Investigational Agents for HCV: I Thought This Was Going To Get Easier

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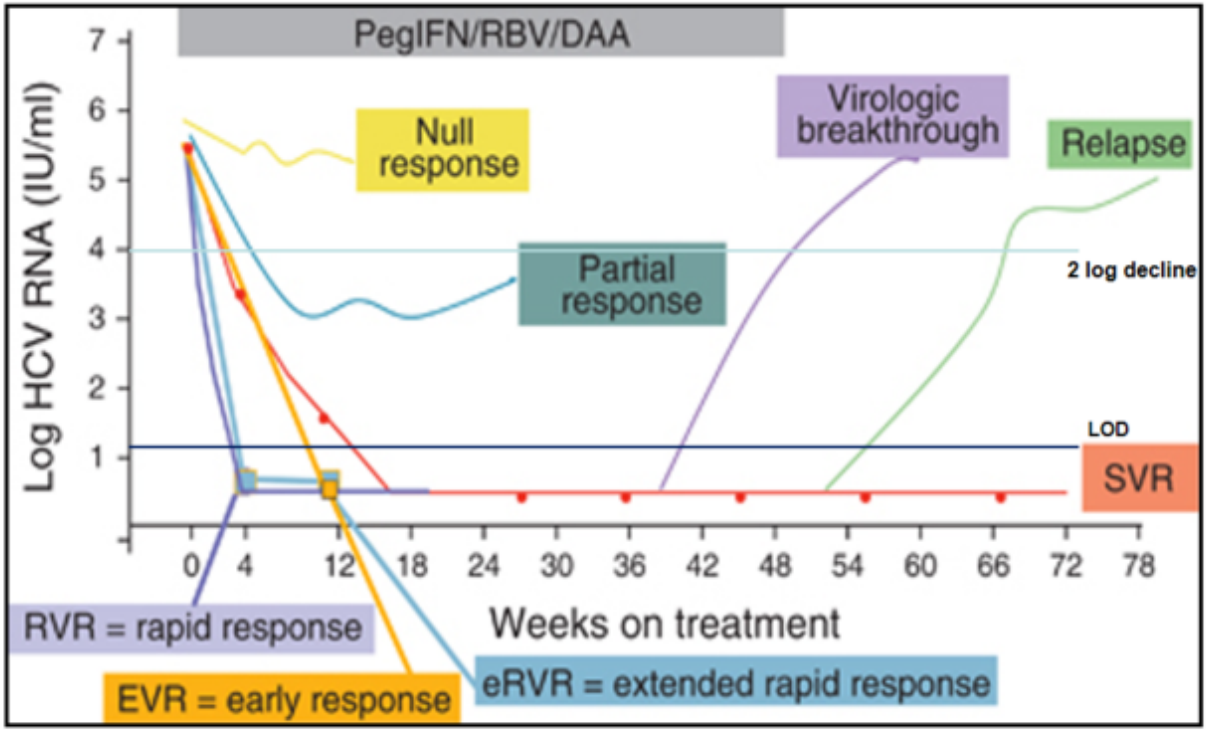
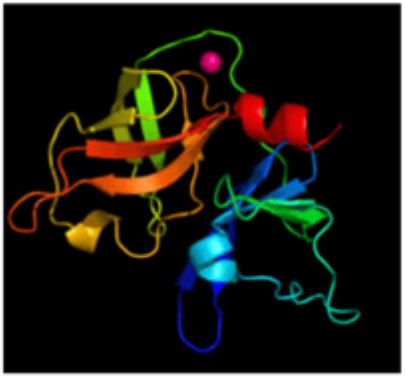
On Treatment Viral Kinetics



Adapted from Yee H et al. Amer J of Gastroenterology 2012

NS3 Protease Inhibitors

- Serine protease (HIV aspartyl)
- Peptidomimetic
  - Linear
  - Macrocyclic
- High Potency
- Low barrier to resistance
- First Wave GT 1
- Second Wave Multigenotypic (GT 3)

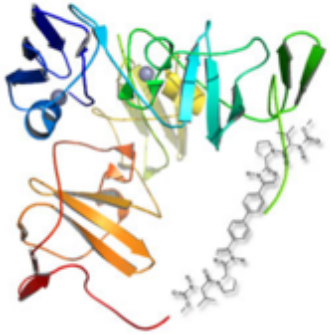


NS5B Polymerase Inhibitors

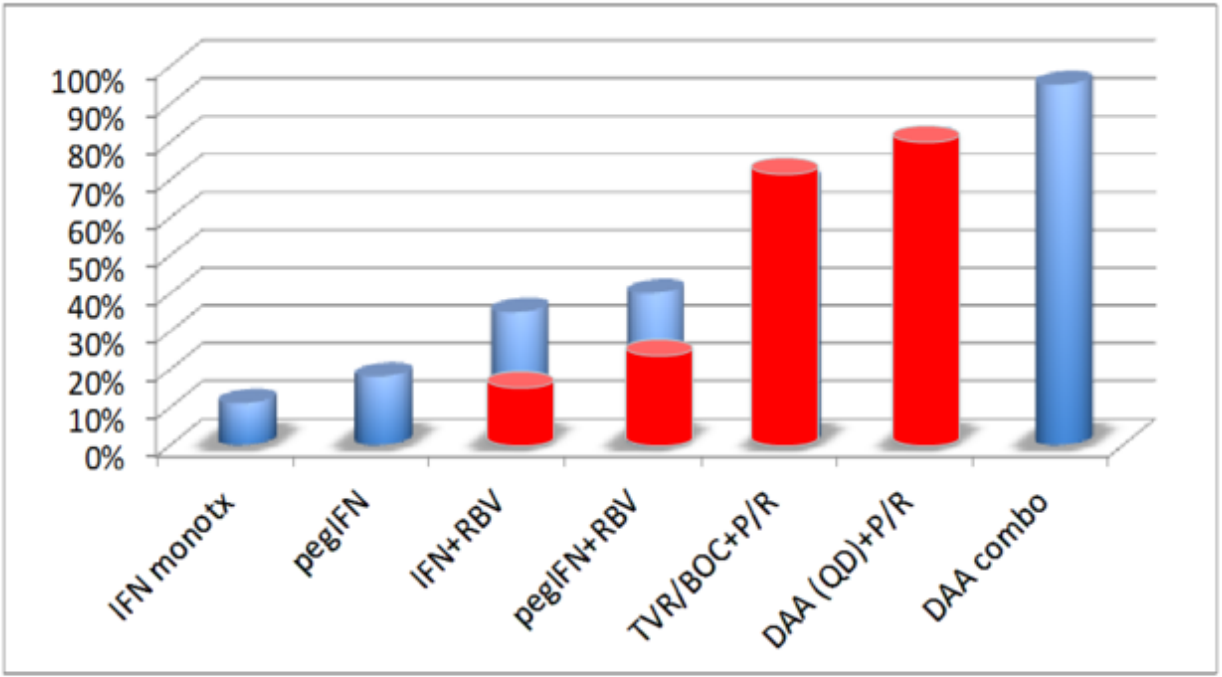
- Nucleoside (NI) vs Non-nucleoside (NNI)
  - Moderate-High potency
  - Higher genetic barrier to resistance
  - Multi- or pangenotypic
- Use in combination therapy
  - 2-3 drugs
- Use in IFN-sparing/free

NS5A Inhibitors

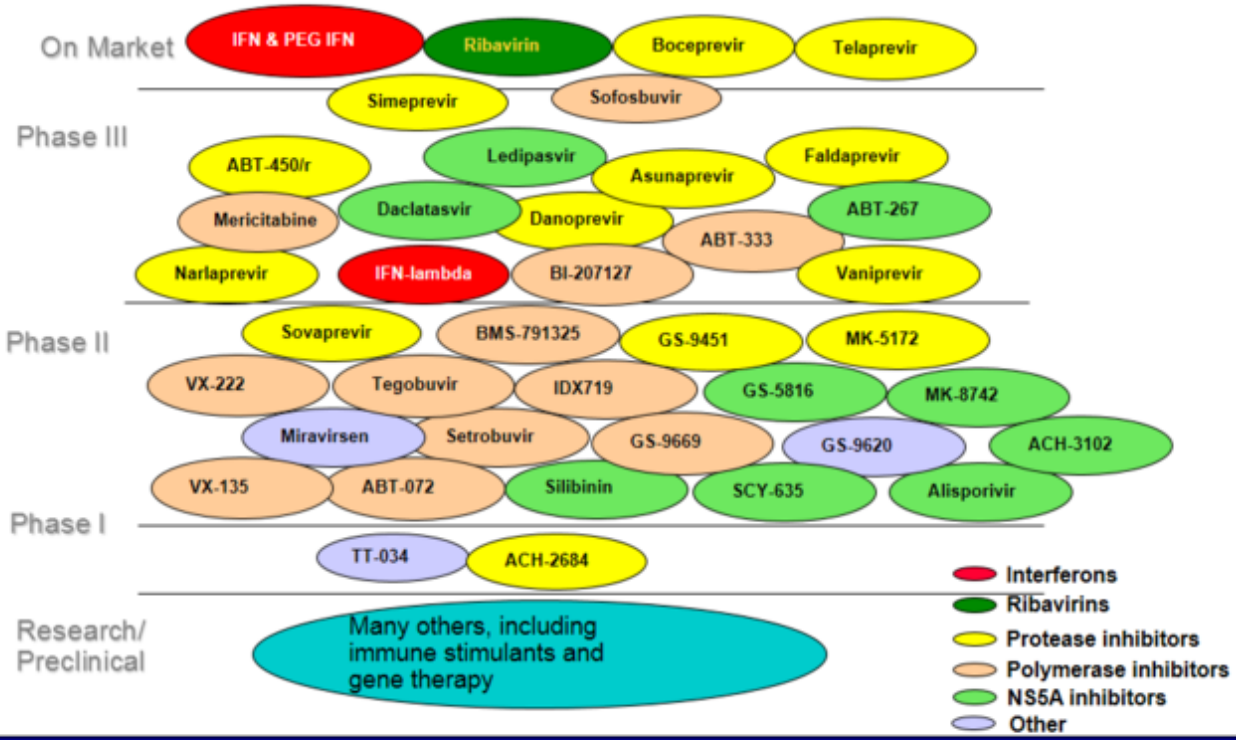
- Activity in replication unknown
  - Multiple possible mech of action
- Multi- to pangenotypic
- Moderate
  - Potency
  - Barrier to resistance
- Use in IFN-sparing/free



Treatment Response in DAA Era



Hepatitis C Drug Development–2013

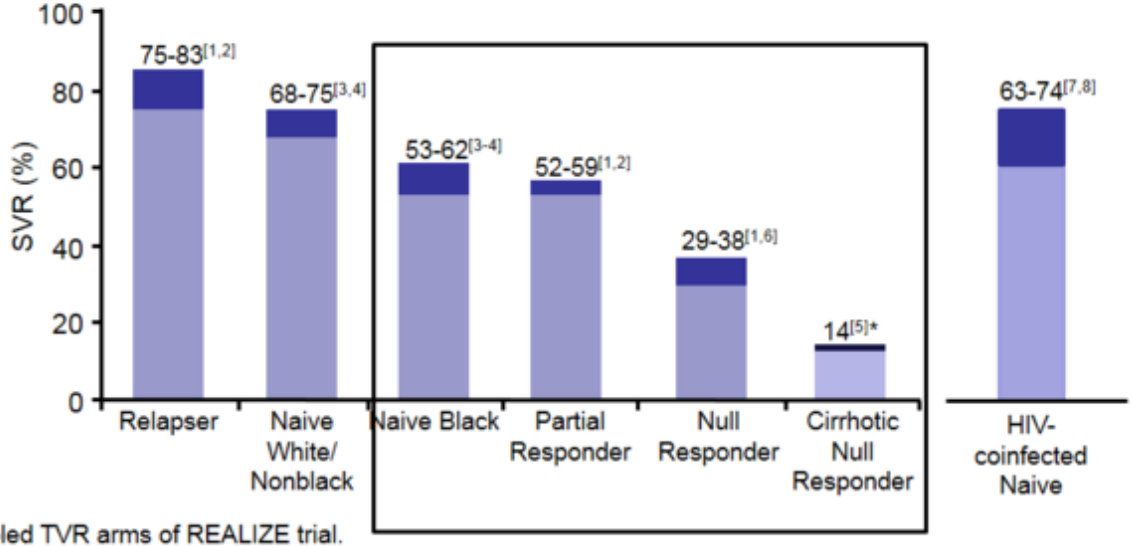


Note: Not a complete list of products in development.
Information from public sources.
Graphic courtesy of Dr. John McHutchison.

The current triple therapies provide the best cure rates for which population of patients?

1. Treatment naïve
2. Prior relapse
3. Prior null responder
4. Cirrhotic
5. HCV mono-infected

Telaprevir and Boceprevir in HCV Mono-Infected Subgroups: Phase III Summary



*Pooled TVR arms of REALIZE trial.

1. Zeuzem S, et al. N Engl J Med. 2011;364:2417-2428. 2. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217. 3. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. 4. Poordad F, et al. N Engl J Med. 2011;364:1195-1206. 5. Zeuzem S, et al. EASL 2011 Abstract FI-6. 6. Vierling JM, et al. AASLD 2011. Abstract 931. 7. Sulkowski MS, et al. Lancet Inf Dis 2013 [Epub]. 8. Sulkowski MS, et al. Ann Int Med 2013 [Epub].

PK Interactions: Telaprevir & ART

ART	Effects on ART		Effects on TVR		Recommendations
	AUC	C_{min}	AUC	C_{min}	
Efavirenz	No significant Δ		↓ 26%	↓ 47%	↑ telaprevir dose
Etravirine*	No significant Δ		↓ 16%	↓ 25%	Use standard doses
Rilpivirine*	↑78%	↑93%	↓ 11%	↓ 5%	Use standard doses
Atazanavir/r	-	↑ 85%	↓ 20%	↓15%	Use standard doses
Darunavir/r	↓ 40%	↓ 42%	↓ 35%	↓ 32%	Do Not Co-Administer
FPV/r	↓ 47%	↓ 56%	↓ 32%	↓ 30%	Do Not Co-Administer
Lopinavir/r	↓ 34%	↓ 43%	↓ 54%	↓ 52%	Do Not Co-Administer
Maraviroc	↑ 950%	-	No significant Δ		Decrease dose of MVC to 150mg BID
Raltegravir	↑ 31%	-	No significant Δ		Use standard doses
Dolutegravir	↑ 25%	↑ 19%	No significant Δ		Use standard doses

Van Heeswijk et al. CROI 2011 Ab#119, ICAAC 2011 Ab# A1-1738a; Kakuda Clin Pharm 2012 Ab# O_18 Johnson Clin Pharm 2013 Ab#O_07, Vourvahis Clin Pharm 2013 Ab#O_17

PK Interactions: Boceprevir & ART

ART	Effects on ART		Effects on BOC		Recommendations
	AUC	C_{min}	AUC	C_{min}	
Efavirenz	↑ 20%	-	↓ 19%	↓ 44%	Do Not Co-Administer
Etravirine	↓ 23%	↓ 29%	↑ 10%	-	Use standard doses
Atazanavir/r	↓ 51%	↓ 34%	↓ 22%	↑ 87%	Use with Caution ??
Darunavir/r	↓ 44%	↓ 59%	↓ 29%	↓ 35%	Do Not Co-Administer
Lopinavir/r	↓ 34%	↓ 43%	↓ 44%	↓ 35%	Do Not Co-Administer
FPV/r, TPV/r	No PK Data, Interaction Possible				Do Not Co-Administer
Maraviroc	↑ 300%	-	No significant Δ		Decrease dose of MVC to 150mg BID
Raltegravir	↑ 57%	↓ 45%	No Δ	↑ 50%	Use standard doses
Dolutegravir	↑ 7%	↑ 8%	Not available		Use standard doses

Kasserra et al. 18th CROI 2011 Ab# 118; Hulskotte et al. 19th CROI 2012 Ab# 771LB; Hammond Clin Pharm 2012 Ab# O_15 Garraffo Clin Pharm 2013 Ab#O_15, , Vourvahis Clin Pharm 2013 Ab#O_17

Disclosure

- Dr Naggie has received research support from Abbott Laboratories, Anadys Pharmaceuticals, Inc, Bristol-Myers Squibb, Gilead Sciences, Inc, Medtronic, Synexis, and Vertex Pharmaceuticals, Inc. She has served as a scientific advisor to Abbott Laboratories, Boehringer Ingelheim Pharmaceuticals, Inc, Gilead Sciences, Inc, Janssen, and Vertex Pharmaceuticals, Inc. (Updated 06/12/13)

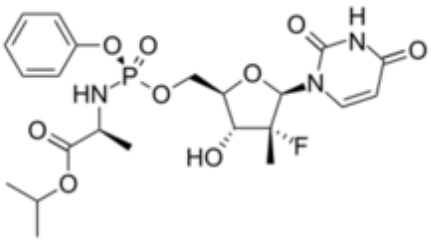
Question

Which genotype have we recently learned is "more difficult" to treat than expected with direct acting antivirals?

1. 1
2. 2
3. 3
4. 4

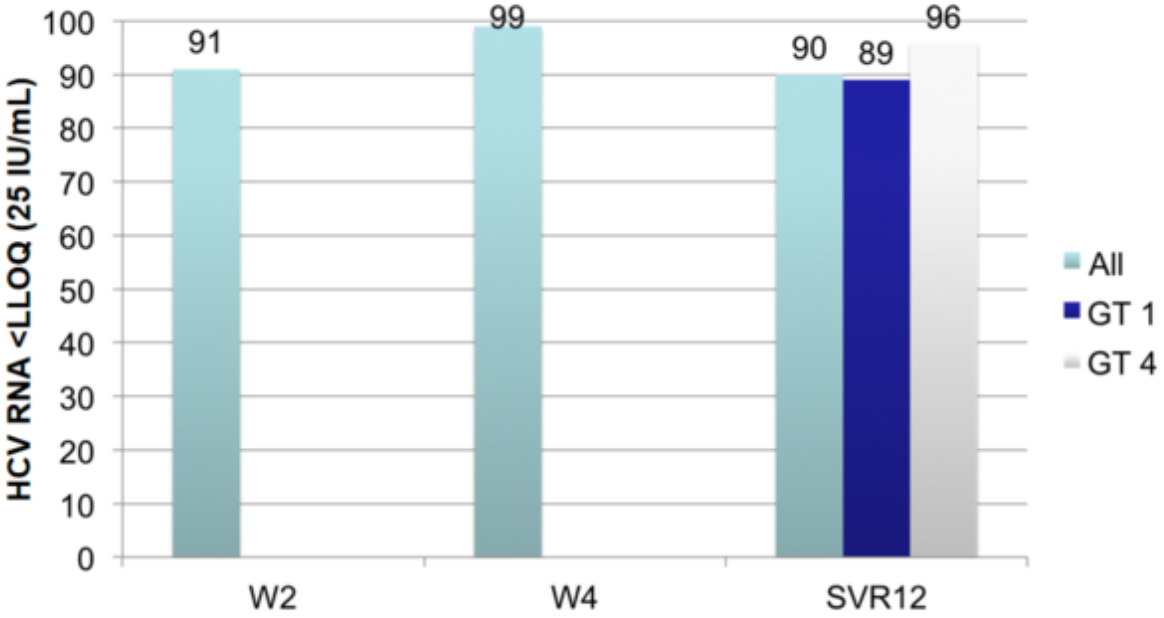
Sofosbuvir (GS-7977)

- Pan-genotypic NS5B nucleotide analogue
- Studied in over 2000 patients
  - No viral breakthrough
  - 1 patient with S282T
- No significant DDI
- No concerning safety signals
- NDA submission April 2013



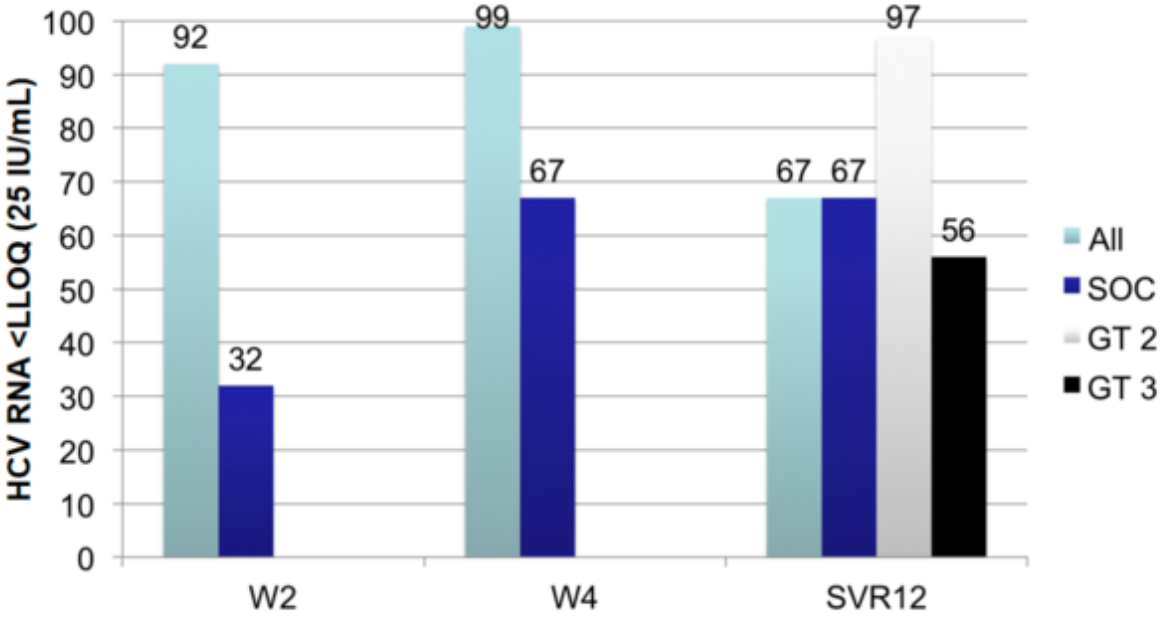
Rodrigues-Torres et al. 52nd ICAAC 2012; Abstract H1921a

NEUTRINO: SOF + P/R
Treatment Naïve Genotype 1,4,5,6



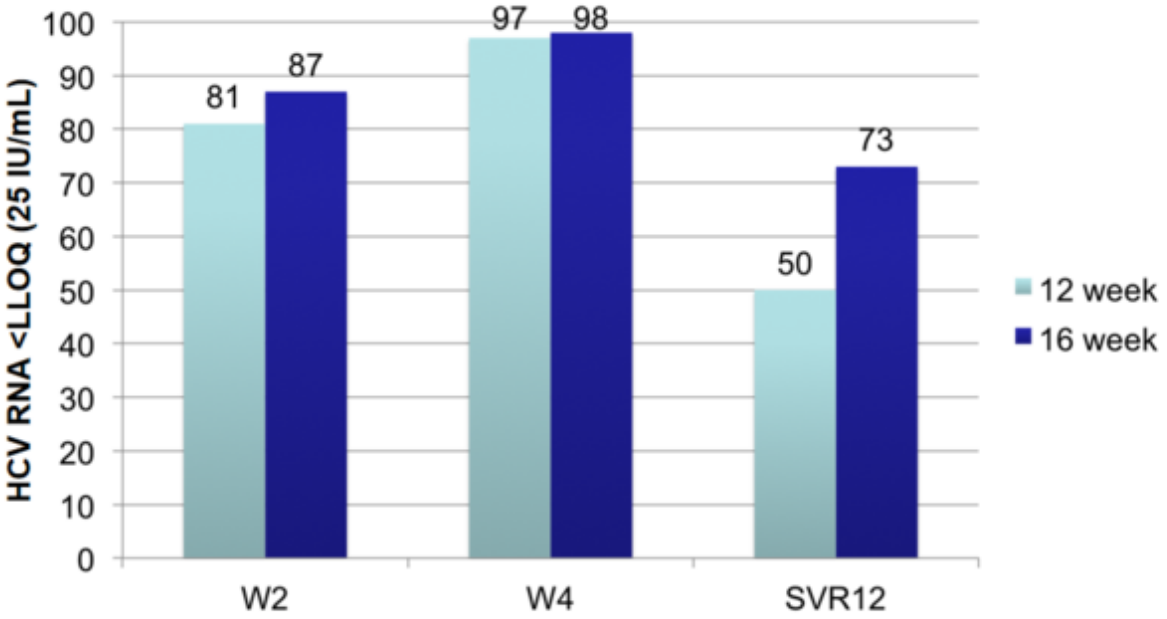
Lawitz et al. NEJM April 23, 2013

FISSION: SOF + WBR
Treatment Naïve Genotype 2,3



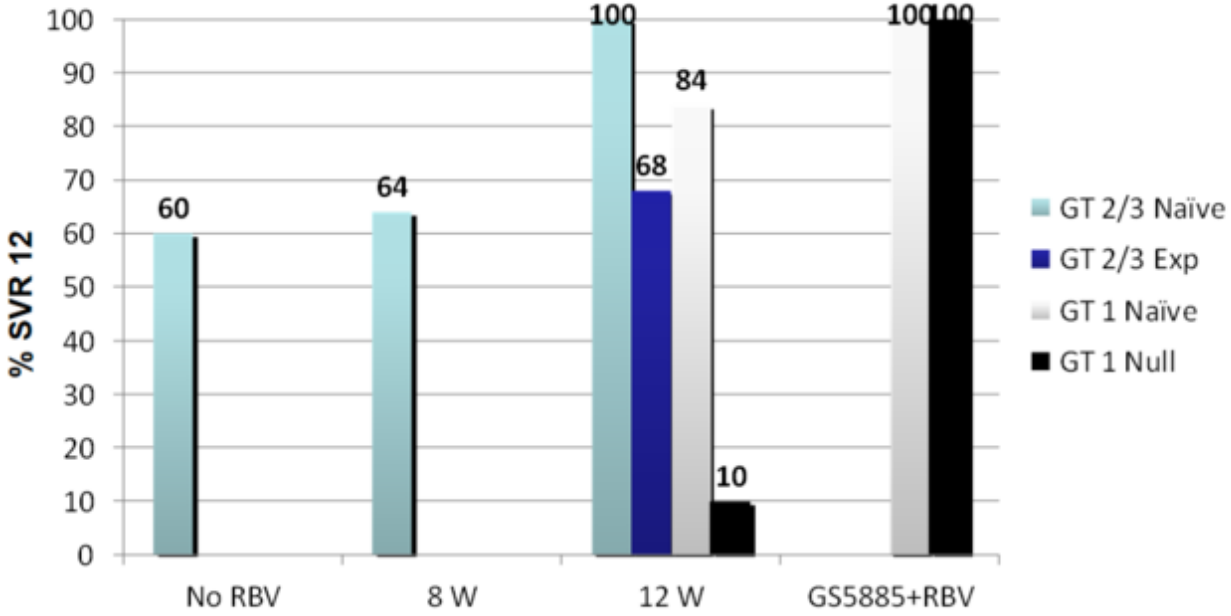
Lawitz et al. NEJM April 23, 2013

FUSION: SOF + WBR
Treatment Experienced Genotype 2,3



Jacobson et al. NEJM April 23, 2013

ELECTRON Study: IFN-free with Sofosbuvir +/- Ledipasvir +/- RBV



Gane et al. CROI 2013 Abstract #41

What about SOF in HIV/HCV?

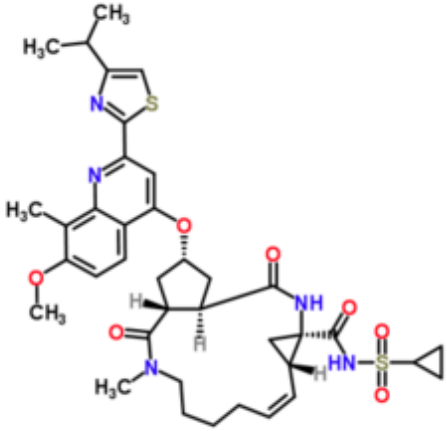
	ARV		SOF	
ARV	**AUC**	**Cmax**	**AUC**	**Cmax**
ATR	N/A	N/A	▼6%	▼19%
DRV/r	▼3%	▼3%	▲37%	▲45%
RAL	▼27%	▼43%	▼5%	▼2%
RPV	▲6%	▲5%	▲10%	▲21%
TDF	▼2%	25%	N/A	N/A
EFV	▼3%	▼5%	N/A	N/A

- Phase IIB
  - SOF + P/R X 12W
  - Naïve, GT 1-3
  - NCT01565889
- Phase III
  - SOF + WBR X 12-24W
  - Naïve GT 1-4, Experienced GT 2,3
  - 20% Cirrhotic

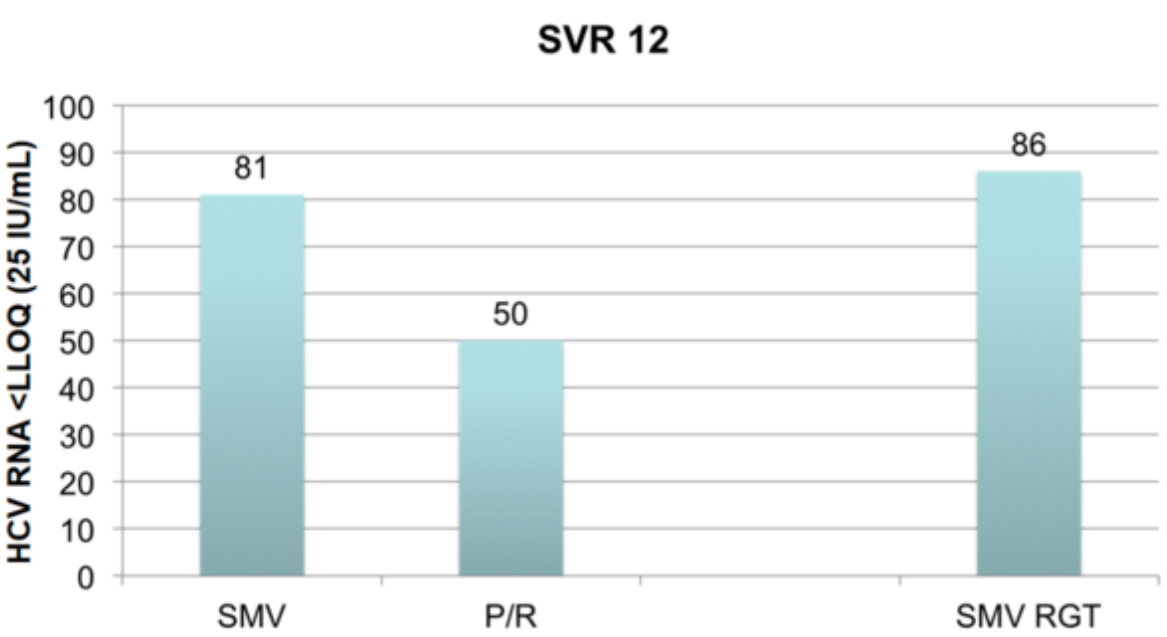
Kirby et al. AASLD 2012 Abstract #1877

Simeprevir (TMC-435)

- Multi-genotypic NS3/4A Protease Inhibitor
- Second Wave PI
- + DDI with ARVs
- No concerning safety signals
- NDA submission April 2013

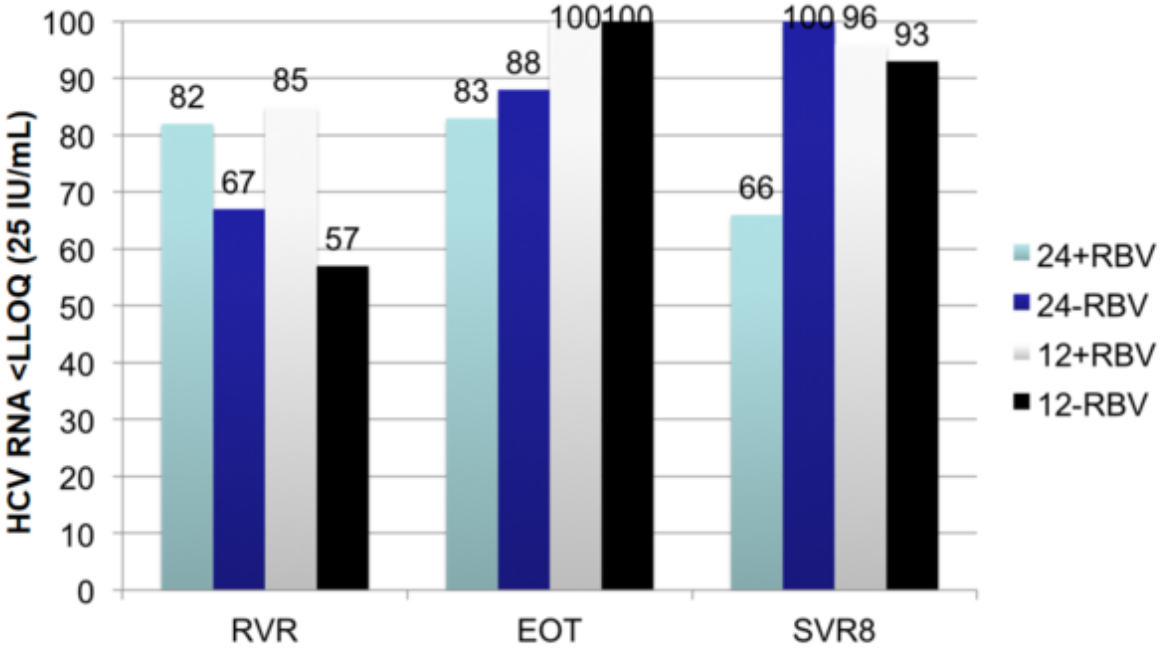


QUEST 1&2: SMV + P/R
Genotype 1 Treatment Naive



Manns et al. EASL 2013 Abstract 1413
Jacobson et al. EASL 2013 Abstract 1425

COSMOS: SOF + SMV ± RBV
GT 1 Null Responders 12 vs 24 weeks



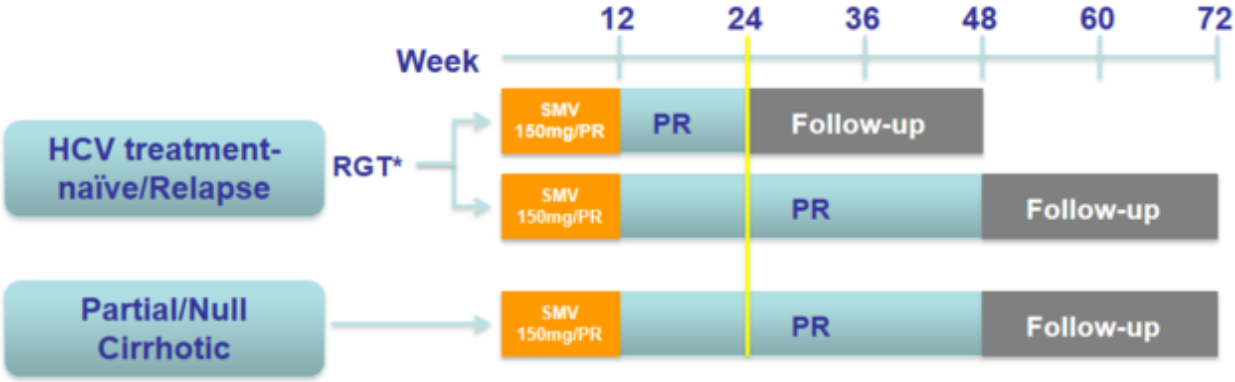
Lawitz et al. CROI 2013 Abstract 155

Goals

- Background
  - Epidemiology/Natural history
  - Virology
  - Mechanism of Action
- HCV treatment landscape
  - Investigational Agents
  - IFN-sparing
  - IFN-free

Simeprevir QD + P/R: Interim analysis

- NS3/4A protease inhibitor, multi-genotypic
- Phase III, open-label (TMC435-C212 Study)
- Treatment naïve and experienced
- RGT = <LLOQ week 4 and <LLOD week 12



Dieterich et al. CROI 2013 Abstract 154
NCT01479868

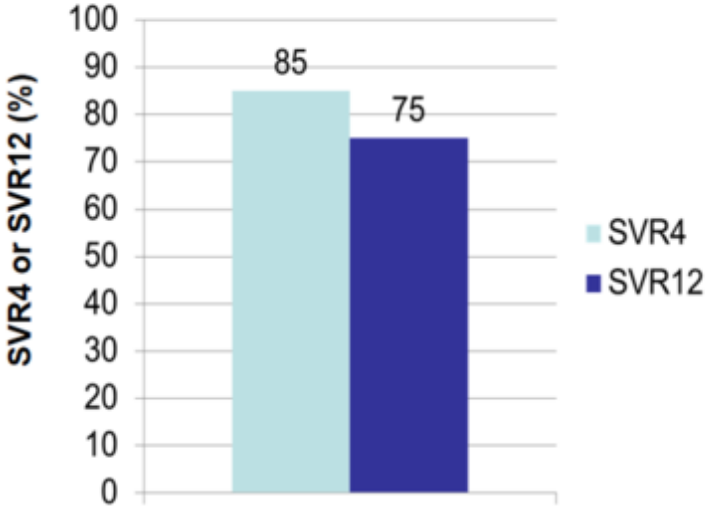
Simeprevir and ART?

	ARV		SOF		Recommendation
ARV	**AUC**	**Cmax**	**AUC**	**Cmax**	
EFV	▼10%	▼3%	▼71%	▼51%	Do not co-administer
DRV/r	▲18%	▲4%	▲259%	▲79%	Do not co-administer
RAL	▲8%	▲3%	▼11%	▼7%	Use standard doses
RPV	▲12%	▲4%	▲6%	▲10%	Use standard doses
TDF	▲18%	▲19%	▼14%	▼15%	Use standard doses

Phase III Study: Rilpivirine (15%), Raltegravir (87%), Maraviroc, Enfuvirtide, NRTIs

SVR12 Simeprevir QD + P/R

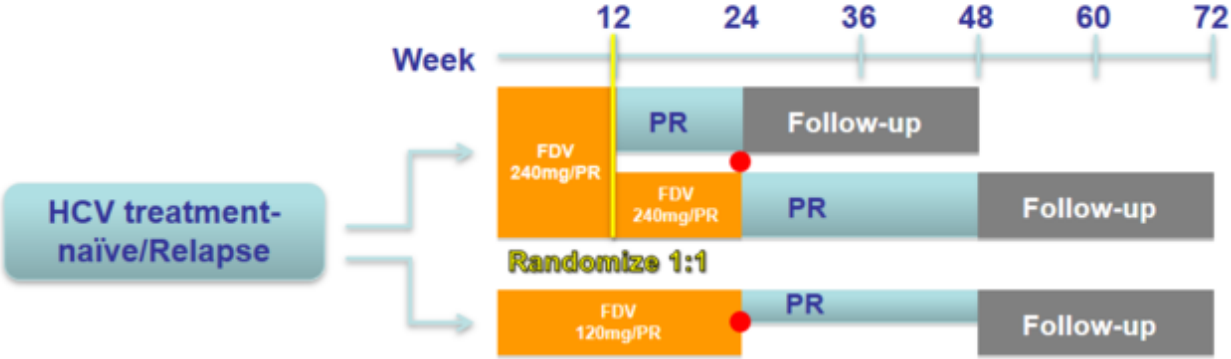
52/59 (88.1%) met RGT criteria and ended treatment at Week 24 (non-cirrhotic)



Dieterich et al. CROI 2013 Abstract 154

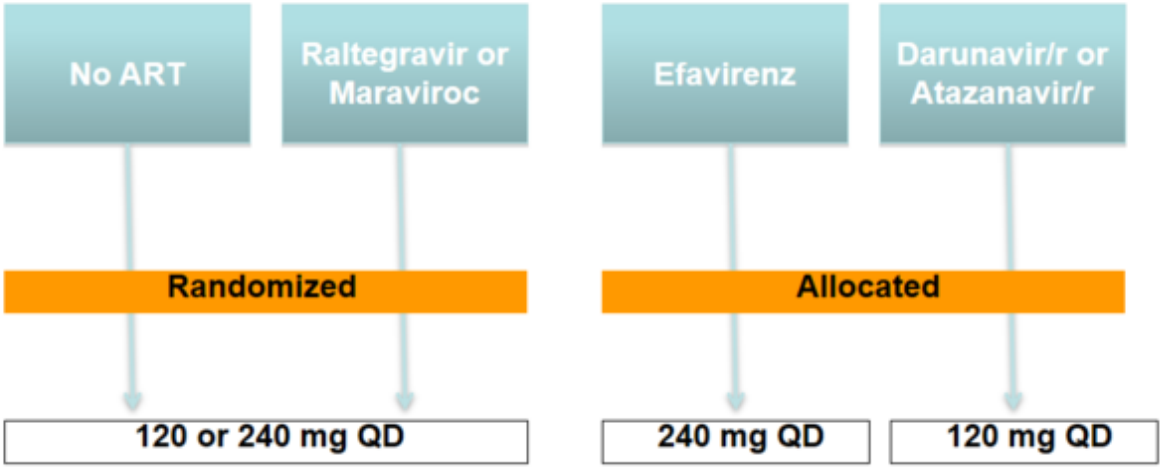
STARTVerso 4: Interim analysis of Faldaprevir + P/R

- NS3/4A protease inhibitor, once daily dosing
- Phase III, open-label
- Treatment naïve and prior relapse
- RGT = <LLOQ week 4 and <LLOD week 8 = ETS



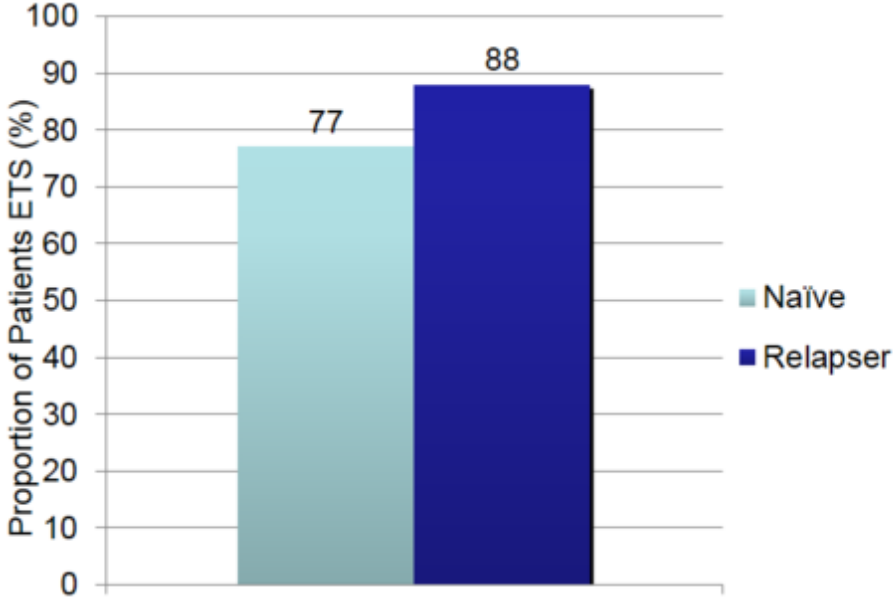
Dieterich et al. CROI 2013 Abstract# 40
DDI abstract #35

STARTVerso 4: Interim analysis of faldaprevir + P/R



Dieterich et al. CROI 2013 Abstract# 40
DDI abstract #35

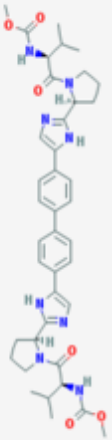
Early Treatment Response



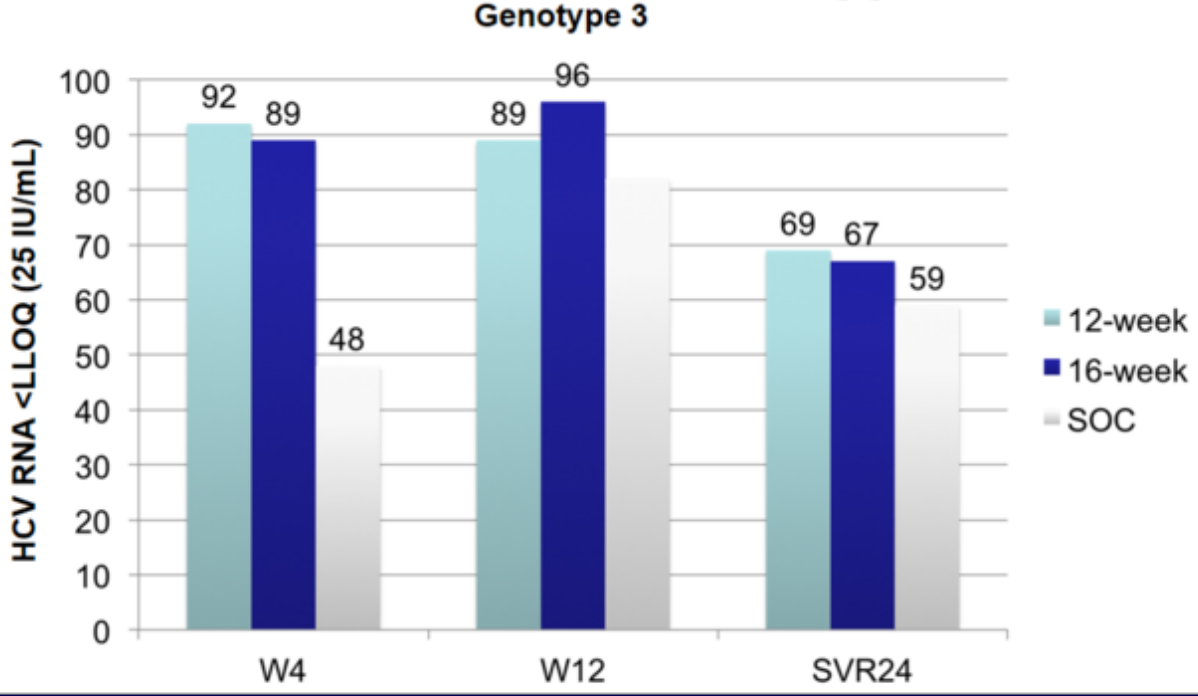
Dieterich et al. CROI 2013 Abstract# 40
Sabo et al. CROI 2013 Abstract #35

Daclatasvir (BMS-790052)

- Pangenotypic NS5A
- Studied in over 4000 patients
- No concerning safety signals
- + DDI with ARVs
- Use in “nucleotide” sparing regimens

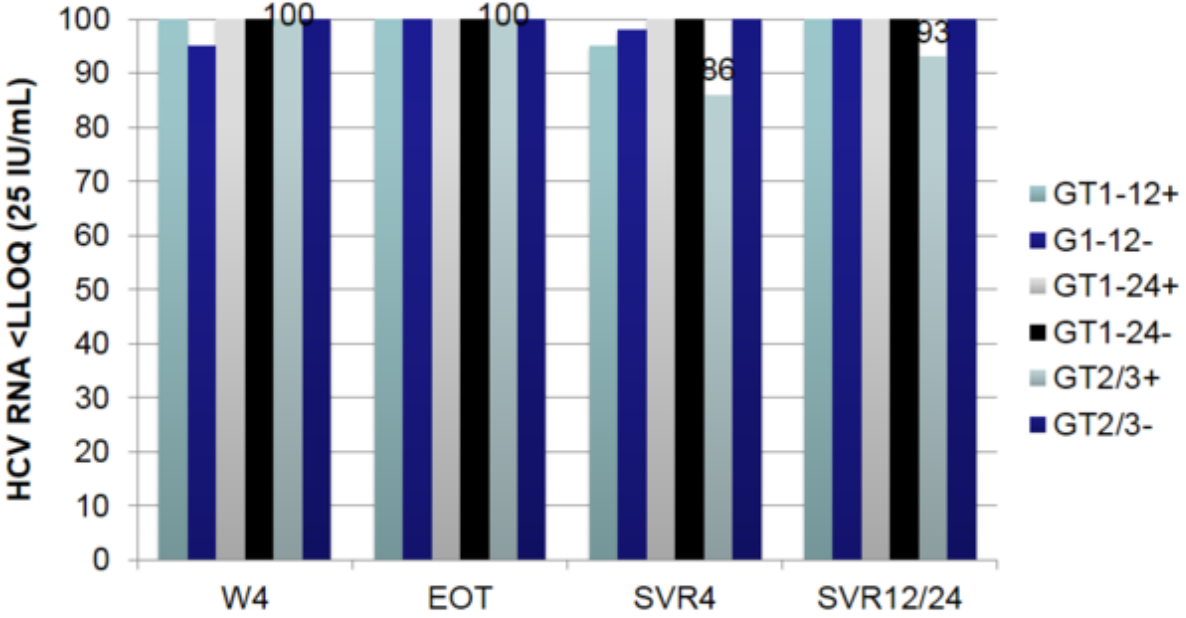


COMMAND: DCV + P/R for 12, 16, 24 Weeks Treatment Naïve Genotype 2,3



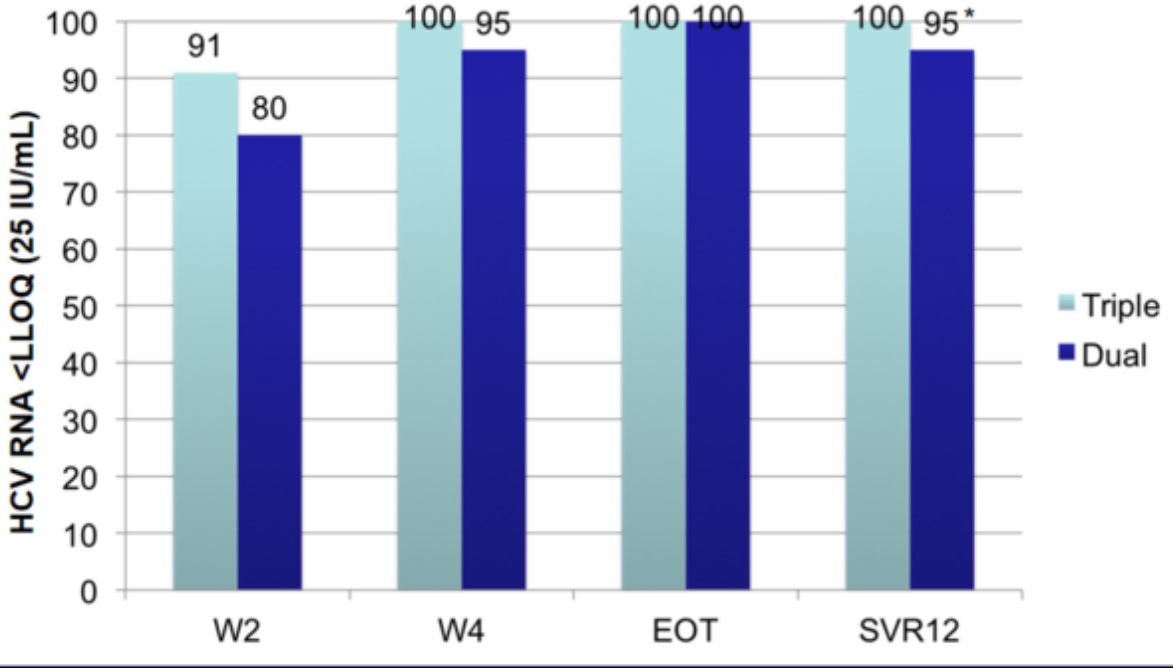
Dore et al. EASL April 2013, Abstract 1418

SOF + DCV ± RBV for 12 or 24 weeks
GT 1, 2, 3 Tx Naive



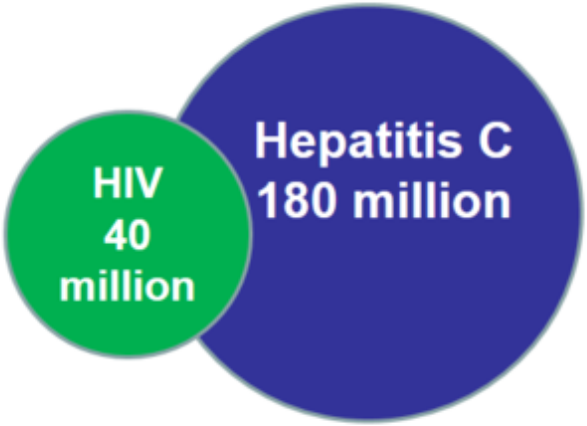
Sulkowski et al. AASLD 2012 Abstract LB-2

SOF + DCV ± RBV for 24 weeks
GT 1 Triple therapy failures



Sulkowski et al. EASL 2013 Abstract 1417

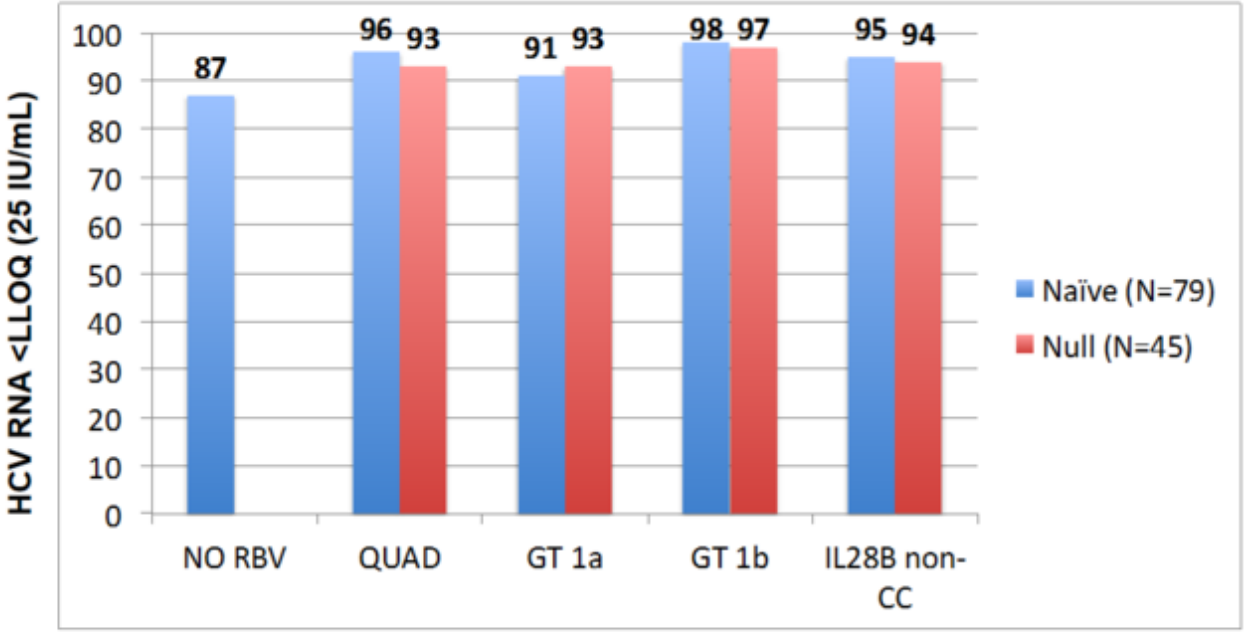
HIV & HCV



- 10 million people worldwide
- 30% of US patients with HIV have HCV

Staples CT. *Clin Infect Dis* 1999

AVIATOR: IFN sparing with ABT 450/r + 267 + 333 ± RBV X 12W

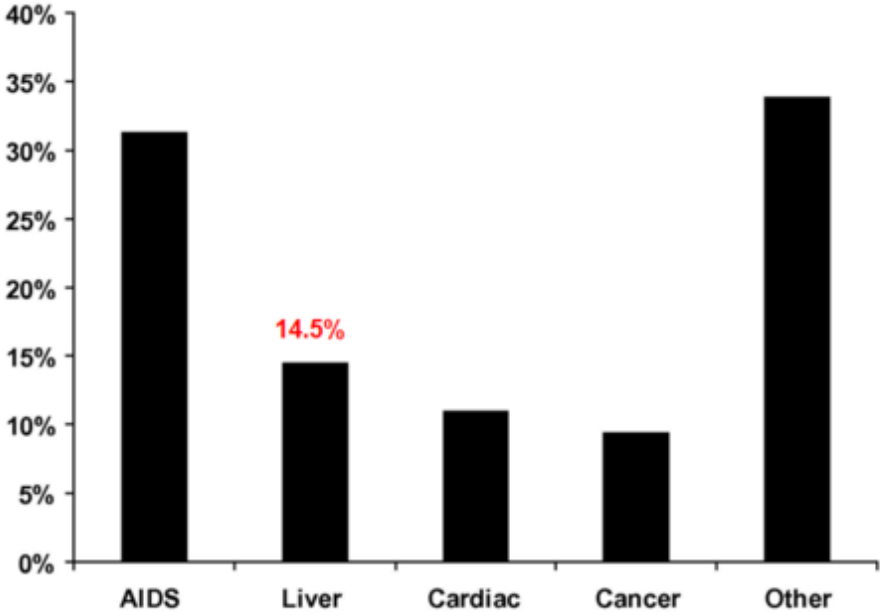


Kowdley et al. EASL 2013 Abstract #3

In a nutshell…

- Many phase III trials in co-infection
- IFN-free is coming for GT 2
  - Naïve and experienced
  - Cirrhotics?? 24 weeks vs add IFN
- IFN-sparing is coming for GT1, GT3
- IFN-free for others…
  - Will require at minimum 2 DAA
  - May still require >12 weeks
  - Addition of IFN may shorten therapy??

D:A:D Study: Liver-Related Deaths in Persons with HIV

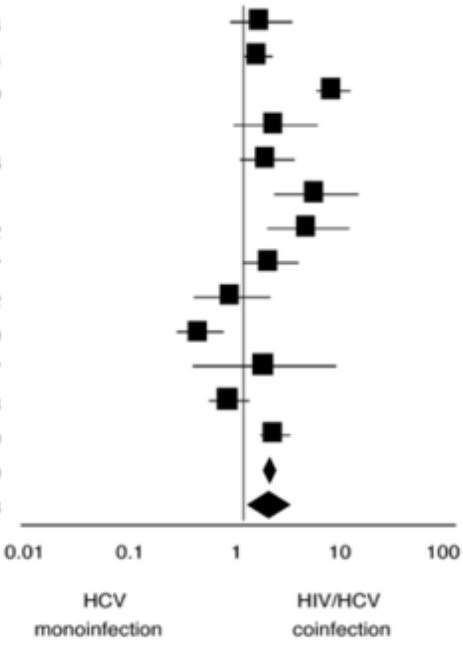


DAD Study Group, Arch Intern Med 2006

HAART Era: Cirrhosis Risk

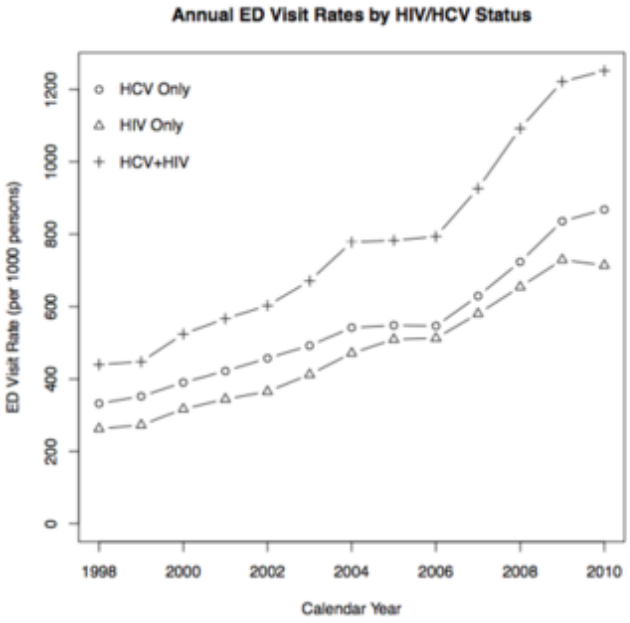
(b)

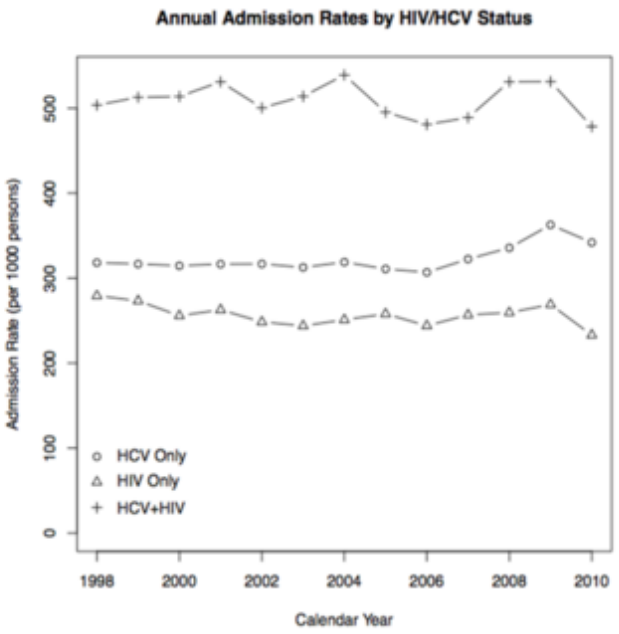
Benhamou, 1999	1.484	0.733	3.004	1.096	0.273
Brau, 2006	1.404	1.010	1.951	2.019	0.044
Gaslightwala & Bini, 2006	7.289	4.938	10.760	9.998	0.000
Gonzalez, 2006	2.037	0.789	5.254	1.471	0.141
Macias, 2005	1.698	0.911	3.165	1.666	0.096
Marine'-Barjoan, 2004	5.000	1.940	12.887	3.332	0.001
Martinez-Sierra, 2003	4.195	1.665	10.567	3.042	0.002
Mohsen, 2003	1.814	0.958	3.434	1.830	0.067
Monto, 2005	0.778	0.327	1.854	-0.566	0.572
Rodriguez-Torres, 2006	0.384	0.225	0.656	-3.501	0.000
Sarmento-Castro, 2007	1.595	0.322	7.904	0.572	0.567
Valle Tovo, 2007	0.727	0.457	1.156	-1.346	0.178
Verma, 2006	2.015	1.421	2.858	3.928	0.000
Fixed effects	1.754	1.509	2.038	7.329	0.000
Random effects	1.723	1.059	2.804	2.191	0.028



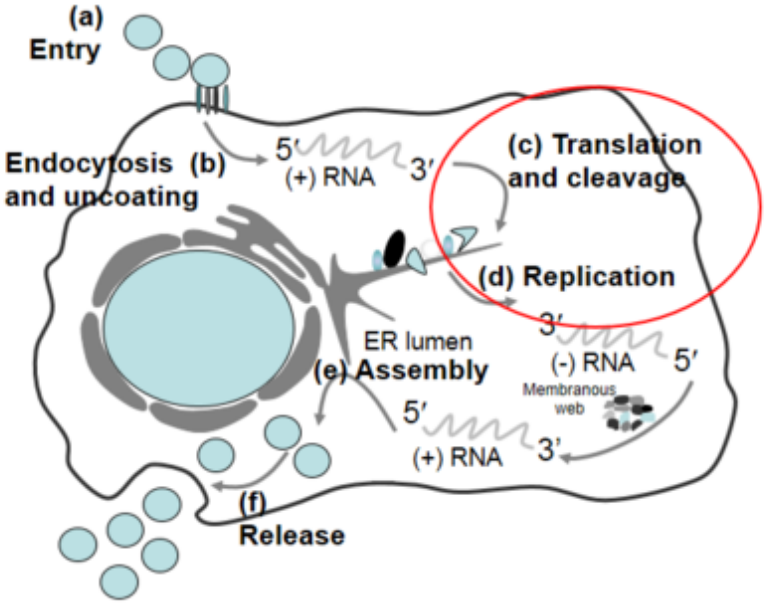
Thein et al. AIDS 2008; 22:1979

Higher Health Care Utilization for HIV/HCV





Hepatitis C Virus: Life Cycle



Hepatitis C Virus