

# 2011 Update in HIV/HCV Management in the Era of Direct Acting HCV Antivirals

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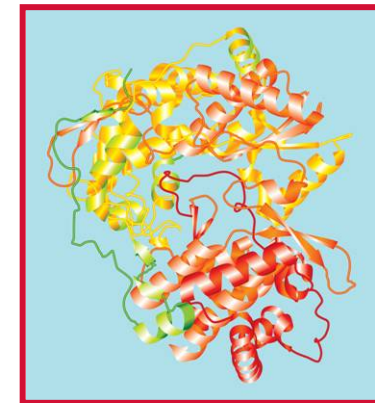
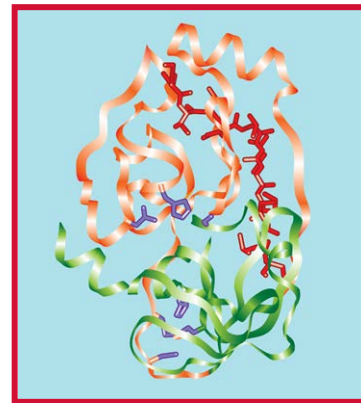
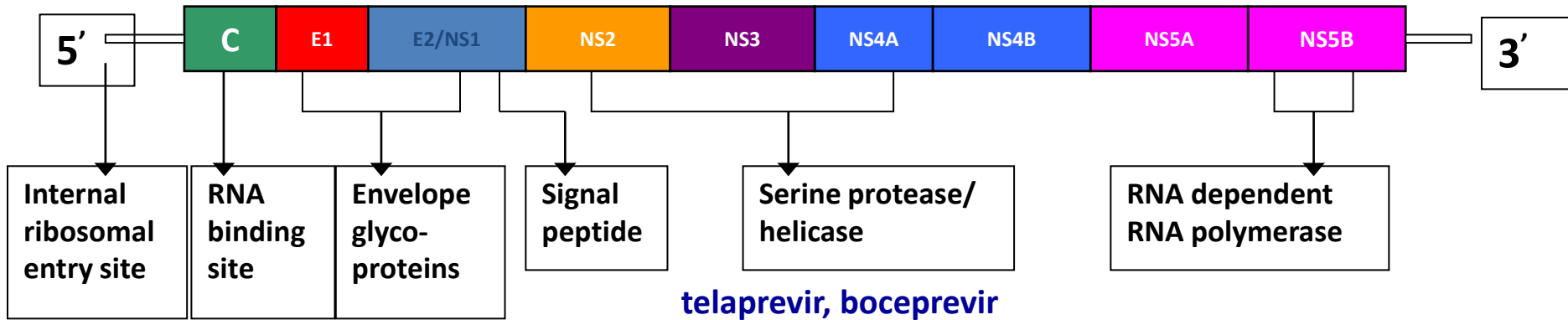
**HEPATITIS C TREATMENT EXPANSION INITIATIVE  
2<sup>nd</sup> ANNUAL ALL GRANTEE MEETING  
WASHINGTON, DC - NOVEMBER 29<sup>th</sup> - 30<sup>th</sup> 2011**



# Areas of Advancement in HIV/HCV Therapy

- Specific HCV antiviral therapy trials
- Limitations of Predictive Biomarkers
- Implications of HCV drug resistance

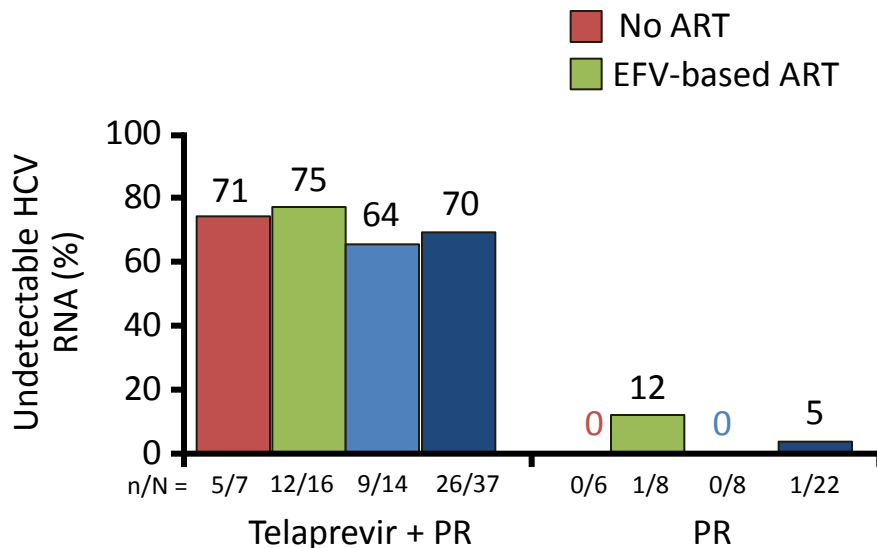
# Potential HCV antiviral targets



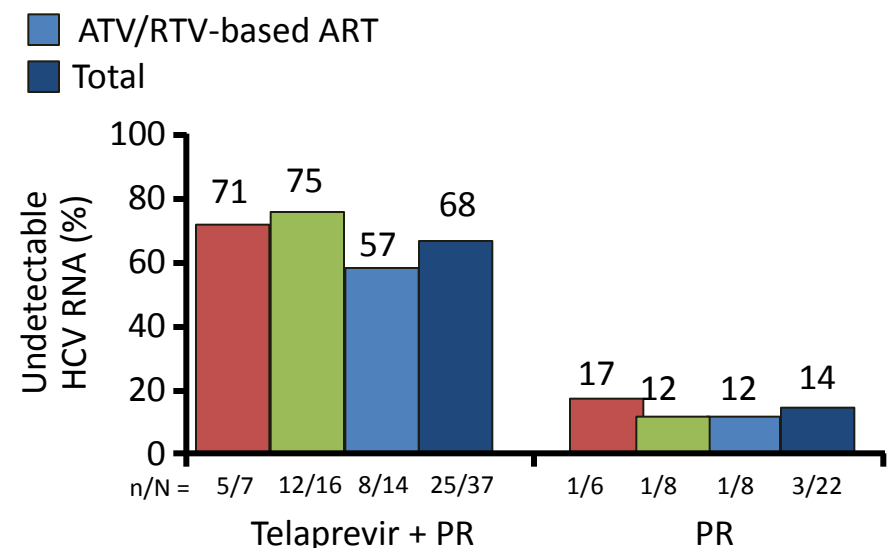
# Study 110: High Rates of Early Response With TVR + PR in Coinfected Patients

- Similar efficacy results observed with or without concurrent ART
- Nausea, pruritus, dizziness, fever more common with TVR vs placebo
- Pharmacokinetic interactions with ATV or EFV not clinically significant

Undetectable HCV RNA, **Week 4 (ITT)**



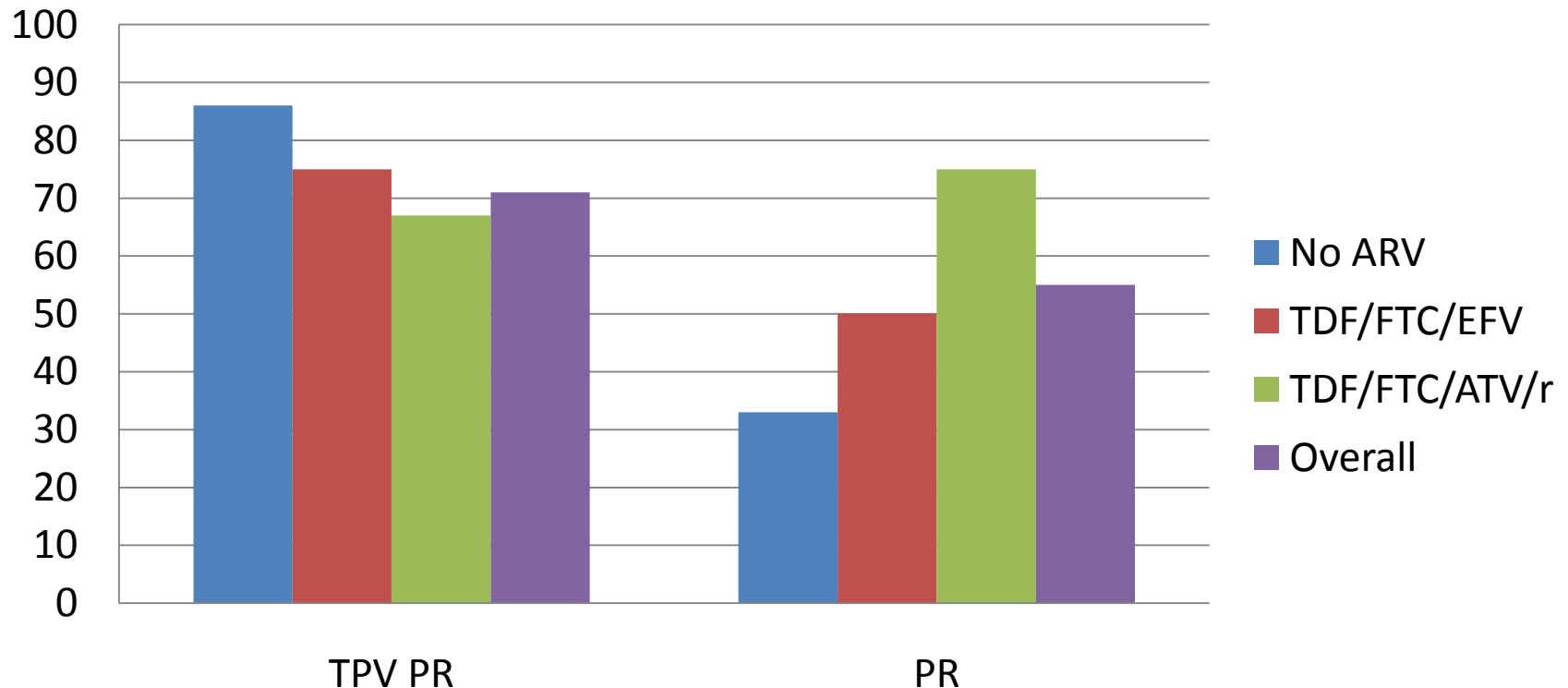
Undetectable HCV RNA, **Week 12 (ITT)**



Sulkowski M, et al. CROI 2011. Abstract 146LB. Graphics used with permission.

# Telaprevir plus PegINF and Ribavirin in HIV/HCV Infected Patients – Week 24

## Undetectable HCV Viral Load at Week 24



Sherman, KE et al.. AASLD Conference November 2011 – Late Breaker Abstract 8

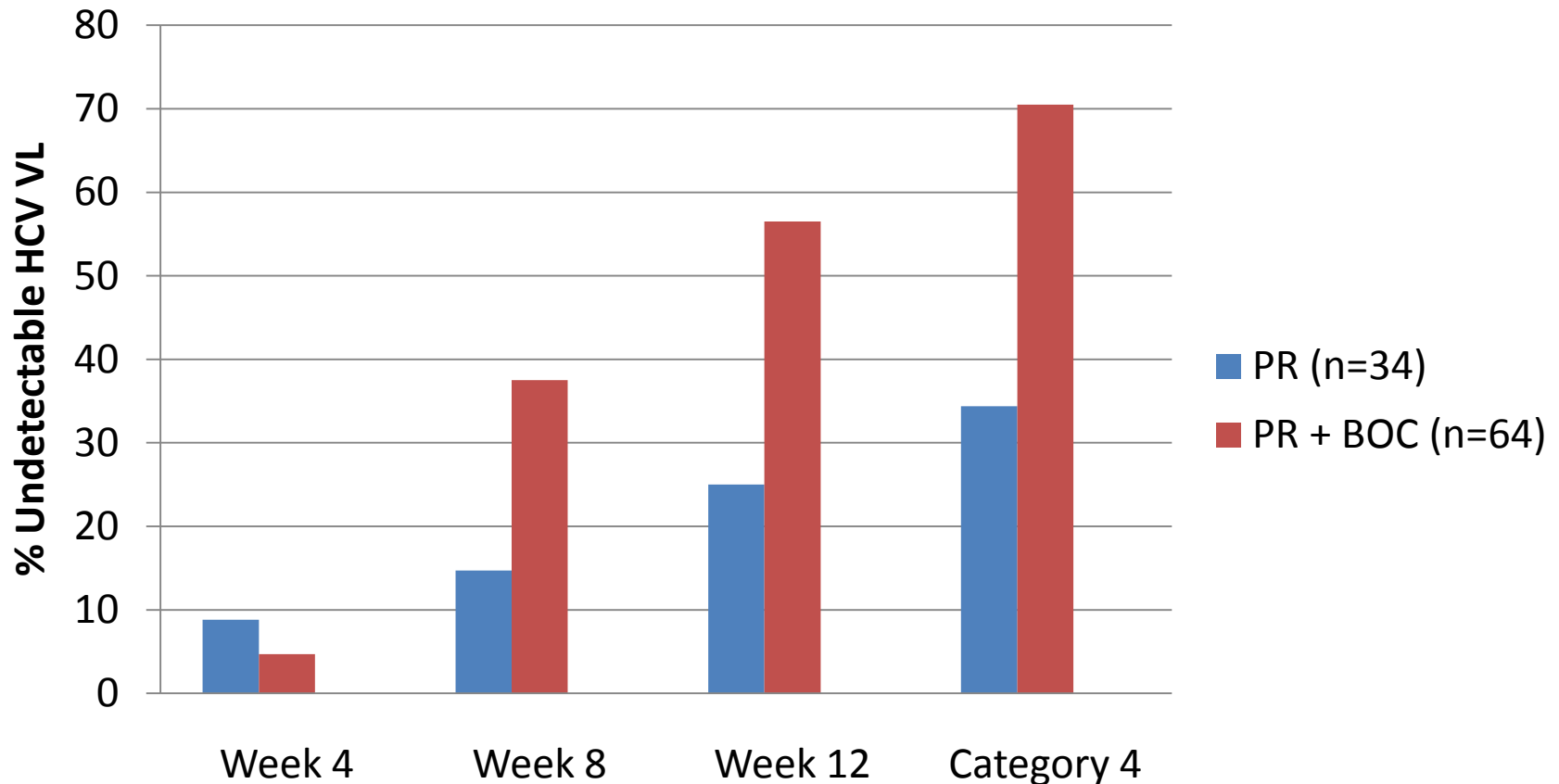
# Telaprevir plus PegINF and Ribavirin in HIV/HCV Infected Patients – Side Effects

Adverse Effect	TVR+PR	PR
Pruritis or Itching	39%	9%
Headache	37%	27%
Nausea	34%	23%
Skin Rash*	34%	23%
Fever	21%	9%
Anemia	13%	18%
Depression	21%	9%
Insomnia	13%	23%

\*no cases of severe rash

Sherman, KE et al.. AASLD Conference November 2011 – Late Breaker Abstract 8

# Boceprevir in Addition to Pegylated INF alfa 2a in HIV/HCV Patients on ARVs



Sulkowski, M. ISDA Late Breaker Abstract LB 37 October 2011

# Boceprevir Interactions with HIV Medications

- No clinically relevant changes in boceprevir exposure when co-administered with ethinyl estradiol or tenofovir .
  - increased tenofovir maximum concentration (C<sub>max</sub>) by about 30%.
- Boceprevir AUC and C<sub>max</sub> decreased, minimum concentration (C<sub>min</sub>) fell by about 40% when administered with efavirenz.
- Boceprevir slightly increased efavirenz AUC and C<sub>max</sub> (by about 20% and 10%, respectively)
- Ritonavir (Norvir) had a minimal effect on steady-state boceprevir exposure, and actually decreased boceprevir AUC by about 20%

*CROI 2011*

*Abstract 118: Merck & Co, Inc, Kenilworth, NJ.*



# Telaprevir Interactions with HIV PIs

- Telaprevir AUC and Cmin decreased by only about 15% when administered 750 mg 3-times-daily with boosted atazanavir.
- Telaprevir levels fell by about 50% when administered at the same dose with lopinavir/ritonavir.
- Telaprevir levels decreased by about 30% when taken with darunavir/ritonavir or fosamprenavir/ritonavir.
- Conversely, darunavir and fosamprenavir levels fell by more than half when co-administered with telaprevir.
- Atazanavir Cmin nearly doubled when taken with 750 mg telaprevir.

*CROI 2011*

*Abstract 119: Tibotec BVBA, Beerse, Belgium; Vertex Pharmaceuticals Inc, Cambridge, MA*

# Telaprevir dosing Recommendations

- Based on these findings, researchers chose 750 mg 3-times-daily telaprevir plus atazanavir/ritonavir, or telaprevir 1125 mg 3-times-daily with efavirenz as regimens to evaluate in clinical trials of HIV/HCV coinfecting patients.

*CROI 2011*

*Abstract 119: Tibotec BVBA, Beersel, Belgium; Vertex Pharmaceuticals Inc, Cambridge, MA*

# Telaprevir Interactions with Efavirenz

- Therapeutic levels of all drugs were maintained when the telaprevir dose was upped to 1250 mg 3-times-daily in combination with efavirenz and tenofovir.
- Telaprevir AUC remained high but Cmin fell by half when using 1250 mg twice-daily.
- Based on these findings, researchers chose 750 mg 3-times-daily telaprevir plus atazanavir/ritonavir, or telaprevir 1125 mg 3-times-daily with efavirenz as regimens to evaluate in clinical trials of HIV/HCV coinfecting patients.

*CROI 2011*

*Abstract 119: Tibotec BVBA, Beersel, Belgium; Vertex Pharmaceuticals Inc, Cambridge, MA*

## Main features of new specifically targeted hepatitis C virus drugs.

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Drug class, feature

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Protease inhibitors

- Interact with the catalytic triad

- Genotype-dependent activity for some drugs

- Rapid selection of resistance

Nucleoside analogues

- Analogues of natural substrates

- Need to be phosphorylated

- Inhibitory competition

- Chain terminators

- Similar activity against all genotypes

- High genetic barrier to resistance

Nonnucleoside inhibitors

- 5 Target sites at the polymerase

- Allosteric inhibition

- Genotype-dependent activity

- Rapid selection of resistance

- Polymorphisms may influence susceptibility

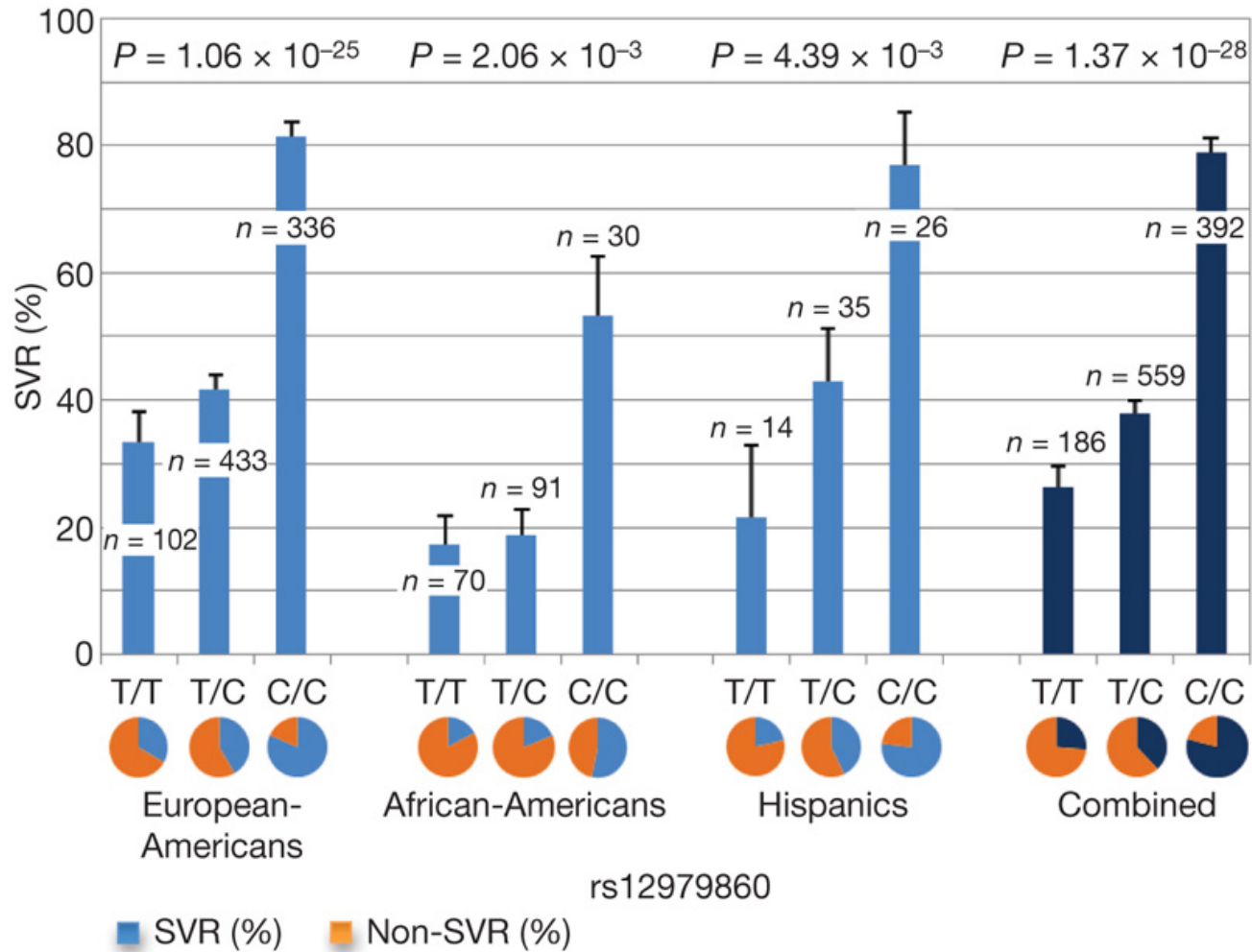
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Soriano V et al. Clin Infect Dis. 2009;48:313-320

# IL-28B Polymorphism and Treatment Response

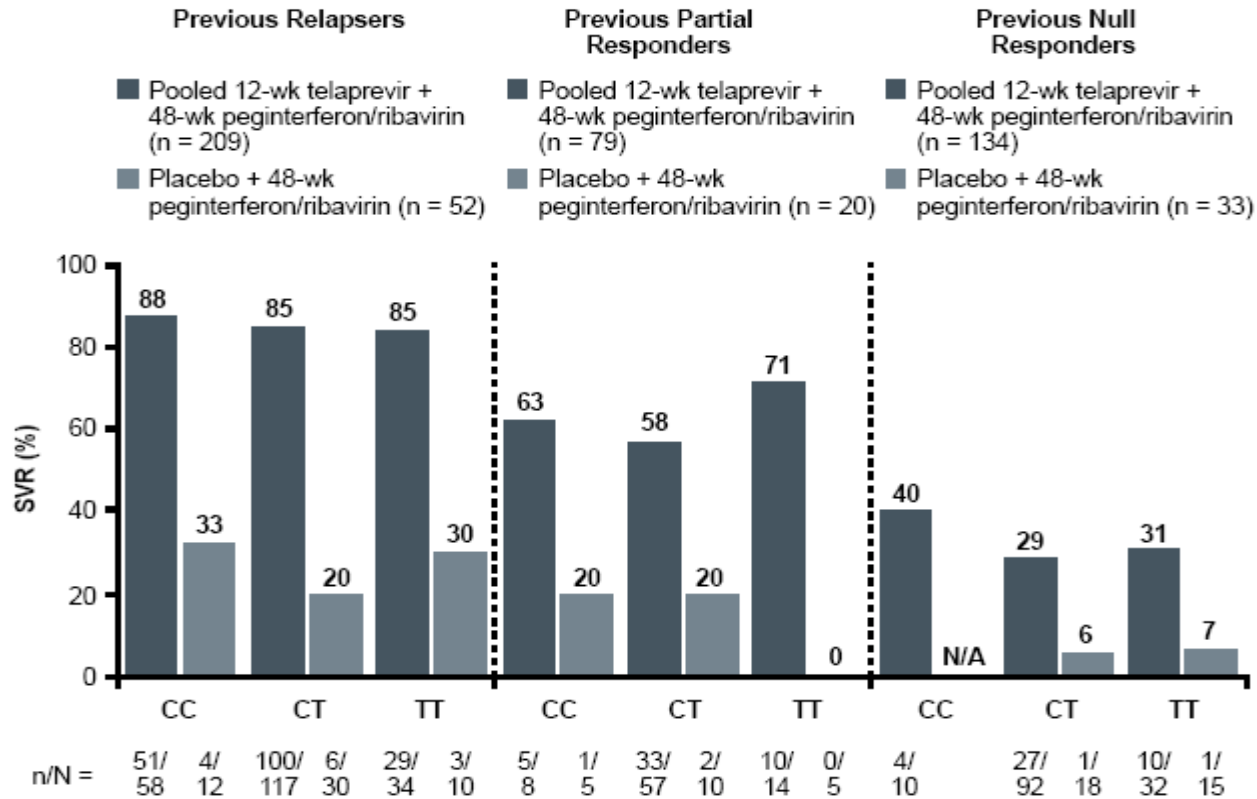
- Polymorphisms near the IL-28B gene are strong predictors of both spontaneous clearance of HCV and response to treatment

# Percentage of SVR by genotypes for IL-28B region



DL Ge *et al.* *Nature* **461**, 399-401 (2009)

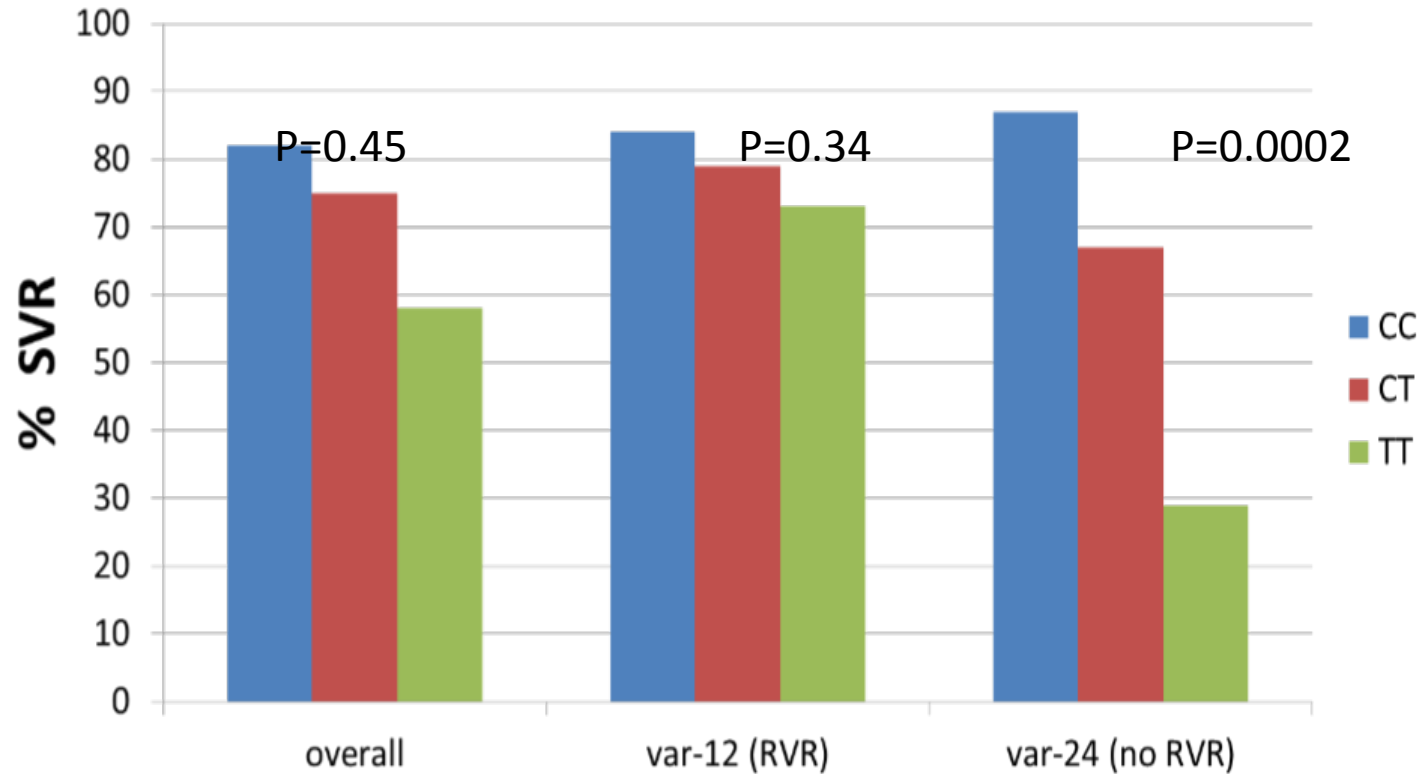
# SVR to Telaprevir by Response Category and *IL28B* Genotype



Genetic testing from 527/662 (80%) patients.

Pol S, et al. EASL 2011. Abstract O-13..

# Effect of unfavorable IL28b genotype is less in Caucasian genotype 2/3 HCV infection



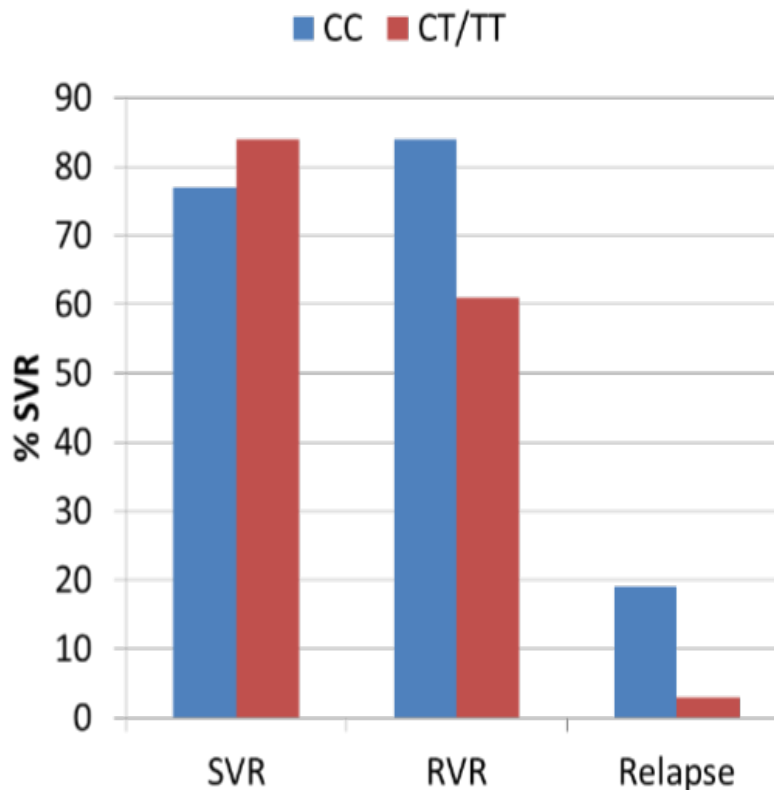
Genotype 2, N=213; Genotype 3, N=55

Mangia A, et al. Gastroenterology 139 (3) 821-827 (2010)



# Favorable IL28b genotype may be associated with relapse of genotype 3 HCV infection

- 281 genotype 3, Scandinavian
- Overall SVR 80%
- CC relapse:
  - 13/64 (20%) 14wk
  - 7/43 (16%) 24 wk



Moghaddam A, et al. Hepatology 53(3) 746-54 (2011)

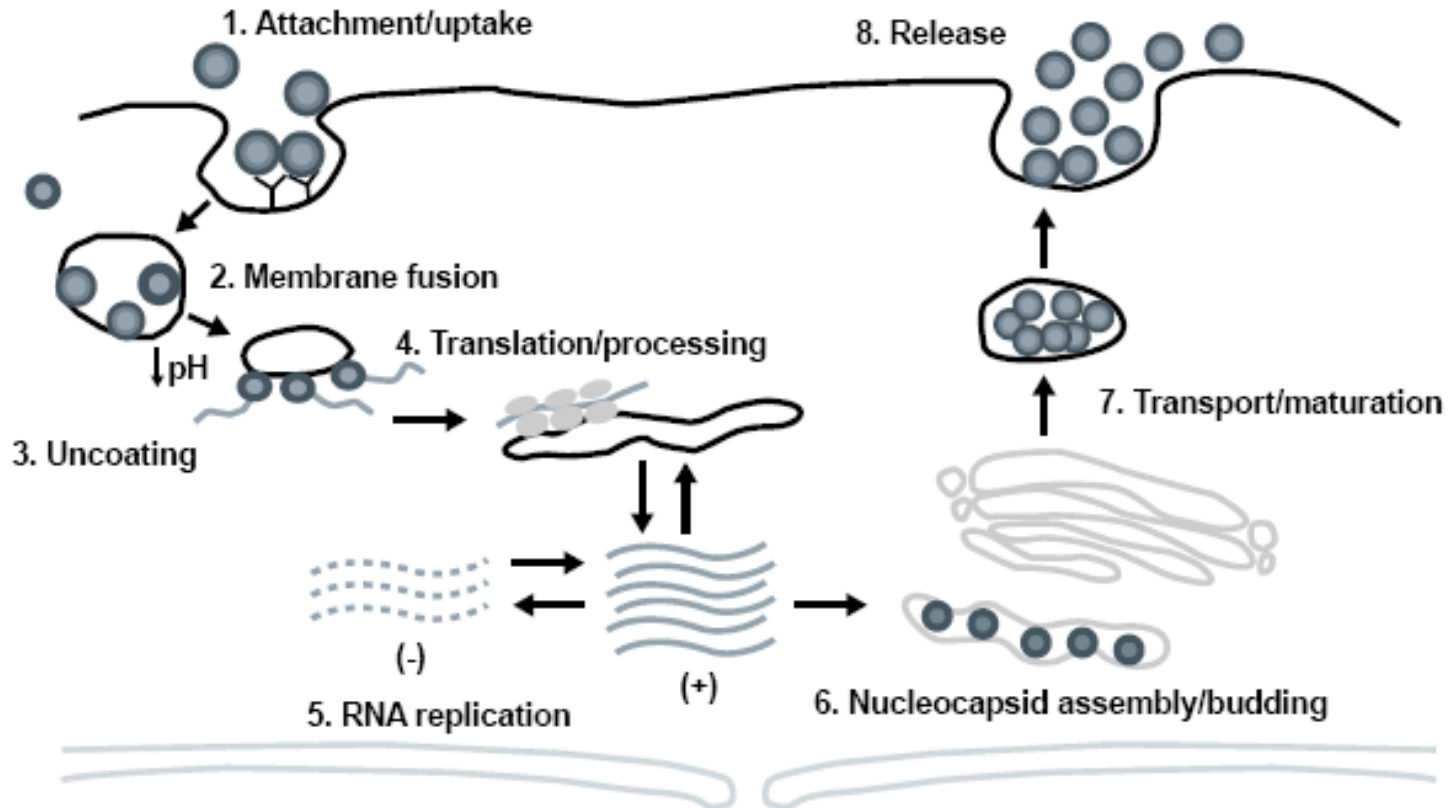
# Predictors of Liver Cirrhosis in Human Immunodeficiency Virus (HIV)–Hepatitis C Virus (HCV)–Coinfected Patients, by Logistic Regression Analysis

Variable	OR (95% CI)	P-value
Age (per year)	1.05 (0.99-1.12)	0.08
Male Sex	1.20 (0.42-3.44)	0.72
Prior EtOH >60g/d	1.97 (0.95-4.06)	0.07
ALT (per IU/L)	0.99 (0.94-1.06)	0.93
Nadir CD4	0.98 (0.99-1.01)	0.63
Receipt of ARVs	2.04 (0.42-9.93)	0.38
<b>IL28B CC vs CT/TT</b>	<b>2.32 (1.22-4.41)</b>	<b>0.01</b>

Barreiro P et al. J Infect Dis. 2011;203:1629-1636

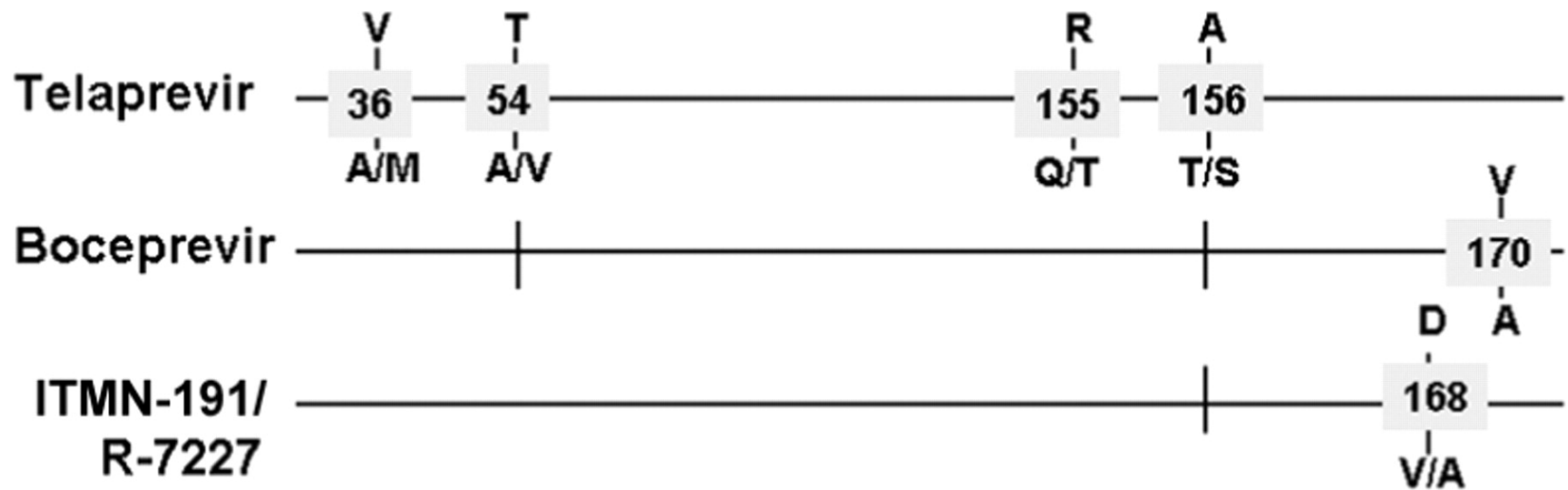


# HCV Life Cycle



From Clinical Care Options 2011 HIV/HCV Annual Symposium; Stuart Ray, MD

# Primary mutations conferring resistance to NS3/4A protease inhibitors.



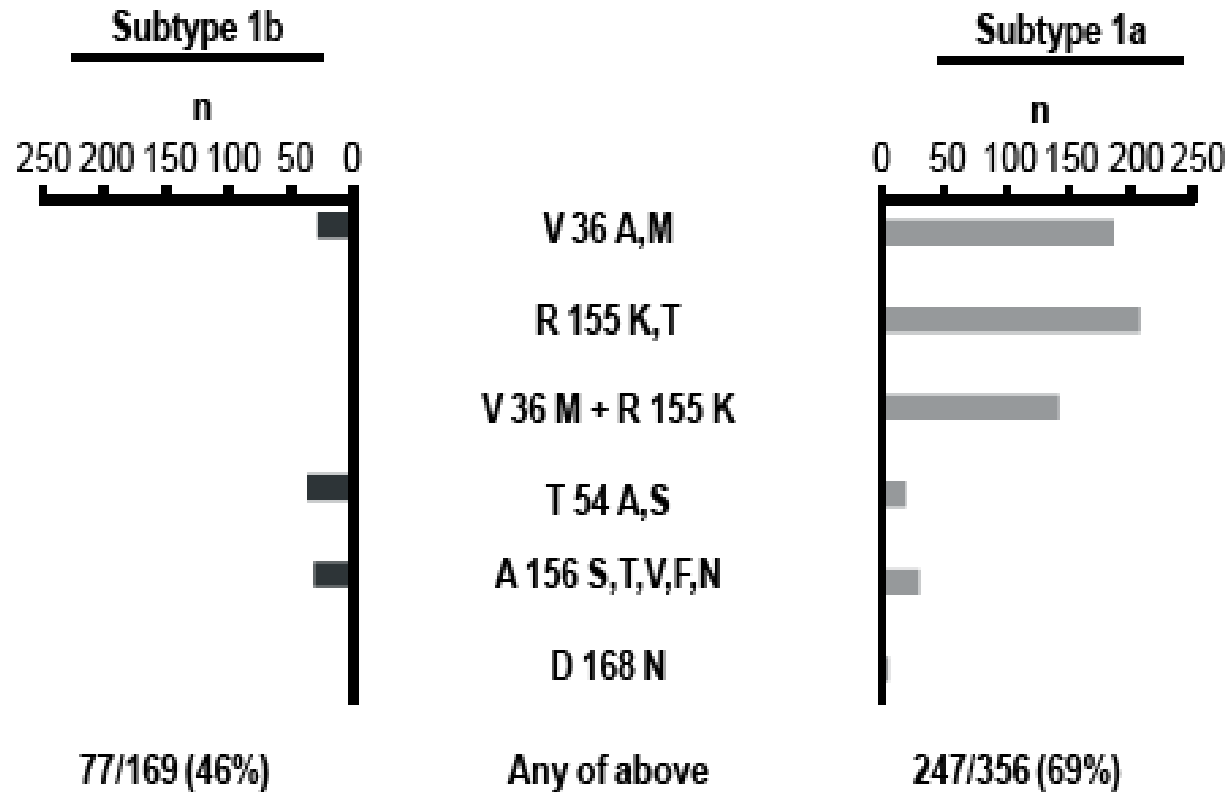
# Subtype Impacts Genetic Barrier to Resistance

Example: codon 155 of the HCV protease

	Step 1	Step 2
Subtype 1a	R155K: <u>AGG</u> → <u>AAG</u>	
Subtype 1b	R155K: <u>CGG</u> → <u>AGG</u> → <u>AAG</u>	

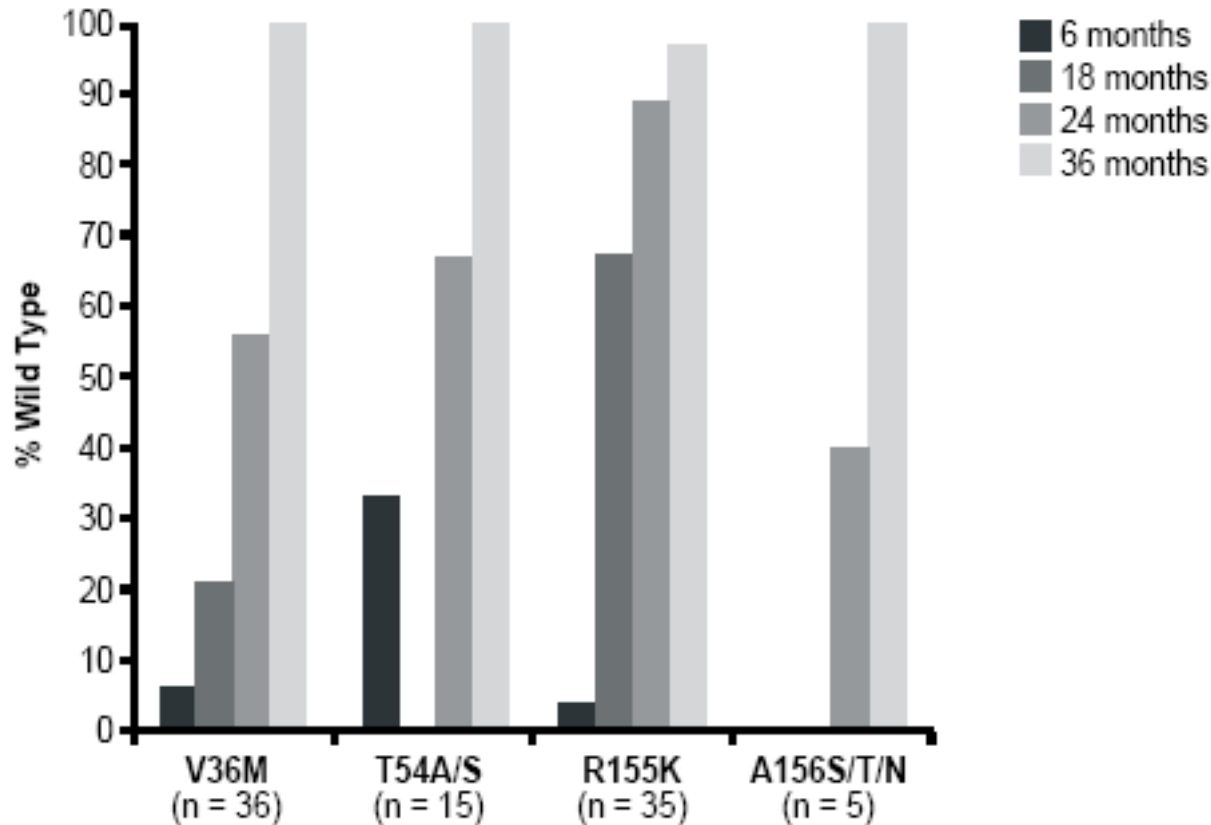
From Clinical Care Options 2011 HIV/HCV Annual Symposium; Stuart Ray, MD

# Relevance of Subtype in HCV Protease Inhibitor Resistance



US DHHS. Advisory committee briefing document for NDA 201-917 telaprevir 375 mg tablets.

# Reversion of Drug Resistance Mutations Following Telaprevir Failure



US DHHS. Advisory committee briefing document for NDA 201-917 telaprevir 375 mg tablets.



# The Direct Acting HCV Antiviral Pipeline

- 10 agents in Phase 1 trials
- 19 agents in Phase 2 trials
- 5 agents in Phase 3 trials
- Multiple trials involving combination therapy with investigational agents
- Trials are exploring virologic efficacy AND duration of treatment
- All agents are protease or polymerase inhibitors plus one entry inhibitor (phase 1)

[http://www.hcvadvocate.org/hepatitis/hepC/HCVDrugs\\_2011.pdf](http://www.hcvadvocate.org/hepatitis/hepC/HCVDrugs_2011.pdf) accessed: November 28, 2011

# Indirect Acting HCV Drug Pipeline

- 12 agents in Phase 1 trials
- 22 agents in Phase 2 trials
- 3 agents in Phase 3 trials
- Mechanisms of action include
  - Immunomodulators
  - Oral or alternative interferons
  - TLR antagonists
  - Therapeutic Vaccines
  - Interfering RNAs
  - Existing Antimicrobials
  - Anti-cancer agents

[http://www.hcvadvocate.org/hepatitis/hepC/HCVDrugs\\_2011.pdf](http://www.hcvadvocate.org/hepatitis/hepC/HCVDrugs_2011.pdf) accessed: November 28, 2011