The future of Hepatitis C therapy

Vicente Soriano
Department of Infectious Diseases
Hospital Carlos III, Madrid, Spain

A new era for hepatitis C – new diagnostic tools & new weapons

Diagnosis	Therapy
• IL28B alleles • Non-invasive liver fibrosis methods • Viral load • HCV geno/subtyping • Drug resistance	• Protease inhibitors • Polymerase inhibitors • NS5A inhibitors • Interferon lambda • Alisporivir

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 (G1a<G1b)
Resistance barrier	Low	High	Low	Low
Cross-resistance	High	Low	Split out in 4-5 families	high
Drug interactions	PK	pharmacodynamic	PK	PK

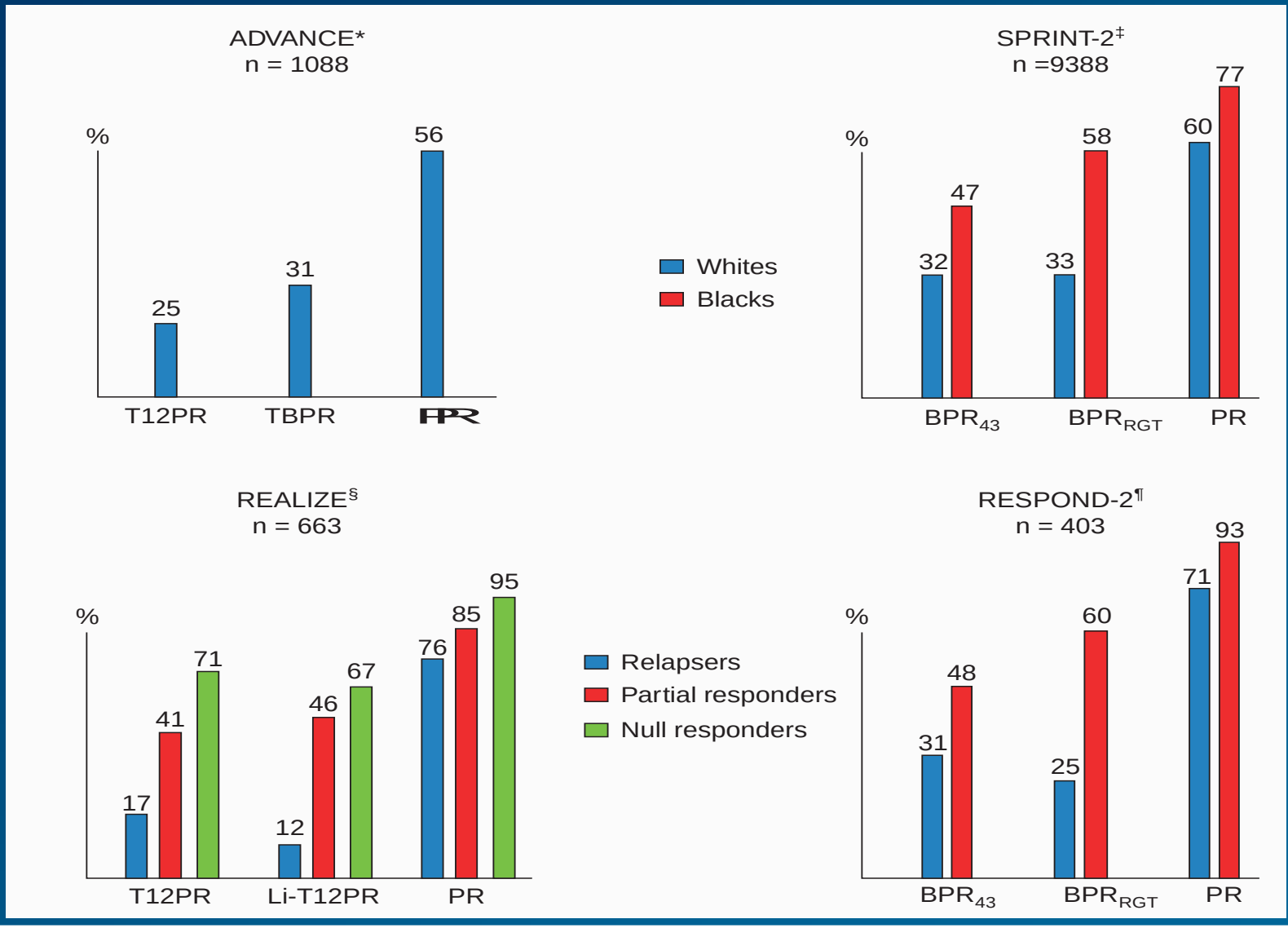
HCV protease inhibitors

	1st generation PIs (telaprevir, boceprevir)	2nd generation PIs (simeprevir, danoprevir, BI-1335)
Mechanism of inhibition	covalent	Non-covalent
Dosing	Q8h/TID	QD
Safety	Rash, anaemia	GI
Shortened treatment duration	40–60%	80–90%
SVR	~70%	Potential for >80%

Treatment failure with new hepatitis C drugs

Vincent Soriano†, Eugenia Vispo, Eva Poveda, Pablo Labarga & Pablo Barreiro
Hospital Carlos III, Infectious Diseases Department, Madrid, Spain

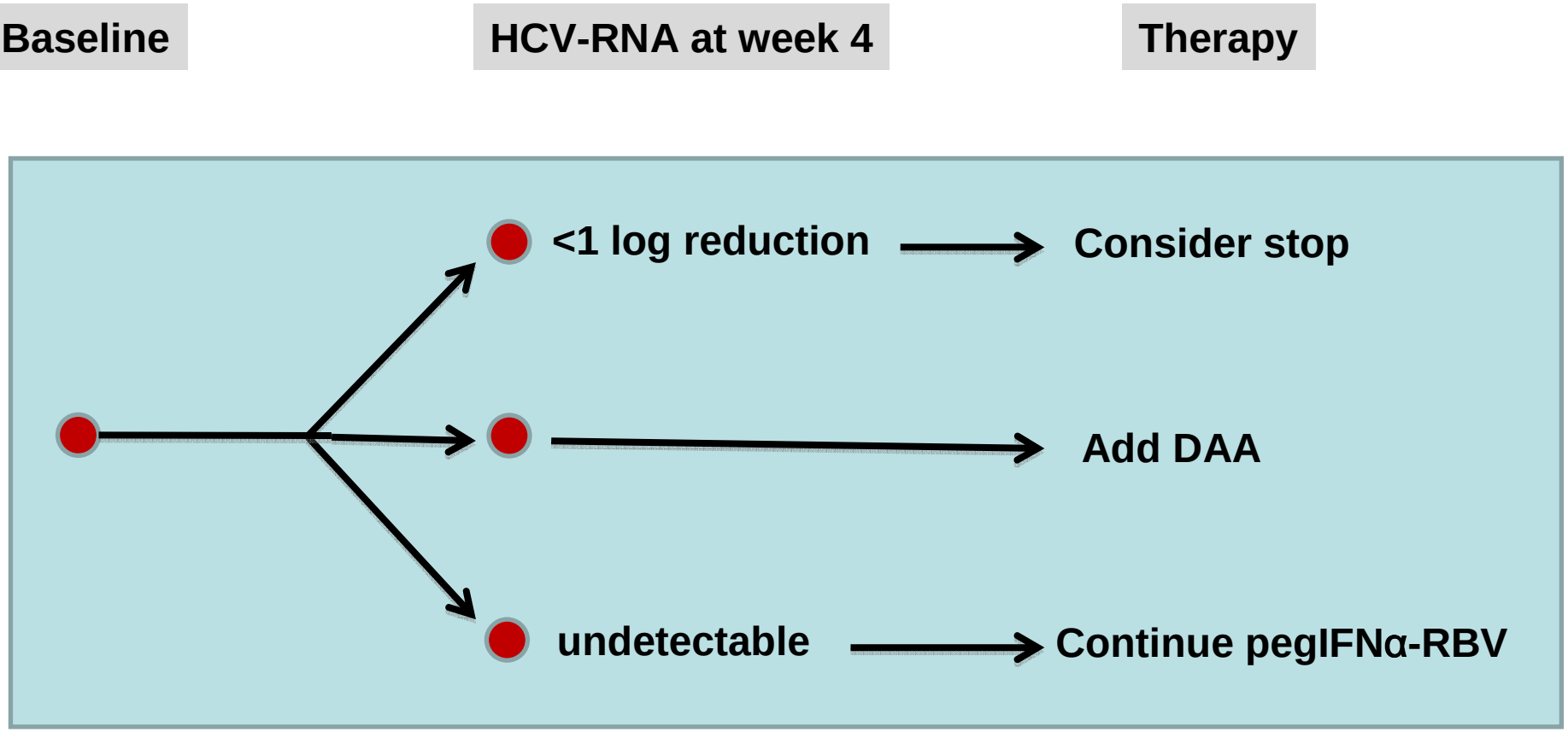
Expert Opin Pharmacother 2012; 13: 313-23.



HCV special populations

Population	Caveat
Liver transplantation	Drug-drug interactions; rejection
Advanced liver disease	DAA metabolism; enhanced toxicity
Prior IFN non-responders	Scarce information
IFN and/or RBV intolerant	Wait for IFN and/or RBV sparing combinations
Non-1 HCV genotypes	Poor or null activity
Hemodyalisis	No data
Children	Dose adjustments
Acute hepatitis C	No data
Inherited hematological disorders: thalassemia, hemophilia	Toxicities: anemia, bleeding
Socially dysfunctional groups (i.e., homeless, illegal immigrants)	Difficult-to-reach and keep on satisfactory drug adherence
Active intravenous drug users	Concerns about drug adherence and transmission of drug-resistant HCV mutants

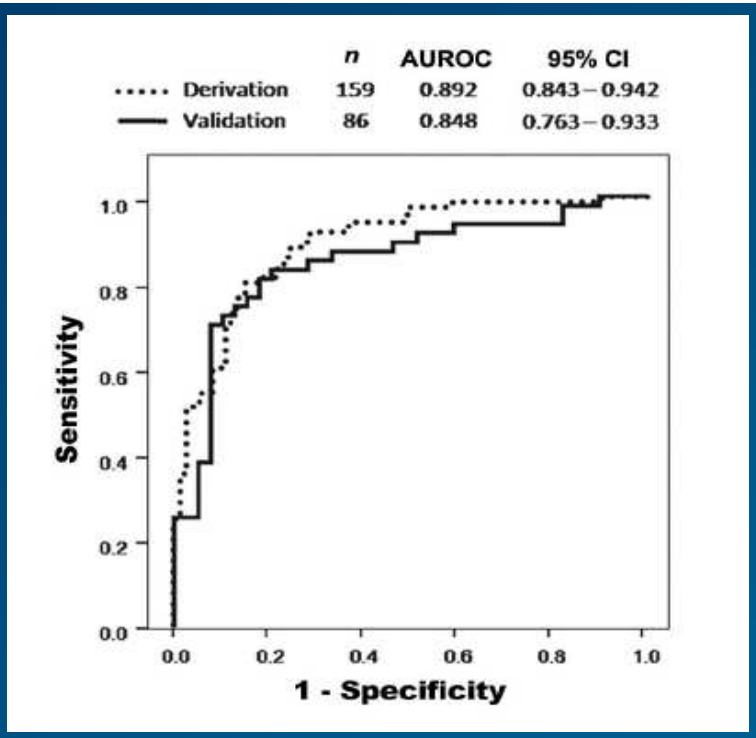
Proposed treatment strategy with a lead-in phase of peginterferon-ribavirin therapy.



Modeling the Probability of Sustained Virological Response to Therapy with Pegylated Interferon plus Ribavirin in Patients Coinfected with Hepatitis C Virus and HIV

Clinical Infectious Diseases 2010;51(10):1209–1216

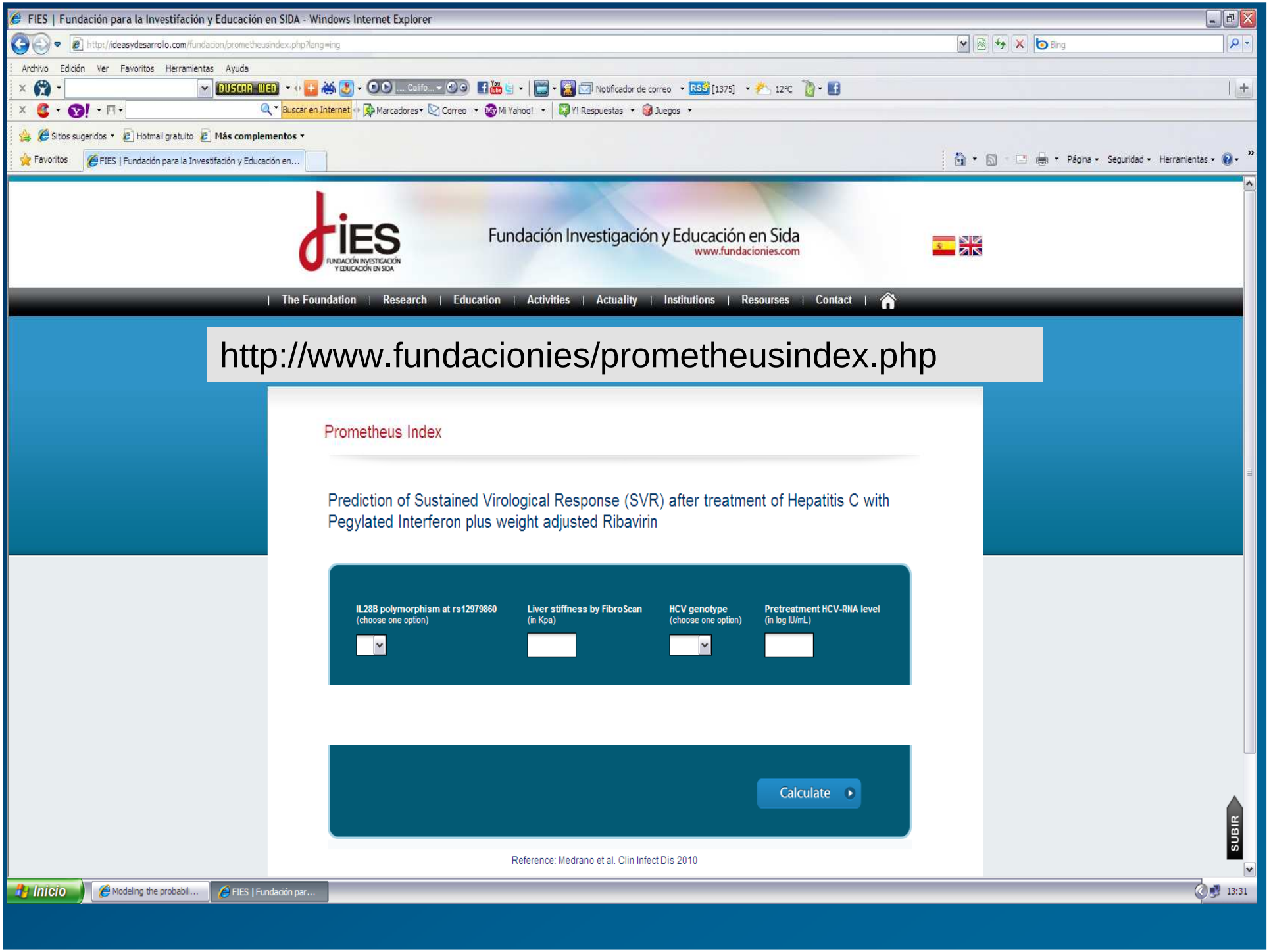
Jose Medrano,[1] Karin Neukam,[3] Norma Rallón,[1] Antonio Rivero,[4] Salvador Resino,[2] Susanna Naggie,[6] Antonio Caruz,[5] Aida Calvino,[2] Juan Macías,[3] Jose Miguel Benito,[1] Carlos Sánchez-Piedra,[1] Eugenia Vispo,[1] Pablo Barreiro,[1] John McHutchison,[6] Juan Antonio Pineda,[3] and Vincent Soriano[1]



Prometheus index

- HCV genotype
- Fibrosis stage (KPa)
- Serum HCV-RNA
- IL28B SNPs

http://www.fundacionies/prometheusindex.php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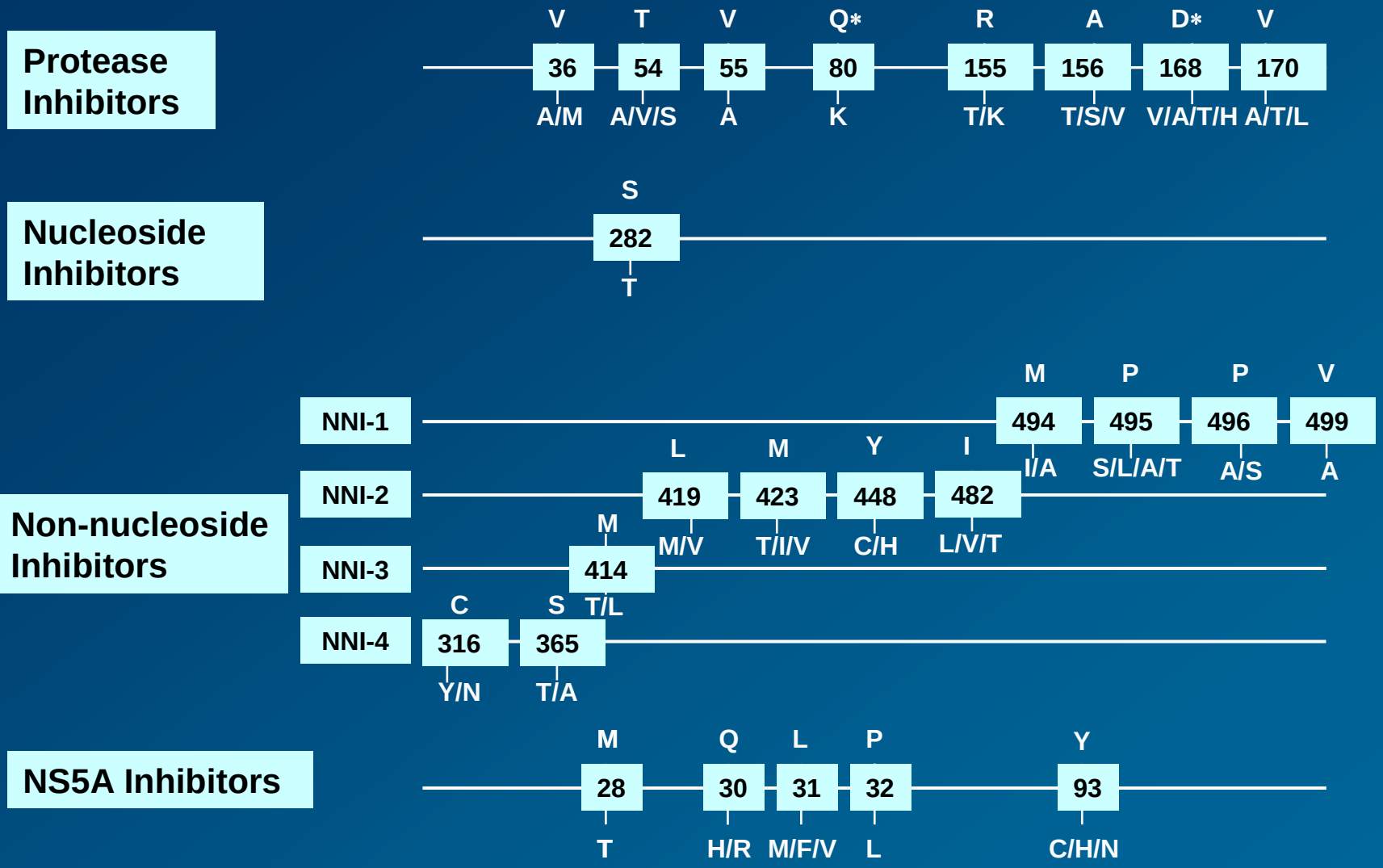
Prometheus Index
Prediction of Sustained Virological Response (SVR) after treatment of Hepatitis C with Pegylated Interferon plus weight adjusted Ribavirin
IL28B polymorphism at rs12979860 (choose one option)
Liver stiffness by FibroScan (in Kpa)
HCV genotype (choose one option)
Pretreatment HCV-RNA level (in log IU/mL)
Calculate
Reference: Medrano et al. Clin Infect Dis 2010
SUBIR

Main HCV resistance mutations to DAA



∗Protease Q80K is a natural polymorphism found in ~44% of HCV-1a and is associated with resistance to simeprevir.

∗Protease D168Q is found in all HCV-3

Poveda et al. Future Virol (in press)

Prevalence of natural polymorphisms that may influence DAA susceptibility across HCV genotypes/subtypes

Drug family	Key mutations associated with DAA resistance*	1a	1b	2	3	4	DAA affected by specific polymorphisms
NS3 protease inhibitors (no. NS3 sequences: 1612†)	T54A/S	1.4% S	1% S	0	0	5.5% S	Telaprevir, boceprevir
	V55A	1.2% A	0	0	0	0	Boceprevir
	Q80K	39.7% K	0	0	0	0	Simeprevir
	D168A/H/T/V/Q	0	0	0	99.2% Q	0	Simeprevir
NS5B non- nucleoside analogues (no. NS5B sequences: 1025†)	S15G	0	0	76.3% G	0	0	PSI35261 (NUC) PSI352938 (NUC)
	C316Y/N	0	36% N	0	0	0	ABT-333 (NNI-4) ABT-072 (NNI-4)
	M414T/L	0	0	0	0	34.2%L	Setrobuvir (NNI-3)
	L419M/V	0	0	2.7% V	0	0	VCH-759 (NNI-2)
	M423T/I/V	1.8% I	0	0	0	0	Filibuvir (NNI-2) VCH-759 (NNI-2) VHC-916 (NNI-2)
	I482L/V/T	0	0	100% L	100% L	100% L	VCH-759 (NNI-2)
	V494I/A	0	0	100% A	5.2%A	0	VCH-759 (NNI-2)
	V499A**	96.2% A	10.5%A	91% A	100%A	100%A	Tegobuvir (NNI-1) BI-7127 (NNI-1)
NS5A inhibitors (no. NS5a sequences: 3153†)	Q30H/R	0	0	0	0	51.3% R	Daclatasvir
	L31M/V/F	0	0	83.5 % M	0	92% M	Daclatasvir
	Y93C/H/N	0	2% H	0	1%H	5.4%H	Daclatasvir

*Only changes with a prevalence >1% are recorded. **V499A confers low-level resistance to NNI-1.

† NS3 protease, NS5B polymerase and NS5A sequences were obtained from Los Alamos database.

No mutations associated with resistance to NS5B nucleos(t)ide analogues are found as natural polymorphisms.

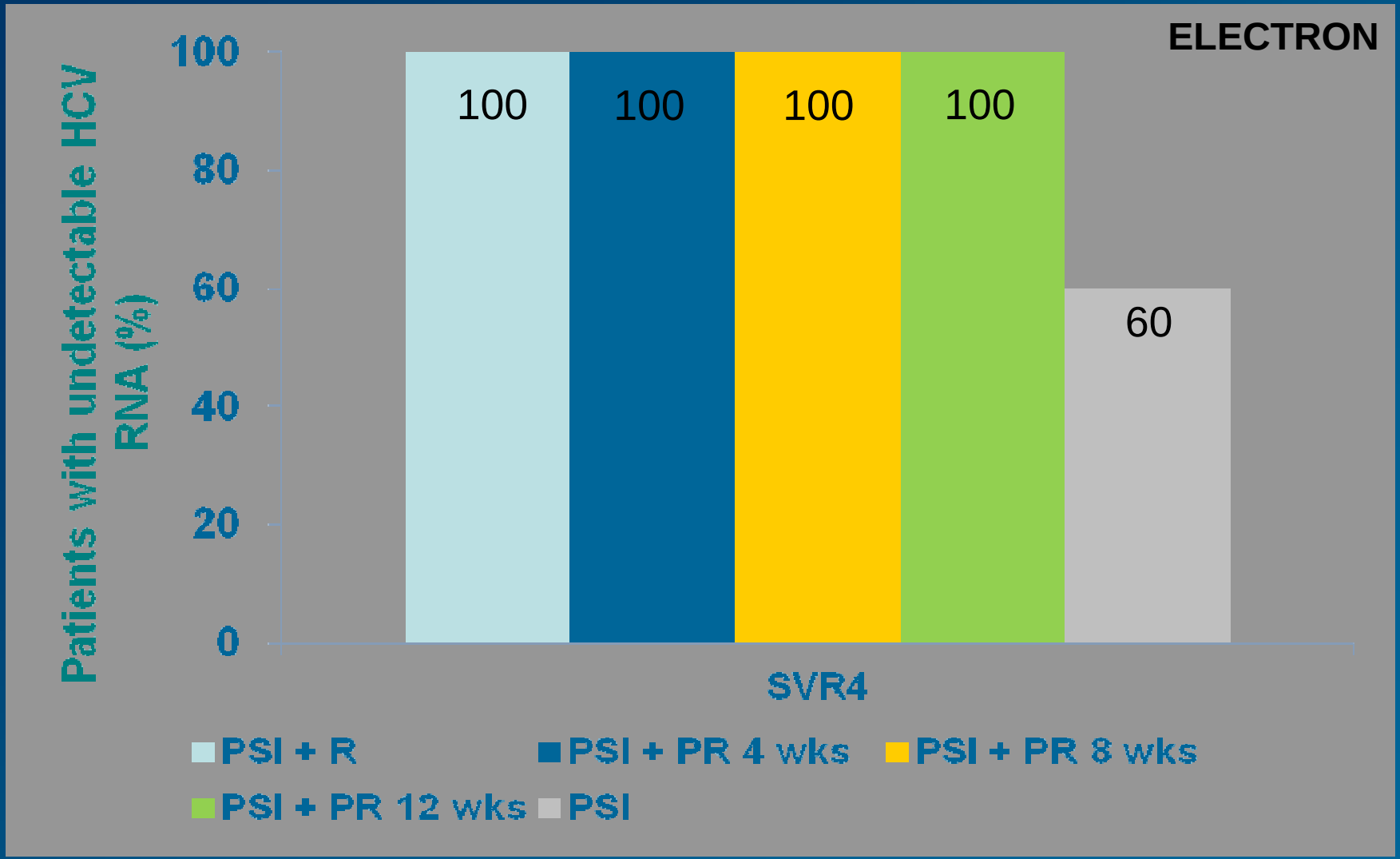
Poveda et al. Future Virol (in press)

AASLD Nov 2011

- Simeprevir (PILLAR trial)
- Danoprevir/r
- Asunaprevir
- BI-1335
- Daclatasvir
- Combos IFN-free

PSI-7977 

PSI-7977 + RBV (GT-2/3) (n=10 per arm)



Gane et al. AASLD 2011. Abstract 34

PSI-7977

- Uridine analogue
- 400 mg QD with/out food
- Pan-genotypic activity
- High barrier to resistance
- No influence IL28B SNPs
- No drug-related side effects

PROTON: 121 G1; triple 12w+PR 12w+RGT
91% SVR (rebounds upon dc PSI)

Ongoing trials using DAA combination therapy against HCV

Company	DAA-1 (protease inhibitor)	DAA-2 (polymerase or NS5A inhibitors)
Roche	Danoprevir	Mericitabine*
Boehringer	BI-1335	BI-7127**
Vertex	Simeprevir	VX-222**
Gilead	GS-9256	Tegobuvir**
BMS	Asunaprevir	Daclatasvir***
Idenix	IDX-320	IDX-184***
Abbott	ABT-450	ABT-072**

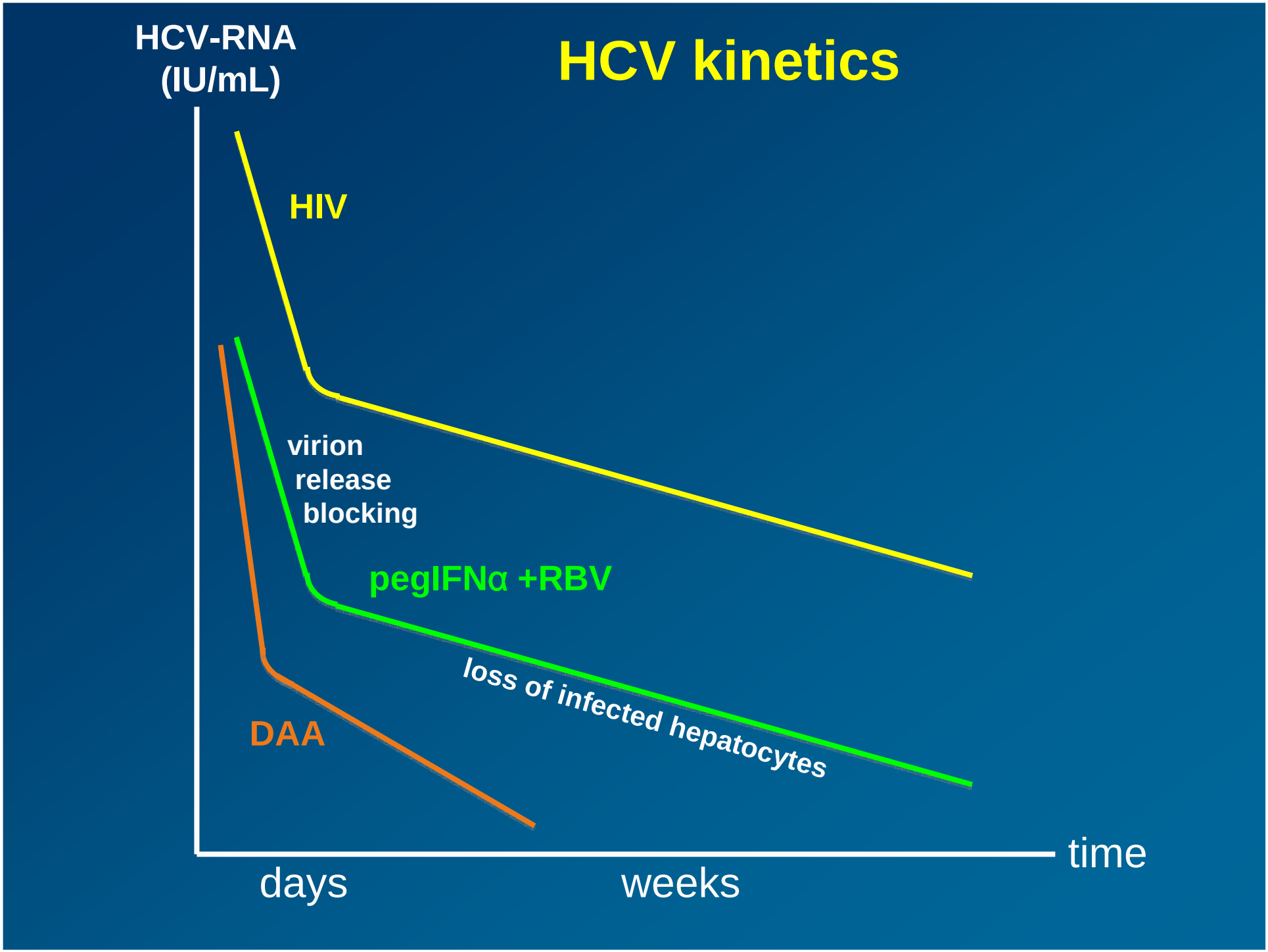
**nucleoside analogue; *non-nucleoside analogue; ***NS5A inhibitor*

Challenges and opportunities for hepatitis C drug development in HIV–hepatitis C virus-co-infected patients

AIDS 2011, **25**:2197–2208

Vincent Soriano[a], Kenneth E. Sherman[b], Juergen Rockstroh[c], Douglas Dieterich[d], David Back[e], Mark Sulkowski[f] and Marion Peters[g]

- More elevated HCV load. More virological failures?
- Faster selection of drug resistance?
- Drug-drug interactions
- Overlapping toxicities – rash & anemia
- Drug compliance with polymedication
- Additional cost

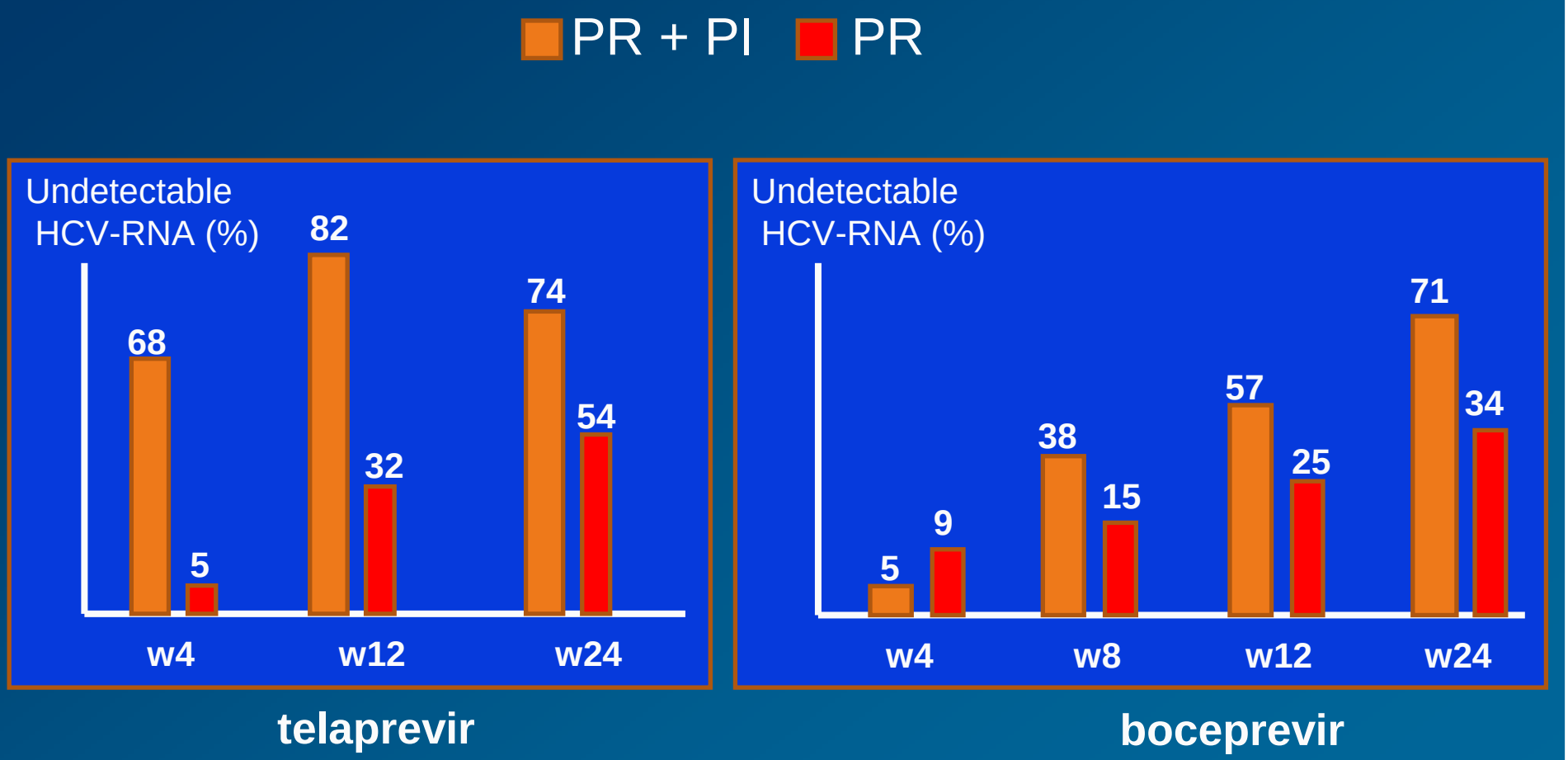

HCV-RNA
(IU/mL)
HCV kinetics
HIV
virion
release
blocking
pegIFNα +RBV
loss of infected hepatocytes
DAA
time
days
weeks

DDI Between HCV-DAA and Common HIV Drugs

	Telaprevir		Boceprevir	
TDF	≈	↑30%*	≈	↑5%*
EFV	↓25% (tid) ↓48% (bid)	↓10% (tid) ↑10% (bid)	↓40%	↑20%*
ATV/r	↓15%	↑85%	≈	↓49%
DRV/r	↓32%	↓42%	↓32%*	↓59%
FPV/r	↓30%	↓56%	--	--
LPV/r	↓52%	↑14%	↓45%*	↓43%
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*	

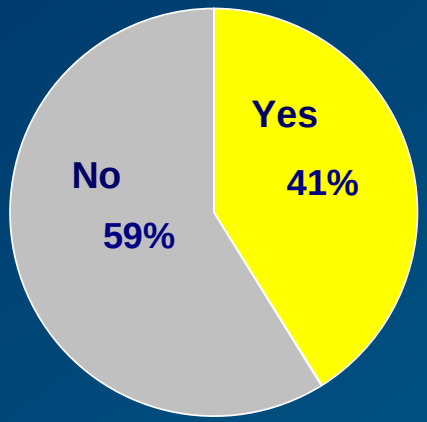
Variation in Cmin, (*or in AUC)

Telaprevir & Boceprevir in HIV/HCV-coinfected patients

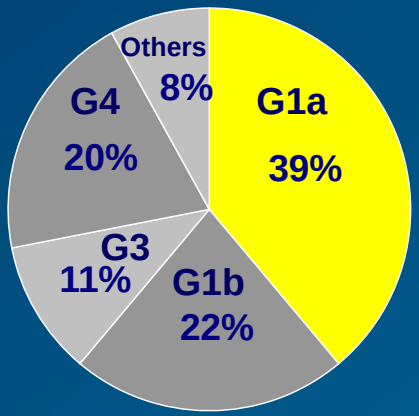


Current profile of HIV/HCV coinfected patients using DAA

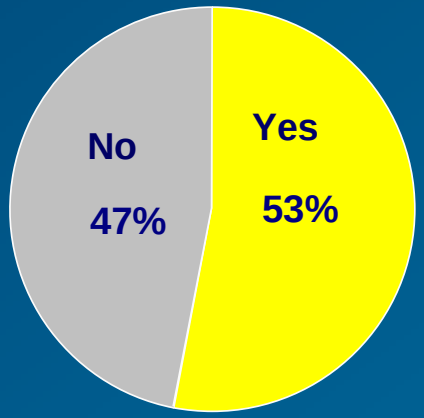
IFN experience



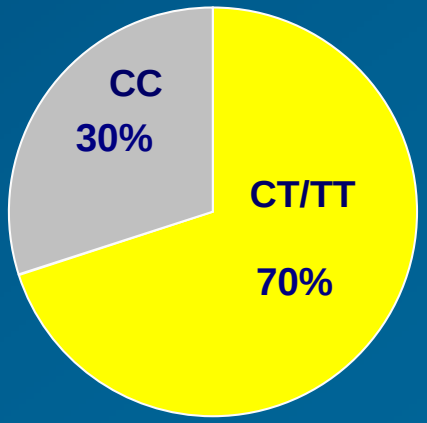
HCV genotype



Advanced liver fibrosis

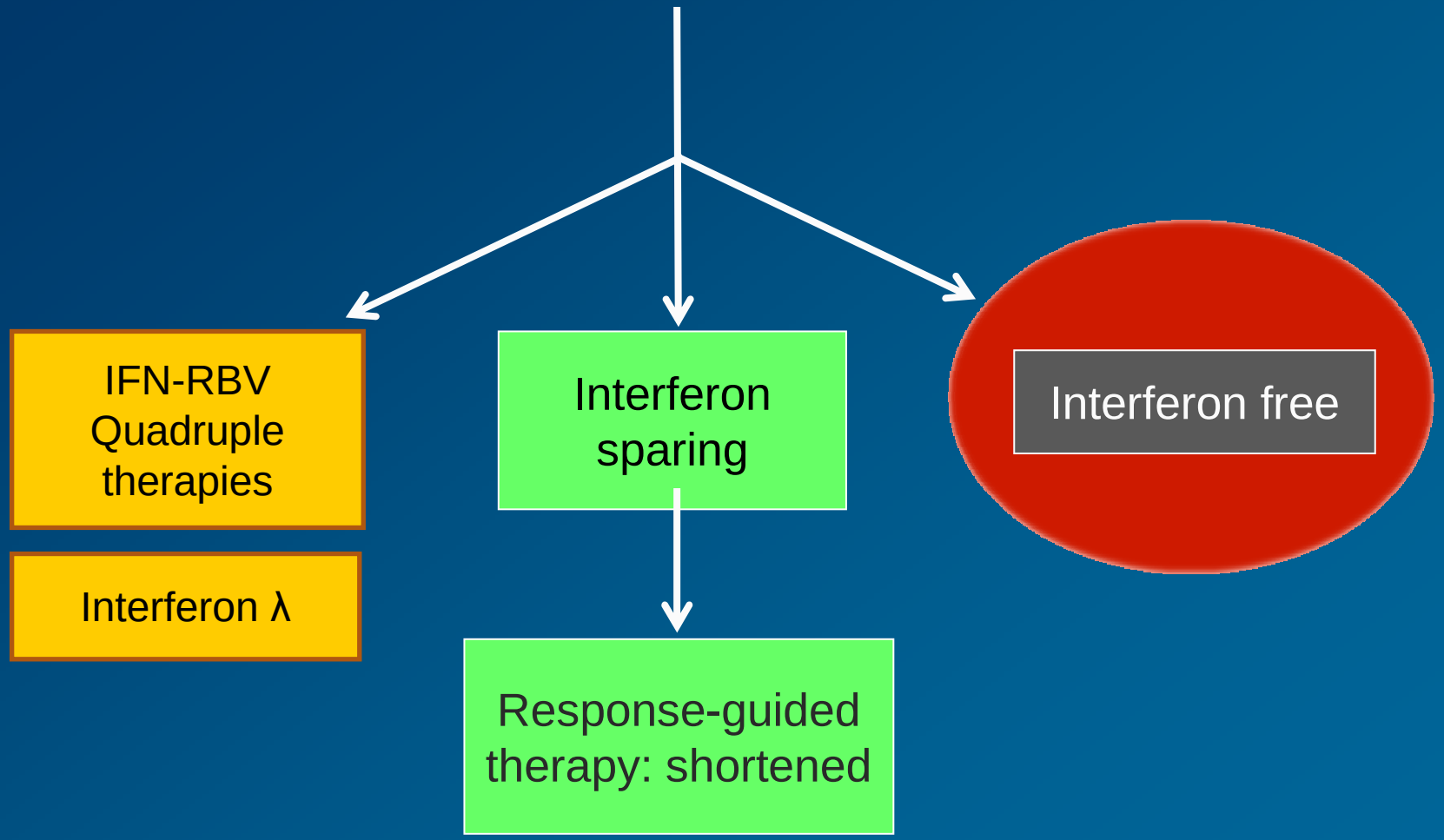


IL28B



Poveda et al. Antivir Ther (in press)

Development of new HCV regimens

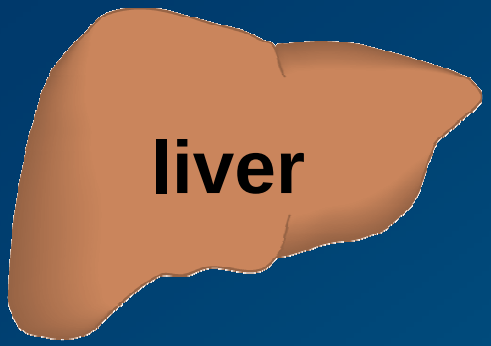


Naive, non-responders, interferon-intolerant, cirrhosis, special populations

Implications of widespread use of DAA

- Shift in HCV genotypes in the infected population, being other genos replacing geno 1.
- Changes in HCV-infected populations, with accumulation in poor regions and/or communities within rich countries.
- Growing number of patients with drug-resistant mutant viruses and potential for transmission.

A shift in care providers for hep C



hepatologist

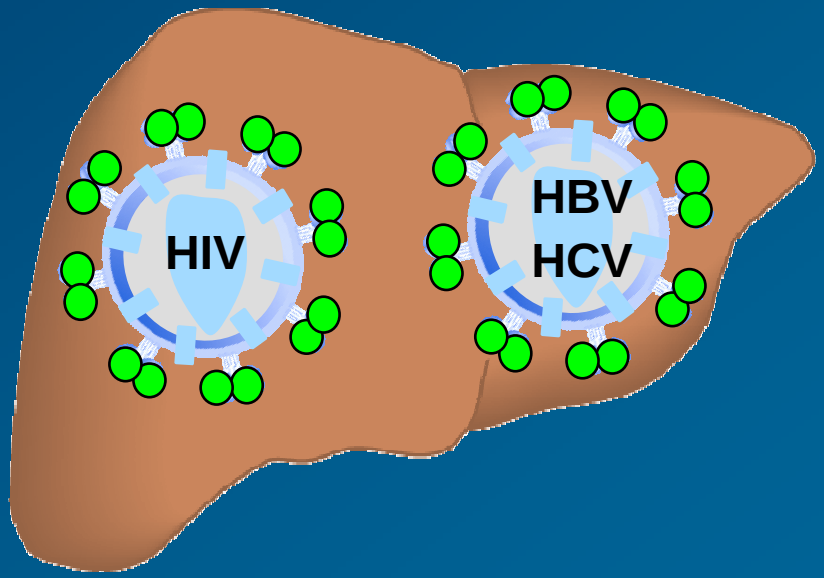
infectologist

The HCV doctor

Take home messages

- IL28B testing remains important to predict DAA response. All hep C patients must be tested.
- HCV subtype 1a responds less than 1b, even to IFN-free, oral DAA combinations.
- DAA resistance – no matter after failure but may be important at baseline for some drugs.
- Shorter treatment durations (3 to 6 months) and more convenient regimens (QD) will replace current triple combinations based on first-generation drugs within 2 years.
- Combinations using IFN-free oral drugs are coming and is the way to go.

8th International Coinfection Workshop
Madrid, May 30 - June 1, 2012



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Agradecimientos

Clinica

Pablo Barreiro
Pablo Labarga
Luz Martin-Carbonero
Eugenia Vispo
Jose V Fernandez

Laboratorio

Norma Rallon
Ana Treviño
Carmen de Mendoza
Eva Poveda
Jose Miguel Benito

Juan Gonzalez-Lahoz