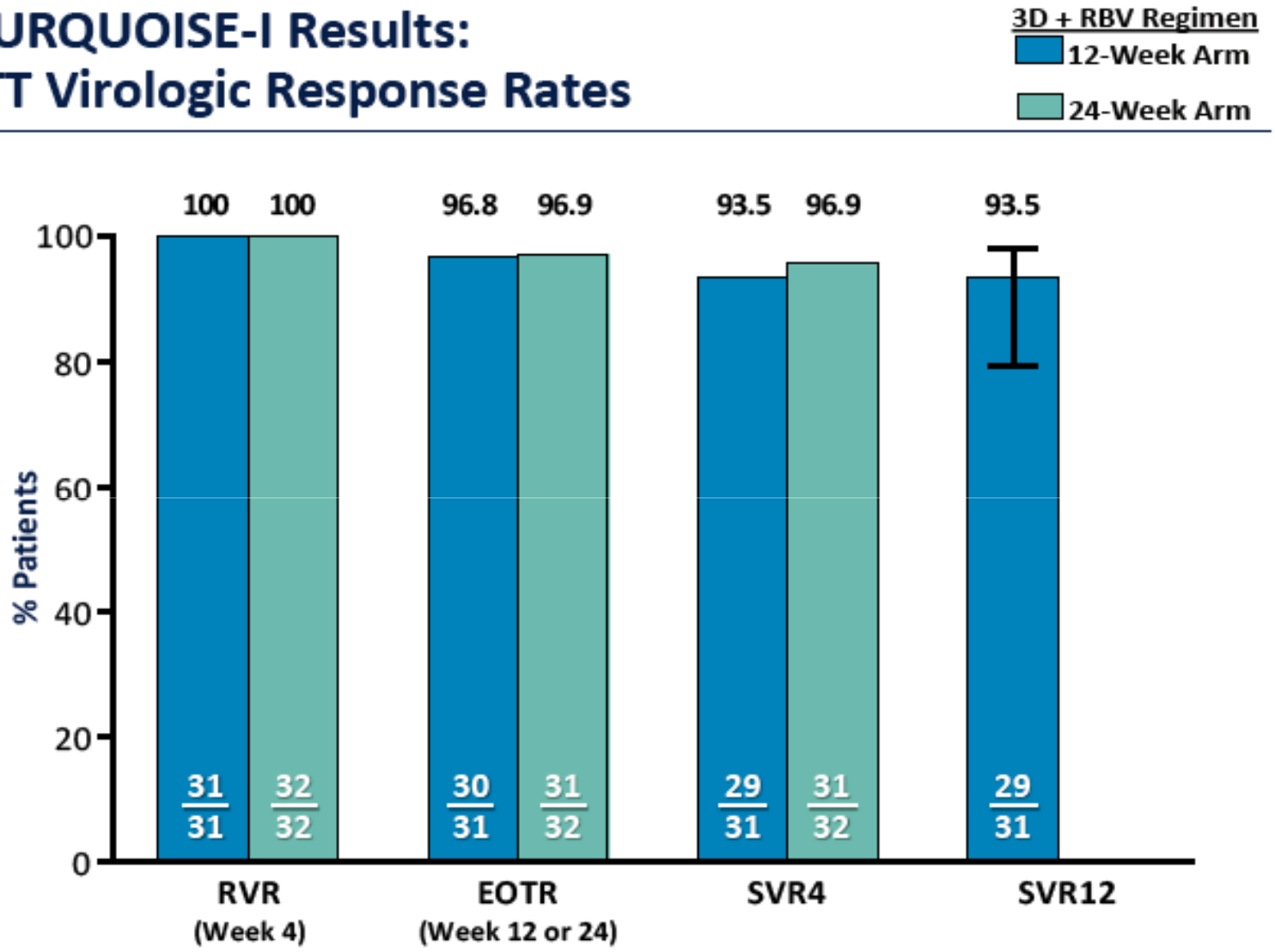
- **Open-label phase II/III trial in GT1, DAA-naive, coinfected pts**
  - **HIV-1 RNA < 40 c/mL *on ATV or RAL regimen;* CD4+ count ≥ 200 or CD4+% ≥ 14%**
- **Primary endpoint: SVR12**
- **19% of patients per arm had cirrhosis**



Paritaprevir/RTV/ombitasvir 150/100/25 mg QD FDC; dasabuvir 250 mg BID; RBV 1000-1200 mg/day.

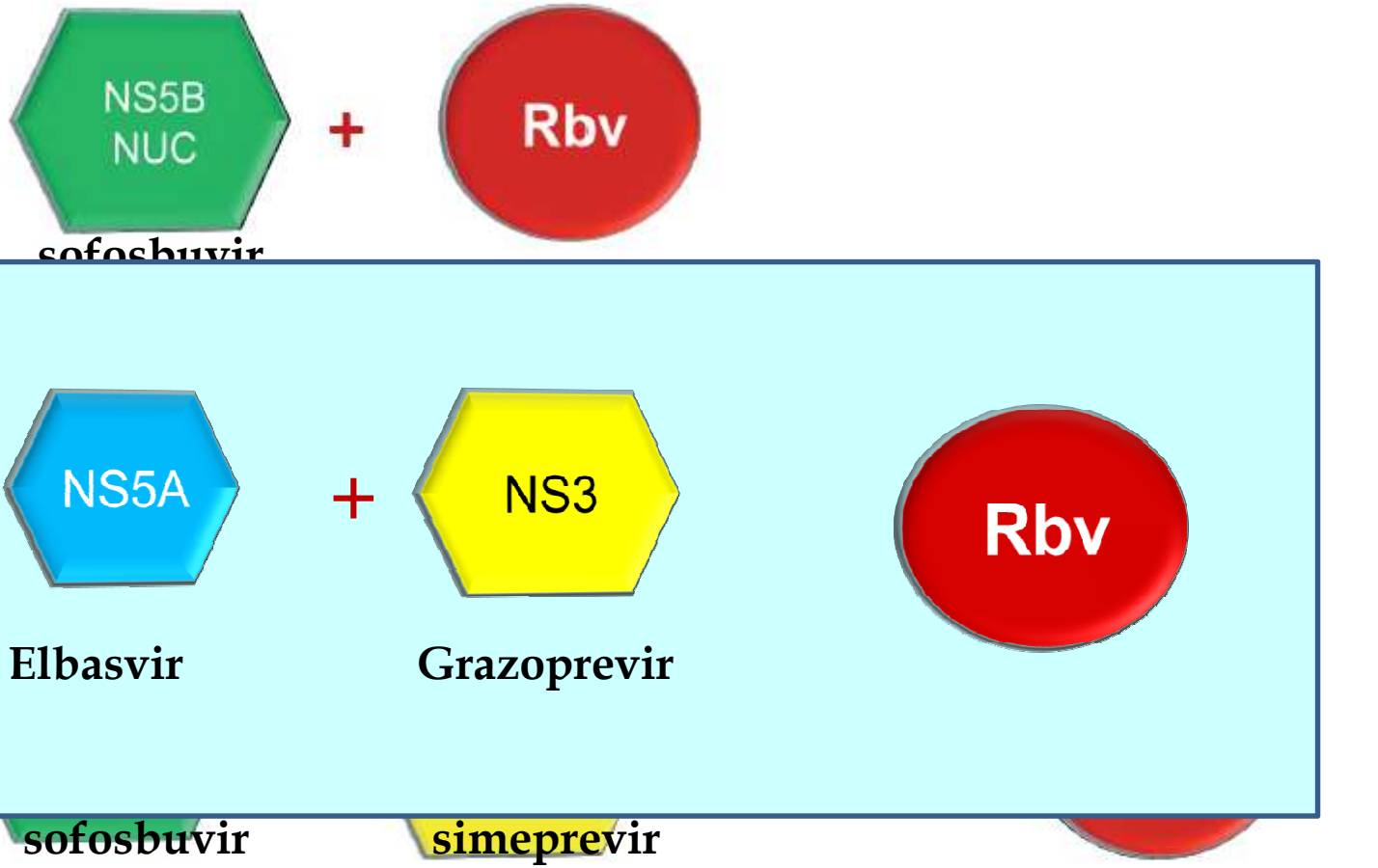
Eron et al, ICAAC 2014 54th Interscience Conferen
September 5-9, 2014, Washington, DC

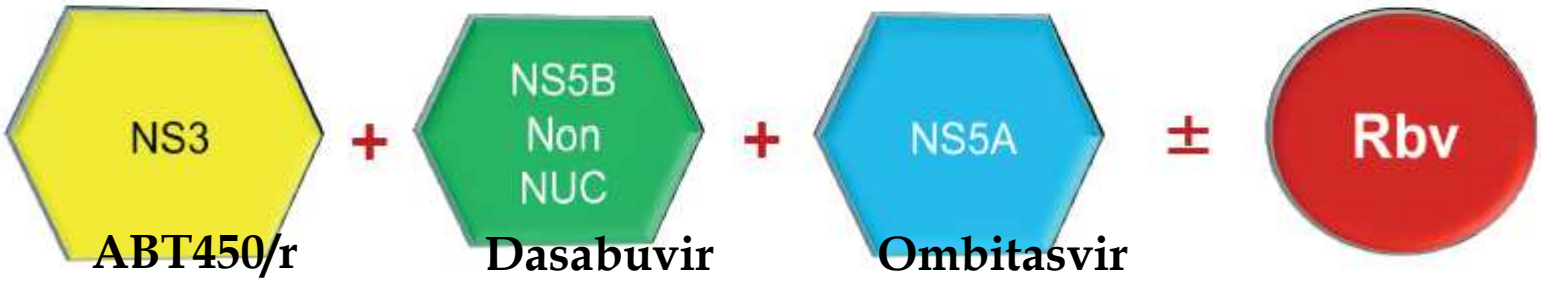
TURQUOISE-I Results: ITT Virologic Response Rates



Eron et al, ICAAC 2014 54th Interscience Conferen
September 5-9, 2014, Washington, DC

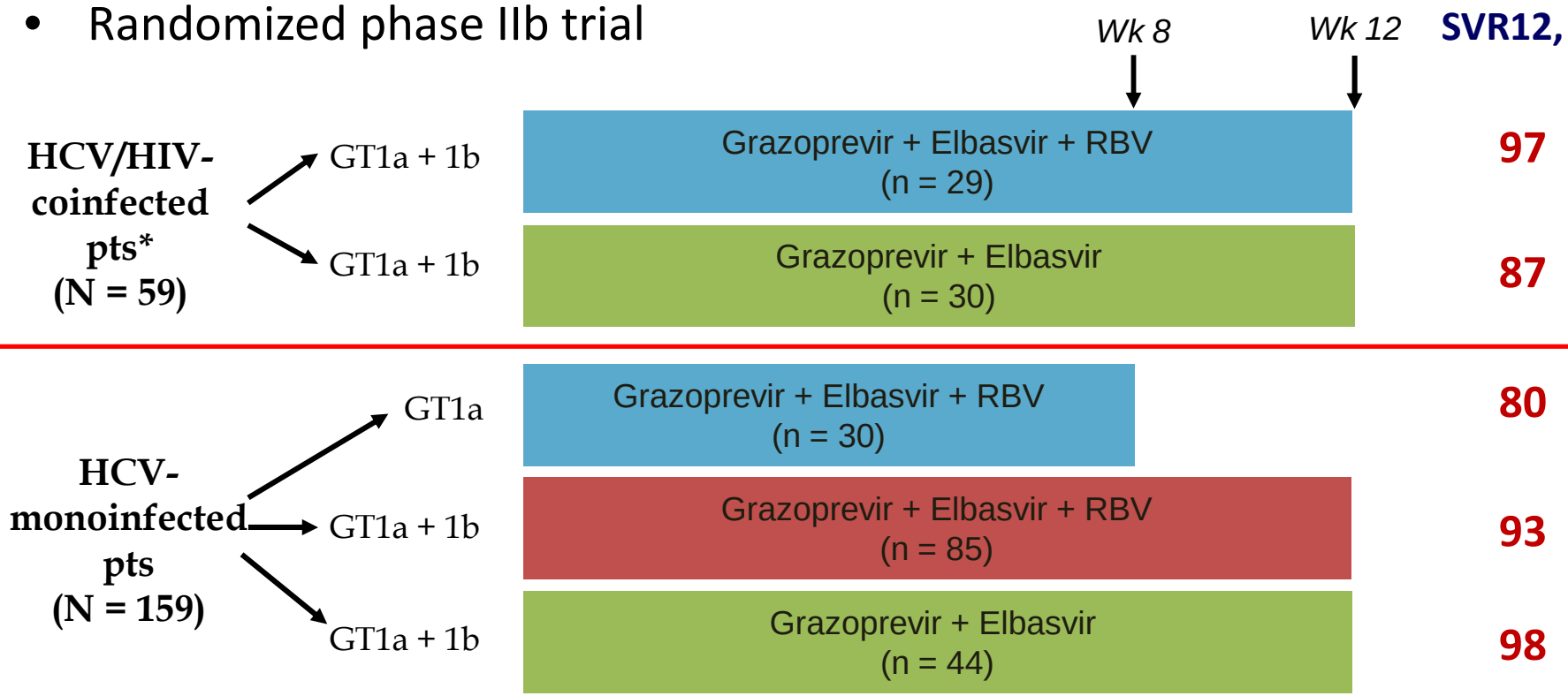
IFN-free regimens





C-WORTHY: Grazoprevir + Elbasvir ± RBV in GT1 Tx-Naive, Noncirrhotic Pts

- Randomized phase IIb trial



Grazoprevir 100 mg QD; elbasvir 20 or 50 mg QD; weight-based RBV 800, 1200, or 1400 mg daily.
*stable on raltegravir + 2 NRTIs for at least 8 wks prior to starting HCV therapy

Sulkowski, MS et al. AASLD 2014. Abstract 236.

SVR rate in HIV/HCV coinfected patients naïve for anti-HCV treatment

	SVR rate in therapy-naive patients			
	Genotype 1	Genotype 2	Genotype 3	Genotype 4
Peg-IFN plus ribavirin	35.6% in 191 patients	72.4% in 152 patients		32.6% in 46 patients
Peg-IFN plus ribavirin+boceprevir	60.7% in 61 patients	///	///	///
Peg-IFN plus ribavirin+telaprevir	74% in 38 patients	///	///	///
Peg-IFN plus ribavirin+sofosbuvir	91% in 23 patients			
Peg-IFN plus ribavirin+simeprevir	79.2% in 52 patients	///	///	///
Peg-IFN plus ribavirin+faldaprevir	73.7% in 227 patients°	///	///	///
Sofosbuvir plus ribavirin	76% in 114 patients*	88% in 26 patients**	67% in 42 patients**	///
Sofosbuvir plus ribavirin	84% in 112 patients	90% in 19 patients	91% in 57 patients	84% in 31 patients
Sofosbuvir plus ledipasvir	100% in 13 patients	///	///	///
Paritaprevir-r/ombitasvir + dasabuvir + ribavirin	93.5% in 31 patients	///	///	///

Coppola N, WJV 2014, submitted

SVR With Single-DAA Regimens by Genotype: Coinfection vs Monoinfection

SVR Range*, %	HIV/HCV Coinfection			HCV Monoinfection		
	GT1	GT2	GT3	GT1	GT2	GT3
Simeprevir + PR	74[1]	NA	NA	80-81[2,3]	NA	NA
Sofosbuvir + PR	89[4]	NA	NA	89[5]	NA	97[6]
Sofosbuvir + RBV	76-88[7,8]	88-89[7,8]	67-91[7,8]	68-90[9]	93[10]	85[10]

*Treatment-naive patients.

52. Dieterich D, et al. CROI 2014. Abstract 24. 53. Jacobson IM, et al. Lancet. 2014;[Epub ahead of print].
54. Manns M, et al. Lancet. 2014;[Epub ahead of print]. 55. Rodriguez-Torres M, et al. ID Week 2013. Abstract 714.
56. Lawitz E, et al. N Engl J Med. 2013;368:1878-1887. 57. Gane EJ, et al. EASL 2014. Abstract 845. 58. Sulkowski MS, et al. JAMA. 2014;312:353-361. 59. Molina JM, et al. AIDS 2014. Abstract MOAB0105LB. 60. Osinusi A, et al. JAMA. 2013;310:804-811. 61. Zeuzem S, et al. N Engl J Med. 2014;370:1993-2001.

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EASL Recommendations on Treatment of Hepatitis C 2014

Recommendations

- Indications for HCV treatment in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection **(Recommendation 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 **(Recommendation A1)**
- The use of cobicistat-based regimens, efavirenz, delavirdine, etravirine, nevirapine, ritonavir, and any HIV protease inhibitor, boosted or not by ritonavir, is not recommended in HIV-infected patients receiving simeprevir **(Recommendation A1)**
- The daily daclatasvir dose should be adjusted to 30 mg daily in HIV-infected patients receiving atazanavir/ritonavir and to 90 mg daily in those receiving efavirenz **(Recommendation B2)**
- No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs **(Recommendation A2)**

DAAs-ART interactions

Table 1 DAAs with acceptable and contraindicated ART regimens

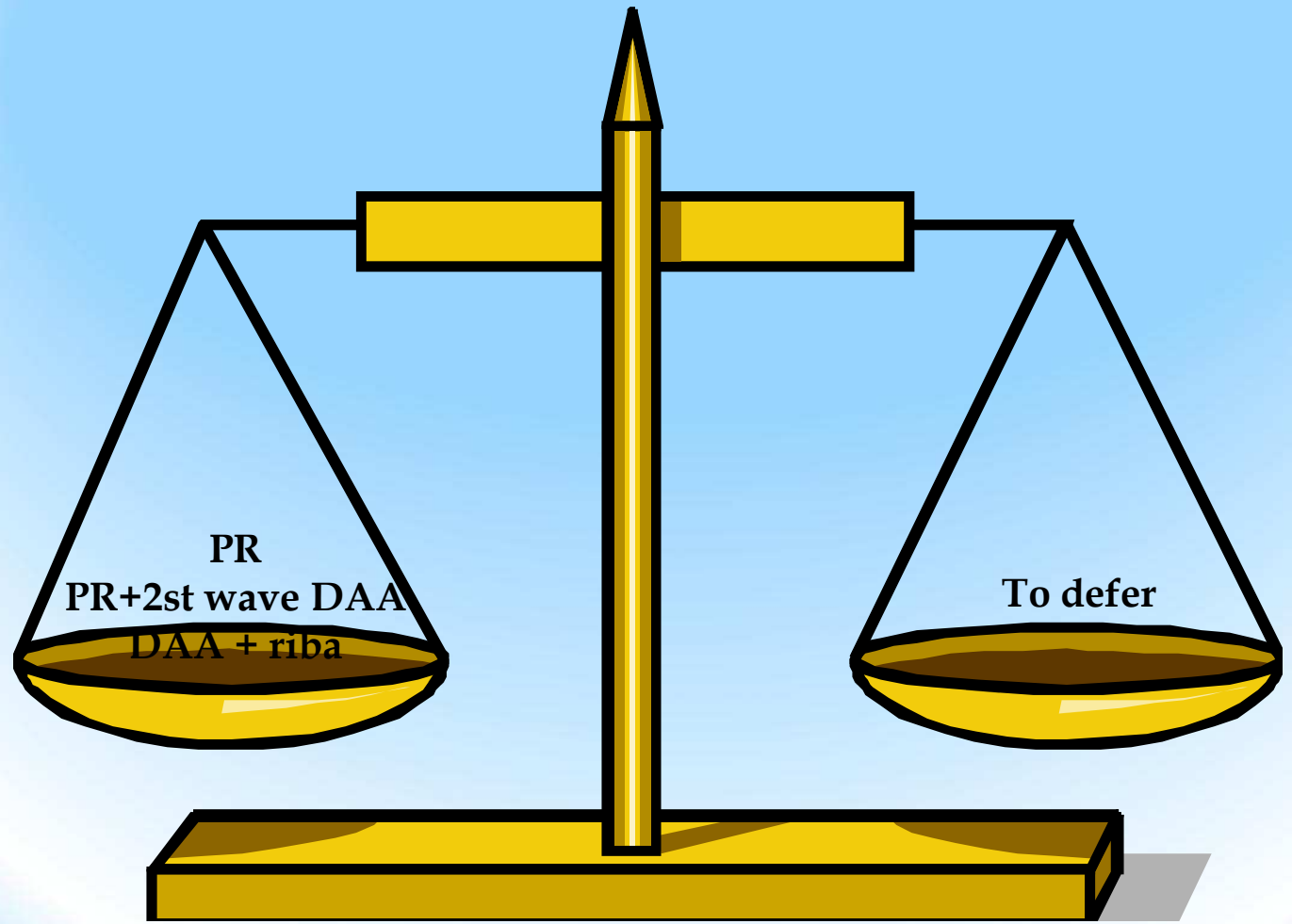
DAA	Type	Acceptable ART regimens	Contraindicated regimens
Telaprevir	NS3/4A protease inhibitor	Atazanavir/r, Tenofovir, Emtricitabine, Efavirenz[a], Etravirine, Rilpivirine[b], Raltegavir	Lopinavir/r, Darunavir/r
Boceprevir	NS3/4A protease inhibitor	Tenofovir, Rilpivirine, Raltegavir	Lopinavir/r, Atazanavir/r, Darunavir/r
Simeprevir	NS3/4A protease inhibitor	Tenofovir, Emtricitibaine, Lamivudine, Abacavir, Rilpiviriine, Raltegavir	All protease inhibitors with or without ritonavir boosting, Efavirenze, Delavirdine, Etravirine, Nevirapine
Sofosbuvir	Non-nucleoside NS5B polymerase inhibitor	Darunavir/r, Tenofovir, Emtricitabine, Efavirenz, Rilpivirine, Raltegavir	Tipranavir/r, Didanosine, Zidovudine
Ledipasvir	NS5A inhibitor	Tenofovir, Emtricitabine, Raltegavir, Rilpivirine	
Faldaprevir	NS3/4A protease inhibitor	Darunavir/r, Tenofovir, Efavirenz, Atazanavir/r	
Daclatasvir	NS5A inhibitor	Atazanavir/r[c], Tenofovir, Efavirenz[d]	
Asunaprevir	NS3/4A protease inhibitor	All NRTIs, rilpivirine, integrase inhibitors, maraviroc	
MK-8742/ MK-5172	NS5A inhibitor and NS3/4A protease inhibitor, respectively	MK-8742: Atazanavir/r, Lopinavir/r, Darunavir/r[e], Efavirenz[f], Raltegavir, Tenofovir.	

Bichoupan K; CurrHIV/AIDS Rep 2014

Challenges With Telaprevir- or Boceprevir-Based HCV Therapy in Coinfected Patients

- Regimen complexity
- High pill burden
  - Long duration, complex RGT rules
  - Multiple drug-drug interactions
  - Overlapping toxicities
  - With/without food dosing requirements
- Tolerability
  - Additional AEs beyond peginterferon/ribavirin

Anti-HCV treatment, November 29, 2014



Advantages of Future HCV Therapies

- Once-daily dosing
- Shorter duration
- Simpler regimens—no response-guided therapy
- Fewer adverse events
- Interferon-free
- High efficacy

Specific Risks of Deferring Therapy in HIV/HCV-Coinfected Patients

- Accelerated rate of HCV-related hepatic fibrosis progression in coinfected patients with increasing immune deficiency
  - Progression to cirrhosis risk 3-fold higher in coinfected vs HCV-monoinfected patients
  - Relative risk of decompensated liver disease 6-fold higher in coinfected vs HCV-monoinfected patients
- Coinfected patients have reduced access to liver transplantation and reduced survival

Importance of Informed Deferral: Know *What* You Are Waiting for

- Need for individualized decision-making and informed consent
- Stepwise progress in HCV therapy anticipated
  - New interferon-based regimens
  - All-oral regimens retaining ribavirin
  - All-oral regimens of just DAAs
- Uncertain timeline
- Initial DAA studies excluded coinfected patients

Factors influencing treatment decision for chronic hepatitis C in HIV/HCV-1 coinfection: treat or defer treatment

Factors
- Age
- severity of liver disease
- stability of HIV infection
-co-morbidities
-contraindications to IFN
- treatment adherence

Some examples in real life :

in young patients with mild chronic hepatitis C
and/or instability of HIV infection
and/or contraindications to IFN
and/or poor adherence to treatments

→ wait for IFN-free regimes

In young patients with severe chronic hepatitis C and controlled HIV infection in the absence of contraindications to IFN

→ treat with IFN-based regimen

Coppola N, WJV 2014 submitted

S.G. 56 anni

- HIV noto da 21 anni
- CDC-93: B1
- In terapia anti-HIV con Abacavir/lamivudina/darunavir-r
- CD4: 360cells/ml
- HIV RNA : negativo
- Anti-HCV noto da 21 anni
- HCV genotipo 1a
- IL28B-CC
- Trattamento con Peg-IFN plus Riba con relapse
- Eco addome: margini irregolari

D.R. 41 anni

- HIV noto da 3 anni
- CDC-93: A1
- In terapia anti-HIV con tenofovir/emtricitabina/rilpivirina
- CD4: 710cells/ml
- HIV RNA: negativo
- Anti-HCV noto da 3 anni
- HCV genotipo 3
- IL28B-TT
- Naive al trattamento anti-HCV
- Biopsia epatica: fibrosi 2 secondo Ishak

Assessing HIV+ Patients for Immediate or Deferred HCV Therapy

HCV Therapy in HIV/HCV-Coinfected, HCV Treatment-Naive Patients		
Liver Fibrosis	**Consider HCV Therapy**	**Eligible to Defer HCV Therapy**
No/minimal fibrosis (F0-F2)[24,25]		●
Advanced fibrosis (F3-F4); cirrhosis[26]	●	

- Antiretroviral therapy for HIV treatment-naive HIV/HCV-coinfected patients
  - CD4+ cell count < 500 cells/mm^3: initiate antiretroviral therapy for HCV treatment optimization[24,25]
  - CD4+ cell count > 500 cells/mm^3: may defer antiretroviral therapy until HCV therapy completed[25]

24. EACS Guidelines, Version 7.0. October 2013. 25. DHHS Antiretroviral Guidelines for Adults and Adolescents. February 2013. 26. Macías J, et al. Clin Infect Dis. 2013;2013;57:1401-1408.

AASLD/IDSA Guidance: Recommended Regimens for HCV/HIV-Coinfected Pts

Genotype	Recommended Regimens
Genotype 1	
HCV treatment naive and prior PR relapsers	
▪ IFN eligible	Sofosbuvir + pegIFN/RBV for 12 wks
▪ IFN ineligible	Sofosbuvir + RBV for 24 wks Sofosbuvir + simeprevir ± RBV for 12 wks
HCV treatment experienced*	Sofosbuvir + simeprevir ± RBV for 12 wks
Genotype 2	
Regardless of HCV treatment history	Sofosbuvir + RBV for 12 wks
Genotype 3	
Regardless of HCV treatment history	Sofosbuvir + RBV for 24 wks
Genotype 4	
Regardless of HCV treatment history	
▪ IFN eligible	Sofosbuvir + pegIFN/RBV for 12 wks
▪ IFN ineligible	Sofosbuvir + RBV for 24 wks
Genotype 5 or 6	
Regardless of HCV treatment history	Sofosbuvir + pegIFN/RBV for 12 wks

*Previous PR nonresponders regardless of IFN eligibility.

AASLD and IDSA. HCV Management Guidance. September 2014.

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EASL European Association for the Study of the Liver

EASL Recommendations
on Treatment of Hepatitis C
2014

Genotype 1 eligible to IFN

Peg-IFN+Riba+Sofosbuvir

Patients infected with HCV genotype 1 can be treated with a combination of weekly pegylated IFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks **(Recommendation A1)**

Peg-IFN+Riba+Simeprevir

Patients infected with HCV genotype 1 can be treated with a combination of weekly pegylated IFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily simeprevir (150 mg) **(Recommendation A1)**

This combination is not recommended in patients infected with subtype 1a who have a detectable Q80K substitution in the NS3 protease sequence at baseline, as assessed by population sequencing (direct sequence analysis) **(Recommendation A2)**

Simeprevir should be administered 12 weeks in combination with pegylated IFN-α and ribavirin. Pegylated IFN-α and ribavirin should then be administered alone for an additional 12 weeks (total treatment duration 24 weeks) in treatment-naïve and prior relapser patients, including cirrhotics, and for an additional 36 weeks (total treatment duration 48 weeks) in prior partial and null responders, including cirrhotics **(Recommendation B1)**

Peg-IFN+Riba+Daclatasvir

- Patients infected with HCV genotype 1, subtype 1b can be treated with a combination of weekly pegylated IFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily daclatasvir (60 mg) 24 weeks **(Recommendation B1)**
- This combination should not be proposed to patients infected with HCV genotype 1, subtype 1a, given the preliminary data available, pending results of on-going large-scale studies **(Recommendation B1)**
- Daclatasvir should be administered 12 weeks in combination with pegylated IFN-α and ribavirin. Daclatasvir should be continued in combination with pegylated IFN-α and ribavirin an additional 12 weeks (total duration 24 weeks) in patients who do not achieve an HCV RNA level <25 IU/ml at week 4 and undetectable at week 10. Pegylated IFN-α and ribavirin should be continued alone between week 12 and 24 (total duration 24 weeks) in patients who achieve an HCV RNA level <25 IU/ml at week 4 and undetectable at week 10 **(Recommendation B2)**

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EASL Recommendations
on Treatment of Hepatitis C
2014

Genotype 1 ineligible to IFN

Sofosbuvir+Riba

Patients infected with HCV genotype 1 who are IFN-intolerant or -ineligible can be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 24 weeks **(Recommendation B2)**

This combination should be proposed to these patients exclusively when no other IFN-free option is available **(Recommendation B2)**

Sofosbuvir+Simeprevir

Patients infected with HCV genotype 1 can be treated with an interferon-free combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg) for 12 weeks **(Recommendation B1)**

Preliminary results do not indicate a major advantage of adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis **(Recommendation B1)**

Sofosbuvir+Daclatasvir

Patients infected with HCV genotype 1 can be treated with an interferon-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) 12 weeks in treatment-naïve patients or 24 weeks in treatment-experienced patients, including those who failed on a triple combination of pegylated IFN-α, ribavirin and either telaprevir or boceprevir (pending data with 12 weeks of therapy in treatment-experienced patients) **(Recommendation B1)**

Preliminary results do not indicate a major advantage to adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis **(Recommendation B1)**

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EASL European Association for the Study of the Liver

EASL Recommendations on Treatment of Hepatitis C 2014

Genotype 2

Peg-IFN+Riba+Sofosbuvir

Recommendations

- Patients infected with HCV genotype 2 must be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks **(Recommendation A1)**
- Therapy should be prolonged to 16 or 20 weeks in patients with cirrhosis, especially if they are treatment-experienced **(Recommendation B1)**

Sofosbuvir+Riba

Recommendation

- Alternatively, cirrhotic and/or treatment-experienced patients could be treated with weekly pegylated IFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks **(Recommendation B1)**

APRIL 2014

EASL European Association for the Study of the Liver

EASL Recommendations
on Treatment of Hepatitis C
2014

Genotype 3

Peg-IFN+Riba+Sofosbuvir

Patients infected with HCV genotype 3 can be treated with a combination of weekly pegylated IFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks **(Recommendation A2)**

Sofosbuvir+Riba

Patients infected with HCV genotype 3 can be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 24 weeks **(Recommendation A2)**

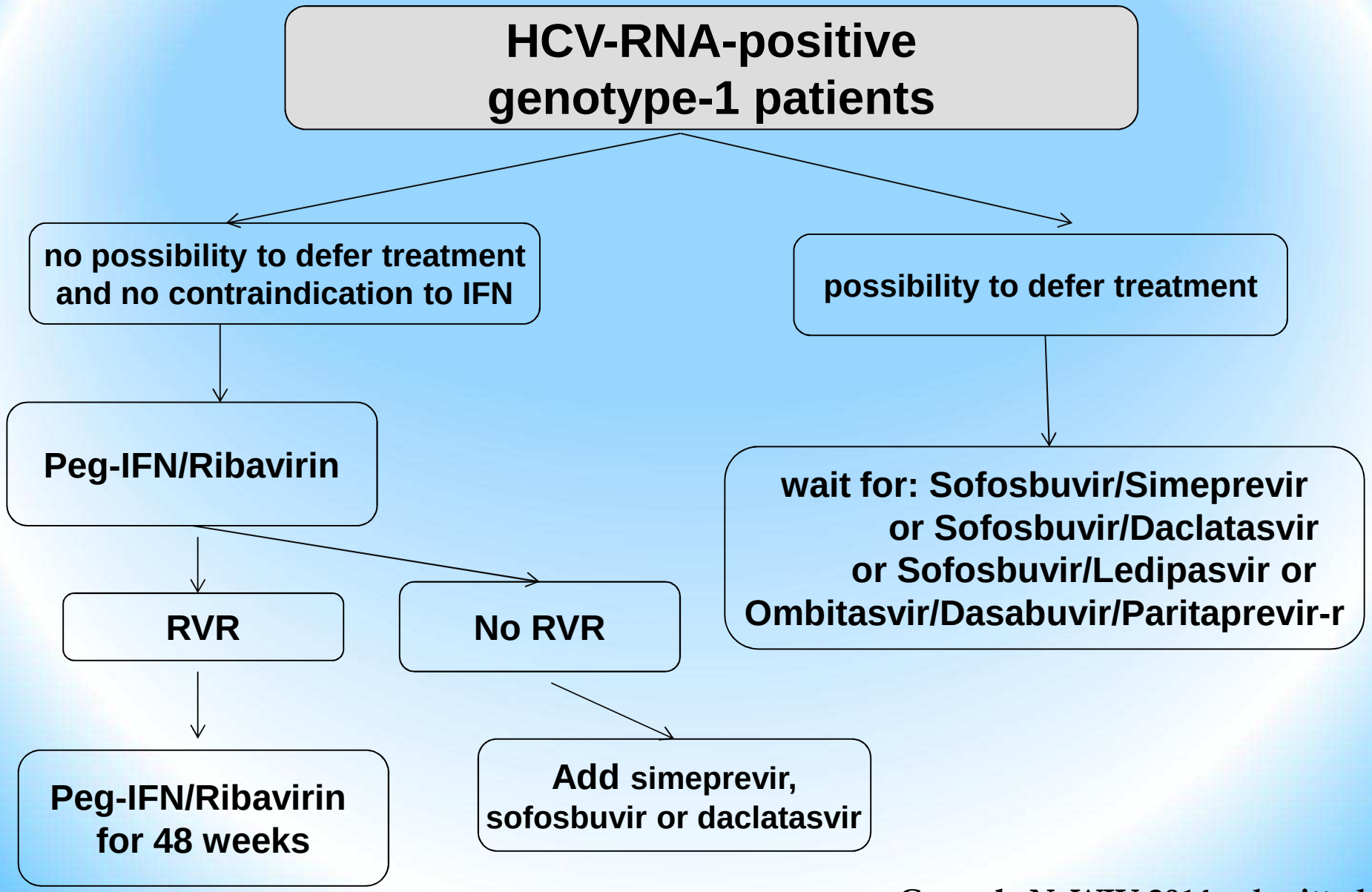
This therapy is suboptimal in treatment-experienced cirrhotics, who should be proposed an alternative treatment option **(Recommendation A2)**

Peg-IFN+Riba+Daclatasvir

Patients infected with HCV genotype 3 can be treated with an interferon-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) 12 weeks in treatment-naïve patients or 24 weeks in treatment-experienced patients (pending data with 12 weeks of therapy in treatment-experienced patients) **(Recommendation B1)**

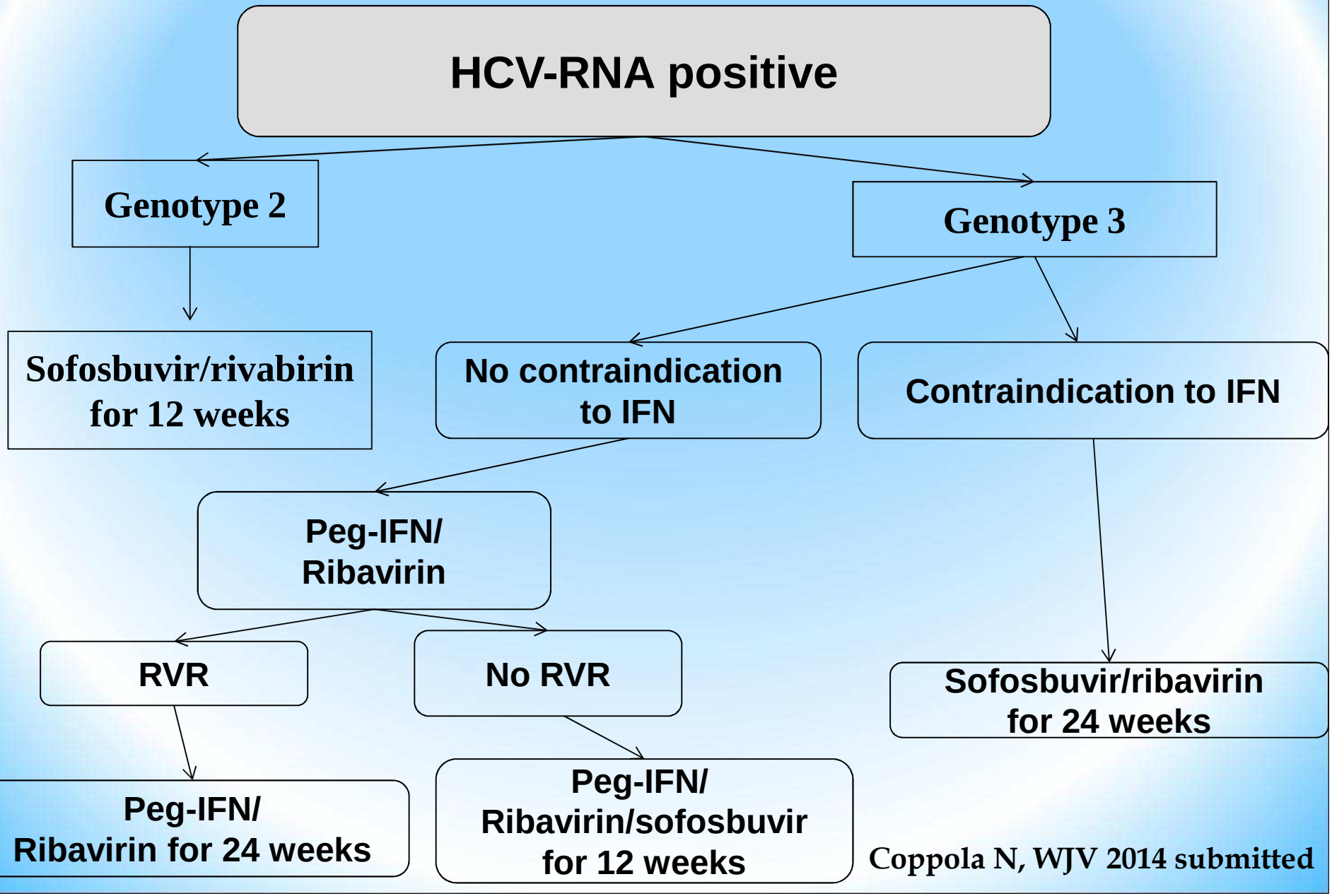
Preliminary results do not indicate a major impact of adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis **(Recommendation B1)**

Treatment of chronic hepatitis C, HCV-genotype 1 or 4, in patients with HIV/HCV coinfection



Coppola N, WJV 2014 submitted

Treatment of chronic hepatitis C, HCV-genotype 2 or 3, in patients with HIV/HCV coinfection



Coppola N, WJV 2014 submitted

Treatment of Chronic hepatitis C – G1

	Hepatitis				Cirrhosis	Decompensated cirrhosis
Fibrosis	No	Mild	Moderate	Severe		
METAVIR	F0	F1	F2	F3	F4	
Ishak's	S0	S 1-2	S3	S4	S5-	

Naives/ Relapsers

Partial/ null

PI non responders

Treatment of Chronic hepatitis C – G1

	Hepatitis				Cirrhosis	Decompensated cirrhosis
Fibrosis	No	Mild	Moderate	Severe		
METAVIR	F0	F1	F2	F3	F4	
Ishak's	S0	S 1-2	S3	S4	S5-	

Naives/ Relapsers

PEG IFN / RIBA ?

Wait

PR + 2nd wave PI or SOF

3D or 2D combos

Partial/ null

3D or 2D combos

PI non responders

2D combos (NS5B +NS5A)

Grazie per l’attenzione

Why Is HCV Therapy Deferred in Many HIV/HCV-Coinfected Patients?

- Challenges with interferon- and/or ribavirin-based regimen
- Anticipated approval of new agents
  - Greater efficacy
  - All-oral regimens
  - Shorter duration
  - Improved tolerability
  - Fewer drug-drug interactions

Phase 2 studies with HCV PI in HIV/HCV

	Telaprevir	Boceprevir
Number of patients	**TVR, 38**; Control, 22	**BOC, 64**; Control, 34
HCV population	Naïve, genotype 1	Naïve, genotype 1
HIV population	CD4 ≥500; HIV ≤100,000 c/mL CD4 ≥ 300; HIV ≤50 c/mL	CD4 ≥ 200 cells/mm^3 HIV RNA <50 c/mL
Antiretroviral therapy	None (n=7) EFV (n=16) or ATV/r (n=15) + TDF/FTC	No NNRTIs ATV/r, (n=20); DVR/r (n=16); DRV/r (n=12); RAL(n=11)
HCV regimen	TLV 750 mg Q8H or 1125 mg Q8H (if EFV co-admin) + pegIFN-2a + RBV 800 mg/day	BOC 800 mg Q8H + pegIFN-2b + weight based RBV (600–1400 mg/day)
PR Lead-in	No	Yes
Duration of PI	12 weeks	44 weeks
Duration of PR (no RGT)	48 weeks	48 weeks
Virologic futility rules	Week-4/8/12 HCV RNA >1000 IU/mL Week-24 Detectable HCV RNA	Week-12 <2 $\log_{10}$ decline Week-24 Detectable HCV RNA
HCV PI PK measured	Yes	Yes
ART PK measured	Yes	No

Naggie S, Gastroenterology 2012

Coinfezione HIV-HCV

-Terapia anti-HCV-

- Perché?
- Come?
  - Duplice terapia (Peg-IFN+Riba)
  - Triplice terapia (Peg-IFN+Riba+DAA)
- Fattori predittivi
- **Problematiche**
  - **Interazioni**
  - **Effetti collaterali**
  - **Resistenze**

DHHS Recommendations on Use of BOC or TVR in Gt 1 HCV/HIV–Coinfected Pts

Patient Group	Recommendation*
Patients not receiving antiretroviral therapy	Use either boceprevir or telaprevir
Patients receiving raltegravir + 2 NRTIs	Use either boceprevir or telaprevir
Patients receiving atazanavir/ritonavir + 2 NRTIs	Use telaprevir at the standard dose; do not use boceprevir
Patients receiving efavirenz + 2 NRTIs	Use telaprevir at increased dose of 1125 mg every 7-9 hrs
*These recommendations may be modified as new drug interaction and clinical trial information become available.	

DHHS Guidelines March 2012. .

Coinfezione HIV-HCV

-Terapia anti-HCV-

- Perché?
- Come?
  - Duplice terapia (Peg-IFN+Riba)
  - Triplice terapia (Peg-IFN+Riba+DAA)
- Fattori predittivi
- **Problematiche**
  - Interazioni
  - **Effetti collaterali**
  - Resistenze

Boceprevir-Related Adverse Events in Clinical Trials

- Most notable adverse events occurring more frequently with boceprevir plus pegIFN/RBV vs pegIFN/RBV alone
  - Anemia, neutropenia, and dysgeusia

Adverse Event, %	Boceprevir + PegIFN/RBV	PegIFN/RBV
Treatment-naive patients	(n = 1225)	(n = 467)
▪ Anemia	50	30
▪ Neutropenia	25	19
▪ Dysgeusia	35	16
Treatment-experienced patients	(n = 323)	(n = 80)
▪ Anemia	45	20
▪ Dysgeusia	44	11

Boceprevir [package insert]. May 2011.

Telaprevir-Related Adverse Events in Clinical Trials

- Most notable adverse events occurring more frequently with telaprevir vs pegIFN/RBV alone
  - Rash, anemia, and anorectal symptoms

Adverse Event, %	Telaprevir + PegIFN/RBV (n = 1797)	PegIFN/RBV (n = 493)
Rash	56	34
Anemia	36	17
Anorectal symptoms	29	7

Telaprevir [package insert]. 2011.

Anemia With Boceprevir or Telaprevir in Phase III Clinical Trials

Outcome, %	Boceprevir Phase III Trial		Telaprevir Phase III Trial	
	Boceprevir + PegIFN/RBV	PegIFN/ RBV	Telaprevir + PegIFN/RBV	PegIFN/ RBV
Hemoglobin ≤ 10 g/dL	49	25-29	36	17
Hemoglobin < 8.5 g/dL	6-10	1-3	14	5
Reduced RBV dose	26	13	32	12
Received erythropoietin	43	24	Not allowed	Not allowed
Received blood transfusion	3	1	5-7	1-2

Barritt AS 4th, Fried MW. Gastroenterology. 2012;142:1314-1323.e1

Management of Telaprevir-Associated Rash

Rash Description	Management
Mild to moderate rashes	Continue all drugs; telaprevir dose should not be reduced or interrupted Monitor for rash progression or development of systemic symptoms Oral antihistamines and/or topical corticosteroids ▪ Systemic corticosteroids are not recommended*
Severe rash	Discontinue telaprevir; continue pegIFN/RBV If no improvement within 7 days (or earlier if indicated), consider discontinuation of pegIFN and/or RBV Oral antihistamines and/or topical corticosteroids ▪ Systemic corticosteroids are not recommended* Consider dermatology consult *Serious skin reactions (Stevens-Johnson syndrome or DRESS):* Discontinue all medications immediately; refer for urgent medical care
All patients with rash	Consider good skin care practices: limit sun exposure, wear loose-fitting clothing, use oatmeal or baking soda baths, apply moisturizers at least twice daily after bathing, launder with mild, unscented detergents

*Systemic corticosteroids and telaprevir drug–drug interactions: with prednisone/methylprednisolone (CYP3A substrates) and telaprevir (potent CYP3A inhibitor) coadministration, plasma concentrations of corticosteroids can be increased significantly. Systemic dexamethasone (induces CYP3A) can decrease telaprevir plasma concentrations (may result in loss of therapeutic effect).

Variants in the ITPA Gene Protect Against Ribavirin-Induced Hemolytic Anemia in HIV/HCV-Coinfected Patients With All HCV Genotypes

The Journal of Infectious Diseases 2012;205:376–83

Susanna Naggie,[1] Norma I. Rallon,[2] José M. Benito,[2] Judith Morello,[2] Sonia Rodriguez-Novoa,[2] Paul J. Clark,[1] Alexander J. Thompson,[1] Kevin V. Shianna,[3] Eugenia Vispo,[2] John G. McHutchison,[1] David B. Goldstein,[3] and Vincent Soriano[2]

Studio includente 161 pazienti coinfetti, precedentemente trattati con pegIFN e RBV tra il 2002 ed il 2008. È stata indagata la correlazione tra i polimorfismi rs1127354 e rs7270101 del gene dell'ITPA e la riduzione dell'Hb alla quarta settimana di trattamento.

Table 4. Regression Models for Quantitative Hemoglobin Reduction at Week 4 and Hemoglobin Reduction >3 g/dL at Week 4

ITPA Variants and Week 4 Quantitative Hb Reduction[a]						
ITPA Variant	Estimate	Standard Error	*P* Value	Adjusted Estimate	Standard Error	Adjusted *P* Value[b]
rs1127354	−1.85	0.42	<.0001	−1.75	0.56	.003
rs7270101	−0.87	0.25	.0008	−1.20	0.40	.004
Composite ITPase Deficiency Variable and Week 4 Quantitative Hb Reduction[c]						
Parameter	Estimate	Standard Error	*P* Value			
ITPase deficiency	−0.97	0.25	.0003			
Creatinine	−1.62	0.78	.043			
Zidovudine exposure	1.79	0.45	.0002			
ITPA Variants and Week 4 Hb Reduction >3 g/dL[a]						
ITPA Variant	OR	95% CI	*P* Value	Adjusted OR	95% CI	Adjusted *P* Value[b]
rs1127354	0.10	.01–.82	.03	0.12	.01–1.38	.089
rs7270101	0.24	.09–.63	.004	0.21	.05–.92	.038
Composite ITPase Deficiency Variable and Week 4 Hb Reduction >3 g/dL[c]						
Parameter	OR	95% CI	*P* Value			
ITPase deficiency	0.24	.08–.73	.012			
Creatinine	0.04	.002–.93	.049			
Zidovudine exposure	14.9	1.6–135	.016			

Adherence

- Triple therapy presents challenges with already busy schedules[143]
  - TID dosing
  - Food requirements
- Data show pegIFN/RBV adherence decreases over time[5]
  - Addition of PIs may exacerbate this trend

Male, 48 years, 80kg

Every week
Peg-IFN: 1fl

Every day
6 am: - 2 tablets of TVR with food or
- 4 tablets of BOC
- 3 tablets of RBV

2 pm: 2 tablets of TVR/ or 4 of BOC with food

6 pm: 3 tablets of RBV

10 pm: 2 tablets of TVR/or 4 of BOC with food

Total tablets: 12-18/day

If ART: 1 table TDF/FTC/EFV or 1 table TDF/FTC + 2 tables RAL or 1 table TDF/FTC+1 RTV+1 ATV
If itch: 1 table of antihistamine
If anemia: eritropietin
If depression: 1 table of paroxetin

Coinfezione HIV-HCV

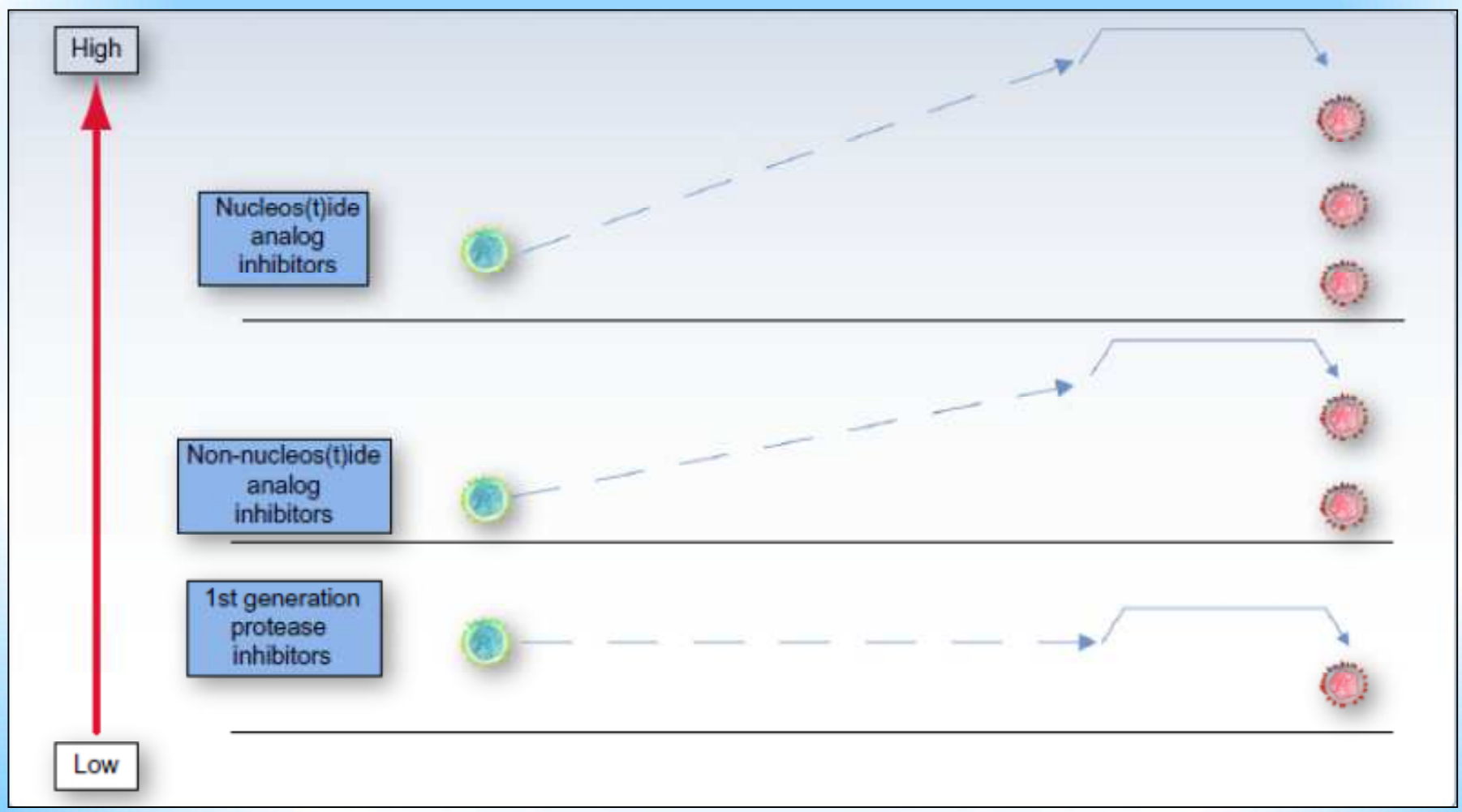
-Terapia anti-HCV-

- Perché?
- Come?
  - Duplice terapia (Peg-IFN+Riba)
  - Triplice terapia (Peg-IFN+Riba+DAA)
- Fattori predittivi
- **Problematiche**
  - Interazioni
  - Effetti collaterali
  - **Resistenze**

Hepatitis C virus resistance to protease inhibitors

- The genetic barrier of the Protease Inhibitors is low
- The Protease-inhibitor mutations occur quickly (less than 15 days) when monotherapy is used.
- Ribavirin prevents viral breakthrough in combination with Pegylated Interferon and protease inhibitors
- Protease inhibitor associated mutations can be present before the treatment and persiste after the end of therapy.

Genetic barriers for HCV Direct Antiviral Agents



Locarnini S, J Hepatol 2011

HCV is the prototype of variable viruses

	HIV	HBV	HCV
Virus			
daily production of virions per day	10^{10}	10^{12}–10^{13}	10^{12}
half-life of free virions (h)	1	3–24	2–3
half-life of intracellular virions	days (dependent on infected cells $t_{1/2}$)	months (dependent on infected cells $t_{1/2}$)	hours (not dependent on infected cells $t_{1/2}$)
Mutation rate	**Very high**	**High**	**Very Very high**
constraints due to ORFs in targeted viral enzymes	moderate	high	none
immune-mediated escape mutants	frequent	infrequent	frequent
Target cells			
half-life of infected cells	days	months	weeks
size of susceptible cells compartment	large	small	probably large
intracellular viral reservoir	yes (integrated cDNA)	yes (cccDNA)	no

Soriano et al., JAC 2008

Why is HCV characterized by a degree of genetic variability?

Their polymerases lack the proof-reading-function

+

High virion production: **>10^{12} virions per day**

Daily generation of a huge number of mutations

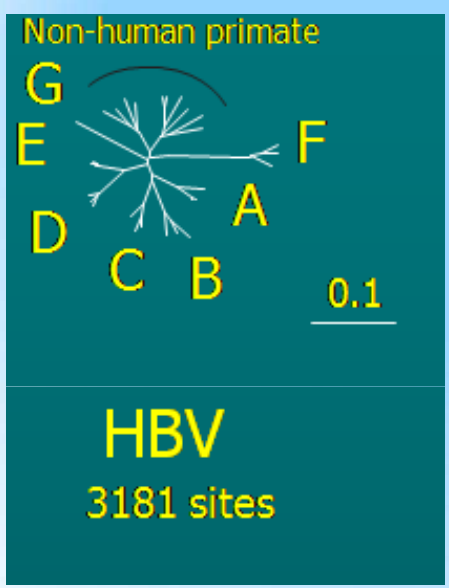
(>10^{10} point mutations produced per day)

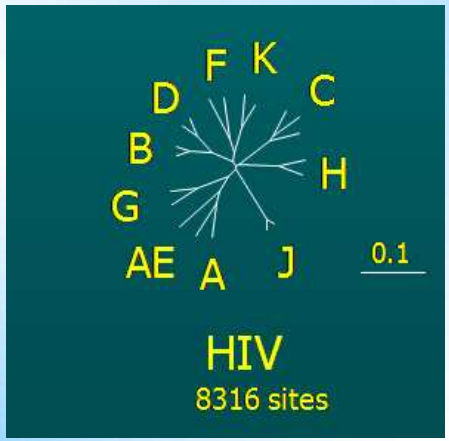
To modify the virological pathogenicity

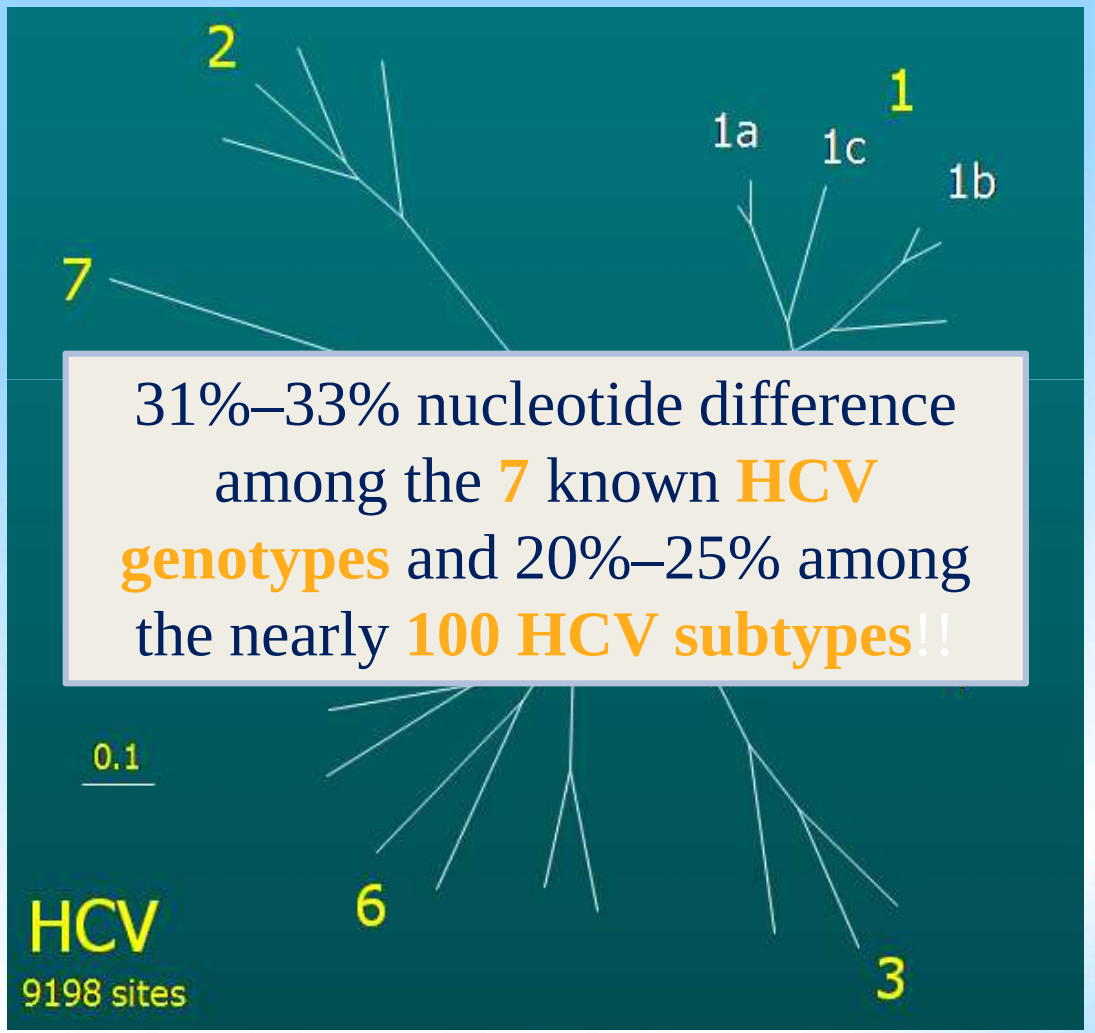
↑ virological fitness

↓ anti-drug susceptibility

Viral dynamics are extremely rapid in HCV







31%–33% nucleotide difference among the 7 known **HCV genotypes** and 20%–25% among the nearly **100 HCV subtypes**!!

Due to this high degree of genetic variability HCV Resistant variants can be present before treatment as minority species

Hepatitis C virus resistance to protease inhibitors

- The genetic barrier of the Protease Inhibitors is low
- The Protease-inhibitor mutations occur quickly (less than 15 days) when monotherapy is used.
- Ribavirin prevents viral breakthrough in combination with Pegylated Interferon and protease inhibitors
- Protease inhibitor associated mutations can be present before the treatment.
- Cross resistance mutations exist between the different protease inhibitors.
- Subtyping of genotype 1 will clarify the different types of resistant variants to the PIs.

Cross resistance to new anti-HCV drugs is widespread and….

	V36A/M	T54A	V55A	Q80R/K	R155K/T/Q	A156S	A156V/T	D168A/V/T/H	V170A
Telaprevir (linear)			*						*
Boceprevir (linear)							*		
SCH900518 (linear)									
BILN-2061 (macrocyclic)									
ITMN191 (macrocyclic)						*	*		
MK7009 (macrocyclic)						*			
TMC435350 (macrocyclic)									
BI-201335 (linear)									
MK5172 (macrocyclic)									
GS-9256 (macrocyclic)									
ABT 450 (macrocyclic)									
BMS-791325 (macrocyclic)									

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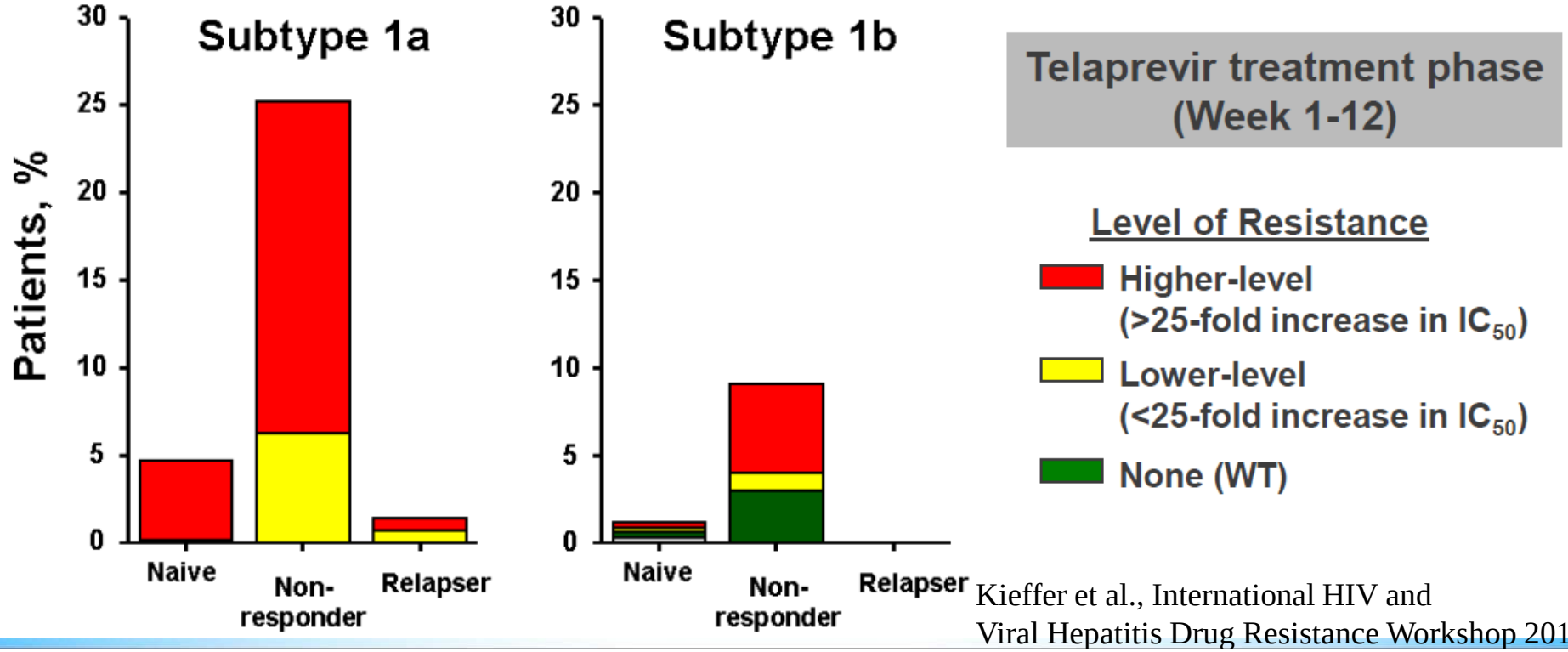
…. subtype-specific

On-Treatment Virologic Failure in Phase 3 Studies by Prior Response and Subtype

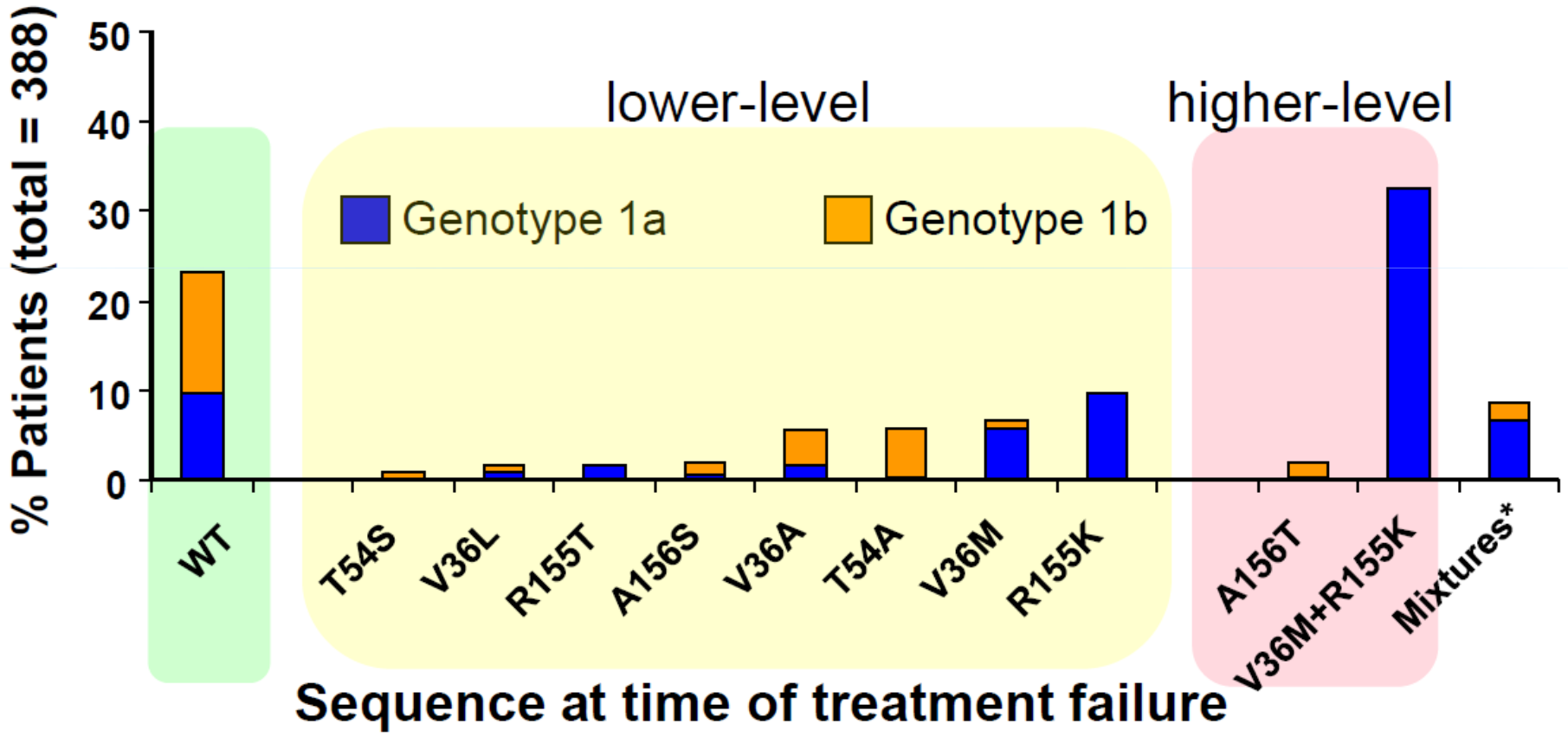
- Overall on-treatment virologic failure rates were low in treatment-naïve (7%) and prior relapsers (1%), but were higher in prior non-responders (36%)
- Associated with higher-level resistant variants during TVR treatment phase, suggesting T/PR suppresses WT and lower-level variants
- **Suggests that virologic failure was due to an insufficient Peg/RBV response to inhibit resistant variants, specifically higher-level resistant variants**



Kieffer et al., International HIV and Viral Hepatitis Drug Resistance Workshop 2011

Frequency of Resistance Profiles in Patients Who Did Not Achieve an SVR in Phase 3 Studies of TVR

Genotype 1a is associated with V36M and R155K variants
Genotype 1b is associated with V36A, T54A/S and A156S/T variants



Variants V36G/I, I132V, R155G/M, A156V/F/N or D168N were also observed at <2%

*Mixtures (n=33): V36A/M, T54A/S, A156S/T, V36L+T54S, V36A/M+T54A/S, V36L+R155K, V36M+A156S/T, T54S+R155K, T54S+A156T, V36A/M+T54S/T+R155K, V36M+R155K+A156S/T/V

Kieffer et al., 2011

Parameters That Affect Resistance

HCV subtype and resistance

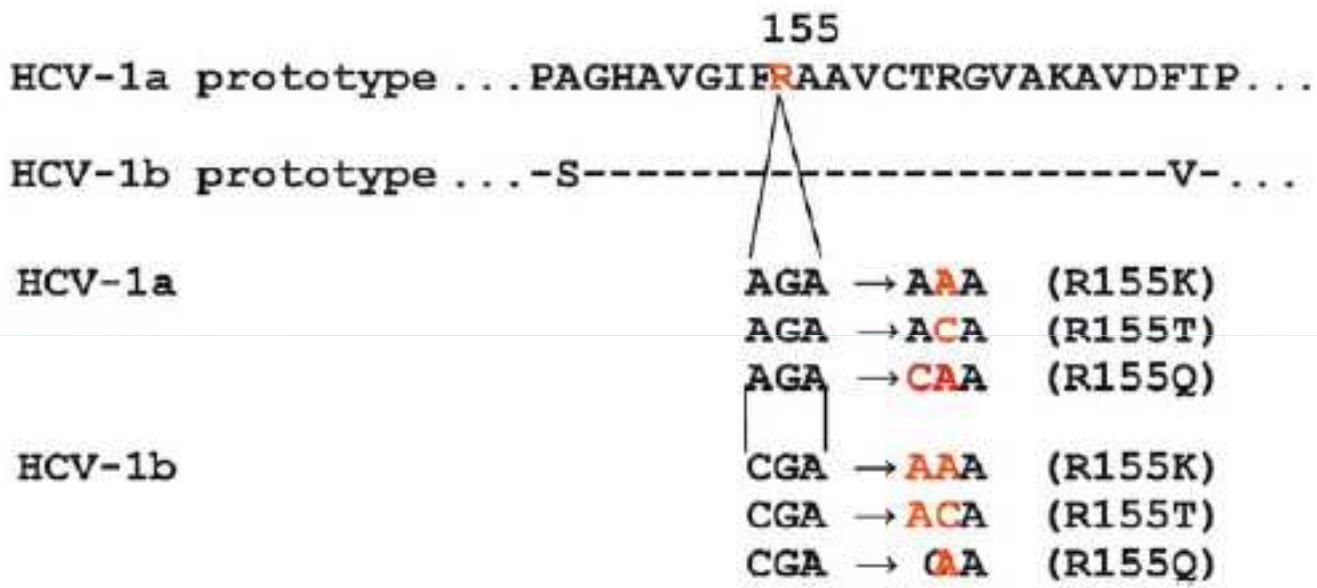


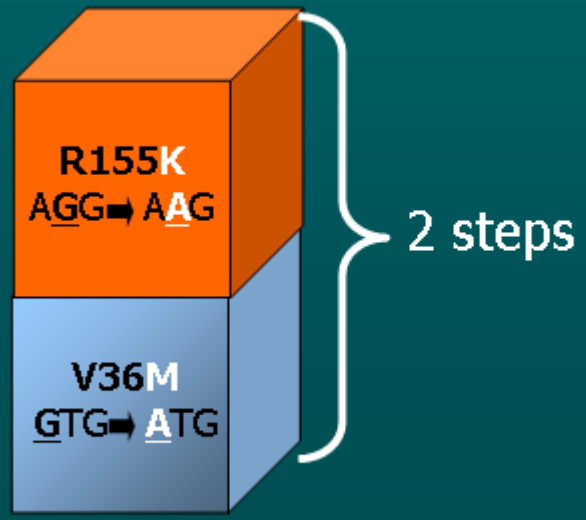
Figure 2. Molecular basis for different probabilities for selection of R155K/T/Q mutations in subtype 1a– vs subtype 1b–infected patients treated with a NS3 protease inhibitor. Selection of R155K/T requires 1 nucleotide exchange in subtype 1a but 2 nucleotide exchanges in subtype 1b patients. Selection of R155Q requires 1 nucleotide exchange in subtype 1b but 2 nucleotide exchanges in subtype 1a patients.

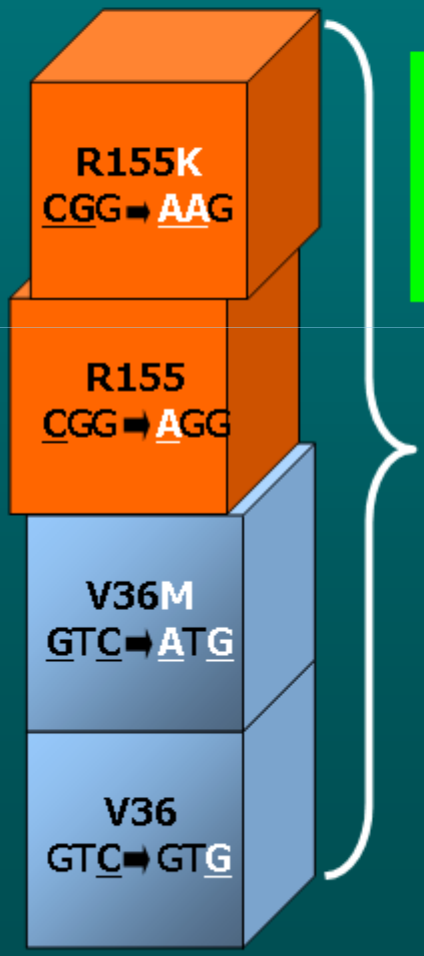
SARRAZIN and ZEUZEM 2010

Clinical Implications Of Genetic Barrier To Resistance – Acquisition Of NS3 Inhibitor Resistant Variant V36M+R155K

Subtype 1a
V36M+R155K variant observed clinically[1,2]

Subtype 1b
V36M+R155K variant not observed clinically





McHutchison JG. *N Engl J Med.* 2009; 360; 18 1827-1838
Hezode C. *N Engl J Med.* 2009; 360; 18 1839-1850

Treatment-Emergent Substitutions During PI-Therapy

pooled analyses of subjects who had on-treatment failure or relapse during clinical trials with boceprevir or telaprevir

Patterns of treatment-emergent substitutions varied by subtype 1a vs 1b

Resistance most common among previous null responders and

HCV Genotype 1 Subtype	Treatment-Emergent Substitutions	
	Telaprevir[1]	Boceprevir[2]
1a	V36M R155K Combination of V36M and R155K	V36M T54S R155K
1b	V36A T54A/S	T54A/S V55A

1. Telaprevir [package insert]. 2011. 2. Boceprevir [package insert]. May 2011.

Hepatitis C virus resistance to protease inhibitors

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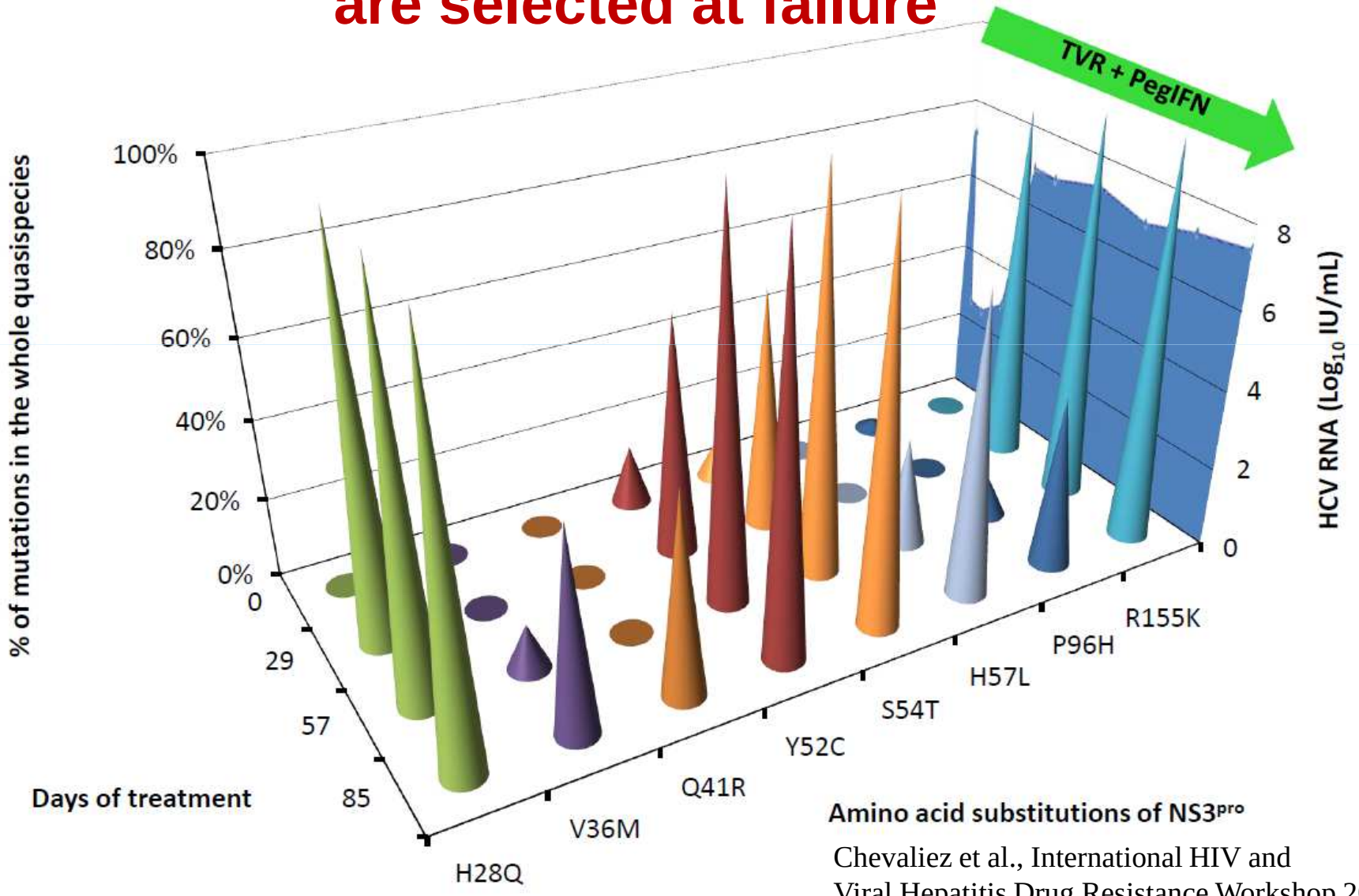
- Protease inhibitor associated mutations can be present before the treatment.
- Cross resistance mutations exist between the different protease inhibitors.
- Subtyping of genotype 1 will clarify the different types of resistant variants to the PIs.

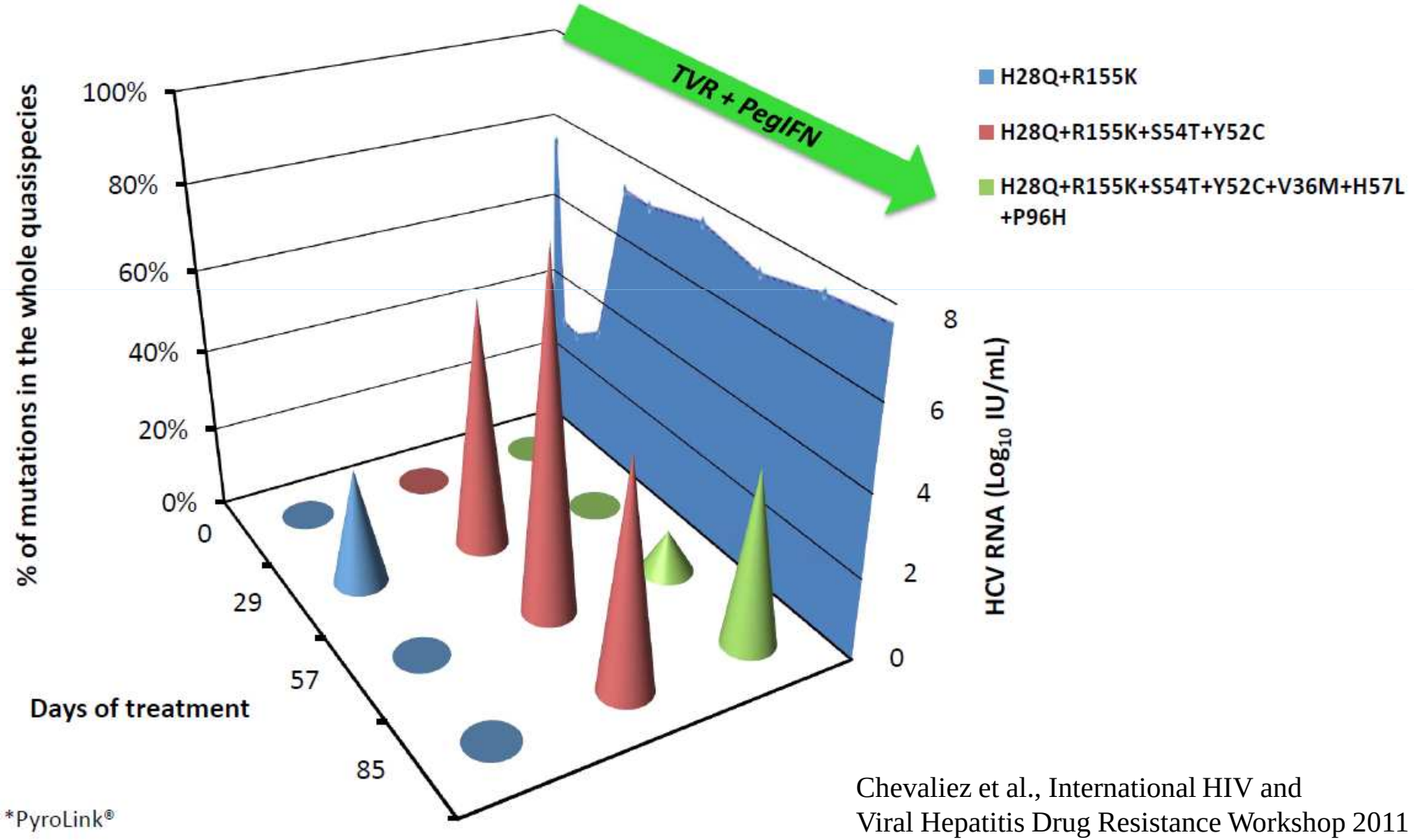
The profiles of anti-HCV drug resistance at failure are highly complex and dynamics

Multiple drug resistance mutations are selected at failure



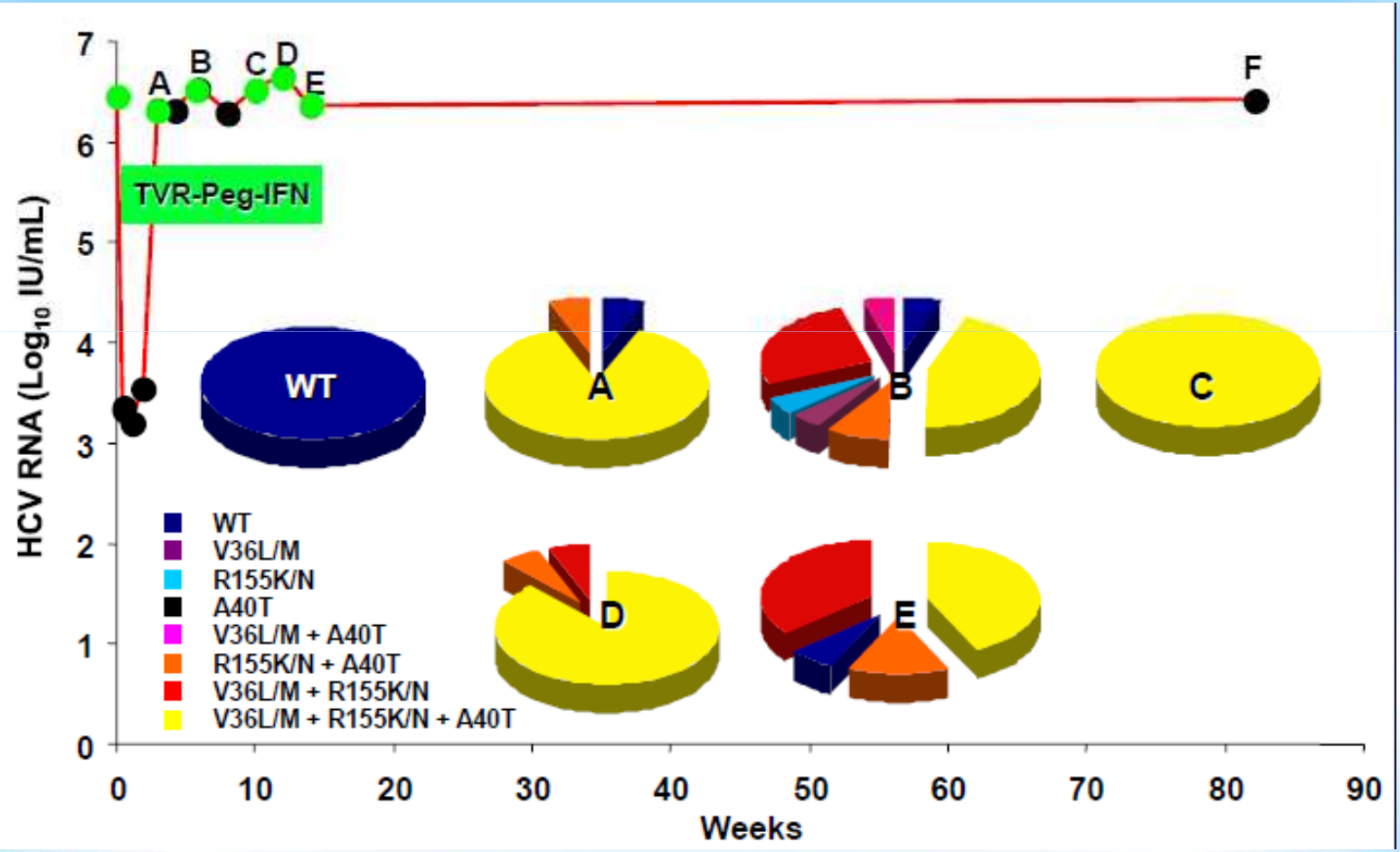
Chevaliez et al., International HIV and Viral Hepatitis Drug Resistance Workshop 2011

Complex patterns of drug resistance mutations are selected at failure



Chevaliez et al., International HIV and Viral Hepatitis Drug Resistance Workshop 2011

Resistant HCV variants keep accumulating mutations

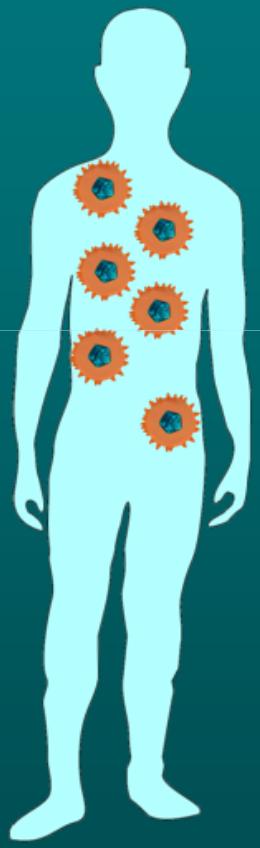


Chevaliez S. et al., EASL 2011, Abstract 67

Say NO To CRAP Therapy

Continued Replication under Antiviral Pressure

- Continued replication in the presence of drug will likely lead to further evolution of the viral population.
- In theory, further evolution can result in a more fit, drug-resistant viral population that may remain enriched in the patient, even in the absence of drug pressure.
- This should be prevented by discontinuing the direct acting antiviral if a patient has a confirmed increase in HCV RNA levels while adhering to therapy.



Dynamics of drug-resistance after PI-treatment interruption

This rises the question:

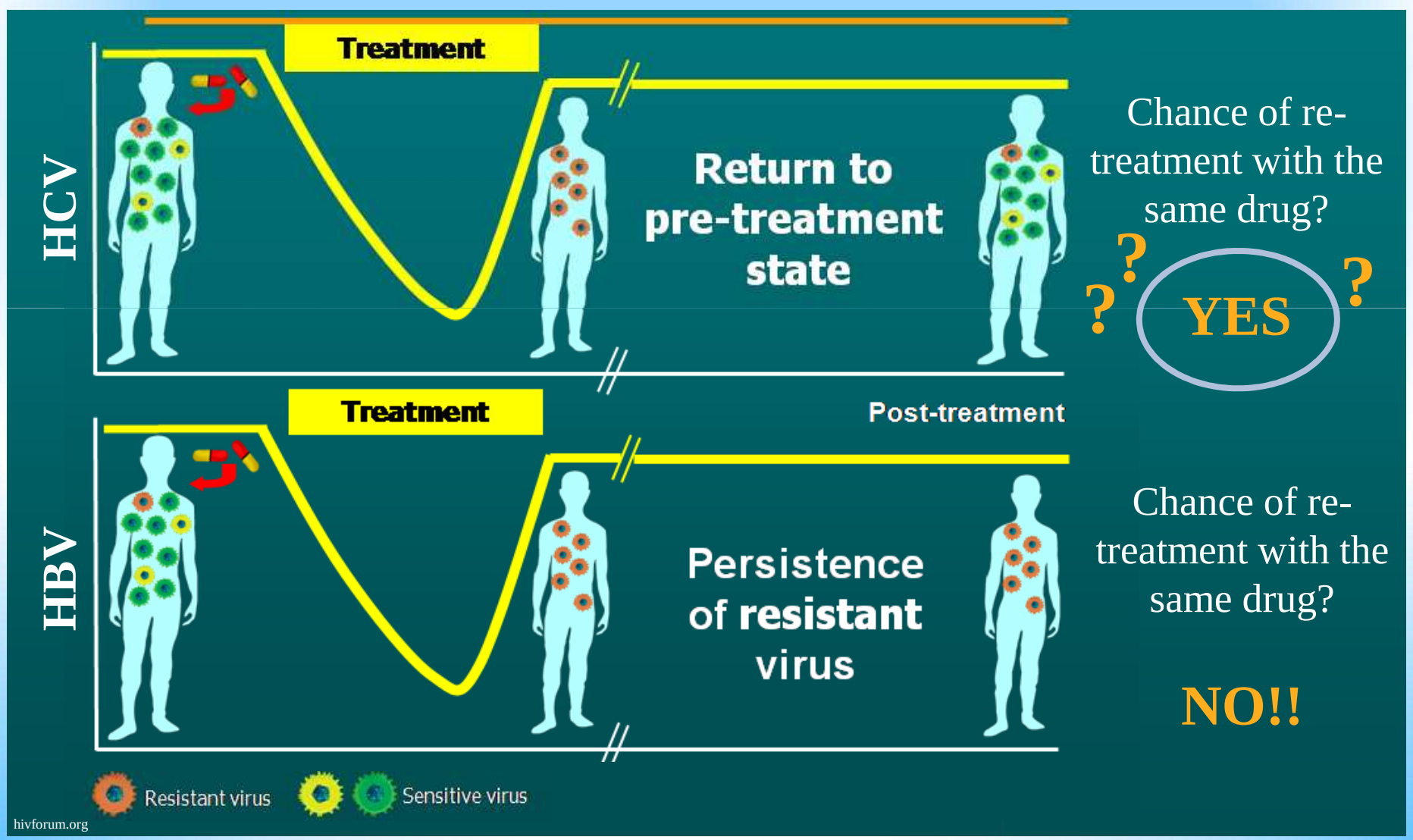
What happens to PI-resistant variants when drug-pressure is interrupted?

HCV has no intracellular reservoirs

	HIV	HBV	HCV
Virus			
daily production of virions per day	10^{10}	10^{12}–10^{13}	10^{12}
half-life of free virions (h)	1	3–24	2–3
half-life of intracellular virions	days (dependent on infected cells $t_{1/2}$)	months (dependent on infected cells $t_{1/2}$)	hours (not dependent on infected cells $t_{1/2}$)
mutation rate	very high	high	very high
constraints due to ORFs in targeted viral enzymes	moderate	high	none
immune-mediated escape mutants	frequent	infrequent	frequent
Target cells			
half-life of infected cells	days	months	weeks
size of susceptible cells compartment	large	small	probably large
intracellular viral reservoir	yes (integrated cDNA)	yes (cccDNA)	no

Soriano et al., JAC 2008

Archiviation of resistant variants can compromise future treatment strategies



Hepatitis C virus resistance to protease inhibitors

- Protease inhibitor associated mutations can be present before the treatment and **persiste after the end of therapy**.

Hepatitis C virus resistance to protease inhibitors

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- Protease inhibitor associated mutations can be present before the treatment and persiste after the end of therapy.
- Cross resistance mutations exist between the different protease inhibitors.
- Subtyping of genotype 1 will clarify the different types of resistant variants to the PIs.
- Detection of resistance should be done using sensitive assays (quasispecies 5-10% of the overall population).

Diagnostic tools used for minor variants determination: description, principle, advantage and drawback

	Clonal sequencing	Single genome sequencing	Allele specific PCR	Ultradeep sequencing
Principle	Molecular cloning Sequencing of numerous clones	Limits dilution (1 single genome) Numerous PCR and sequence	Mismatch amplification mutation assay	Multiples short sequences analyzed 200 to 400 nt
Sensitivity	>10% (1%:100 clones) 0.1%:1000 clones	2%	0.03-0.2%	0.05-1%
Advantages	Reference method All mutations detected Double mutant detected	All mutations detected Double mutant detected	Sensibility +++ Easy to perform Possible quantitation Low cost	Sensibility ++ Automatisation Quantitation
Drawbacks	Errors/recombination during PCR Bad sensitivity Bad NPV Nb of clones and sequences ++ Costly and hard time labour Lack of automatisation	1 single copy of DNA? Costly and hard time labour Lack of automatisation	Known position of resistance Limited number of mutations detected Bad specificity Neighbour polymorphisms few standardisation	Short sequences CV >10^4 copies/ml Availability Equipment/cost ++ Interpretation

Locarnini S, J Hepatol 2011

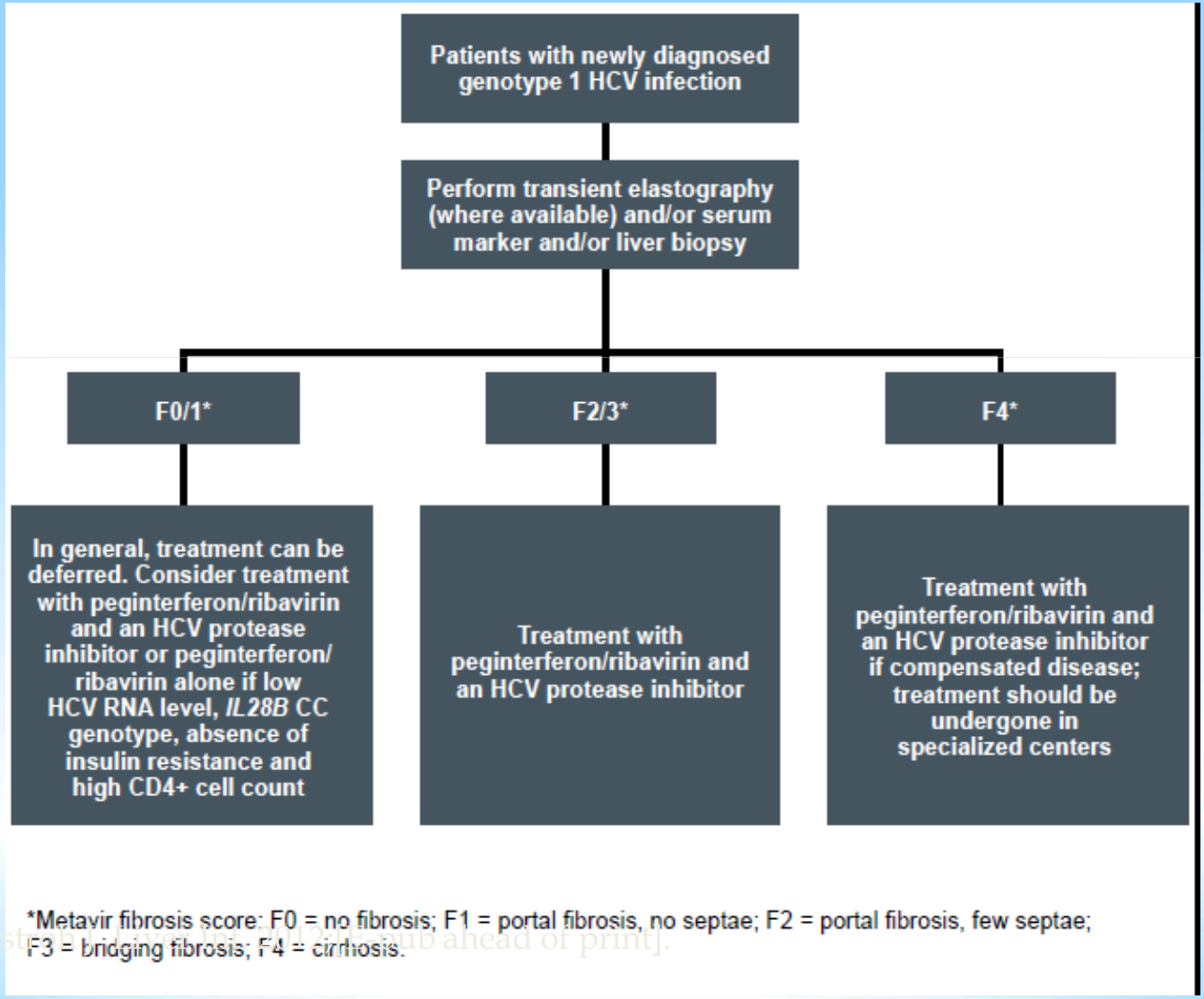
Strategies to Minimize the Risk of Treatment Failure With Resistance

- Stopping-rule should be strictly applied
- Neither boceprevir nor telaprevir should be given as monotherapy. If pegIFN/RBV is discontinued, PI should also be stopped.
- Boceprevir and telaprevir should not be dose reduced or stopped and then restarted
- Importance of medication adherence should be emphasized to patients
- Currently no evidence to support switching from one PI to the other

Futility Rules for Boceprevir and Telaprevir

Time Point	HCV RNA Level Required for Stopping	Action
Boceprevir		
▪ Wk 12	≥ 100 IU/mL	Discontinue boceprevir + pegIFN/RBV
▪ Wk 24	Detectable	Discontinue boceprevir + pegIFN/RBV
Telaprevir		
▪ Wk 4 or 12	> 1000 IU/mL	Discontinue telaprevir + pegIFN/RBV
▪ Wk 24	Detectable	Discontinue pegIFN/RBV

Management of Newly Diagnosed Gt 1 HCV/HIV–Coinfected Pts



Ingiliz P, Rockstroh J. Liver Int. 2012 [Epub ahead of print].

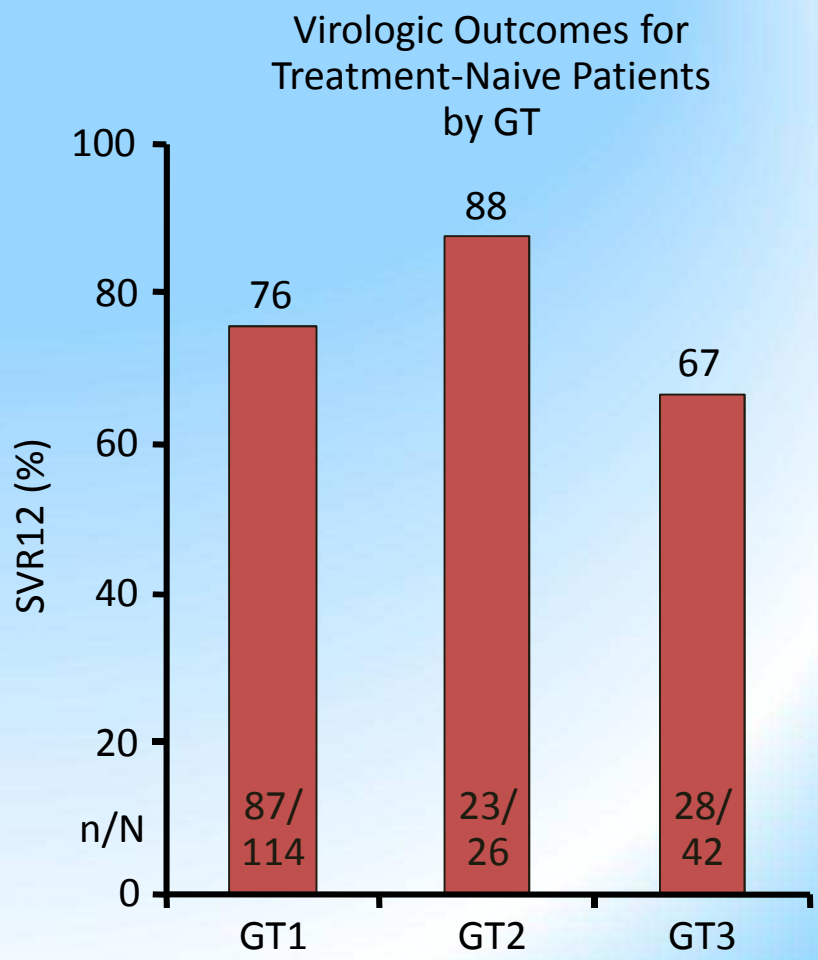
Conclusioni

- HCV patologia con impatto epidemiologico e clinico rilevante nel paziente anti-HIV positivo
- Efficacia limitata, specie per il genotipo 1, della duplice terapia, ma oggi prevedibile
- Dati non conclusivi su schemi terapeutici ed efficacia con DAA
- Problematiche di tossicità, interazione con ART, resistenze dei DAA

Grazie per l’attenzione

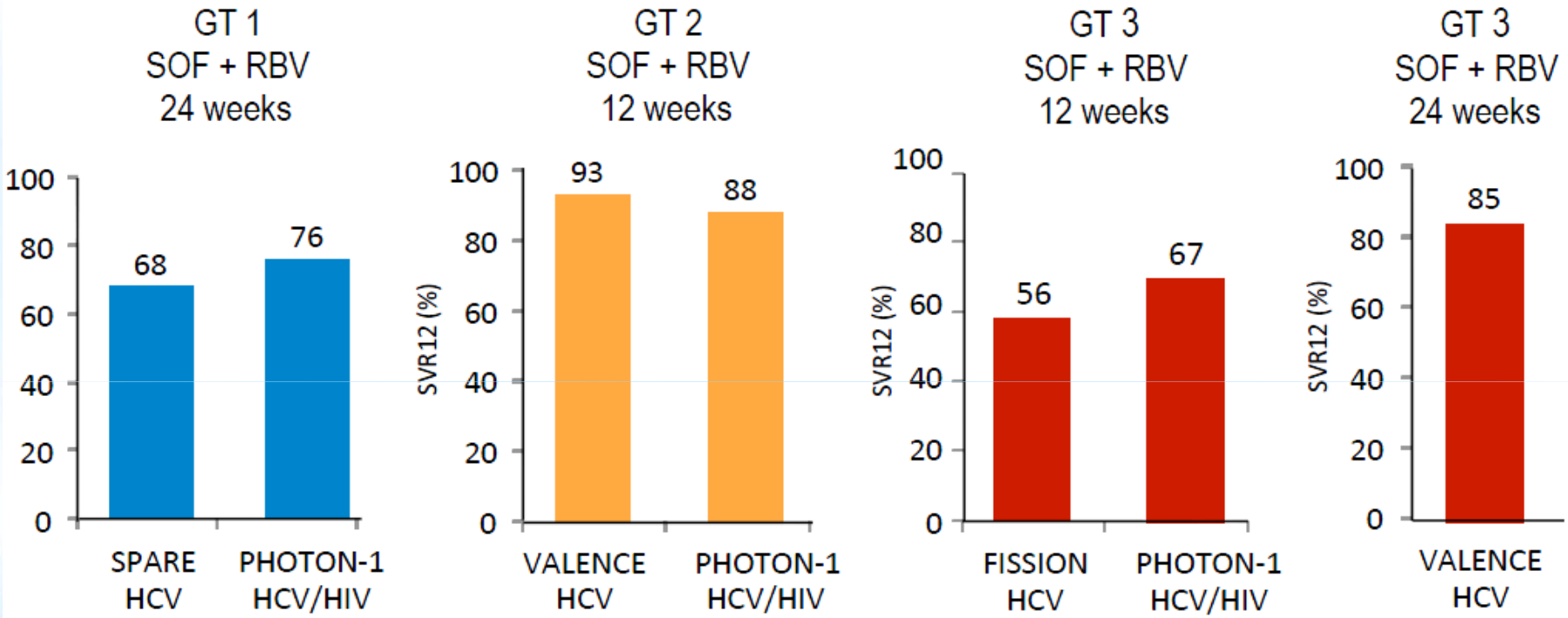
PHOTON-1: Sofosbuvir + RBV in GT1/2/3 HIV/HCV Coinfection

- Phase III open-label study
  - 12- (GT2/3 treatment-naive) or 24-week regimens (GT1 treatment-naive, GT2/3 treatment experienced): sofosbuvir + RBV
- HCV treatment-naive or -experienced HIV+ patients (N = 223)
  - Approx 76% on ART (VL < 50 cells/mL), various standard regimens
- Safety profile similar to monoinfected patients; consistent with RBV
  - Most frequent AEs: fatigue, insomnia, headache, nausea, diarrhea
- 2 patients had transient HIV rebound due to nonadherence



47. Sulkowski MS, et al. AASLD 2013. Abstract 212.

All-Oral SOF+RBV for HCV Mono-infected and HCV/HIV Co-infected Patients



Similar response rates in HCV/HIV co-infected patients compared to HCV mono-infected patients

Osinusi A, et al. *JAMA*. 2013;310(8):804-811.Sulkowski MS, et al. AASLD 2013. Washington, DC. Oral #212. Zeuzem S, et al. AASLD 2013. Washington, DC. #1085. Lawitz E, et al. *N Engl J Med*. 2013 May 16;368(20):1878-87. Sulkowski et al, JAMA. 2014 ; 312:353-61