Treatment of HCV in HIV Disease: New Challenges, New Promise

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Treating HCV in HIV 2011 : On the Cusp of Change?

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Questions

- 1. How many of you are treating HCV in HIV patients now?
- 2. How many of you plan to treat with the new protease inhibitors for HCV?
- 3. How many of you plan to treat HCV monoinfection?
- How many of you think we can cure HCV without interferon?
- How many of you went to CROI?
- How many of you knew that the IAS-USA has changed its name to the International ANTIVIRAL society so that they can treat HCV?

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EASL HIGHLIGHTS
BERLIN 2011 = VANCOUVER 1994

- First ever 2 NUC combo: 5 log decline and no resistance
- First ever SVR data with Peg/RBV and nucleoside: mericitabine
- First ever SVR data with Peg/RBV and NS5A (BMS)
- First ever SVR data with Peg/RBV and cyclophillin inhibitor: alisporivir
- First ever 100% SVR for geno 2 with nucleotide PSI 7977
- First ever 100% SVR for QUAD therapy with PI and NS5A in null responders (BMS)
  - First ever SVR (40%) for 2 DAA's without Peg/RBV- It can be done!

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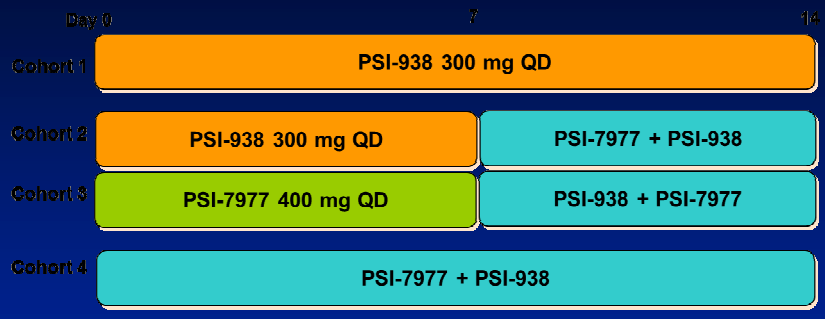
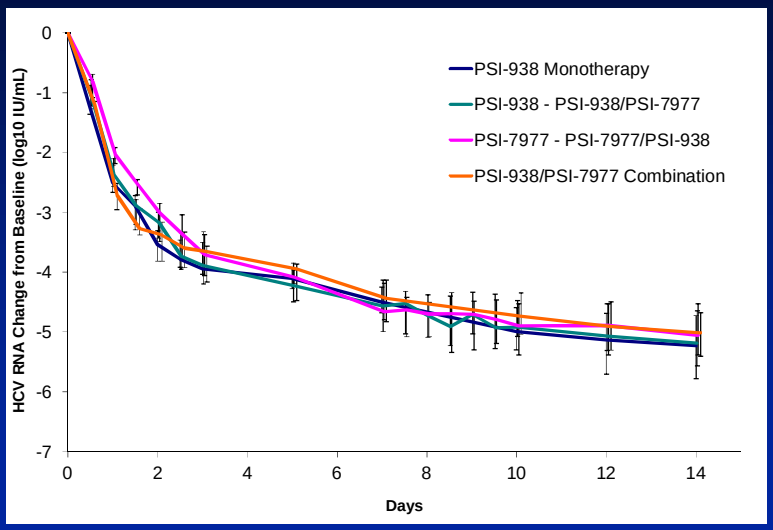
NUCLEAR: PSI-7977 + PSI-938 Combo
First Purine/Pyrimidine Combination Study

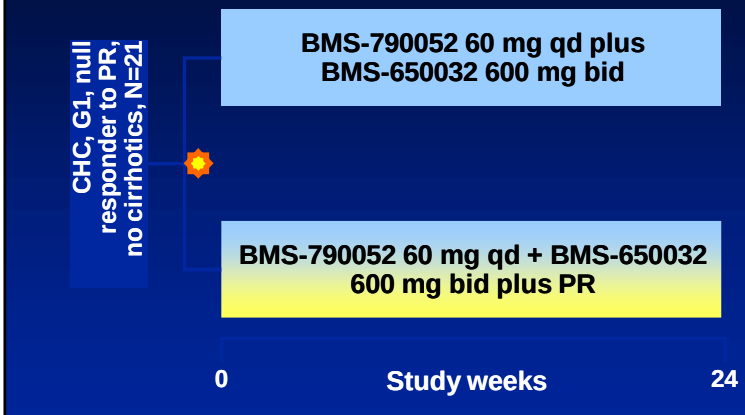


- 40 HCV GT 1, treatment-naïve subjects
  - 8 active and 2 placebo per cohort
- HCV RNA >50,000 IU/mL, no evidence of cirrhosis
- All subjects offered full course of PEG/RBV on day 15

NUCLEAR Cohort 4: PSI-938/PSI-7977 administered in combination x 14d



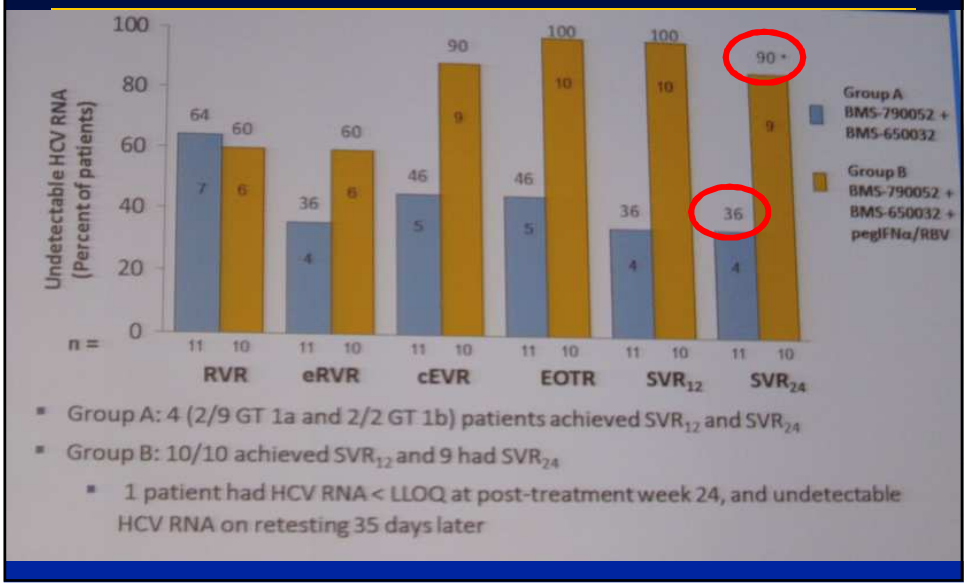
BMS-790052 (NS5A inhibitor) + BMS-650032 (PI) ± PR in null responders: phase IIa study



Randomisation
Null response defined as <2 $\log_{10}$ decline in HCV RNA following 12 weeks of treatment with PR

Lok A, et al. EASL 2011, oral

Virologic Response During and After Treatment



- Group A: 4 (2/9 GT 1a and 2/2 GT 1b) patients achieved SVR_{12} and SVR_{24}
- Group B: 10/10 achieved SVR_{12} and 9 had SVR_{24}
  - 1 patient had HCV RNA < LLOQ at post-treatment week 24, and undetectable HCV RNA on retesting 35 days later

Change in Causes of Death in Patients with HIV

- Swiss HIV Cohort Study (SHCS)
  - 446 deaths between 2005 and 2009
    - 76% men, median age at death = 47 years, duration of HIV infection = 14 years, 93% received ART X 9.5 years, $CD4^+$ before death= 251, 45% co-infected with HCV and 11% co-infected with HBV
  - Causes of death
    - #1 Non-AIDS defining cancers (n=85, 19.1%) including HCC (n=13, 2.8%)
    - #2 AIDS (n=73, 16.4%)
    - #3 Liver Diseases (n=67, 15%)

Ruppik M. et al. Changing patterns of causes of death in the SHCS 2005-2009. CROI 2011. Poster # 789. Available at: http://www.retroconference.org/2011/PDFs/789.pdf.

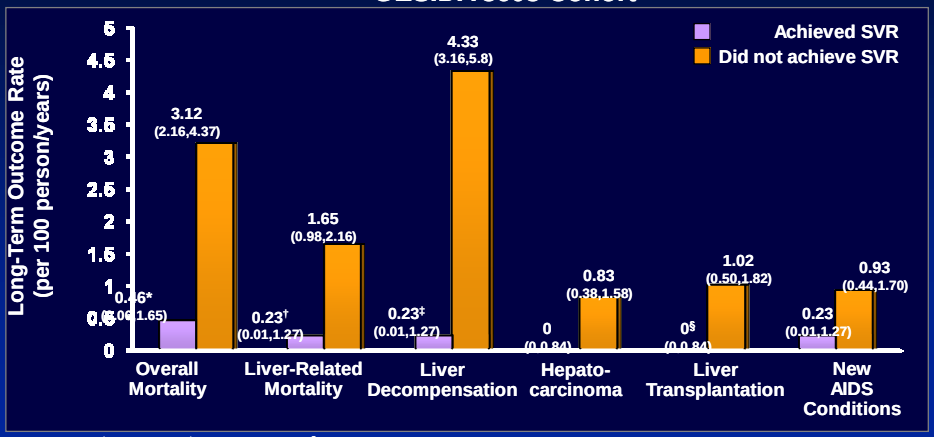
Change in Causes of Death in Patients with HIV

- When deaths due to HCC are included among liver-related deaths (instead of non-AIDS defining cancers)
  - Liver Diseases = #1 Cause of Death (17.9%)

Ruppik M. et al. Changing patterns of causes of death in the SHCS 2005-2009. CROI 2011. Poster # 789. Available at: http://www.retroconference.org/2011/PDFs/789.pdf

Achieving Sustained Virologic Response: Impact on Long-Term Outcomes in HIV/HCV-Coinfection

GESIDA 3603 Cohort



*P=0.003, †P=0.028, ‡P<0.001, and §P=0.034 versus not attaining a sustained virologic response.
n=711 HIV/HCV-coinfected patients receiving interferon (peg or conventional) + ribavirin.

Berenguer J. et al. Hepatology 2009.

Predictive Factors of Response to HCV Treatment: What's New?

- Traditional Factors of Response to Treatment
  - Genotypes 2,3 vs 1,4
  - Low Baseline Viral Load
  - Low Fibrosis Stage
  - Women vs men
  - Young Age
  - Caucasians
  - Absence of Steatosis
  - Low BMI
  - Optimal HIV control
- New Factors of Response to Treatment with pegIFN/RBV
  - IL28B CC Genotype
  - Absence of Insulin Resistance
  - Vitamin D?

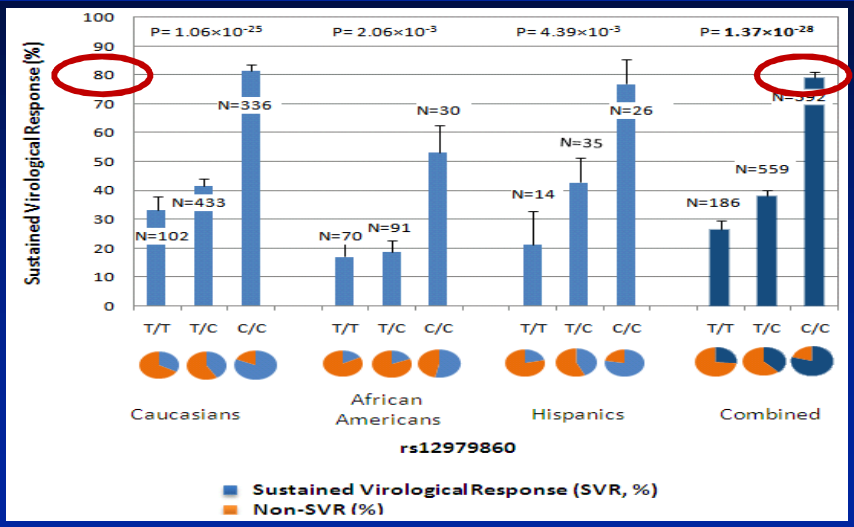
Soriano V. et al. AIDS 2007.

Genome-wide association study for predictors of treatment response

- **Adherence criteria (clinical phenotype critical*)**
  - **SVR – all included**
  - **NR – only those who were > 80% adherent to pegIFN and > 80% adherent to RBV were included**
    - **336 (21%) were excluded**
- **Race was defined by genetic ancestry, not self-report, to control for population stratification**
  - **Caucasians (C), African Americans (AA), Hispanics (His)**
  - **130 (8%) patients were re-classified**

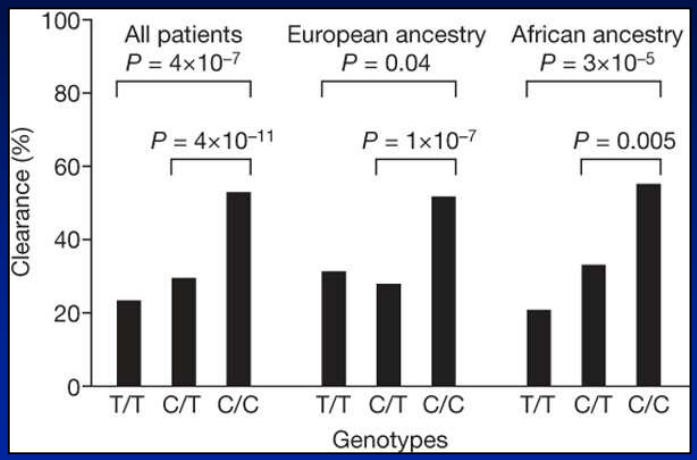
Ge, Nature, 2009

C allele is associated with SVR



Ge, Nature, 2009

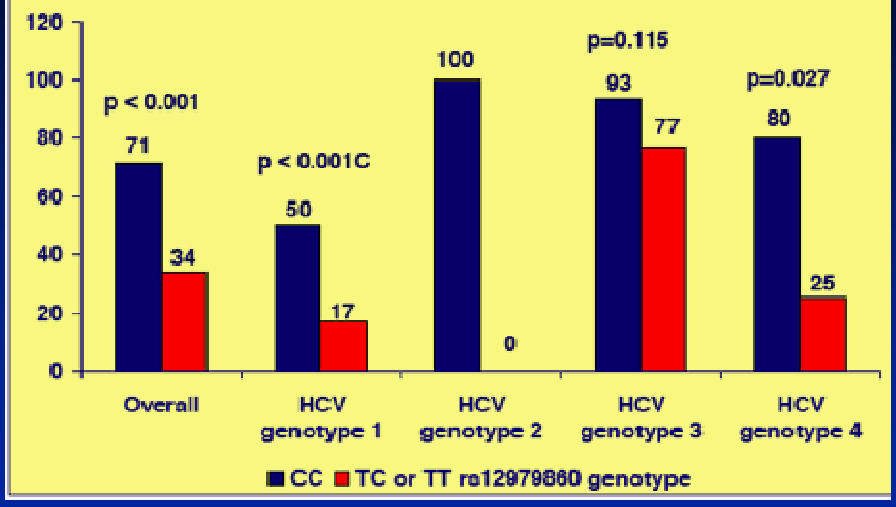
C Allele Increases Probability of Spontaneous Clearance of HCV



Thomas DL. et al. Nature 2009

SVR in HIV HCV Pts According to IL28b

Figure 2: Rate of SVR according to HCV and rs12979860 genotypes

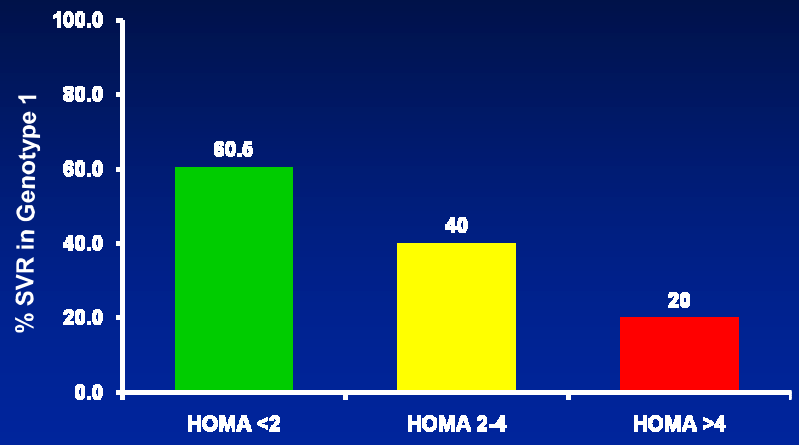


Pineda,J;Cruz,W; Camarcho,E et. al.

Factors Associated with SVR in HIV HCV Treated Pts.

Variable	SVR no. (%)	p univariate	Adjusted OR (95% CI)	p multivariate
Gender				
Male	60 (48)			
Female	17 (71)	0.026	4.28 (1.08-16.96)	0.039
Advanced liver fibrosis[§]				
Yes	24 (41)			
No	51 (55)	0.090	1.99 (0.82-4.83)	0.129
HCV genotype				
1-4	33 (32)			
2-3	44 (86)	<0.001	13.98 (4.87-40.11)	<0.001
Baseline HCV-RNA load (IU/mL)				
≥600000	36 (39)			
<600000	41 (66)	0.001	1.99 (1.18-3.34)	0.009
Daily dose of RBV (mg/kg)*				
≤ 15	36 (44)			
> 15	41 (56)	0.123	2.19 (0.81-5.51)	0.124
Exposure to planned HCV therapy				
< 80%	2 (20)			
≥ 80%	75 (52)	0.050	4.78 (0.77-30.30)	0.094
rs12979860 genotype				
TT or TC	39 (34)			
CC	48 (71)	<0.001	5.05 (2.04-12.5)	<0.001
Baseline LDL cholesterol				
≤ 100 mg/dL	42 (44)			
> 100 mg/dL	29 (58)	0.149	2.85 (0.73-11.1)[†]	0.130[†]
Concomitant ART[‡]				
Yes	63 (47)			
No	14 (70)	0.055	2.22 (0.51-9.61)	0.286
Abacavir therapy				
Yes	7 (29)			
No	70 (54)	0.026	3.66 (0.92-14.52)	0.064
Zidovudine therapy				
Yes	7 (35)			
No	70 (52)	0.150	1.36 (0.30-6.08)	0.688

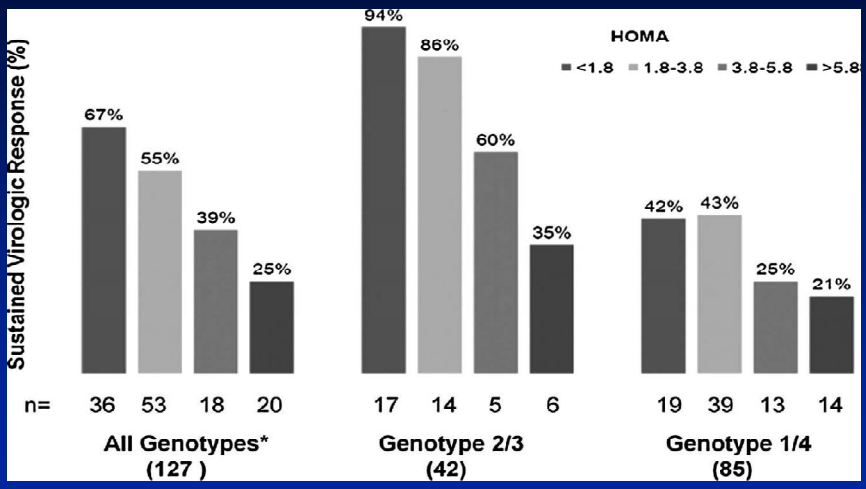
Insulin Resistance in HCV: Impact on Response to Treatment with PegIFN/RBV



HOMA: Homeostasis model of assessment of insulin resistance

Romero-Gomez, M et al. *Gastroenterology* 2005.

Insulin Resistance Influences Response to Treatment with PegIFN/RBV in HIV/HCV Co-Infected Patients



Ryan P. et al. JAIDS 2010.

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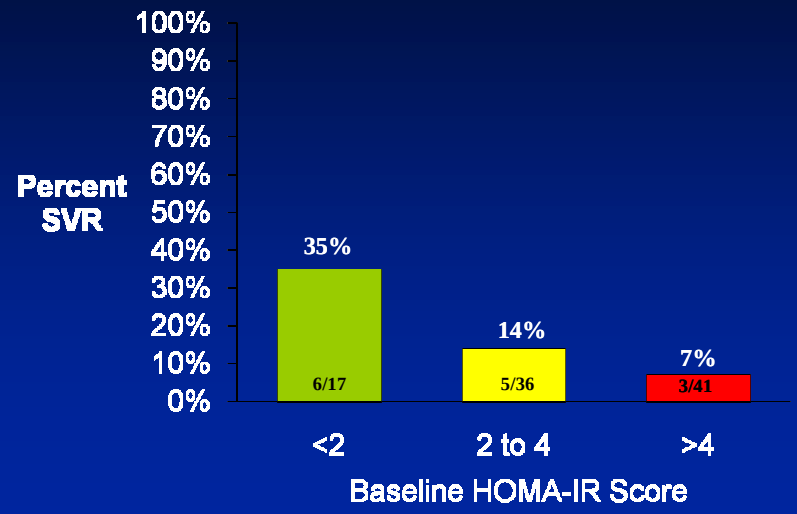
Insulin Resistance Influences Response to Re-Treatment with PegIFN/RBV in HIV/HCV Co-Infected Patients



Vachon, ML. et al. J hepatol 2011.

Insulin Resistance Predicts Non-Response to Re-Treatment with pegIFN/RBV in HIV/HCV Co-Infected Patients

Multi-variable Analysis
Outcome = SVR

	AOR (95%CI)	p-value
HOMA- IR		
≤ 2	1	
>2	0.17 (0.05-0.64)	0.009
Log_{10} HCV RNA	0.36 (0.14-0.93)	0.04

Vachon, ML. et al. J Hepatol 2011.

Does Vitamin D Play a Role?

- Vitamin D is an immune modulator
- HCV-infected patients have a high prevalence of 25(OH)D deficiency[1,2]
- Among HCV mono-infected patients, 25(OH)D deficiency is related to severe liver fibrosis and low response to HCV treatment with pegIFN and RBV[1,2]
- Vitamin D supplementation can improve SVR[3]
- 25(OH)D deficiency is prevalent in HIV-infected patients[4,5]
- The impact of vitamin D deficiency and supplementation before or after HCV treatment in HIV/HCV co-infected patients is unknown

1. Petta S. et al. Hepatology 2010; 2. Lange CM. et al. J Hepatol 2011; 3. Mouch SA. et al. (abstract) J Hepatol 2011; 4. Mueller NJ. Et al. AIDS 2010; Childs KE. et al. AIDS Res Hum Retroviruses 2010.

European Recommendations for Treatment of Acute HCV

1. **Pegylated IFN and weight-based ribavirin is recommended for the treatment of acute hepatitis C in HIV-infected patients (grade A, level II).**
2. **Duration of treatment should be based on RVR [negative HCV-RNA at week 4 (evidence based on using a 615 IU/ml cut-off to define negative HCV-RNA)], regardless of HCV genotype.**
   - **a. In patients with RVR, treatment duration should be 24 weeks (AII).**
   - **b. In patients without RVR, treatment duration of 48 weeks should be considered (BIII).**
   - **c. In non-RVR patients not achieving a 2 log10 drop in HCV-RNA at week 12, treatment can be discontinued (BIII).**

Acute hepatitis C in HIV-infected individuals: recommendations from the European AIDS Treatment Network (NEAT) consensus conference. AIDS. 25(4):399-409, February 20, 2011.

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			

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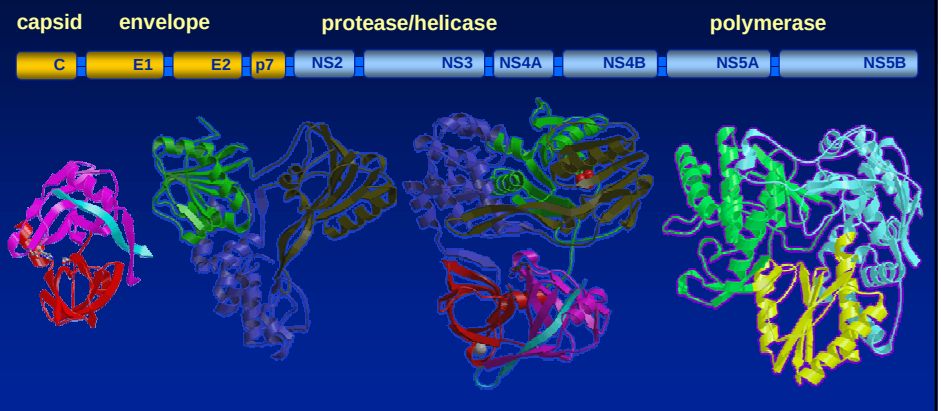
Targets of New Hepatitis C Antivirals



NS3 Protease domain | NS3 Helicase domain | NS3 Bifunctional protease / helicase | NS5B RNA-dependent RNA polymerase

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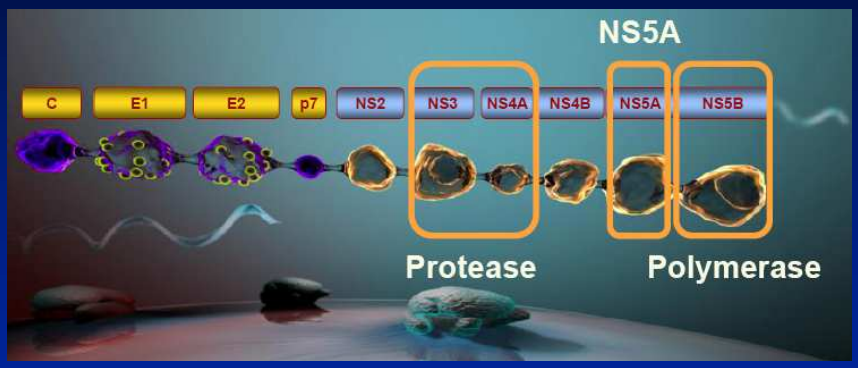
HCV Targets



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36 DAA's at AASLD: 15 Proteases

Drug	Company	Phase
Telaprevir	Vertex	III
Boceprevir	Merck	III
TMC 435	Tibotec, Medivir	IIb
BI 1335	Boehringer Ingelheim	IIb
Vaniprevir (MK 7009)	Merck	II
Narleprevir	Merck	IIa (discontinued)
Danoprevir	Roche/Genentech	II
BMS-850032	BMS	I
ACH 1625	Achillion	Ib
GS 9256	Gilead	Ib
ABT 450	Abbott/Enanta	I
IDX 320	Idenix	I (FDA hold)
GS 9451	Gilead	I
ACH 2684	Achillion	I
MK 6172	Merck	I

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5 Non Nucleoside Polymerase Inhibitors

Drug	Company	Phase
GS 9190	Gilead	II
Filibuvir	Pfizer	II
ABT 333	Abbott	I
IDX 375	Idenix	I
ANA 598	Anadys	IIb

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4 Nucleoside Analogue Polymerase Inhibitors

Drug	Company	Phase
RG 7128	Roche/Genentech/ Pharmasset	II
IDX 184	Idenix	II
PSI 938	Pharmasset	IIb
INX 198	Inhibitex	I

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4 NS5A Inhibitors

Drug	Company	Phase
BMS 790052	BMS	II
PPI 461	Presidio	I
GS 5885	Gilead	I
BMS 82493	BMS	I

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3 Other Classes

Drug	Company	Phase	Class
SCY 235	Scynexis	IIa	Cyclophilin inhibitor
GI 5005	Globimmune	II	Therapeutic vaccine
GS 9450	Gilead	II(withdrawn)	Caspase inhibitor

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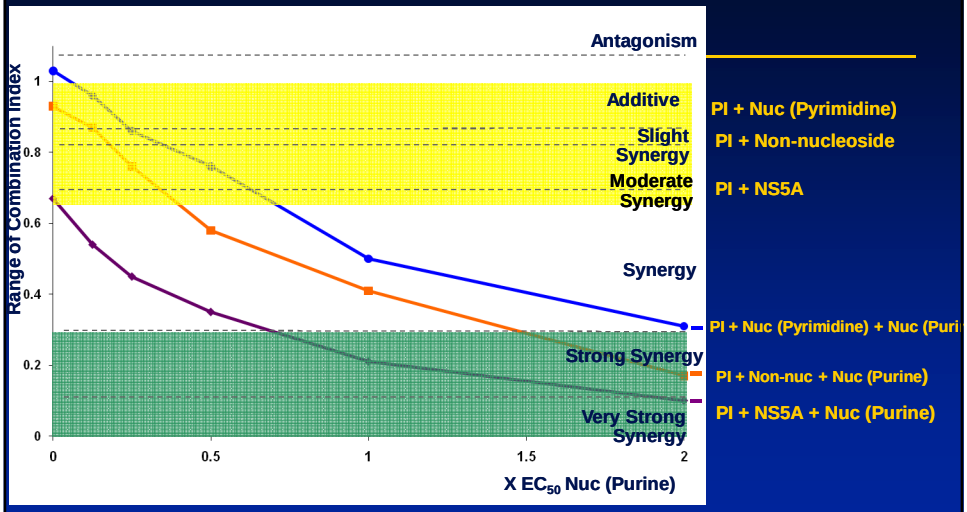
The Most Profound *In Vitro* Synergy is Achieved With Triple Combination of HCV DAA with Different Mechanisms of Action



Two-drug and three-drug combinations tested at equivalent concentrations (EC_{50}s) in the HCV Replicon model

Source: Idenix preclinical studies

Hepatitis C – The Competitive Landscape

Pre-clinical	Phase 1a	Phase 1b	Phase 2a	Phase 2b	Phase 3
Intermune	VPY-376	ACH-1625	Danoprevir ITMN-191	TMC435	Telaprevir VX-950
Taigen	PHX1766		ABT-450	BI201335	Boceprevir SCH-503034
Novartis	IDX320		BMS-650032	Vaniprevir MK-7009	
Vertex	MK-5172		GS-9256		
AVL-181,192					
ACH-2684					

HCV PI's in combination with SoC

- Combinations of DAA agents:
  - Telaprevir in phase 2a in combination with VX-222 (NNRTI) +/- SoC
  - Danoprevir in phase 2a in combination with RG7128 (NI) +/- SoC
  - BMS-650032 in phase 2a in combination with BMS-790052 (NS5A inh) +/- SoC
  - GS-9256 in combination with GS-9190 (NNRTI) +/- Ribavarin
  - BI 1335 and BI polymerase 34
- Danoprevir and ABT-450 employ ritonavir-boosting

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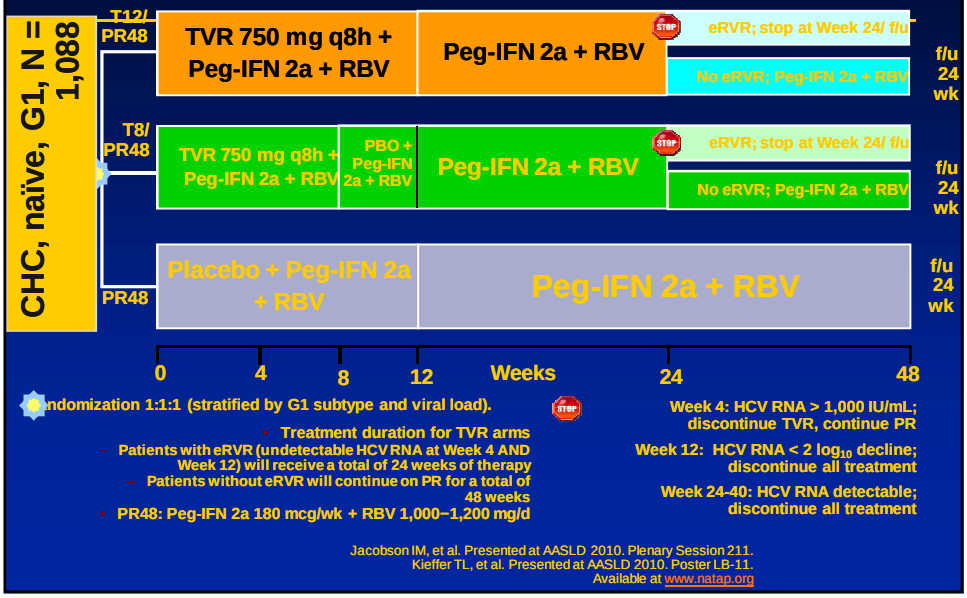
HCV Treatment: A Lexicon of Acronyms

- RAV: Resistance-Associated Variants
- IL28B: IL28B polymorphism (rs12979860) genotype test
- LLQ: lower limit of quantitation (usually < 25 IU)
- LLD: lower limit of detection (usually < 10 IU)
- NA: nucleoside analog polymerase inhibitors
- NNI: nonnucleoside polymerase inhibitors
- MV: minority variants
- PI: protease inhibitors
- UDPS: ultradeep pyrosequencing
- vBT: viral breakthrough > 1 log rise in HCV RNA
- RGT: response-guided therapy
- Null responder < 2 log drop at week 12 (<1 log at wk4)
- Partial responder > 2 log drop, but never < 25 IU
- Relapser < 25IU at EOT (end of therapy) but relapses
- eRVR: extended RVR (HCV negative at weeks 4 and 12(TVR) 8 and 24 for BOC

ADVANCE
Study Design



Randomization 1:1:1 (stratified by G1 subtype and viral load).

- Treatment duration for TVR arms
  - Patients with eRVR (undetectable HCV RNA at Week 4 AND Week 12) will receive a total of 24 weeks of therapy
  - Patients without eRVR will continue on PR for a total of 48 weeks
- PR48: Peg-IFN 2a 180 mcg/wk + RBV 1,000–1,200 mg/d

Week 4: HCV RNA > 1,000 IU/mL; discontinue TVR, continue PR

Week 12: HCV RNA < 2 $\log_{10}$ decline; discontinue all treatment

Week 24-40: HCV RNA detectable; discontinue all treatment

Jacobson IM, et al. Presented at AASLD 2010. Plenary Session 211.
Kieffer TL., et al. Presented at AASLD 2010. Poster LB-11.
Available at www.natap.org

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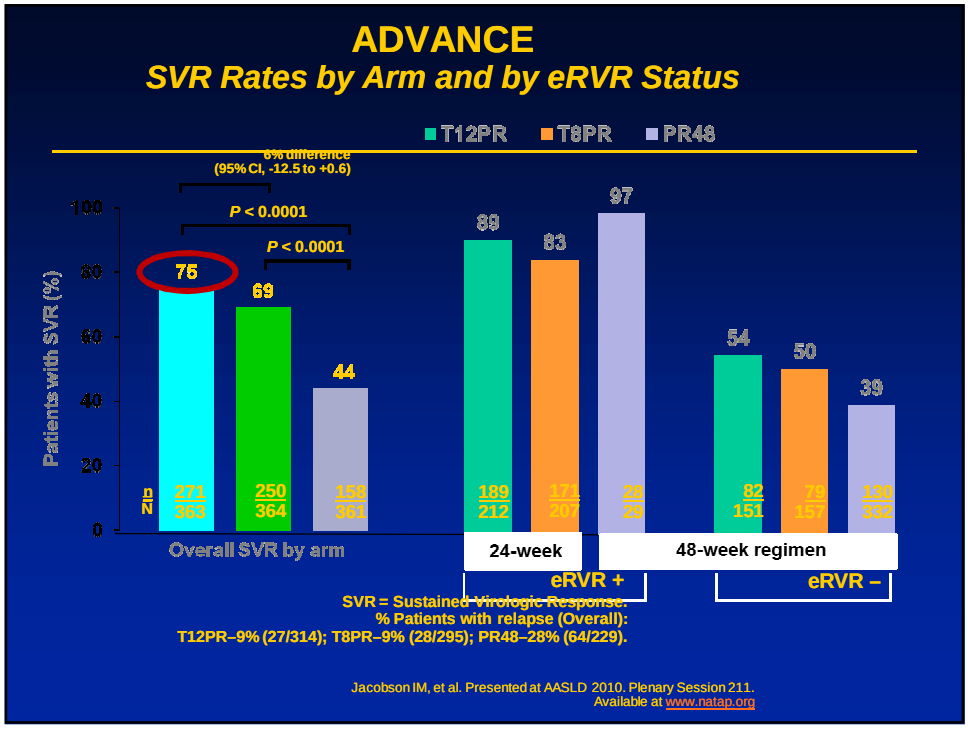

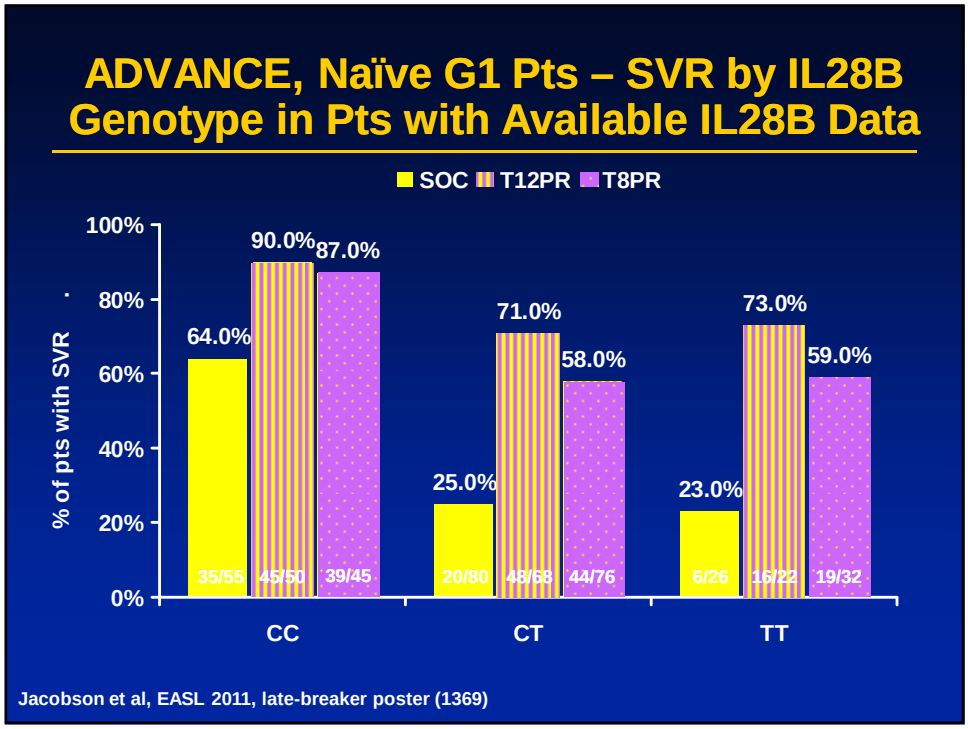

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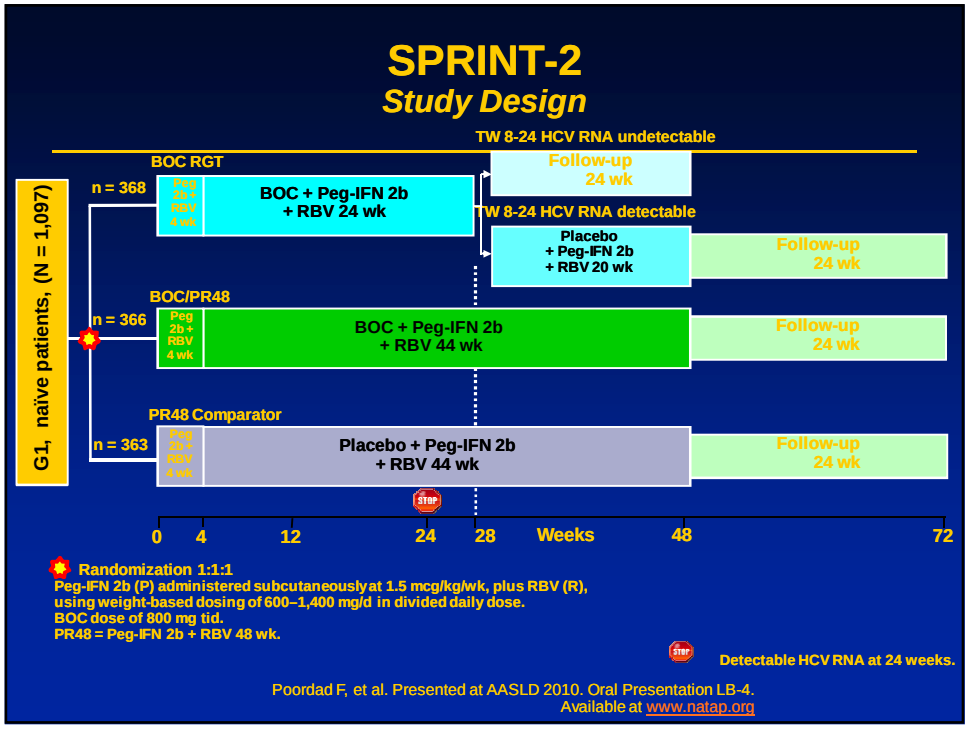

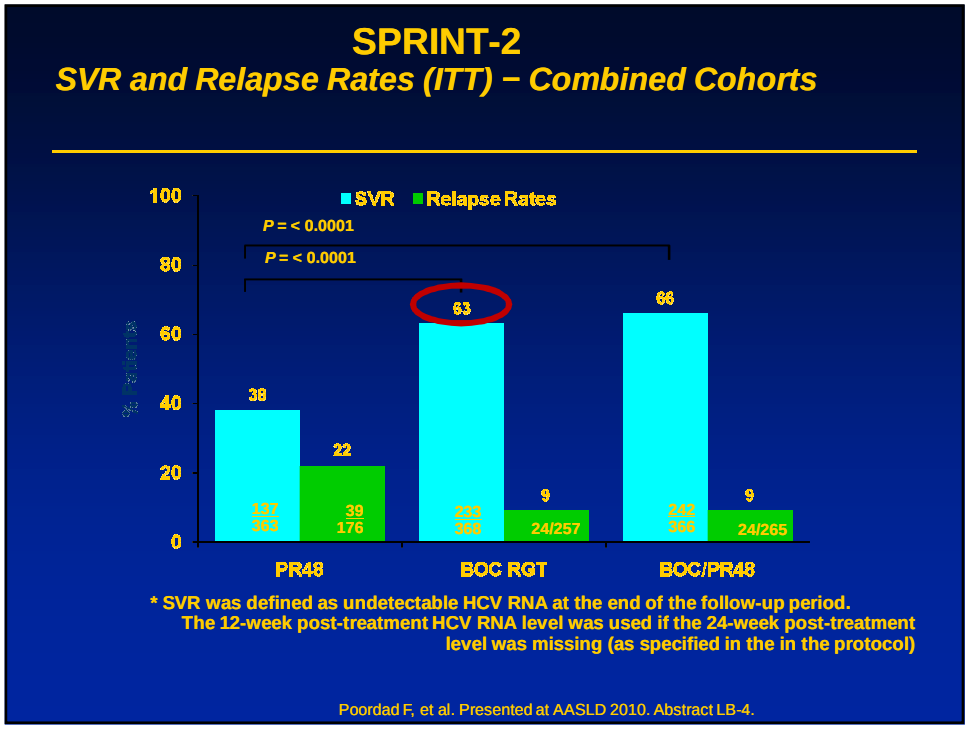

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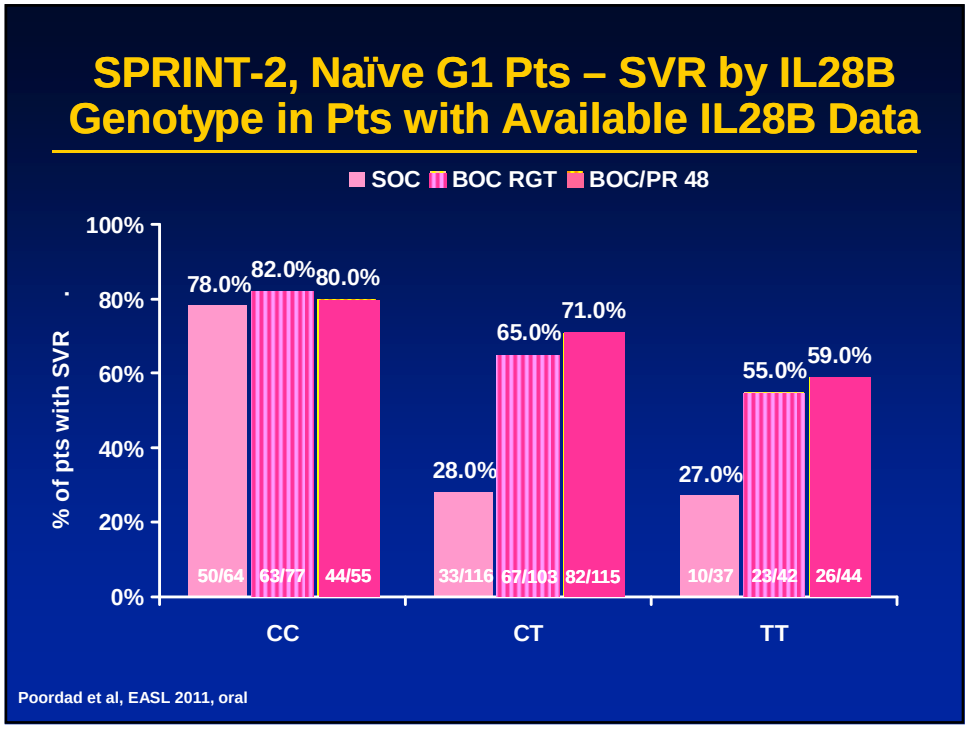
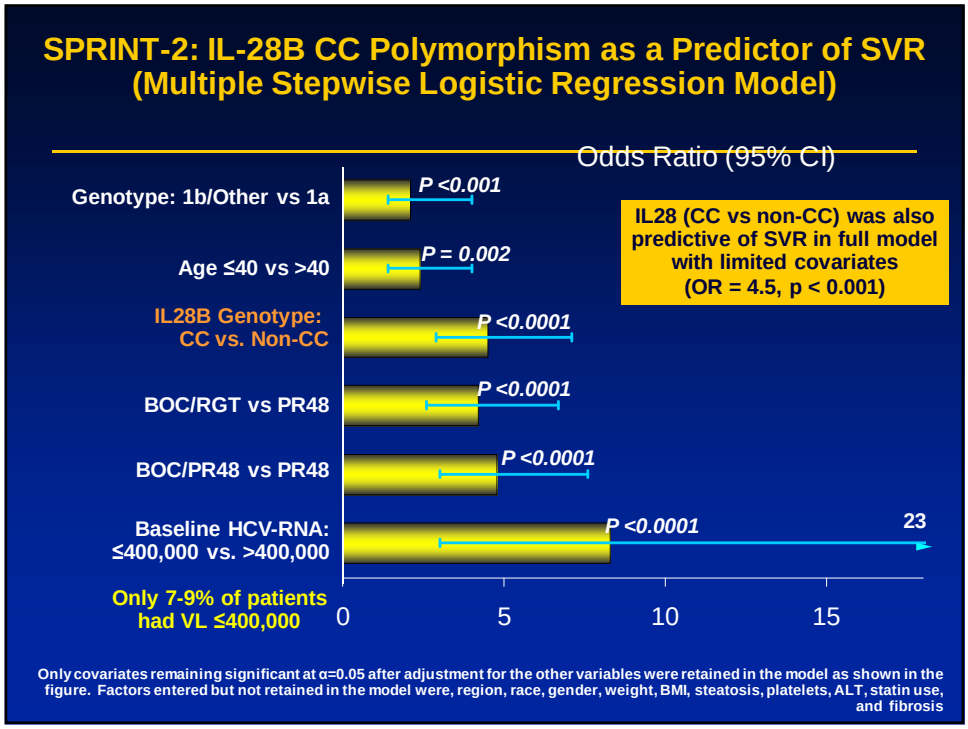
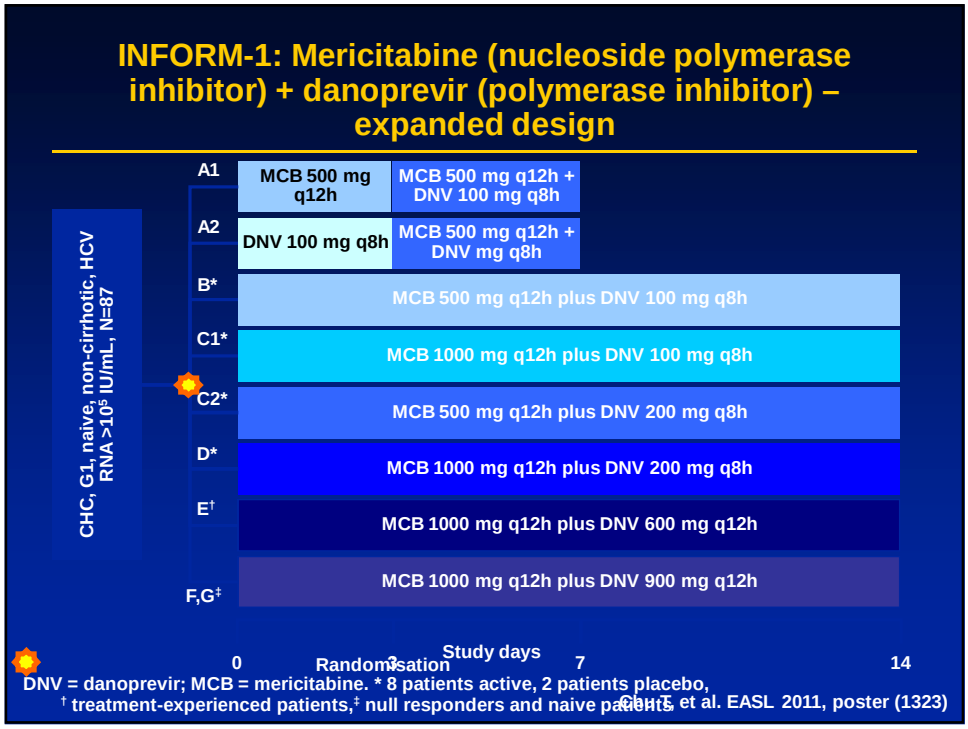
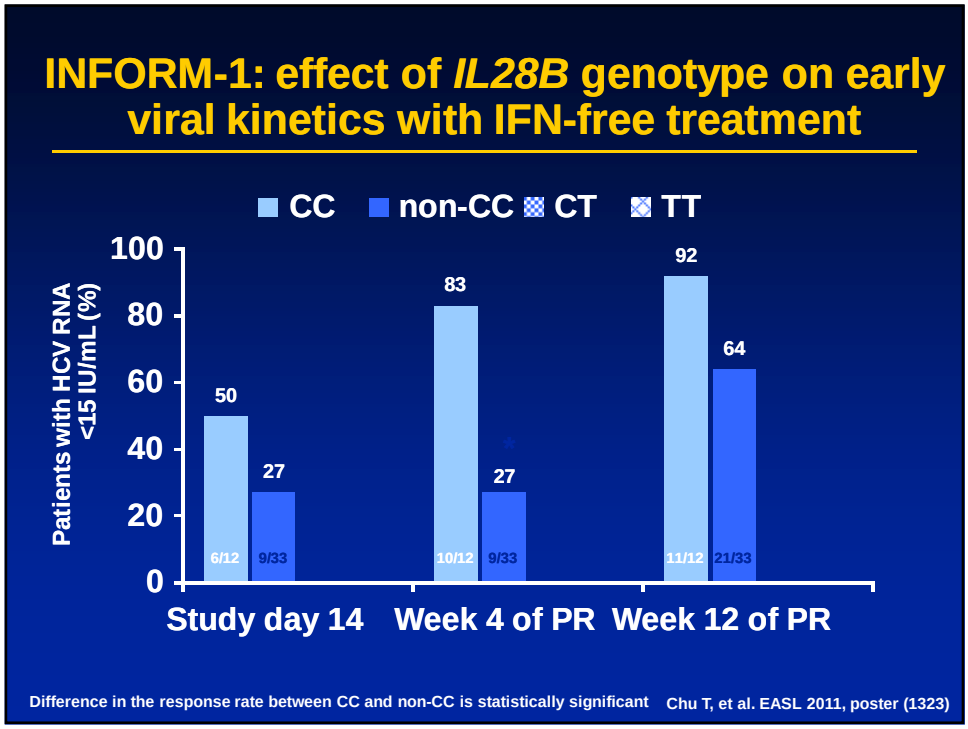

SPRINT-2, Naïve G1 Pts – SVR by IL28B Genotype in Pts with Available IL28B Data
SOC
BOC RGT
BOC/PR 48
% of pts with SVR
100%
80%
60%
40%
20%
0%
78.0%
82.0%
80.0%
28.0%
65.0%
71.0%
27.0%
55.0%
59.0%
50/64
63/77
44/55
33/116
67/103
82/115
10/37
23/42
26/44
CC
CT
TT
Poordad et al, EASL 2011, oral


SPRINT-2: IL-28B CC Polymorphism as a Predictor of SVR (Multiple Stepwise Logistic Regression Model)
Odds Ratio (95% CI)
Genotype: 1b/Other vs 1a
P <0.001
Age ≤40 vs >40
P = 0.002
IL28B Genotype: CC vs. Non-CC
P <0.0001
BOC/RGT vs PR48
P <0.0001
BOC/PR48 vs PR48
P <0.0001
Baseline HCV-RNA: ≤400,000 vs. >400,000
P <0.0001
23
IL28 (CC vs non-CC) was also predictive of SVR in full model with limited covariates (OR = 4.5, p < 0.001)
Only 7-9% of patients had VL ≤400,000
0
5
10
15
Only covariates remaining significant at α=0.05 after adjustment for the other variables were retained in the model as shown in the figure. Factors entered but not retained in the model were, region, race, gender, weight, BMI, steatosis, platelets, ALT, statin use, and fibrosis





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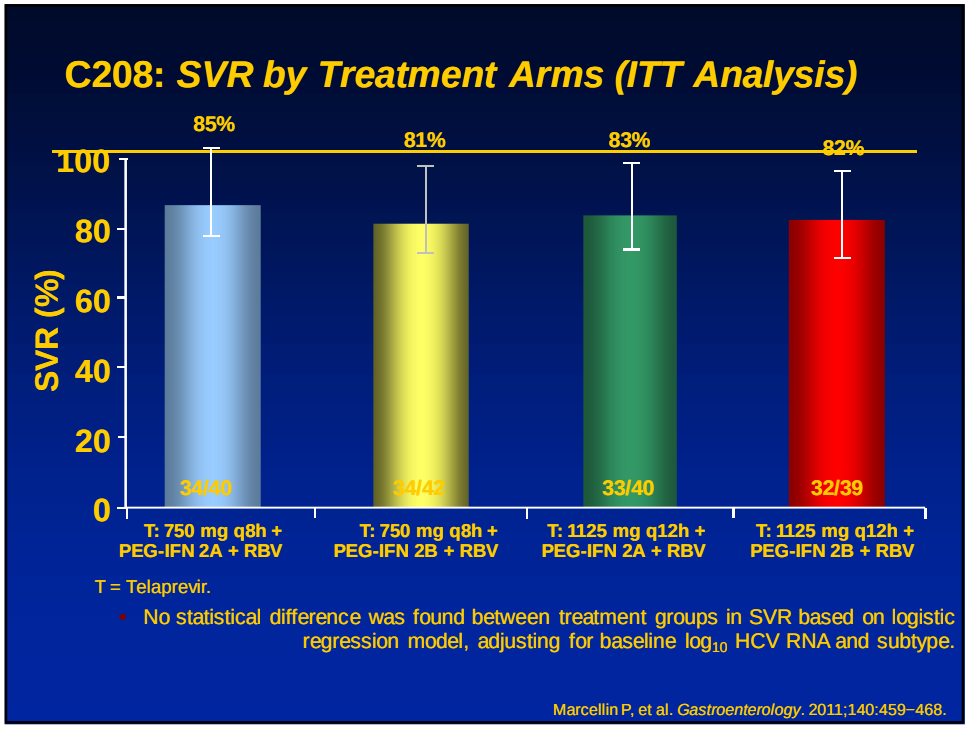
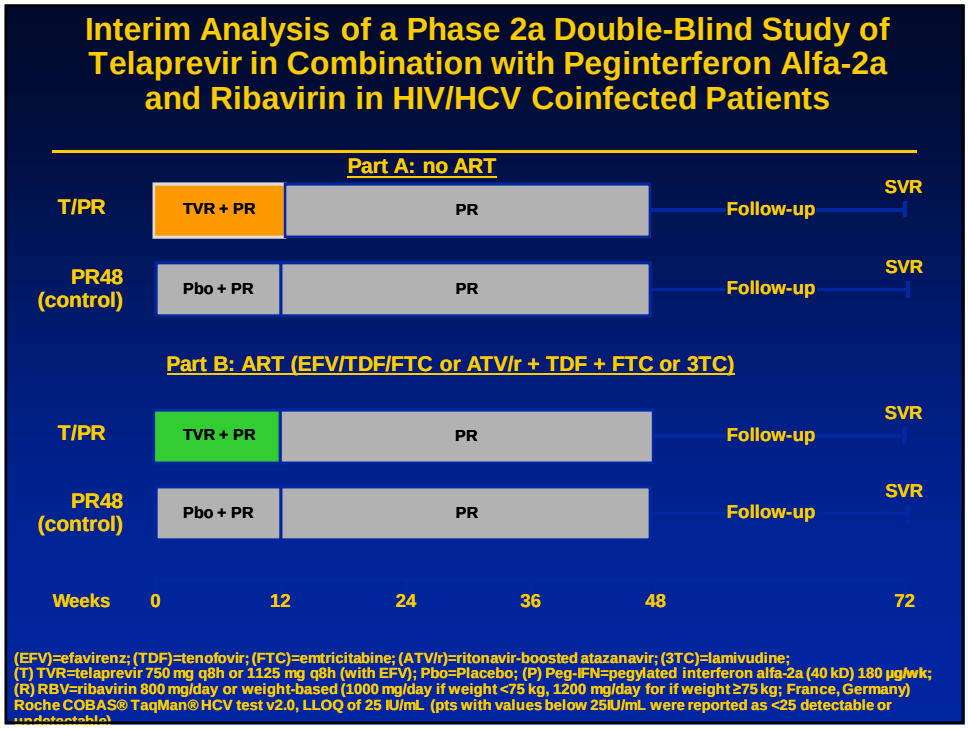
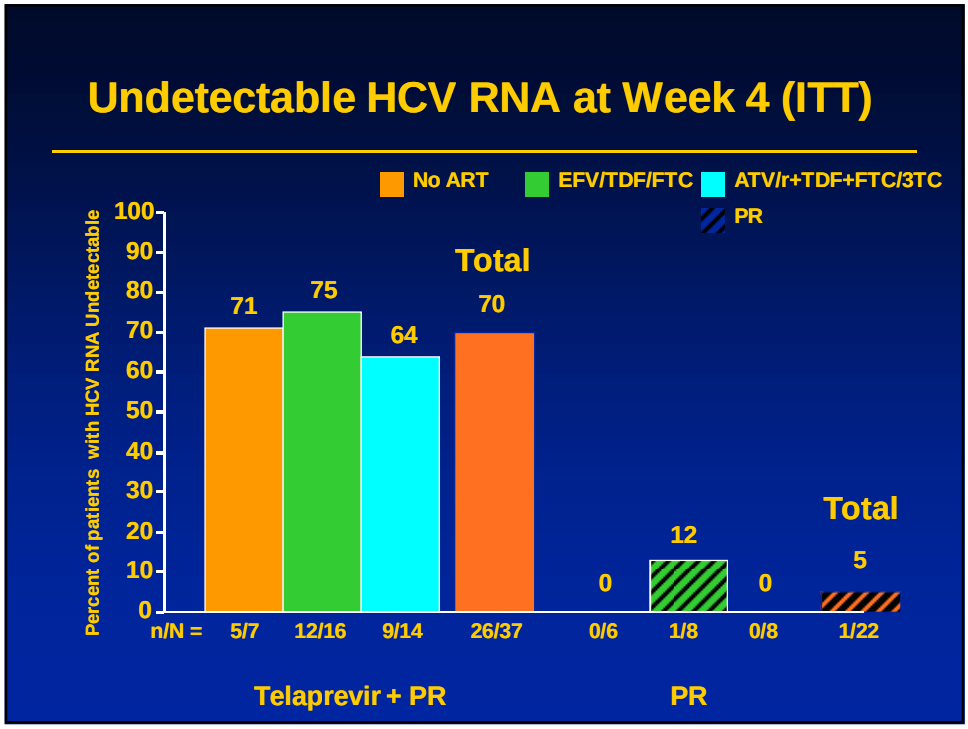
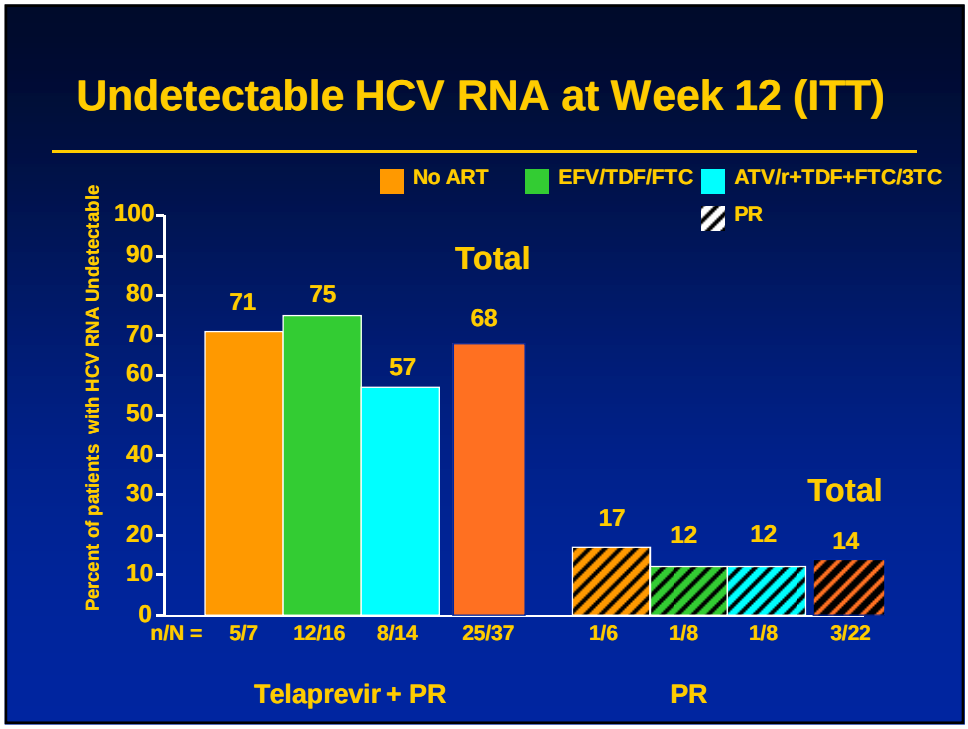

C208: SVR by Treatment Arms (ITT Analysis)
SVR (%)
100
80
60
40
20
0
85%
81%
83%
82%
34/40
34/42
33/40
32/39
T: 750 mg q8h + PEG-IFN 2A + RBV
T: 750 mg q8h + PEG-IFN 2B + RBV
T: 1125 mg q12h + PEG-IFN 2A + RBV
T: 1125 mg q12h + PEG-IFN 2B + RBV
T = Telaprevir.
No statistical difference was found between treatment groups in SVR based on logistic regression model, adjusting for baseline log10 HCV RNA and subtype.
Marcellin P, et al. Gastroenterology. 2011;140:459–468.


Interim Analysis of a Phase 2a Double-Blind Study of Telaprevir in Combination with Peginterferon Alfa-2a and Ribavirin in HIV/HCV Coinfected Patients
Part A: no ART
T/PR
TVR + PR
PR
Follow-up
SVR
PR48 (control)
Pbo + PR
PR
Follow-up
SVR
Part B: ART (EFV/TDF/FTC or ATV/r + TDF + FTC or 3TC)
T/PR
TVR + PR
PR
Follow-up
SVR
PR48 (control)
Pbo + PR
PR
Follow-up
SVR
Weeks 0 12 24 36 48 72
(EFV)=efavirenz; (TDF)=tenofovir; (FTC)=emtricitabine; (ATV/r)=ritonavir-boosted atazanavir; (3TC)=lamivudine;
(T) TVR=telaprevir 750 mg q8h or 1125 mg q8h (with EFV); Pbo=Placebo; (P) Peg-IFN=pegylated interferon alfa-2a (40 kD) 180 µg/wk;
(R) RBV=ribavirin 800 mg/day or weight-based (1000 mg/day if weight <75 kg, 1200 mg/day for if weight ≥75 kg; France, Germany)
Roche COBAS® TaqMan® HCV test v2.0, LLOQ of 25 IU/mL (pts with values below 25IU/mL were reported as <25 detectable or





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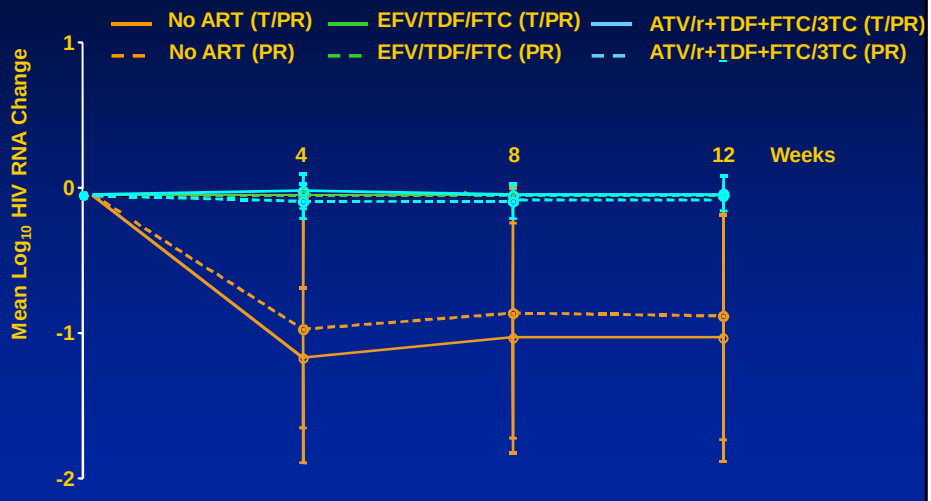
Mean HIV RNA Changes from Baseline



Most Common Adverse Events*

%	T/PR N=37	PR N=22
Fatigue	38%	41%
Nausea	**35**	**14**
Pruritus	**35**	**5**
Headache	32	27
Dizziness	**22**	**5**
Pyrexia	**22**	**9**
Anorexia	**19**	**9**
Vomiting	**19**	**9**
Diarrhea	19	18
Chills	16	18

*Reported in ≥ 15% of patients regardless of severity in any treatment arm, in bold event occurring at ≥ 10% points in any T group vs PR

Mild and moderate rash events occurred in 16% and 11% of T/PR patients, respectively and in 14% and <1% of PR patients

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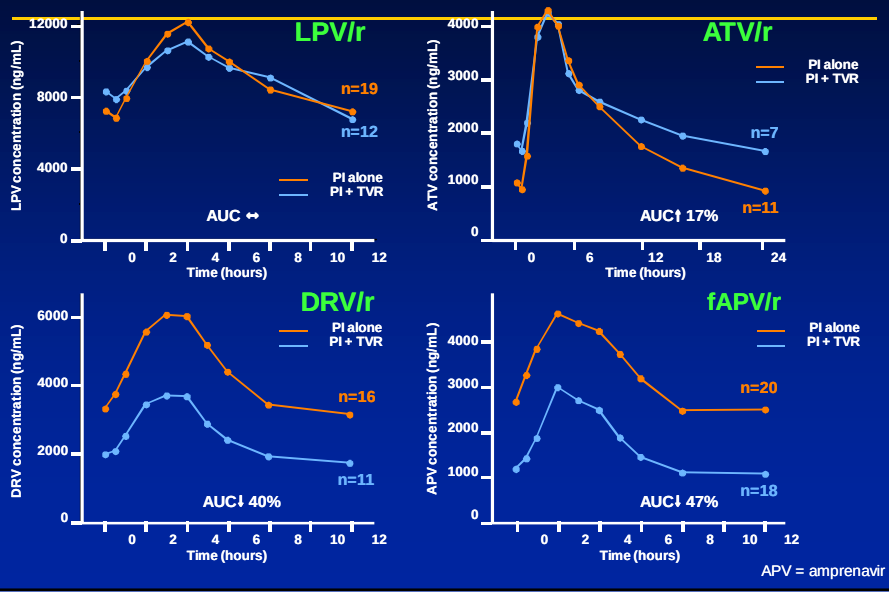
Interim Analysis Summary

- In this interim analysis, the most common adverse events in telaprevir patients with or without concurrent ART were fatigue, nausea, and headache; no severe rash events were reported
- Patients in the T/PR arms in both parts exhibited a higher on-treatment HCV RNA response at week 4
  - T12/PR: 26 of 37 patients (70%)
  - PR: 1 of 22 patients (5%)
- No unexpected trends in HIV viral loads and/or CD4 counts were observed
- No clinically significant PK interactions were observed

Mean HIV PI PK Profiles TVR



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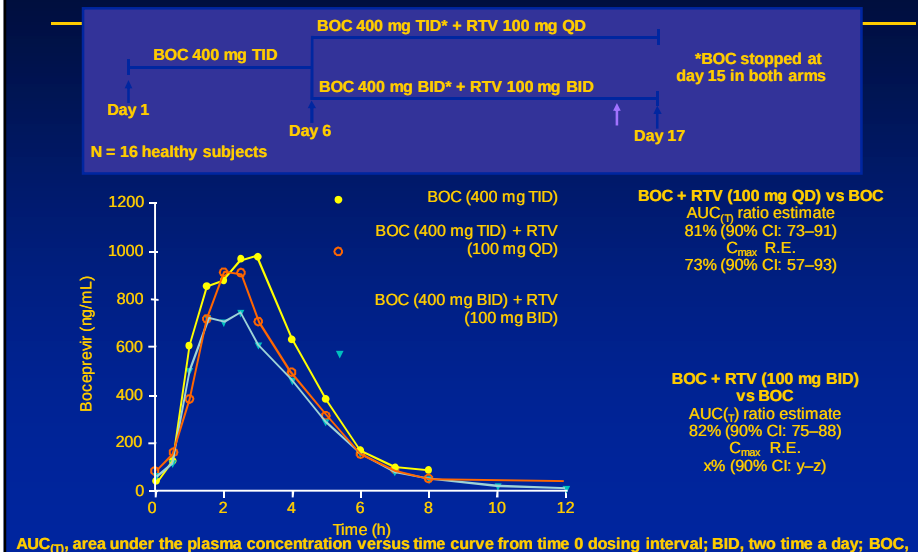
TVR DDI's

- RTV-boosted HIV PIs + TVR 750 mg q8h
  - (Mutual) drug interactions were observed
    - Reduced exposure to TVR, variable effect s on HIV PIs
  - Protein displacement may play a role in reduction of total concentrations (in-vitro evaluation ongoing)
  - Appropriate doses have not been established
- EFV and Tenofovir + TVR 1125 mg q8h
  - Small changes in TVR, EFV and tenofovir exposure
  - Higher TVR dose (1125 mg q8h) partly offset interaction with EFV

Sulkowski et al. CROI 2011; Abstract 146LB

Ritonavir and BOC



$AUC_{(T)}$, area under the plasma concentration versus time curve from time 0 dosing interval; BID, two time a day; BOC, boceprevir;
CI, confidence interval; RTV, ritonavir; TID, three times a day.

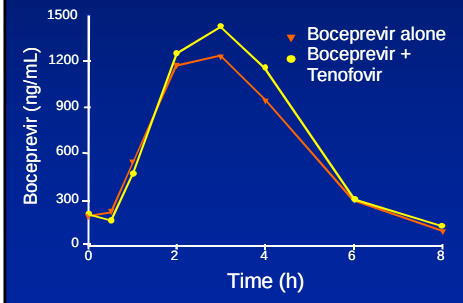
Tenofovir and BOC

A: BOC (800 mg) TID
B: TFV (300 mg) QD
C: BOC + TFV

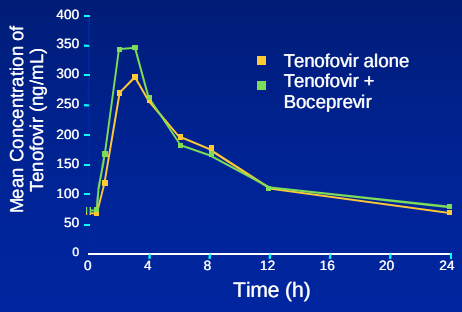
A or B or C for 7 days → ≥7 days → A or B or C for 7 days → ≥7 days → A or B or C for 7 days

N = 18 healthy subjects (n = 2 discontinued due to vomiting and viral infection)

BOC vs BOC + TFV
$AUC_{(0\text{-}8h)}$ ratio estimate 108% (90% CI: 102–114)
C_{max} R.E. 105% (90%CI: 98–112)



TFV vs TFV + BOC
$AUC_{(0\text{-}8h)}$ ratio estimate 105% (90% CI: 101–109)
C_{max} R.E. 132% (90% CI: 119–145)



$AUC_{(0\text{-}8\ h)}$, area under the plasma concentration-time curve from 0 to 8 hours; BOC, boceprevir; CI, confidence interval; QD, once daily; TFV, tenofovir; TID, three times a day.

Efavirenz decreased BOC Cmin

Days 1–5: BOC 800 mg TID
Day 6: BOC 800 mg single dose
N = 12 healthy volunteers

Washout ≥7 days

Days 1–10: •EFV 600 mg QD

Days 11–15: BOC 800 mg TID
Day 16: BOC 800 mg single dose
Days 11–16: EFV 600 mg QD

	Treatment	LS Mean[a]	Ratio Estimate, % (90% CI)
Effect of EFV (600 mg QD) on BOC (800 mg TID)			
C_{max} (ng/mL)	BOC	2038	92 (78–108)
	BOC + EFV	1871	
$AUC_{(0\text{-}8h)}$ (ng·h/mL)	BOC	6913	81 (75–89)
	BOC + EFV	5630	
C_{min} (ng/mL)	BOC	94.4	56 (42–74)
	BOC + EFV	52.5	
Effect of BOC (800 mg TID) on EFV (600 mg QD)			
C_{max} (ng/mL)	EFV	4573	111 (102–120)
	EFV + BOC	5077	
$AUC_{(0\text{-}24h)}$ (ng·h/mL)	EFV	78667	120 (115–126)
	EFV + BOC	94655	

[a]Model-based (least squares) geometric mean; ANOVA extracting the effects due to treatment and subject.
AUC, area under the plasma concentration-time curve; BOC, boceprevir; CI, confidence interval; C_{max}, maximum observed plasma concentration; C_{min}, minimum observed plasma concentration; EFV, efavirenz; LS, least squares; QD, once daily; TID, three times a day.

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Boceprevir DDI's

- Metabolic inhibitors (even in combination) did not alter BOC PK profile substantially to change BOC's dose or schedule
- Ritonavir (CYP 3A4 inhibitor) did not substantively affect exposure to BOC
- No dosage adjustment is needed for the coadministration of BOC with tenofovir or peginterferon
- Clinical implications of a ↓ mean BOC trough concentration when coadministered with efavirenz will be clearer as data from coinfected populations are obtained

AKR, aldo-keto reductase; BOC, boceprevir; CYP3A4, cytochrome P450 3A4; P-gp, P-glycoprotein; PK, pharmacokinetics.

Telaprevir and Methadone

- No effect of methadone on TVR pharmacokinetics.
- Exposure to R-methadone (AUC24h) decreased by 29% with TVR.
- Although the total R-methadone Cmin was reduced, the median unbound concentration was not affected
- Co-administration with TVR increased the median free fraction of R-methadone by 26%.
- unbound concentration of R-methadone was unchanged the reduction not considered to be clinically relevant
- Nov withdrawal symptoms in this study.
- No dose adjustment of methadone is necessary when initiating co-administration of TVR

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Telaprevir and Methadone

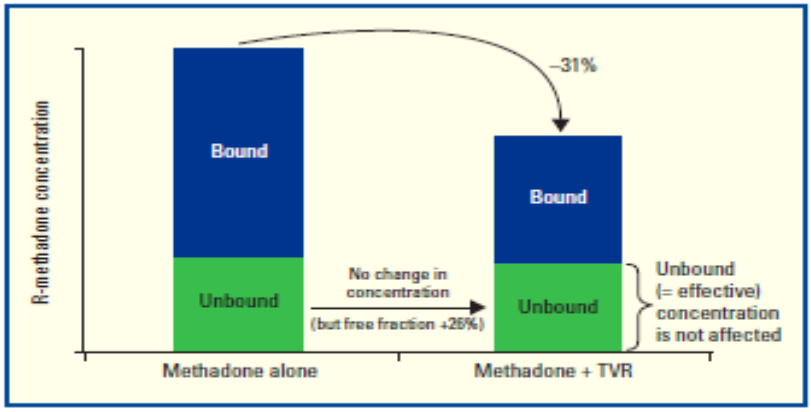

Figure 6. Representation of Effect of Protein Displacement by TVR on R-methadone Concentration (Bound and Unbound Fractions).

Berlin, Germany, 30 March–3 April 2011.

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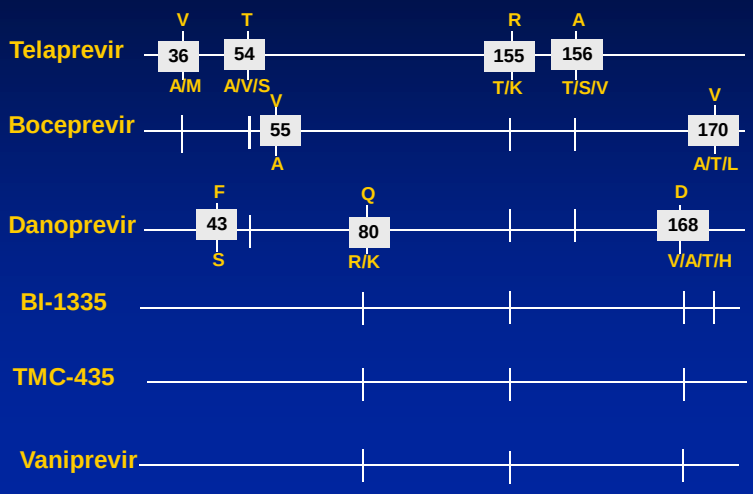
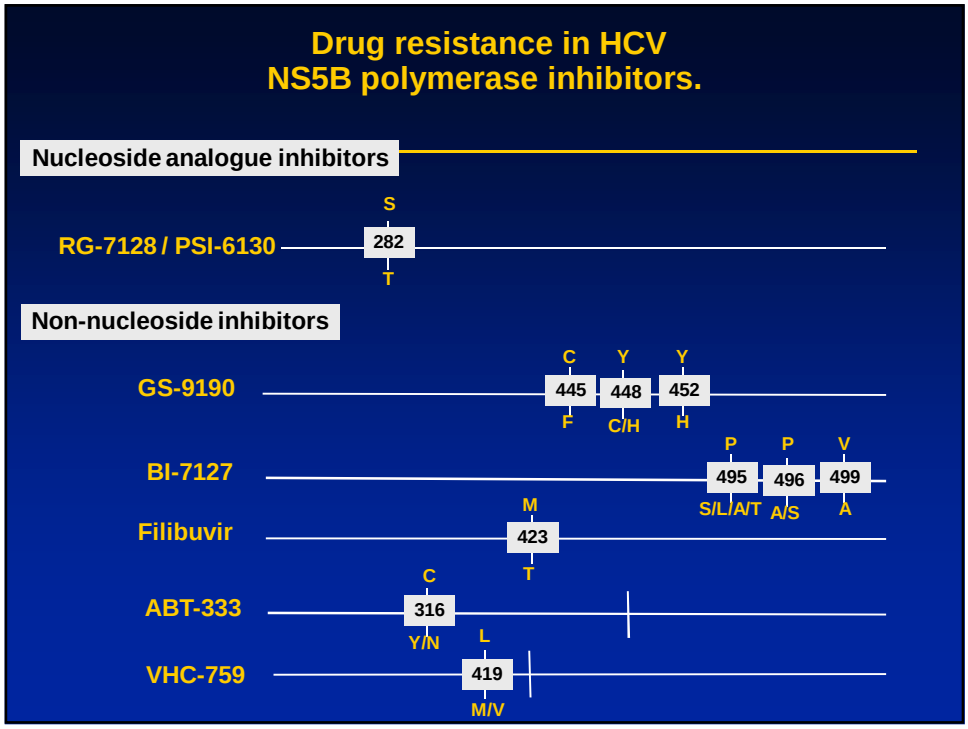
Drug resistance in HCV Protease inhibitors.





Tailoring HCV therapy.

		pegIFN +/- RBV	PI	NA	NNA	NS5A
IL28B CC		+++				
HCV genotypes	1a	+	++	++	++	++
	1b	+	+++	++	+++	++
	2	+++	++	++	-	++
	3	++	-	++	-	++
	4	+	-	++	-	++

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How to use HCV Protease Inhibitors and avoid resistance

- Make sure your patients are taking all 3 doses of TLV and BOC (both TID drugs)
- Don't continue the DAA if there is not an RVR!
- Don't re-treat with the same or another protease with the same resistance pattern
- Not every patient needs to be treated right away
- Triage, and treat the sicker patients first, but the decompensated cirrhotics should not be treated unless listed for liver transplant first
- There are other drugs coming that will be active against PI failures, so don't worry too much about resistance

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Conclusions

- HCV is a major, if not the major cause of morbidity and mortality in HIV+ patients today
- Successful treatment of HCV (cure) in HIV+ patients is possible and even likely with pegylated interferon and ribavirin
- Data is being generated with DAA's in HIV
- DDI's with HIV medications appear manageable
- Awaiting data on BOC in HIV
- Early efficacy data with TVR in HIV is promising

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