Controversias en Hepatitis Viral
Curso de Biologia Molecular para clinicos VIH y Hepatitis

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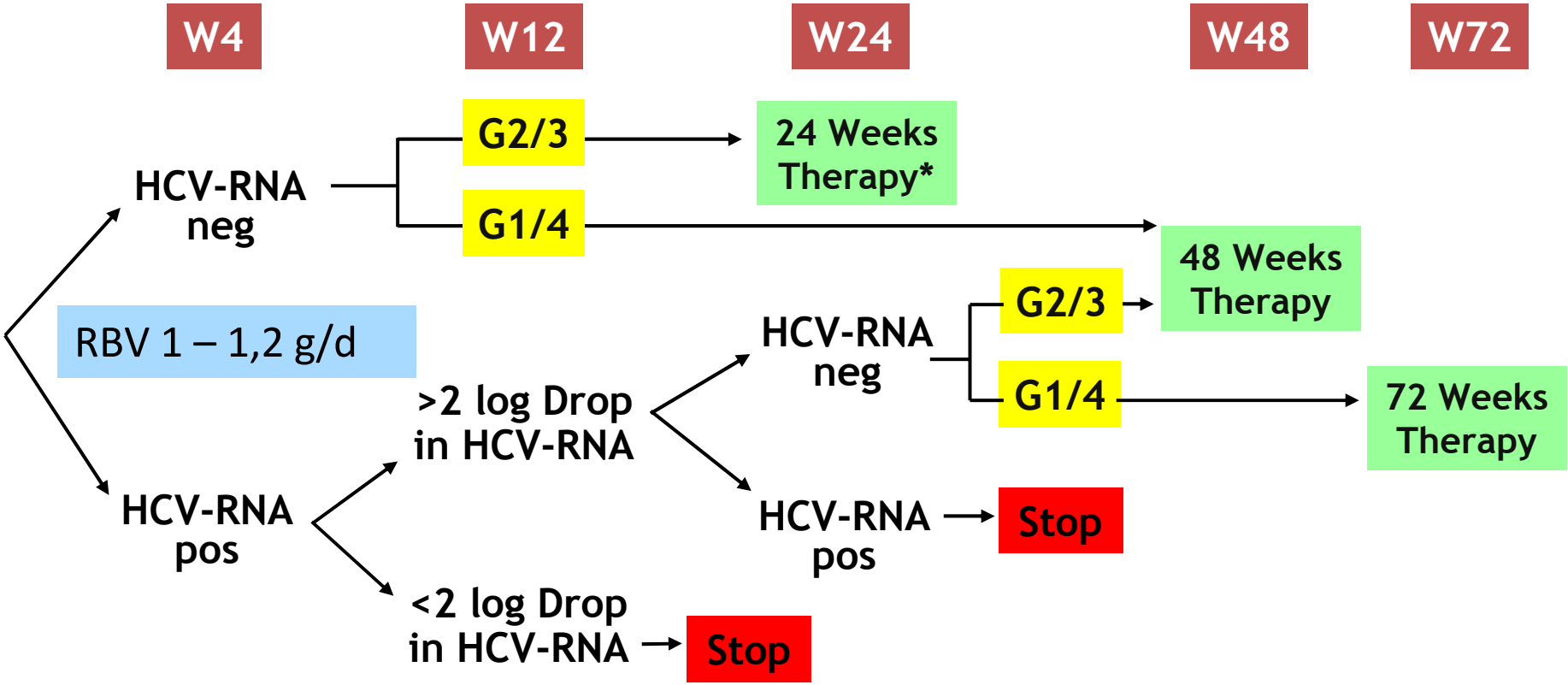
Vigo, 4 Fevereiro

Terapêutica Actual em Co-Infectados VIH/VHC



*In patients with baseline low viral load and minimal liver fibrosis.

Guidelines EACS v6, Outubro 2011

Factores predictivos de resposta ao tratamento do VHC

- Genótipo VHC (antes)
- RNA-VHC basal (antes)
- Grau de fibrose hepática (antes)
- RVR (durante)
- RVP (VPN- 98-100%)

- IL28b polimorfismo

Controversias en Hepatitis Viral

- **Clinical Case**
  - 700 CD4/mm3; RNA-VIH 10 000 cp/ml
  - Male gender
  - 32 yrs (age less 40)
  - HCV G1a
  - HCV-RNA- 550 000 UI/ml ($<4x10^5$)
  - HOMA-IR -2
  - FS – 9,6 Kpa (F3)
  - IL 28B - *CC*

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RESPONSE TO PEG-IFN PLUS RBV IN HIV/HCV-COINFECTED PATIENTS

STUDY	ACTG A5071 [82]	APRICOT [84]	PEREZ-OLMEDA et al. [79]	LAGUNO et al. [85]	RIBAVIC et al. [83]
Nº patients	66	289	68	52	205
Type of peg-IFN	alpha-2a	alpha-2a	alpha-2b	alpha-2b	alpha-2b
RBV dosage	Escalating 600→1000mg/d	800 mg/d	800 mg/d	800 to 1200 mg/d	800 mg/d
IDU	80%	62%	94%	75%	81%
Cirrhosis	11%	15%	14%	11%	18%
Genotypes 1-4	77%	67%	70%	63%	69%
Median CD4	492	520	546	624	525
With ARV	85%	84%	94%	94%	82%
Premature stop	12%	25%	22%	25%	36%
ETR (ITT)	41%	49%	50%	52%	36%
SVR (ITT)	27%	40%	28%	44%	27%

ETR, end-of-treatment response; SVR, sustained virological response; ARV, antiretroviral therapy; Peg-IFN, pegylated interferon; RBV, ribavirin; ITT, intention to treat.

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G1 – RVS 14-36%*

*Presco, 192 pt G1

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Controversias en Hepatitis Viral

- Indivíduos com fibrose significativa (Metavir >F2) têm maior risco de evolução da doença*
- A presença de **fibrose hepática severa** e de cirrose são factores associados a resposta pobre

**Sulkowki M. CROI 2010,#166*

Controversias en Hepatitis Viral

- A imunossupressão agrava a taxa de progressão da fibrose hepática*
- Em indivíduos com infecção VIH controlada (CD4 > 500 cel/mm3 e CV < 400 cp/ml) a progressão da fibrose é semelhante em pessoas com ou sem infecção VIH**

Puoti M. JID 2001; 183: 134 Sulkowski M. Liver Intern 2011, 32(S1): 129*

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Impacto *IL28b* nos coinfectados VIH/VHC

164 HIV-HCV coinfected patients who completed a course of pegIFN-RBV.
HCV genotype distribution: HCV1- 58%, HCV3- 31% and HCV4- 11%.

SVR rate	rs12979860 polymorphisms		p
	CC genotype (n=75)	CT/TT genotype (n=89)	
Global population	75% (56/75)	38% (34/89)	<0.0001
HCV 1 (n=95)	65% (22/34)	30% (18/61)	0.001
HCV 3 & 4 (n=69)	83% (34/41)	57% (16/28)	0.02

Predictors of SVR (multivariate analysis)

	OR	95% CI	p
IL28b alleles (CC vs CT/TT)	3.4	1.4-7.9	0.006
HCV genotypes (3 vs 1/4)	8.1	3.0-21.7	<0.0001
Baseline HCV-RNA (< vs. > 600,000 IU/mL)	13.9	3.9-48.1	<0.001
Liver fibrosis (F0F2 vs. F3F4)	3.4	1.3-9.2	0.016

Rallon et al. CROI 2010

Predictivos de Resposta –papel da IL28B

Genótipo	RVS (%) TT/CT	RVS (%) CC
1	17	50
4	25	80
3	77	93

159 doentes*

A presença do IL28B constitui um factor independente de RVS quer no G1 quer no n-G1

Pineda, CID 2010; 51(7): 788-95

Algoritmo de Resposta ao tratamento

- *Modeling the probability of sustained virological response to therapy*

  – 4 variáveis

  .2 relacionadas com o hospedeiro (rs 12979860 e fibrose)

  .2 relacionadas com o VHC (genótipo e carga viral)

  – 159 doentes terminaram o tratamento

**CID, 2010, 51(10): 1209-16*

Factores predictivos de Resposta ao tt com PEG+R

Valor predictivo	OR (95% CI)	P
VHC-genótipo 1 e 4	0.212	.002
RNA-VHC (log IU/mL)	0.186	<.001
Fibrose (kilopascais)	0.920	0.07
Rs 12979860 (CT ou TT)	0.170	<.001

$$Pr\ (RVS) = \frac{1}{1 + e^{(-x)}}$$

x=[13.940 + (-1.549X genótipo ¼
+(-1.682XRNA-VHC (log) + (-0.084X fibrose) +
(-1.772Xrs 12979860 CT ou TT)]

**Medrano J, CID, 2010, 51(10): 1209-16*


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Prometheus Index
Prometheus Index
http://ideasydesarrollo.com/fundacion/prometheusindex.php
Prediction of Sustained Virological Response (SVR) after treatment of Hepatitis C with Pegylated Interferon plus weight adjusted Ribavirin
IL28B polymorphism at rs12979860
(choose one option)
Liver stiffness by FibroScan
(in Kpa)
HCV genotype
(choose one option)
Pretreatment HCV-RNA level
(in log IU/mL)
Age
(in years)
Gender
(choose one option)
Race
(choose one option)
HIV infection
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Controversias en Hepatitis Viral

Novos fármacos

Controversias en Hepatitis Viral

- Telapravir & Bocepravir

  – Taxas de RVS

  66-75% em naives

  75-88% em *Relapsers*

  52-59% em Respondedores parciais

  38% em Não Respondedores

Main differential features of new DAA against HCV

	NS3 protease inhibitors	NS5B polymerase nucleos(t)ide analogs	NS5B polymerase non-nucleoside analogues	NS5A inhibitors
Mechanism of inhibition	Inhibitory competition	Inhibitory competition	Allosteric	?
Genotype activity	G1 (G1b > G1a)	Across all	G1 (G1b >1a)	Across all
Resistance barrier	Low	High	Low	Low
Cross-resistance	High	Low	Split out in 4-5 families	high
Drug interactions	PK	pharmacodynamic	PK	PK

HCV protease inhibitors

	1st generation PIs (telaprevir, boceprevir)
Mechanism of inhibition	covalent
Dosing	Q8h/TID
Safety	Rash, anaemia
Shortened treatment duration	40–60%
SVR	~70%

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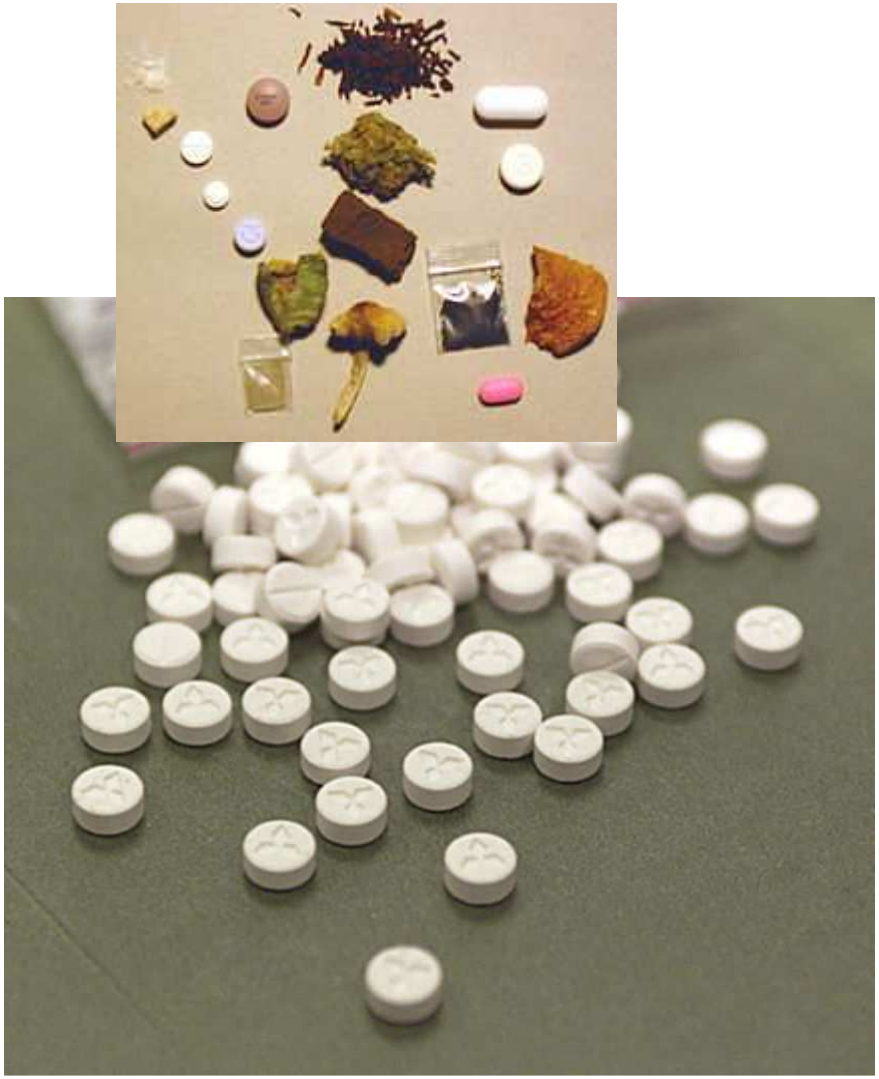
TPV
2 cp 8/8H

BOC
4 cp de
8/8H

+

RBV

Interacções medicamentosas



DDI Between HCV-PIs and Common HIV Drugs

	Telaprevir		Boceprevir	
TDF	≈	↑30%*	≈	↑5%*
EFV	↓25% (tid) ↓48% (bid)	↓10% (tid) ↑10% (bid)	↓40%	↑20%*
ATV/r	↓15%	↑85%	--	--
DRV/r	↓32%	↓42%	--	--
FPV/r	↓30%	↓56%	--	--
LPV/r	↓52%	↑14%	--	--
RTV (low dose)	↓32-75%	--	↓19%*	--
Raltegravir	≈	≈	≈	≈
Methadone	≈	↓31-40%	--	--
Midazolam	--	--	--	↑5.3-fold*
Escitalopram	--	↓42%	--	--
Esomeprazole	≈	--	--	--
Contraceptives (estrog./progest.)	--	--	--	↓24%/↑99%*
Clarithromycin	--	--	↑21%*	--
Ketoconazole			↑3.3-fold*	

Variation in Cmin, (*or in AUC)

Contraindicaçãoes com uso de TPV ou BOC

Class	Telaprevir	Boceprevir
Anxiolytics	**Midazolam p.o**, *triazolam*	**Midazolam p.o**, *triazolam*
Alpha 1 receptor antagonist	Alfuzosin	Alfuzosin
Anti-arrhythmic	Amiodarone, quinidine, flecainide, propafenone, *bepridil*	
Anticonvulsant		Carbamazepine, phenobarbital, phenytoin
Antimycobacterials	**Rifampicin**	Rifampicin
Antihistamines	*Terfenadine, astemizole*	
Antipsychotic	Pimozide	Pimozide
Contraceptives (oral)		**Drospirenone**
Digestive motility stimulants	*Cisapride*	*Cisapride*
Ergot rye derivatives	Dihydroergotamine, *ergonovine*, ergotamine, methylergonovine	Dihydroergotamine, *ergonovine*, ergotamine, methylergonovine
Herbal products	St. John's wort (Hypericum perforatum)	St. John's wort (Hypericum perforatum)
Lipid-lowering (HMG CoA inhibitors)	Simvastatin, *lovastatin*	Simvastatin, *lovastatin*
PDE-5 inhibitors	Sildenafil (Pulmonary arterial hypertension)	Sildenafil, tadalafil (Pulmonary arterial hypertension)

Bold: study done; *Removed /Not available in all countries*

Terapêutica tripla?? neste Caso

- *Overlapping toxicities – rash* /anemia
- Muitos comprimidos/dia (< *Compliance* à terapêutica/ > risco de Resistência)
- Menor probabilidade de RVS no G1a
- Custo adicional

- **RVS estimada com terapêutica tripla de 66-75%**
- **RVS estimada com terapêutica dupla- 87,32%**

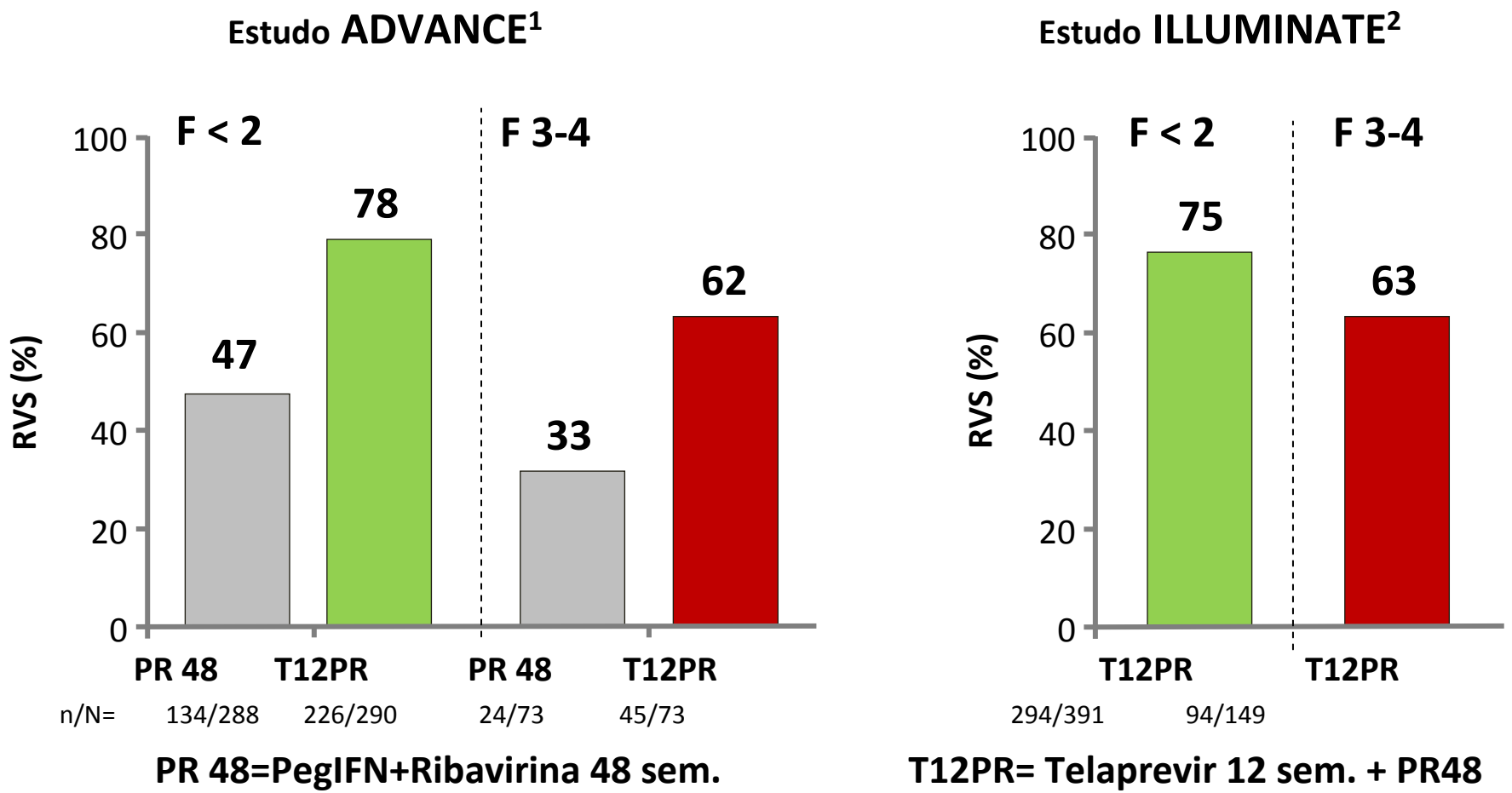
Controversias en Hepatitis Viral

- PegIFN+RBV
- PegIFN+RBV +IP

SI

NO

RVS de acordo com estádios de fibrose: estudos ADVANCE e ILLUMINATE - Telaprevir



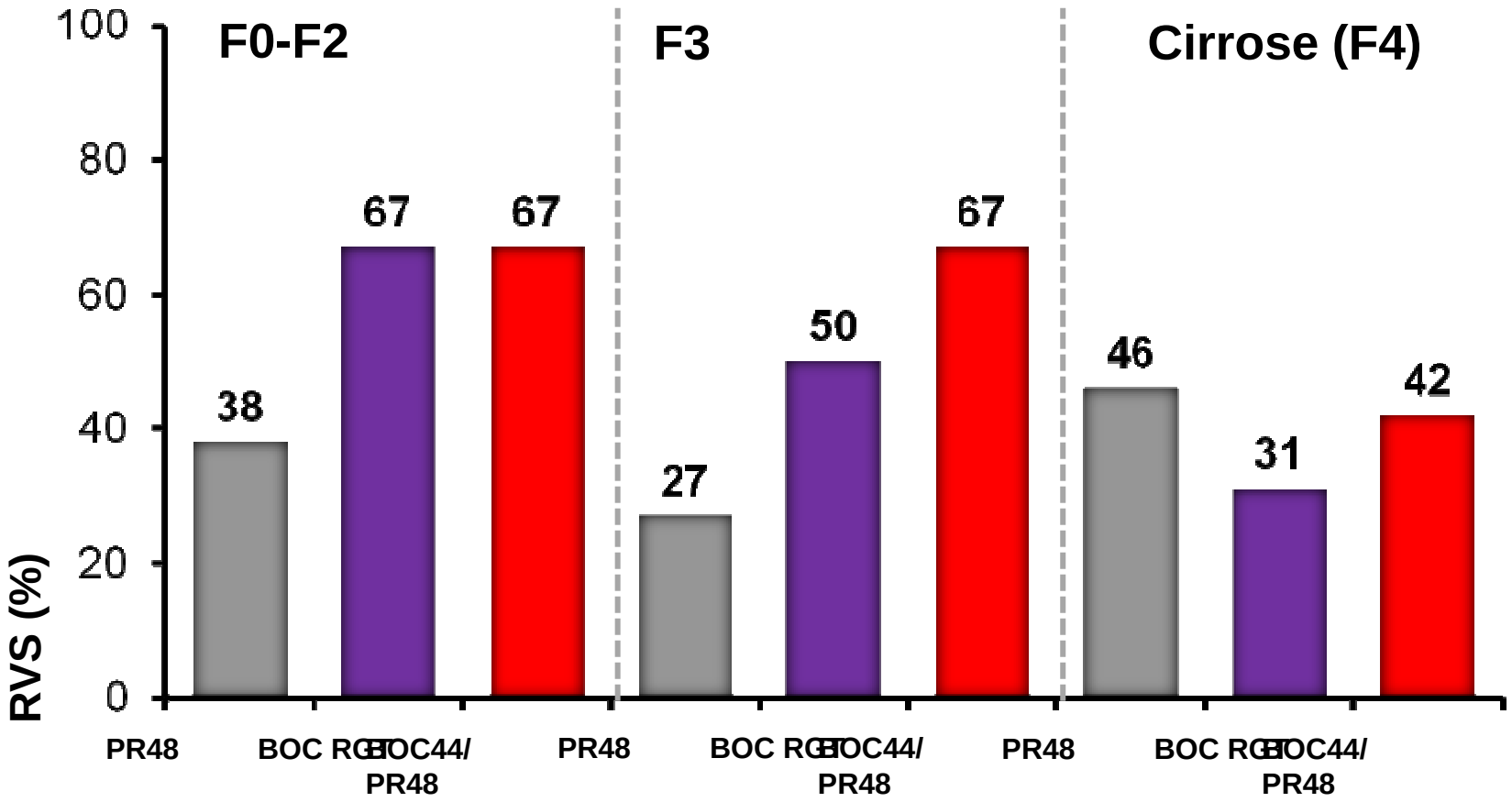
PR 48=PegIFN+Ribavirina 48 sem.

T12PR= Telaprevir 12 sem. + PR48

1. Jacobson IM, et al. Hepatology 2010;52(Sup):427A

2. Sherman KE, et al.Hepatology 2010;52(Supl):401A

RVS de acordo com estádios de fibrose: estudo SPRINT-2 - Boceprevir



Poordad F, et al. N Engl J Med 2011;364:1195–206