Predictors of Response to Hepatitis C Therapy

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A New Era for Hepatitis C—New Diagnostics Tools and New Weapons

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ACS Medicinal Chemistry Letters

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

New & Old
Predictors of HCV treatment response

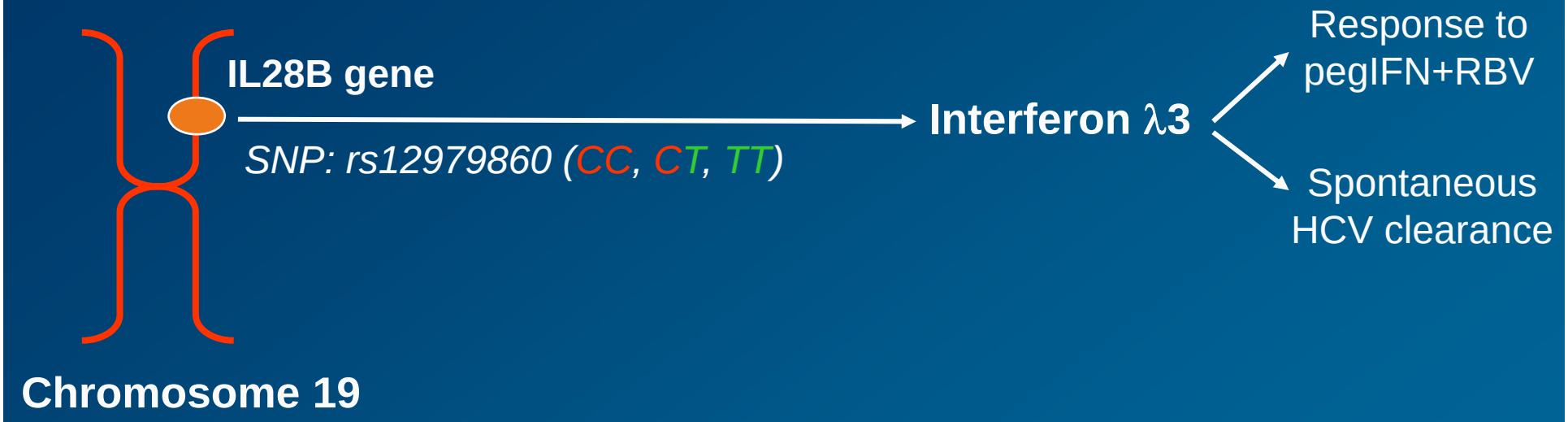
Old

- Genotype
- Viral load
- Fibrosis
- RVR
- Adherence
- Anemia

New

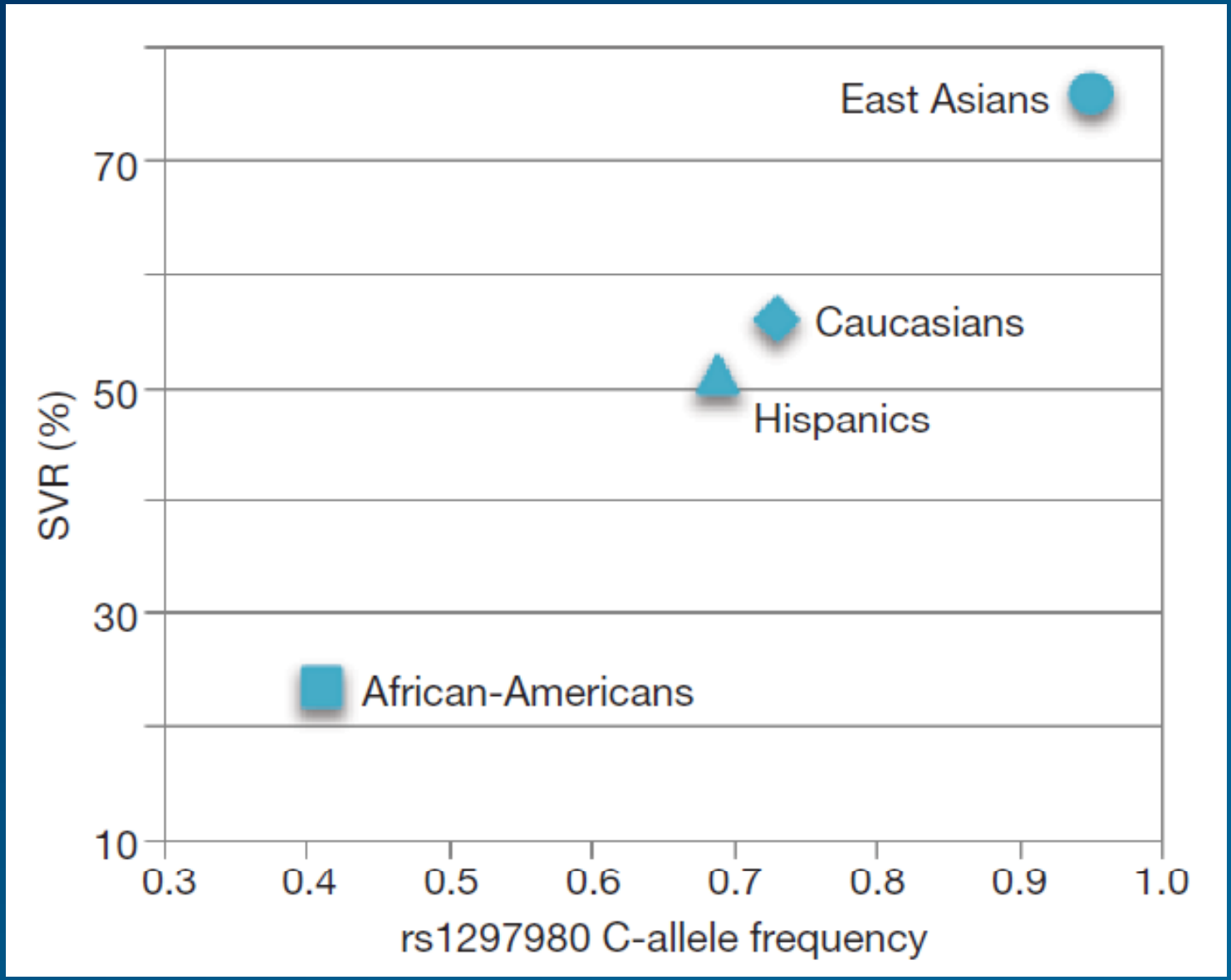
- IL28B
- Polymorphisms
- HCV-1 subtypes

IL28B polymorphisms & hepatitis C outcome



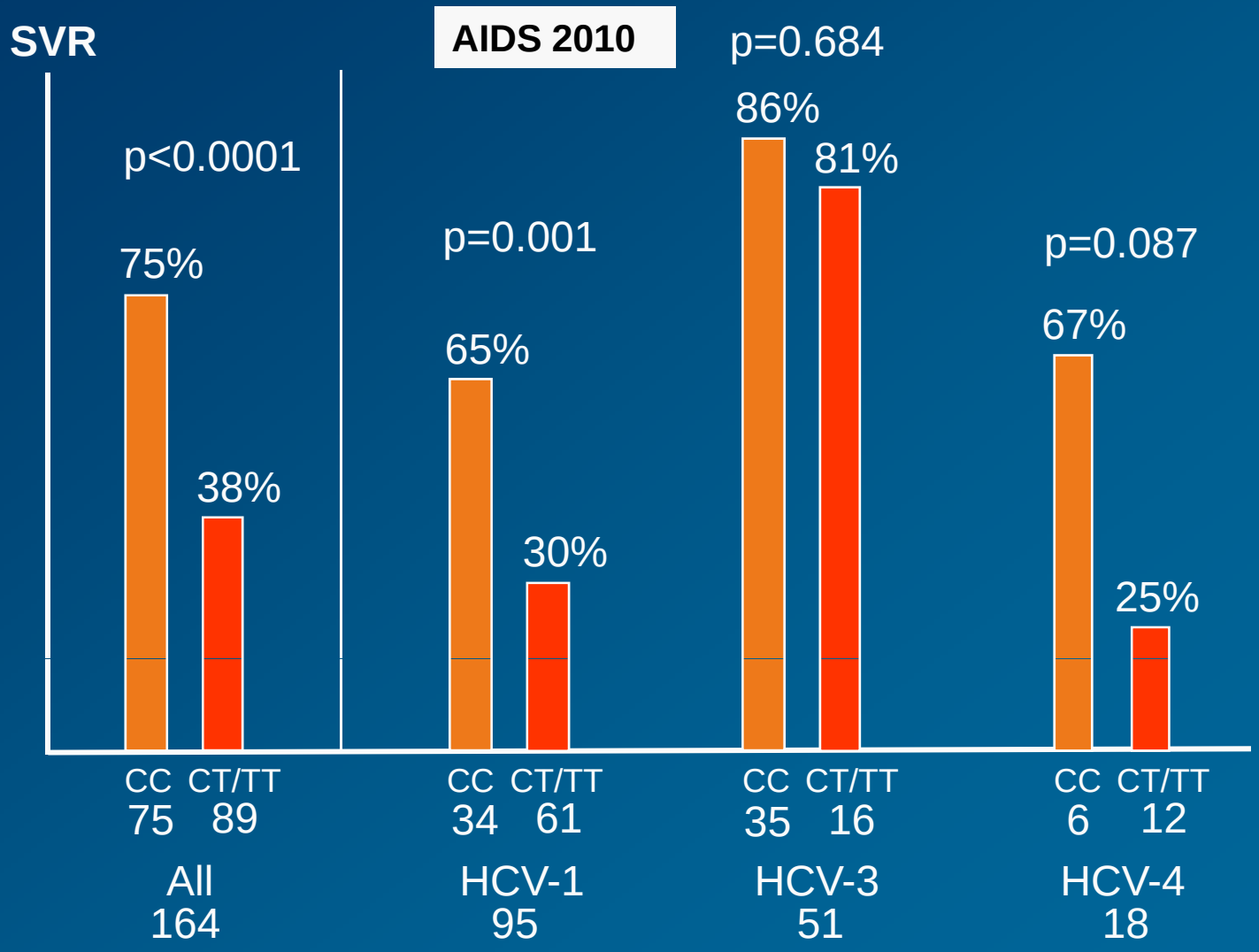
Ge et al. Nature 2009; 461: 399-401.
Suppiah et al. Nature Gen 2009; 41: 1100-4.
Tanaka et al. Nature Gen 2009; 41: 1105-9.
Thomas et al. Nature 2009; 461: 798-802.

IL28B polymorphisms, ethnicity & SVR

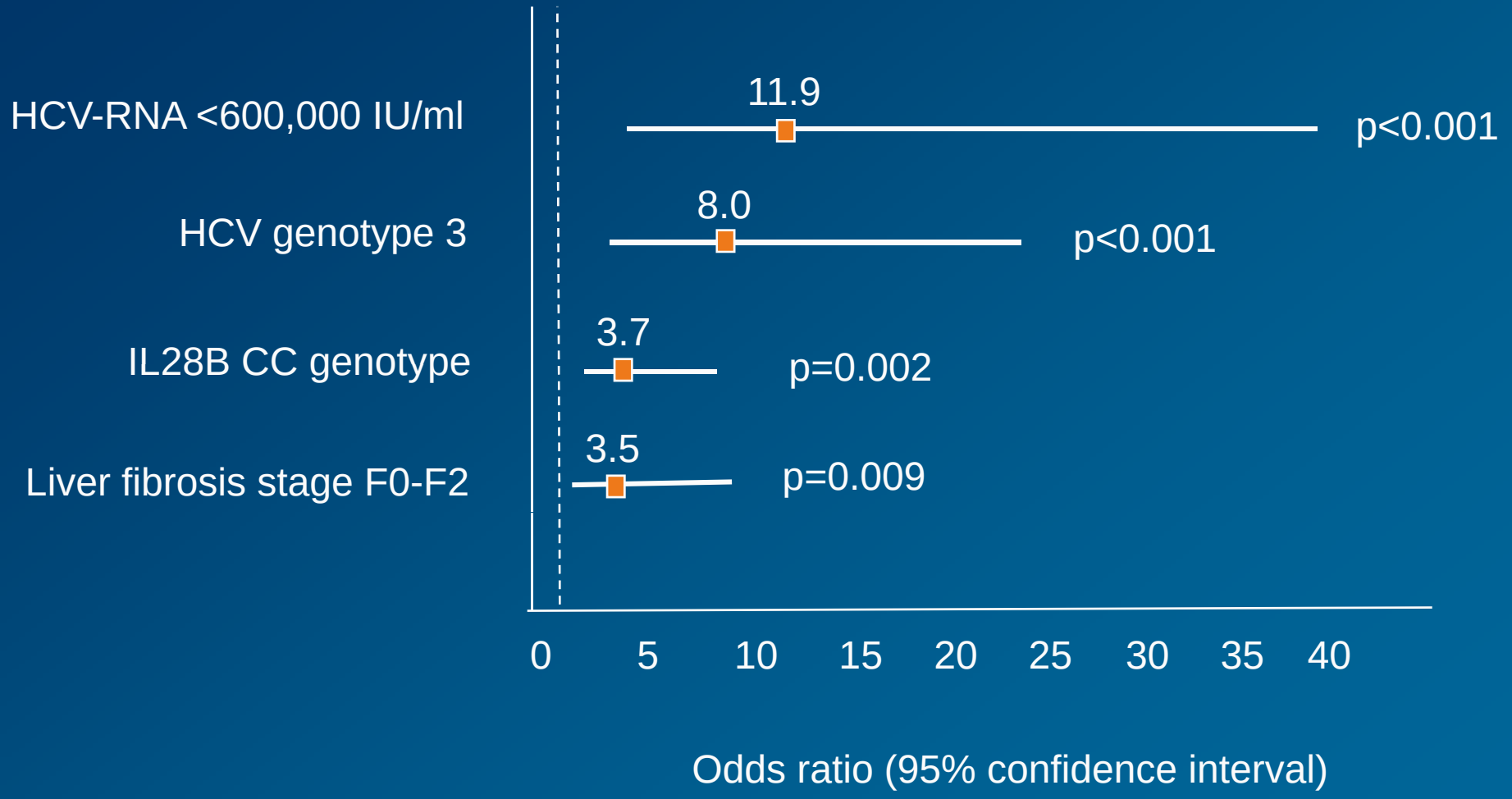


Association of a single nucleotide polymorphism near the interleukin-28B gene with response to hepatitis C therapy in HIV/hepatitis C virus-coinfected patients

Norma I. Rallón[a], Susanna Naggie[b], José M. Benito[a], José Medrano[a], Clara Restrepo[a], David Goldstein[c], Kevin V. Shianna[c], Eugenia Vispo[a], Alex Thompson[b], John McHutchison[b] and Vincent Soriano[a]



IL28B polymorphisms in HIV-HCV coinfection

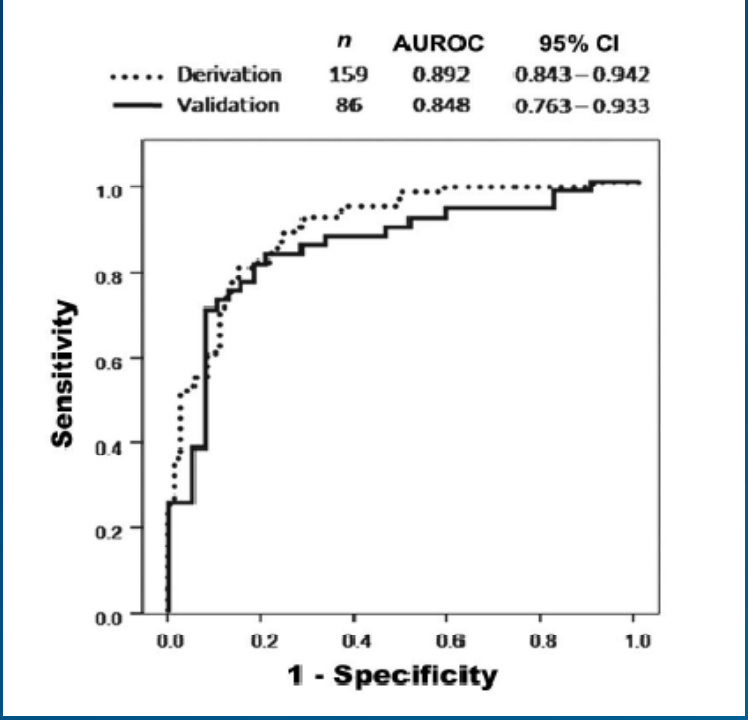


Rallon et al. AIDS 2010

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

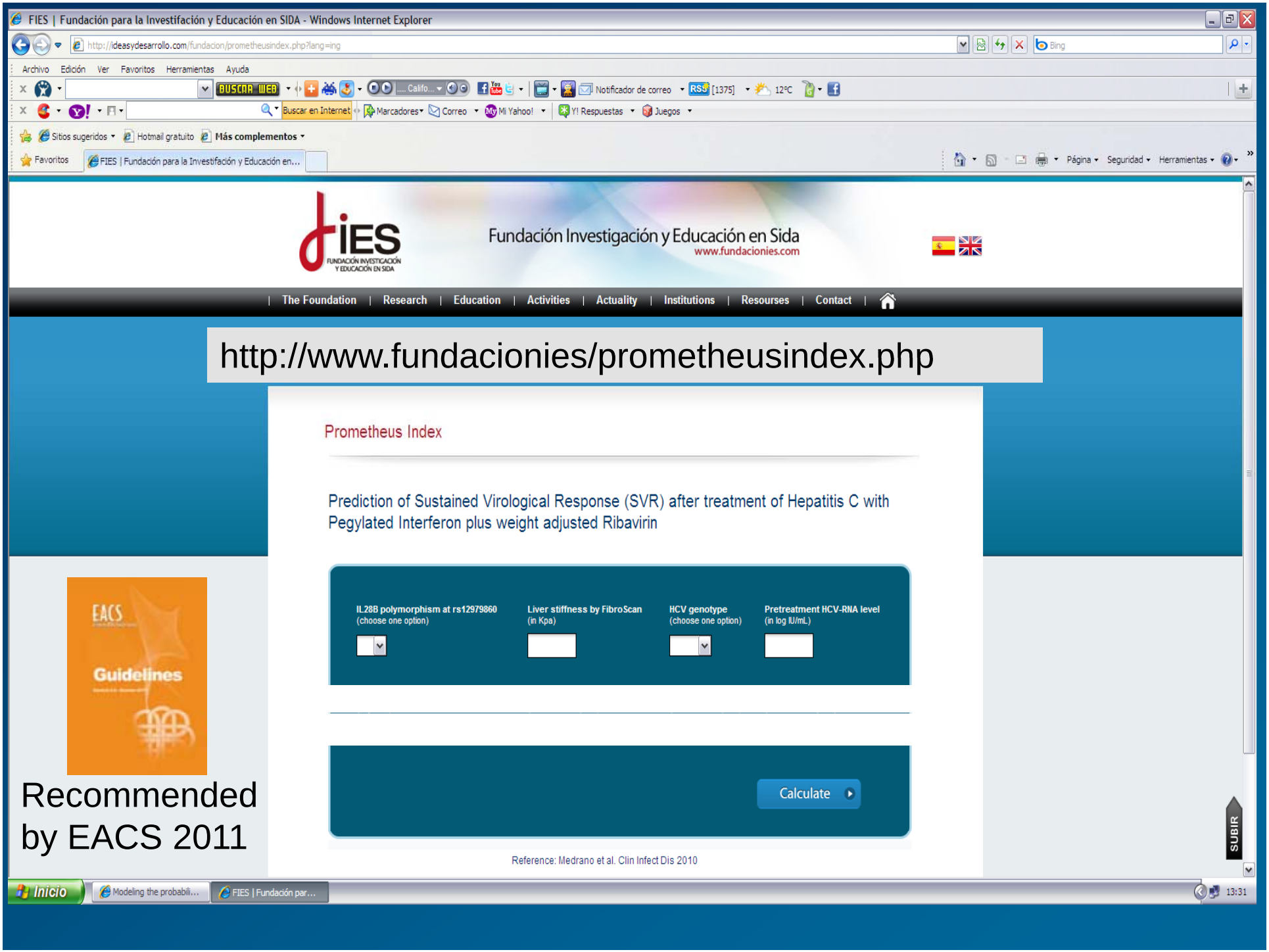
Jose Medrano,[1] Karin Neukam,[3] Norma Rallón,[1] Antonio Rivero,[4] Salvador Resino,[2] Susanna Naggie,[6] Antonio Caruz,[5] Aida Calvino,[2] Juan Macías,[3] Jose Miguel Benito,[1] Carlos Sánchez-Piedra,[1] Eugenia Vispo,[1] Pablo Barreiro,[1] John McHutchison,[6] Juan Antonio Pineda,[3] and Vincent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



Prometheus index

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

http://www.fundacionies/prometheusindex.php


FIES | Fundación para la Investifación y Educación en SIDA - Windows Internet Explorer
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Fundación Investigación y Educación en Sida
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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
EACS Guidelines
Recommended by EACS 2011
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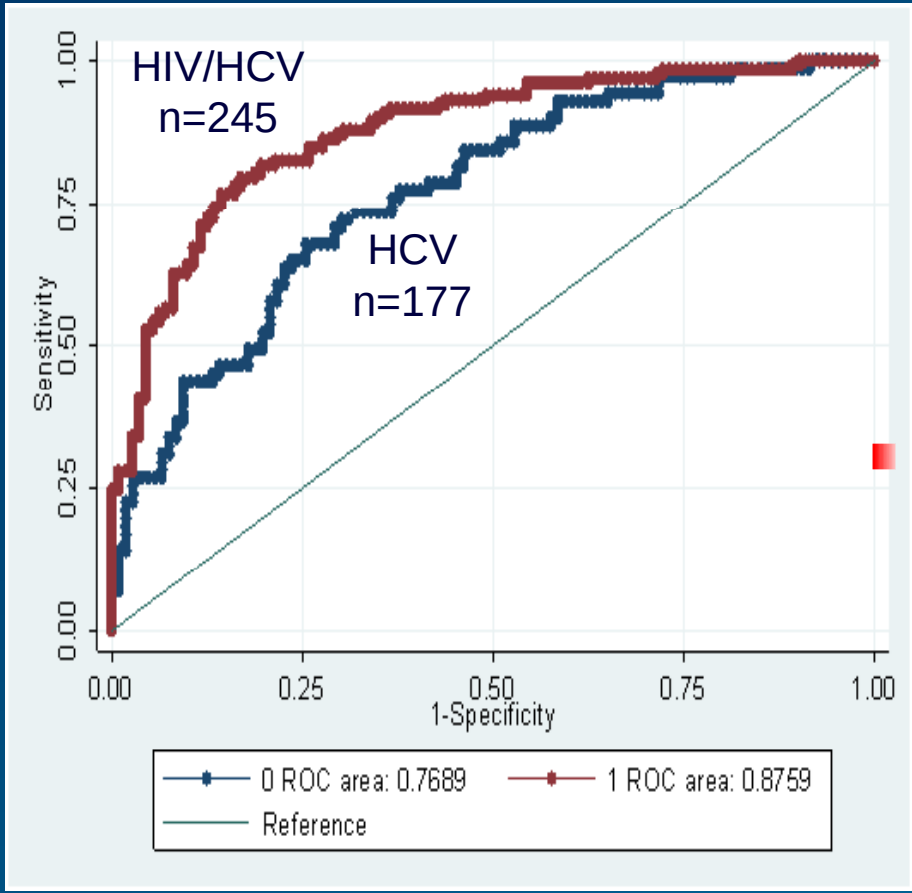
Baseline Prediction of Response to PegIFN+RBV in Chronic Hepatitits C Using the PROMETHEUS Index: Coinfected vs Monoinfected Patients

- To examine the accuracy of the PROMETHEUS index in HCV-monoinfected patients in comparison with HIV-HCV coinfected patients.



The accuracy of the Prometheus Index to predict SVR is significantly lower in HCV-monoinfected than in HIV-HCV coinfected patients.

Updating the Prometheus Index with HIV status should improve the accuracy to predict SVR in HCV-monoinfected patients.

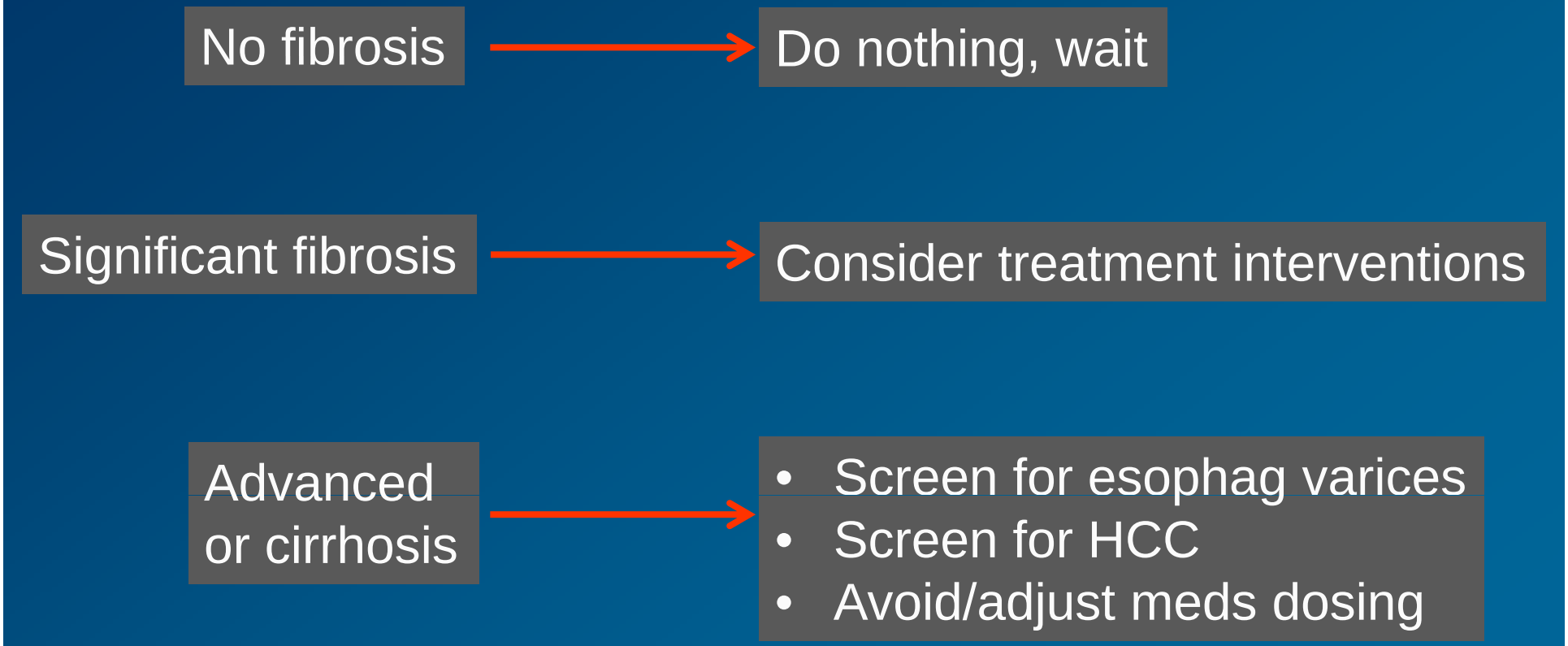
Medrano et al. CROI 2012; abstract 761.

FibroScan®

Metavir	KPa
F0-F1	<7.5
F2	7.5-9.4
F3	9.5-14.4
F4	>14.5

- No fasting
- Examination duration < 10 min
- 10 successful acquisitions
- Median value = correct value
- Results expressed in kPa
- Less reliable with obesity & LEE

Why we need liver fibrosis assessment and which distinctions are relevant?



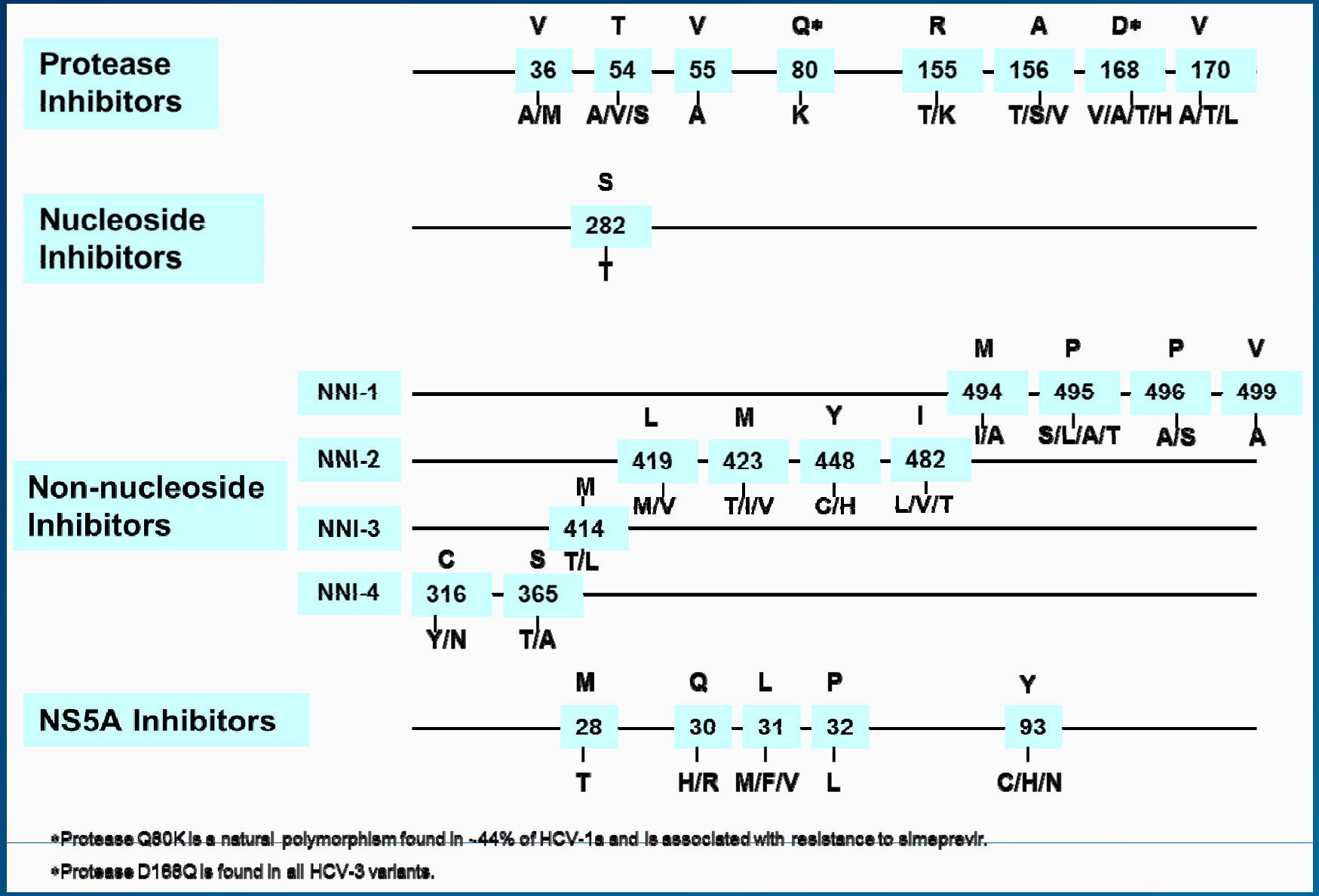
HCV antivirals in most advanced development

Protease inhibitors	Polymerase inhibitors		NS5A inhibitors
	Nucleos(t)ide analogues	**Non-nucleoside analogues**	
•**Telaprevir** •**Boceprevir** •Simeprevir •Danoprevir/r •Asunaprevir •BI-1335 •ABT-450/r	•Mericitabine •GS-7977 •IDX-184	•GS-9190 •Filibuvir •BI-7127 •ANA-598 •VX-222	•Daclatasvir
•GS-9256		•ABT-333	

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

Main Drug Resistance Mutations to DAA



Poveda et al, Future Virology 2012

Natural polymorphisms influencing DAA susceptibility

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	0	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†)	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	0	5.4%H	Daclatasvir

Poveda et al, ICVH NYC 2012

Natural polymorphisms at the NS3 protease

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	0	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

Antivir Ther. 2011;16:413-6.

Natural polymorphisms associated with resistance to new antivirals against HCV in newly diagnosed HIV–HCV-coinfected patients

*Ana Treviño[1], Carmen de Mendoza[1], Patricia Parra[1], Carmen Rodríguez[2], Antonio Madejón[1], Zulema Plaza[1], Jorge del Romero[2], Eva Poveda[1], Vincent Soriano[1]**

HCV isolates containing Q80K displayed significantly reduced susceptibility to TMC-435 (simeprevir)

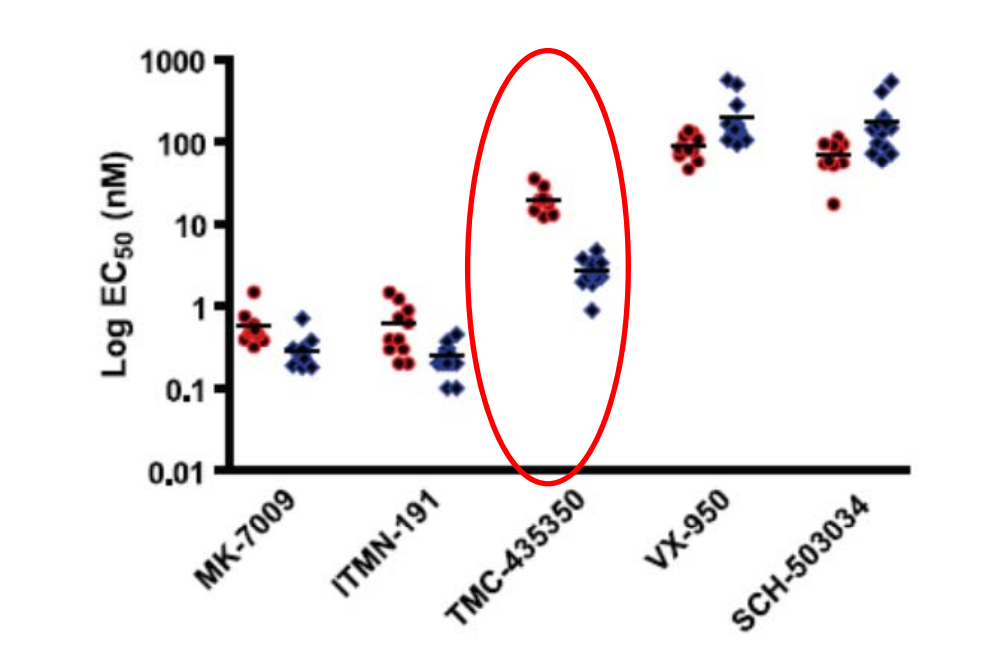


TABLE 4. Susceptibilities of mutants generated by site-directed mutagenesis

NS3 mutant	Fold change in EC_{50}[a]				
	VX-950	SCH-503034	TMC-435350	MK-7009	ITMN-191
T54S	**5.6**	**4.7**	0.7	0.5	1.0
Q80K	1.0	0.9	**10.9**	**6.6**	**6.3**
Q80K/T54S	2.3	1.7	**7.3**	**3.7**	**5.3**

[a] Fold change in EC_{50} = chimeric mutant replicon EC_{50}/wild-type replicon EC_{50}. The values represent the means from 2 or 3 independent experiments; the values in boldface represent >3-fold increases in the EC_{50}.

Bae et al, Antimicrob Agents Chemother 2010

ASPIRE trial (TMC435+pegIFN/RBV, IFN-experienced)

SVR to TMC435 based on HCV subtype (G1a vs. G1b)

and presence or absence of Q80K polymorphism.

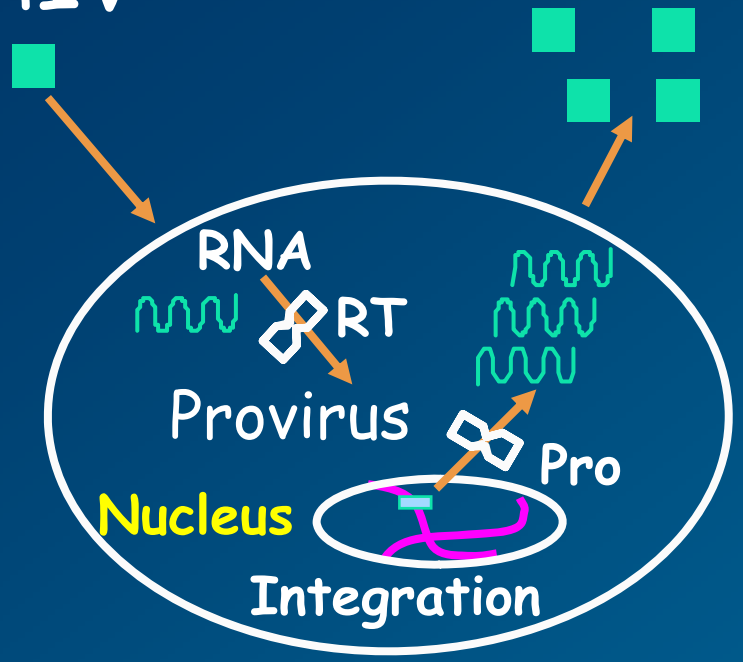
	G1a	GT1a with Q80K	G1a no Q80K	G1b
TMC100mg + P/R N=197	45/81 (55.6)	5/23 (21.7)	40/57 (70.2)	83/113 (73.5)
TMC150mg + P/R N=199	53/84 (63.1)	14/23 (60.9)	39/59 (66.1)	90/112 (80.4)
Placebo + P/R N=66	5/27 (18.5)	1/5 (20)	4/22 (18.2)	10/39 (25.6)

Lenz et al, EASL Barcelona 2012

Therapeutic Strategy

Suppressive

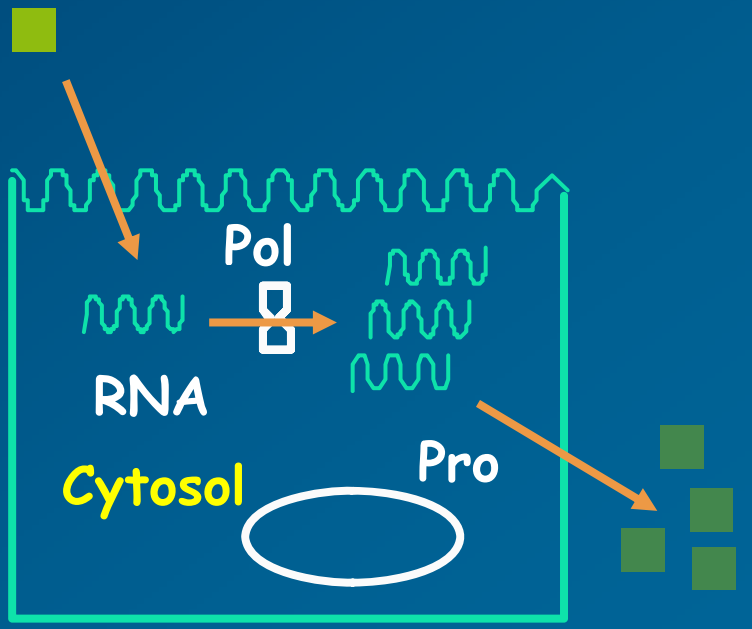
HIV



CD4+ T-lymphocyte

Eradicative

HCV

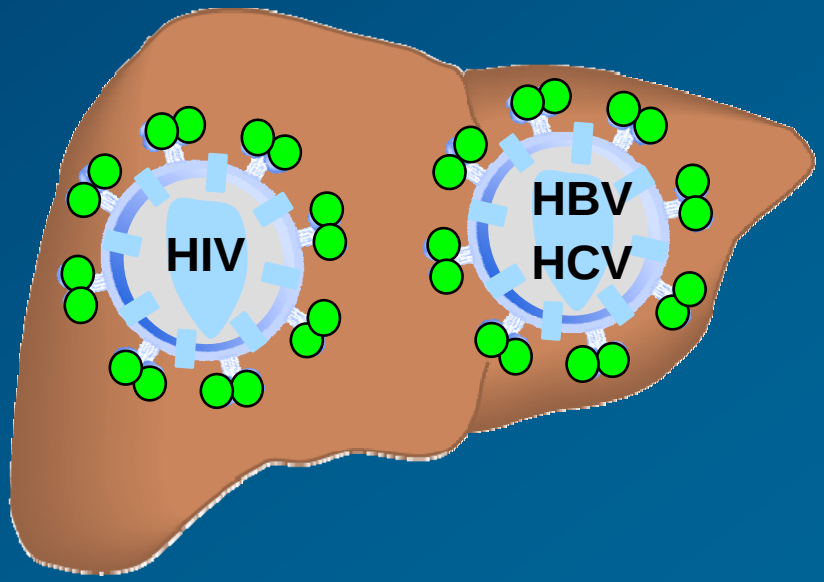


Hepatocyte

Implications of widespread use of DAA

- Significant increments in cost and demands for the health system, including well-trained personnel.
- Shift in HCV genotypes within the infected population, being other genos replacing geno 1.
- Changes in HCV-infected populations, with accumulation in poor regions and/or marginalized communities within rich countries.
- Growing number of patients with drug-resistant mutant viruses and potential for transmission.

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



www.virology-education.com

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