Evidence based medicine
From discovery to market

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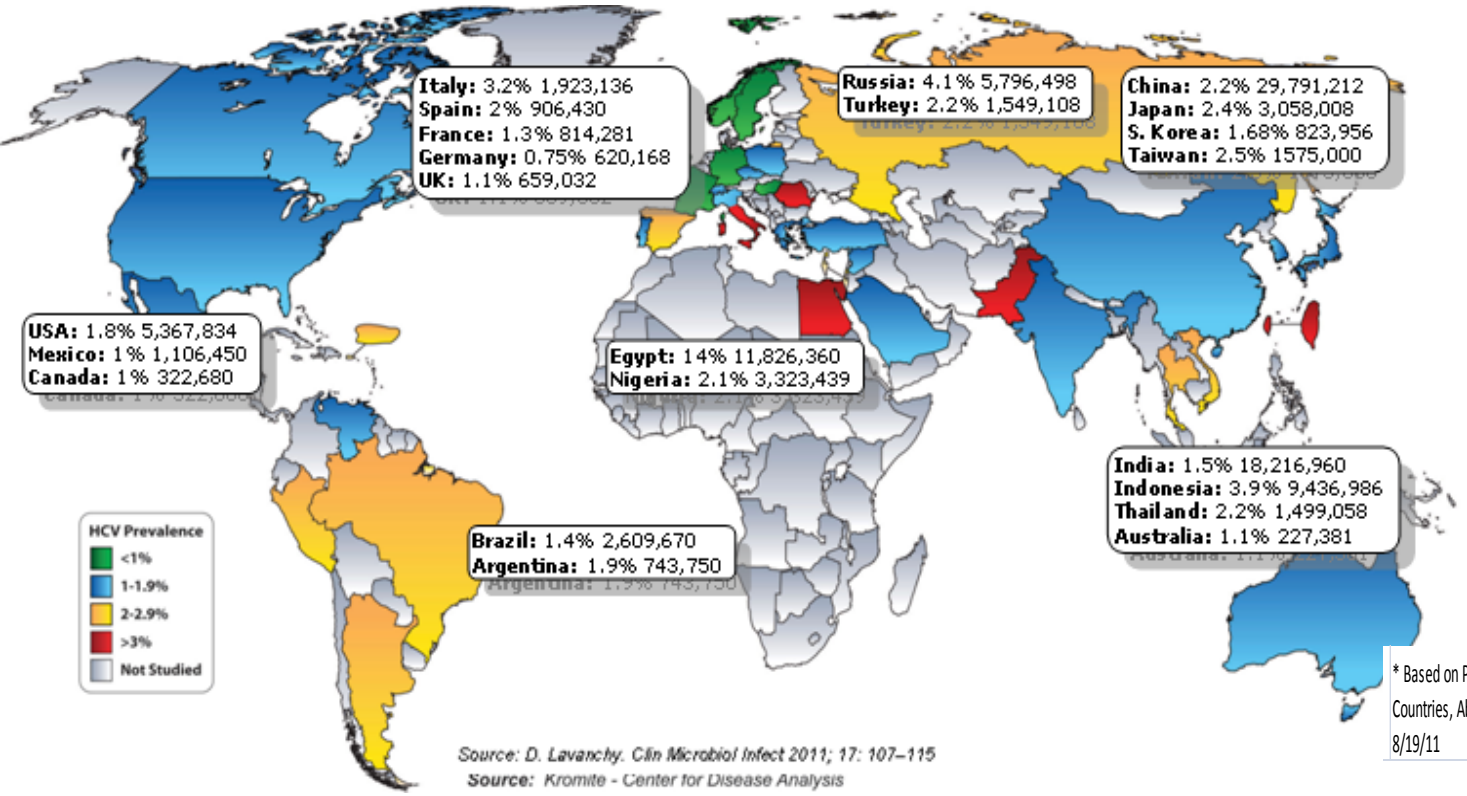
Shah Alam, 10th June 2014

Agenda

- Chronic hepatitis C burden of disease
- Evolution of available treatments
- Limitations of current treatments
- What’s new?

HCV Global Prevalence:

Pandemic with 170 million HCV-infected, 75% undiagnosed and marked genotypic distribution differences across countries and regions



Genotypes* (%)				
	1a	b	2	3
US	56	17	15	7
Japan	3	64	29	1
Germany	21	41	7	28
France	30	27	9	21
China	2	66	14	4
Russia	<1	55	8	35
Italy	8	53	26	7
Spain	24	41	3	20
Brazil	38	40	3	18
UK	30	15	10	40
Taiwan	3	45	33	1
Turkey	10	87	1	1
Mexico	38	32	22	7
S Korea	3	47	45	0
Hungary	26	58	1	3

Prevalence > 25%

* Based on Prevalence and Distribution of HCV Genotypes in Developed and Developing Countries, Abbott Clinical Epidemiology & Analytics, J. Griffith, Pharm.D., Revised 8/19/11

Key Implications

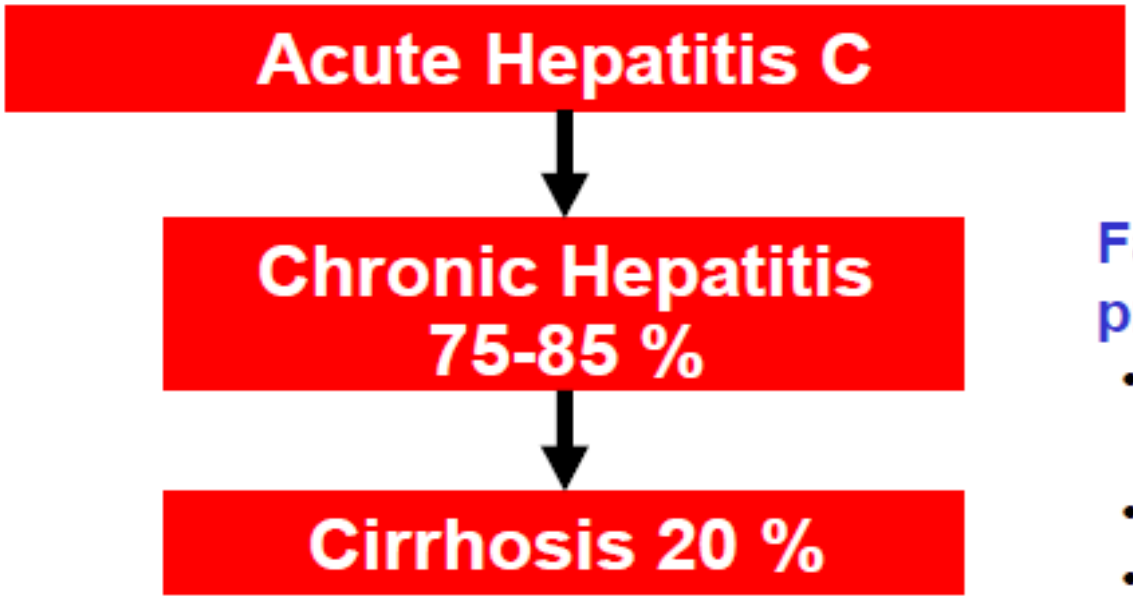
- Response to therapy (Interferon-based) is low and varies by HCV genotype and subgenotype.
- New treatment regimens need to be developed to maximize efficacy, reduce toxicities associated with interferon and minimize duration of therapy.

HCV prevalence

	Malaysia	Singapore	Thailand	Vietnam
Country population	29.6MM	5.3MM	67.0MM	87.8MM
HCV Prevalence	2.1% 622M	Estimated at 0.5% (*KOL) 26M	2.15% 1.46MM	2.9% 2.58MM
Potential Infected Population Genotypes & Sub-genotypes (%)	**1 = 248M (39%)** 2 = 24M (4%) **3 = 342M (56%)** 4 = 6M (1%)	**1 = 20M (75%)** 2 & 3 = 6M (25%)	1a = 97M (6.7%) [11] **1b = 390M (26.7%)** 2a = 32M (2.2%) 2c = 32M (2.2%) **3a = 746M (51.1%)** 3b = 32M (2.2%) 6 = 130M (8.9%)	**1a = 802M (31.15%)** **1b = 466M (17.8%)** 3a = 51M (2.2%) 3b = 77M (3.0%) **6a,e,l = 1.19MM (37.0%)**

**Based on 2013 population

Natural History



20-50 years

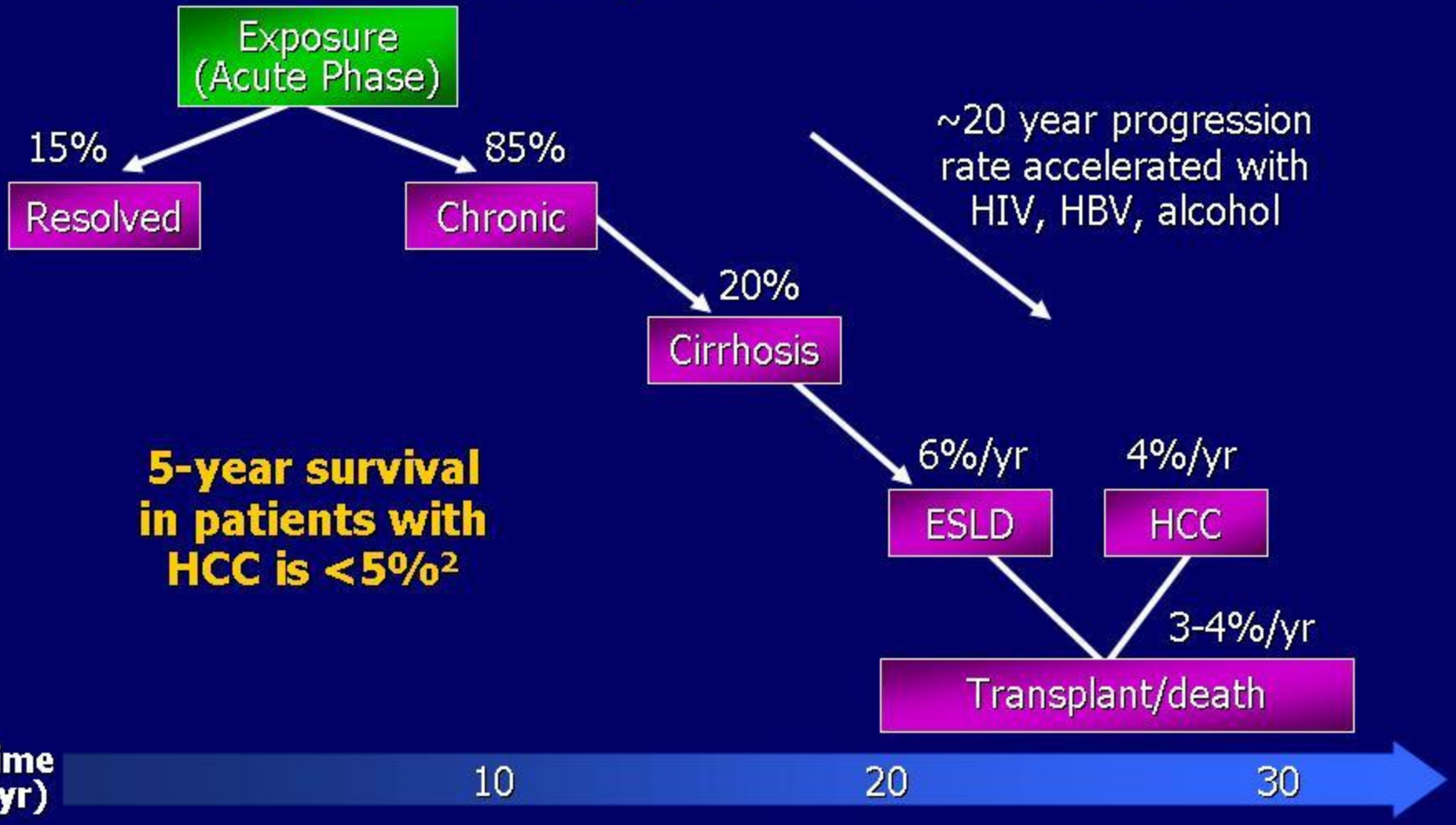
Faster progression

- older age at infection
- alcohol
- HIV infection
- post-transplant

DukeMedicine

Di Bisceglie, Hepatology 2000

Natural History of HCV Infection



HCC = hepatocellular carcinoma

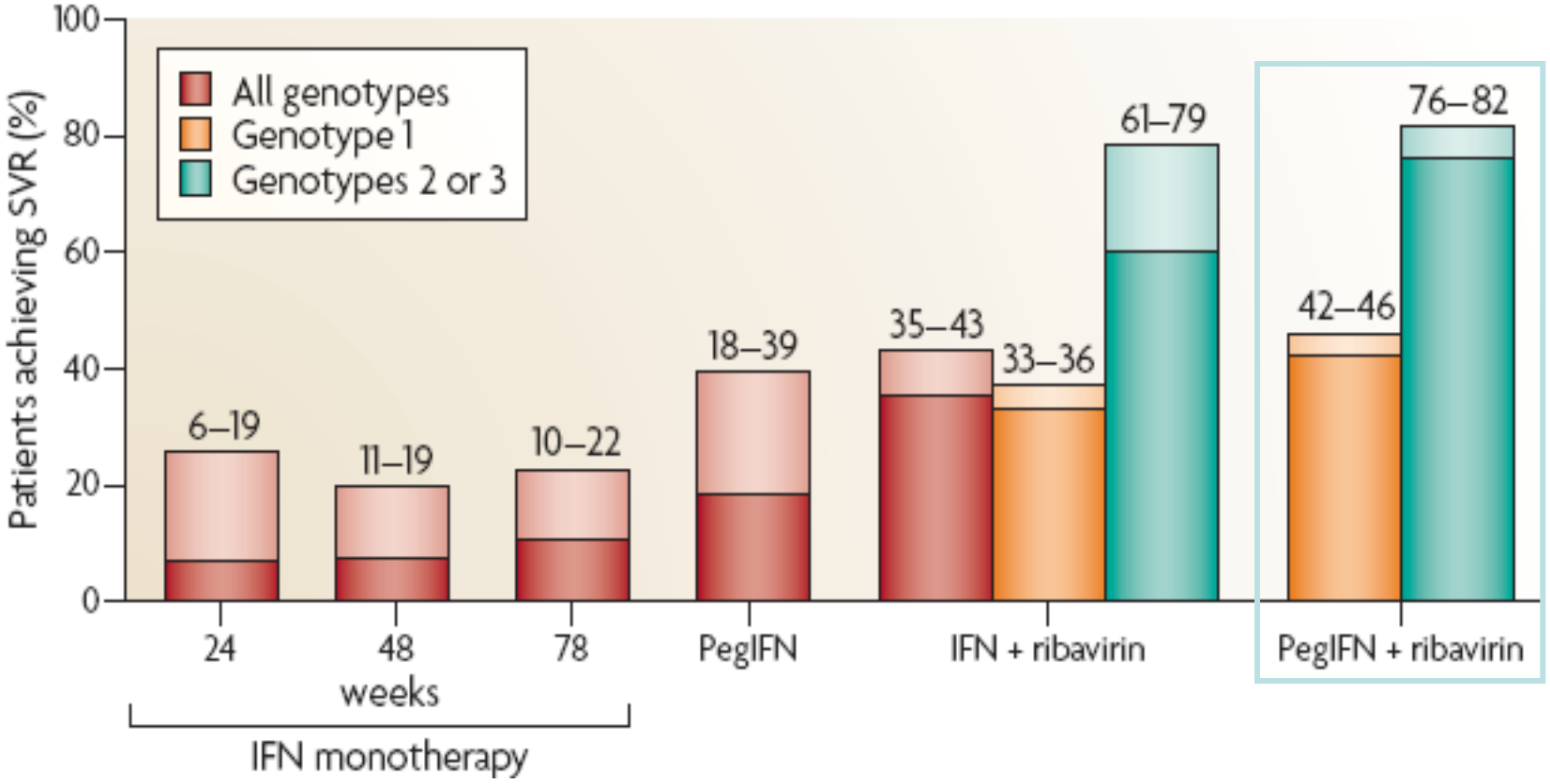
ESLD = end-stage liver disease

DiBisceglie et al. *Hepatology*. 2000;31(4):1014-1018.

Risk Factors for HCV

- Injection drug use (60%)
- Blood transfusion before 1992
- Multiple sex partners
- Iatrogenic (hemodialysis, re-use of vials, etc)
- Intranasal cocaine
- Piercing, tattooing, scarification
- Unknown (10%)

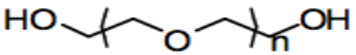
Evolution of Antiviral Therapy for Chronic HCV



Manns MP, et al. *Nat Rev Drug Discovery* 2007; 6:991-1000.
Ghany MG, et al. AASLD Practice Guideline. *Hepatology.* 2009; 49:1335-1374.

What is Pegylation?

- Covalent attachment of polyethelene glycol to peptide



- Increases hydrodynamic size
- Prolonged circulation, delayed renal clearance
- PegIntron (12kd, Schering), Pegasys (40kd, Roche)
- Enzon pharmaceutical
  - Adenosine deaminase
  - Others: Neulasta (GCSF), doxorubicin

Side Effects of PegIFN/Ribavirin

"Interferon Man"

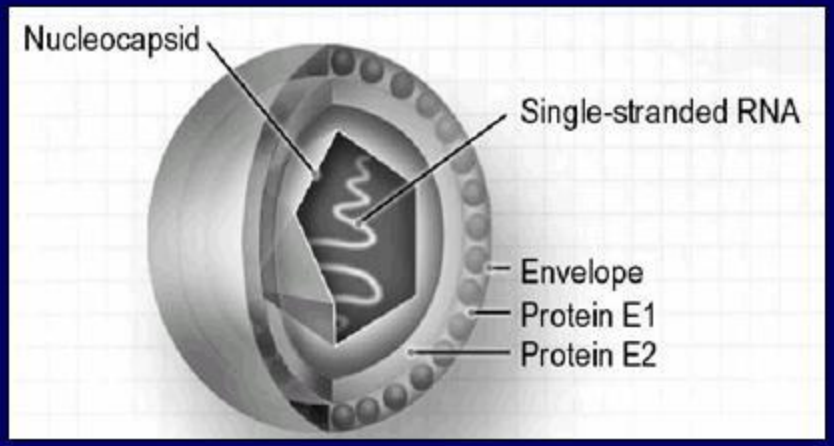
- Depression ranging from mild to suicidality
- Irritability, aggressive behavior
- Worsening of mania
- Fatigue
- Insomnia
- Myalgias, fever, flu-like symptoms
- Hair loss
- Cytopenias

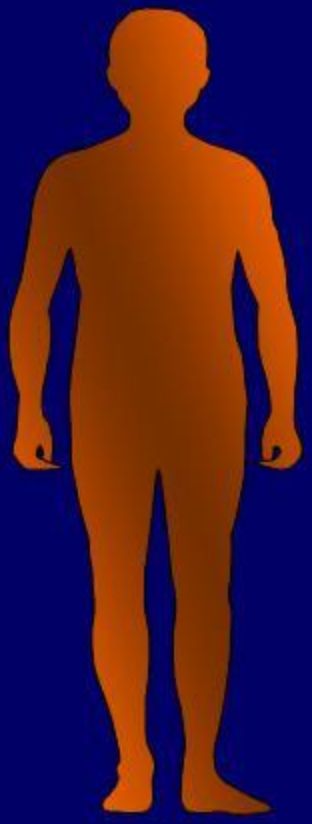
Slide courtesy Chia Wang

Predictors of Virologic Response

Viral Factors

- Genotype
- Viral Load



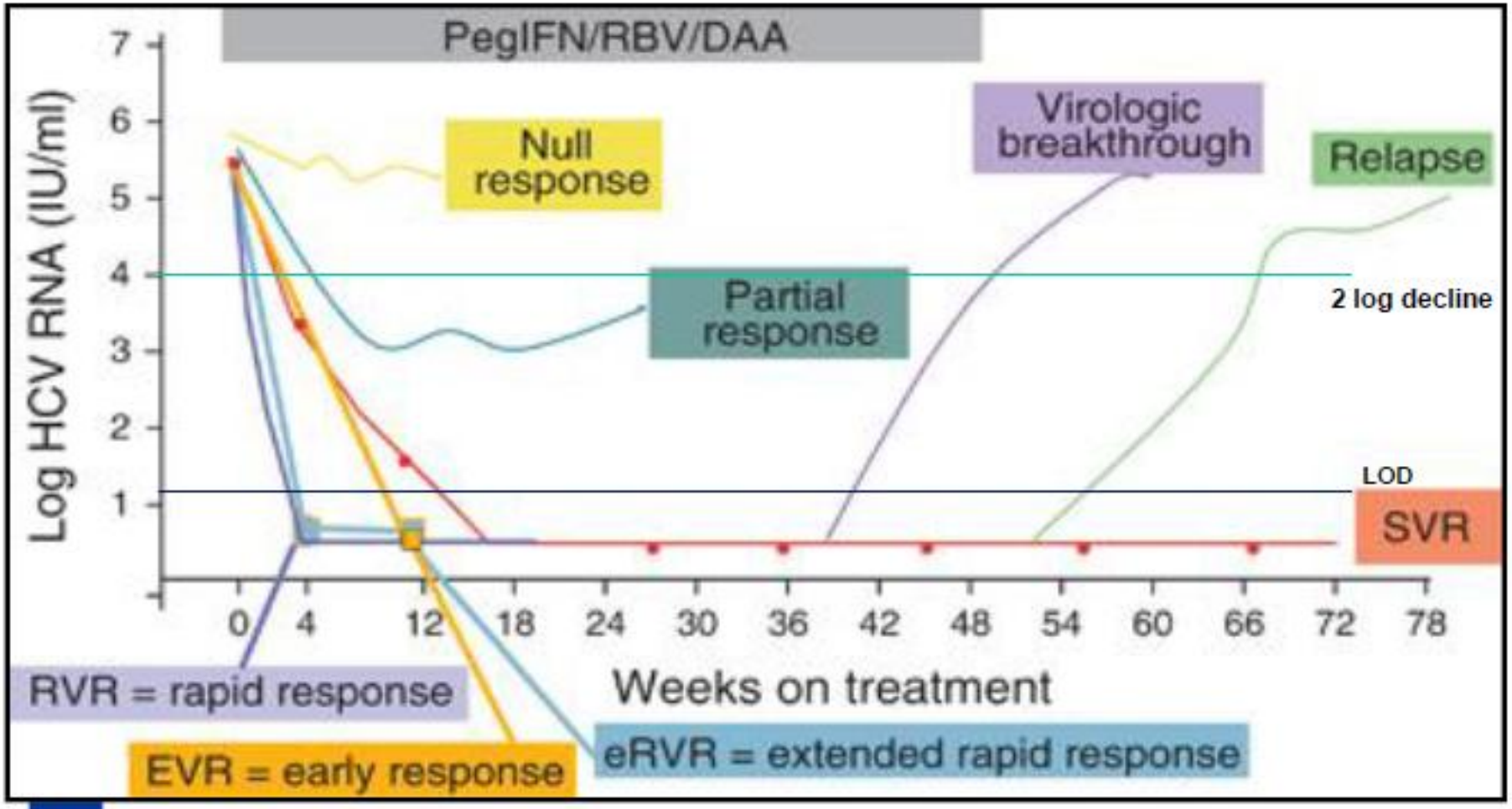


Host Factors

- Age
- Cirrhosis
- Race
- Gender
- Weight
- Hepatic Fe Overload
- Coinfection (HIV, HBV)
- Steatosis
- Hyperinsulinemia

Ferenci. *Semin Liver Dis.* 2004;24(suppl 2):25-31.

On-Treatment Viral Kinetics



DukeMedicine

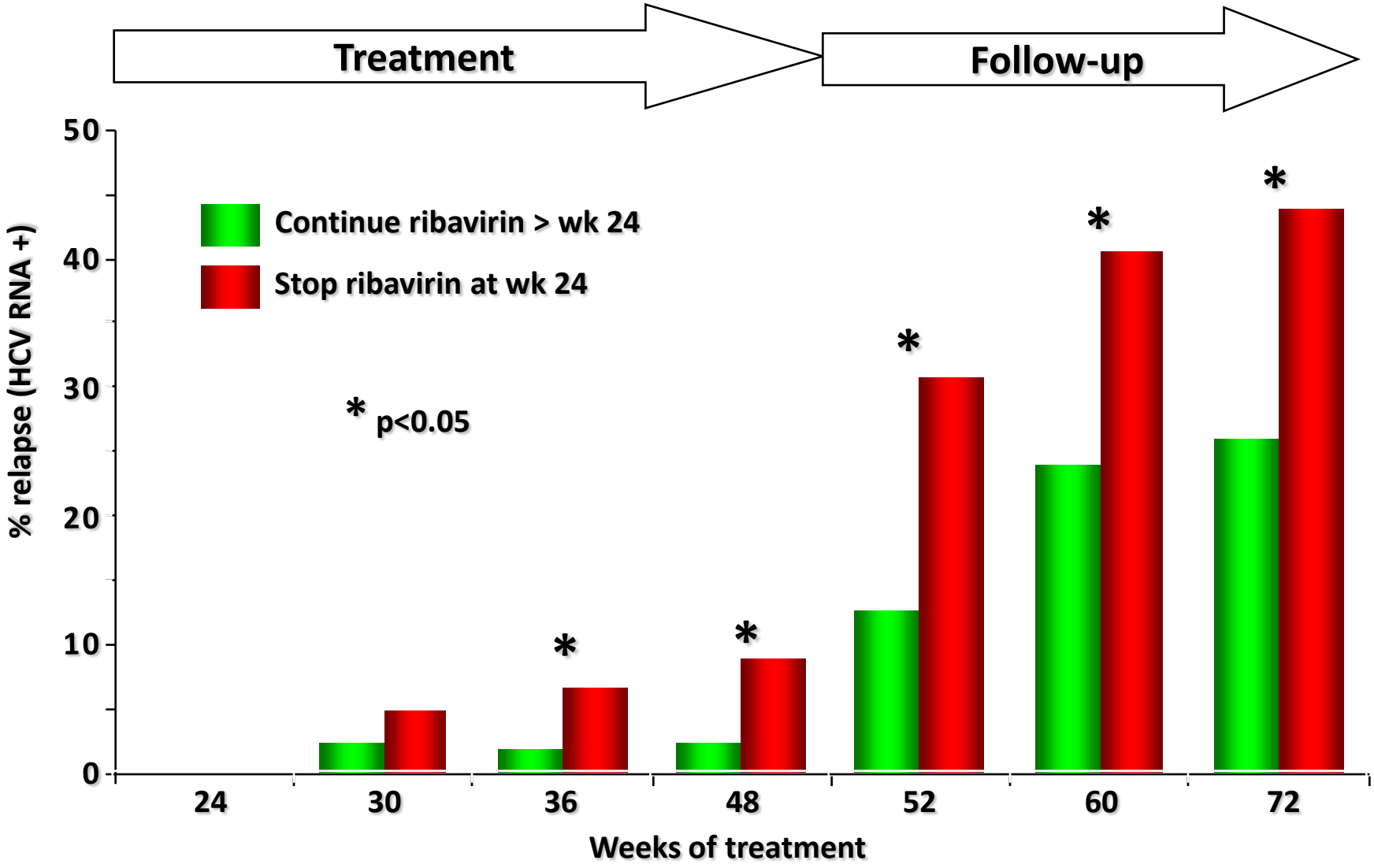
Adapted from Yee H et al. American Journal of Gastroenterology 2012 Used with permission.

Kinetics and SVR : GT 1 (Pegasys + RVN)

Time	HCV RNA status			
Wk 4	Neg	<2 log	<2 log	Any
Wk 12	Neg	Neg	>2 log	Any
Wk 24	Neg	Neg	Neg	Pos
SVR	**91%**	**60%**	**43%**	**2%**

Ferenci P. J Hepatol 2005; 43:425-33

Ribavirin Prevention of Relapse



(Bronowicki et al., Gastroenterology 2006;131:1040-8) slide courtesy of JM Pawlotsky

Remaining questions

- Why doesn’t IFN work in some patients?
- Is IFN necessary if you have two potent antivirals?
- How many antiviral targets are needed and how long is therapy needed?
- Target lipid metabolism?

What have we learnt so far?

Current interferon (IFN)-based therapies for HCV genotype (GT) 1 infection are associated with treatment-limiting toxicity and differing efficacy in patients with HCV GT 1a and GT 1b infection

ABT-450 is a potent NS3/4A protease inhibitor identified by AbbVie and Enanta

- Co-dosing of ABT-450 with ritonavir* (ABT-450/r) increases the peak, trough, and overall drug exposures of ABT-450, and also enables once daily dosing[1]

Ombitasvir (formerly ABT-267) is a potent NS5A inhibitor

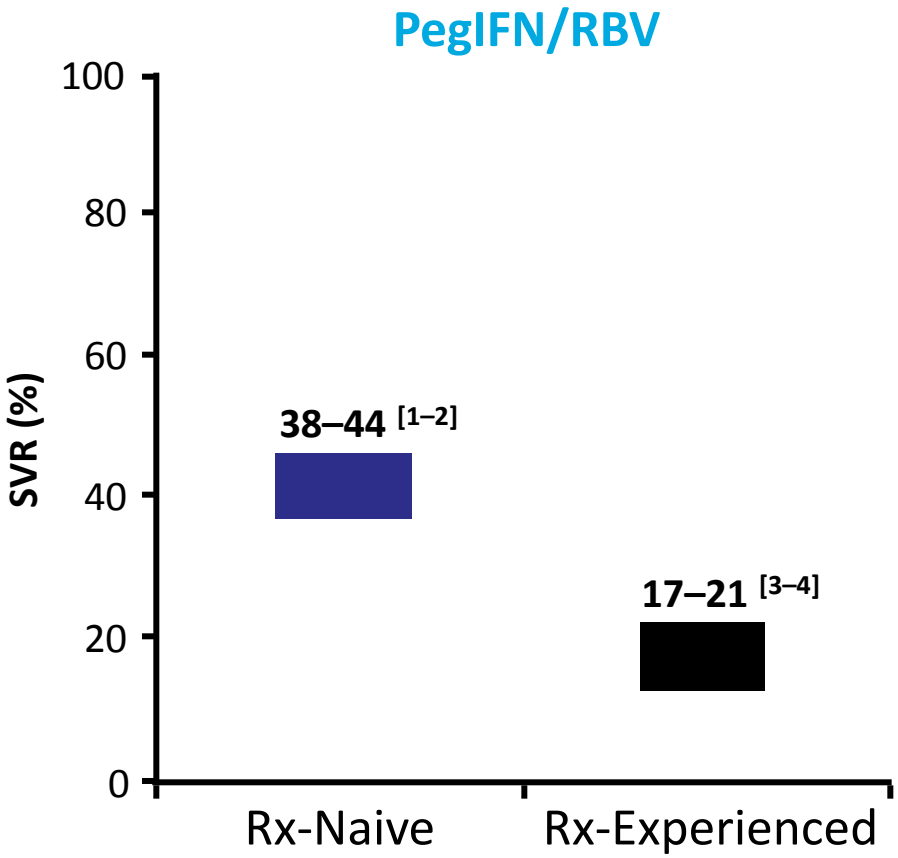
Dasabuvir (formerly ABT-333) is a non-nucleoside NS5B polymerase inhibitor

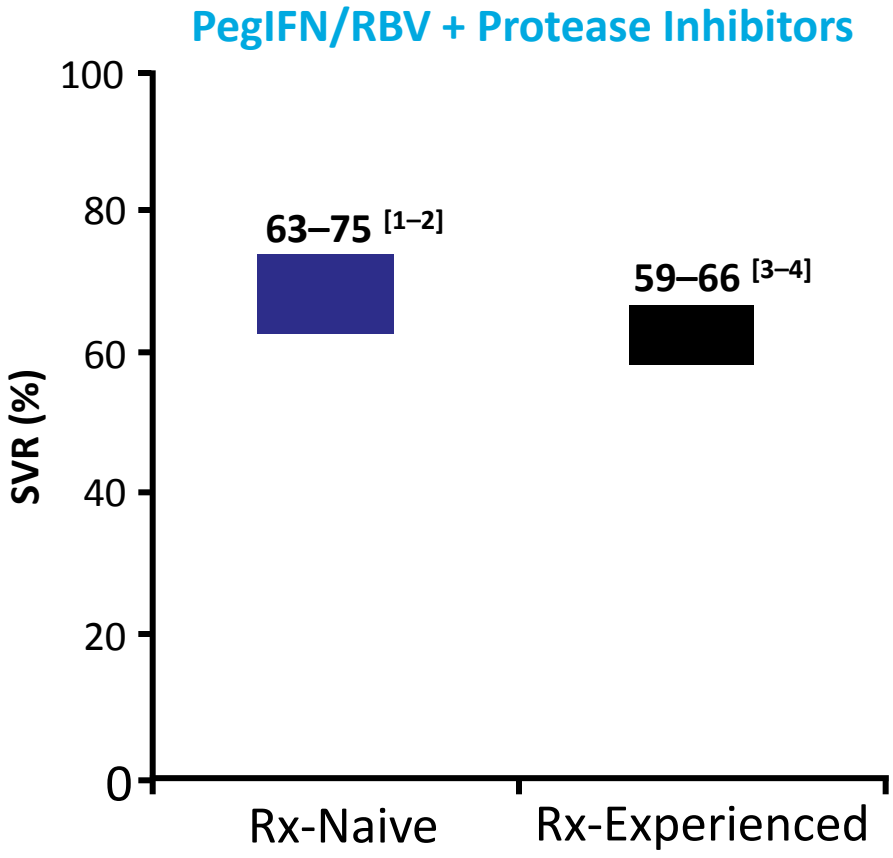
The mean maximum HCV RNA decline observed in patients receiving 3-day monotherapy with ABT-450/r, ombitasvir, or dasabuvir was >4 $\log_{10}$ IU/mL, >3 $\log_{10}$ IU/mL, and ~1 $\log_{10}$ IU/mL , respectively[2-4]

*Ritonavir does not have antiviral activity against HCV.

[1]Menon R, et al. HepDART 2009; [2]Lawitz E, et al. *J Hepatol*. 2012;56(suppl 2):S470. [3]Lawitz E, et al. *J Hepatol*. 2012;56(suppl 2):S469-S470. [4]Poordad F, et al. *J Hepatol*. 2012;56(suppl 2):S478.

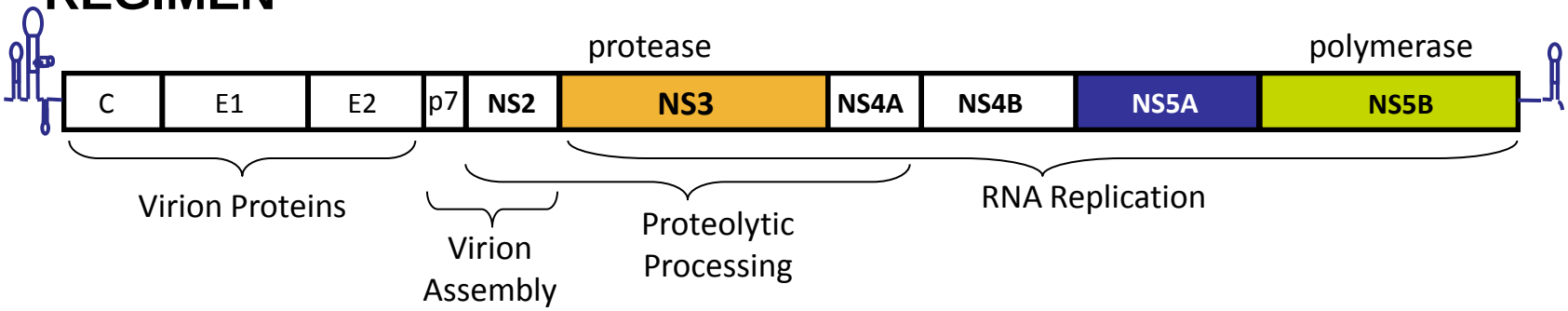
SVR with Boceprevir and Telaprevir in HCV Genotype 1 Treatment-Naive and -Experienced Subjects





Poordad F, et al. *N Engl J Med.* 2011; 364:1195-1206. Bacon B, et al. *N Engl J Med.* 2011; 364:1207-1217. Jacobson IM, et al. *N Engl J Med.* 2011; 364:2405-2416. Zeuzem S, et al. *N Engl J Me.d* 2011; 364:2417-2428. Sherman KE, et al. *N Engl J Med.* 2011; 365:1014-1024.

TARGETING MULTIPLE DOMAINS OF HCV TO INCREASE EFFICACY AND REDUCE RESISTANCE FOR AN IFN-FREE REGIMEN



Likely need combination of two or three drugs hitting separate targets

- Avoid cross-resistance and overlapping toxicities
- Maintain a high barrier to resistance
- Simple regimen to maximize adherence

Drug Development is NOT Easy

Clinical Trials – Timeline for new drug development

	Preclinical Testing	Phase I	Phase II	Phase III	FDA	Total Years	Phase IV
Years	3.5	1	2	3	2.5	12	Post-marketing
Test Population	Laboratory & animal studies	20 to 80 healthy volunteers	100 to 300 patient volunteers	1000 to 3000 patient volunteers	Review process/ Approval		
Purpose	Assess safety and biological activity	Determine safety and dosage	Evaluate effectiveness, look for side effects	Verify effectiveness, monitor adverse reactions from long-term use			

-one for every 1,000 drugs makes it into humans

-One in 5 receive FDA approval

HCV ADVOCATE
www.hcvadvocate.org

Slide courtesy S Polyak

HCV DIRECT ACTING ANTIVIRALS CLINICAL DEVELOPMENT PROGRAMS

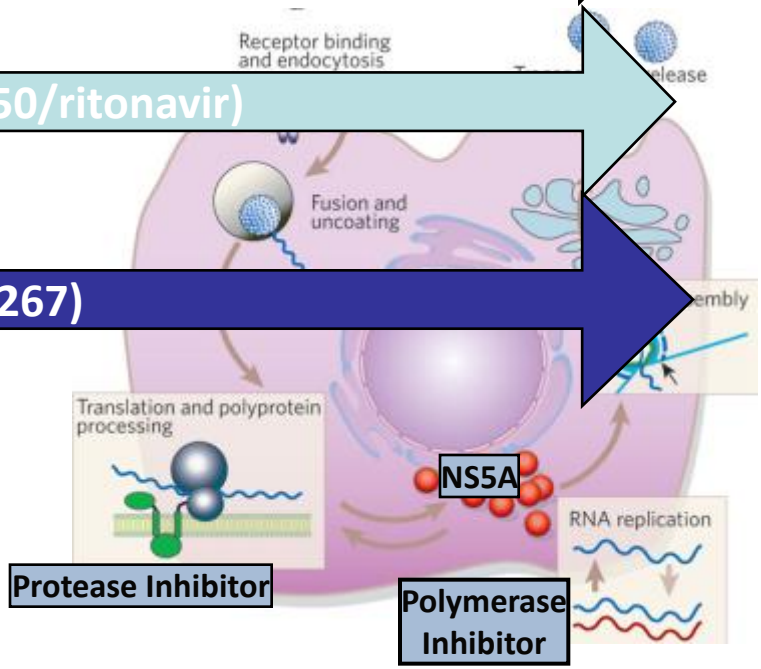
DAAs in Development at AbbVie

Discovery	Non-clinical	Phase 1 SAD	Phase 1 MAD	Phase 2a	Phase 2b	Phase 3

Polymerase Inhibitor (ABT-333)

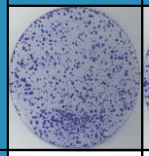
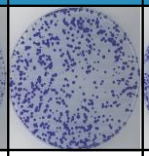
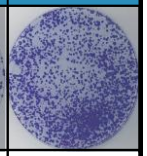
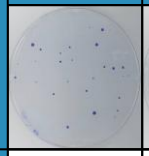
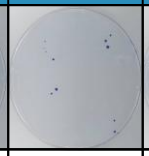
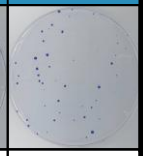
Protease Inhibitor (ABT-450/ritonavir)

NS5A Inhibitor (ABT-267)



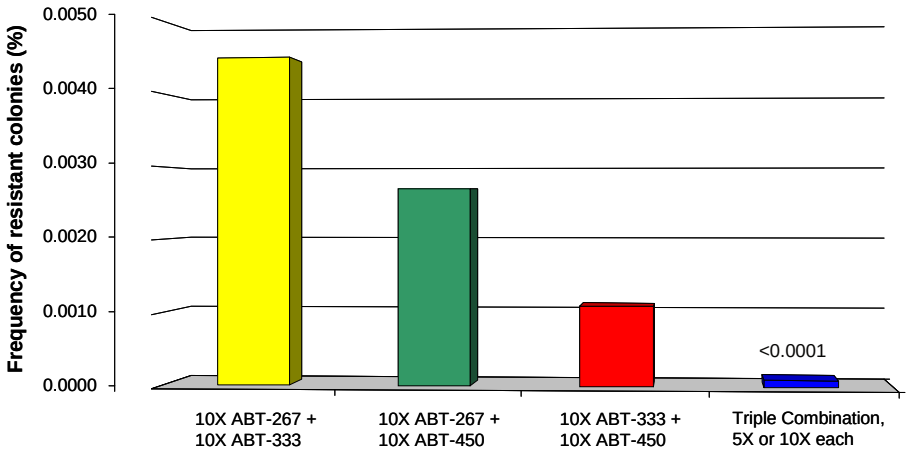
3D HAS A HIGH GENETIC BARRIER TO RESISTANCE

Earlier *in vitro* studies have demonstrated that combination of ABT-450, ABT-267, and ABT-333 are needed to completely eliminate colony growth

10X EC_{50} (10^5 cells)	ABT-450	ABT-267	ABT-333
			
Frequency of resistant colonies	>1%	~ 0.5%	>1%
10X + 10X EC_{50} (10^6 cells)	ABT-450 + ABT-267	ABT-450 + ABT-333	ABT-267 + ABT-333
			
Frequency of resistant colonies	0.0027%	0.0011%	0.0045%
ABT-450 + ABT-267 + ABT-333 (10^6 cells)		5X + 5x + 5X EC_{50}	10X + 10x + 10X EC_{50}
			
Frequency of resistant colonies		<0.0001%	<0.0001%

EC_{50} = median effective concentration.

Genotype 1a replicon



There were no surviving colonies (<0.0001%) when all 3 drugs were used in combination, including at low concentrations (5X above respective EC_{50}s).

Pilot-Matias, T, et al. EASL 2012, April 18–22, 2012, Barcelona, Spain. Poster #867

AbbVie's HCV Clinical Development Program

PHASE 2a

PILOT
GT1 naïve, N=11
ABT-450/r + ABT-072 + RBV

CO-PILOT
GT1 naïve/exp, N=50
ABT-450/r + ABT-333 + RBV

PHASE 2b

AVIATOR
GT1 naïve/exp, N=571
ABT-450/r ± ABT-267 ± ABT-333 ± RBV

NAVIGATOR
GT1, 2, 3 naïve, N=60
ABT-450/r + ABT-267 ± RBV

PEARL-I
GT1b, 4, naïve/exp, N=320
ABT-450/r + ABT-267 ± RBV

PHASE 3

SAPPHIRE-I
GT1 naïve, N=600
ABT-450/r/ABT-267 + ABT-333 + RBV

SAPPHIRE-II
GT1 exp, N=400
ABT-450/r/ABT-267 + ABT-333 + RBV

PEARL-II
GT1b exp, N=210
ABT-450/r/ABT-267 + ABT-333 ± RBV

PEARL III
GT1b naive, N=400
ABT-450/r/ABT-267 + ABT-333 ± RBV

PEARL-IV
GT1a naïve, N=300
ABT-450/r/ABT-267 + ABT-333 ± RBV

SPECIAL PATIENT POPULATIONS

TURQUOISE-I (HIV/HCV)
GT1 naïve/exp, N=300
ABT-450/r/ABT-267 + ABT-333 + RBV

TURQUOISE-II
(Compensated Cirrhosis)
GT1 naïve/exp, N=300
ABT-450/r/ABT-267 + ABT-333 + RBV

M12-999
(Liver Transplant Recipients)
GT1 naïve/exp, N=30
ABT-450/r/ABT-267 + ABT-333 + RBV

ADDITIONAL STUDIES

M13-101 (Virologic Failures)
GT1 failures in previous AbbVie trial, N=150
ABT-450 + RTV + ABT-267 + PegIFN + RBV

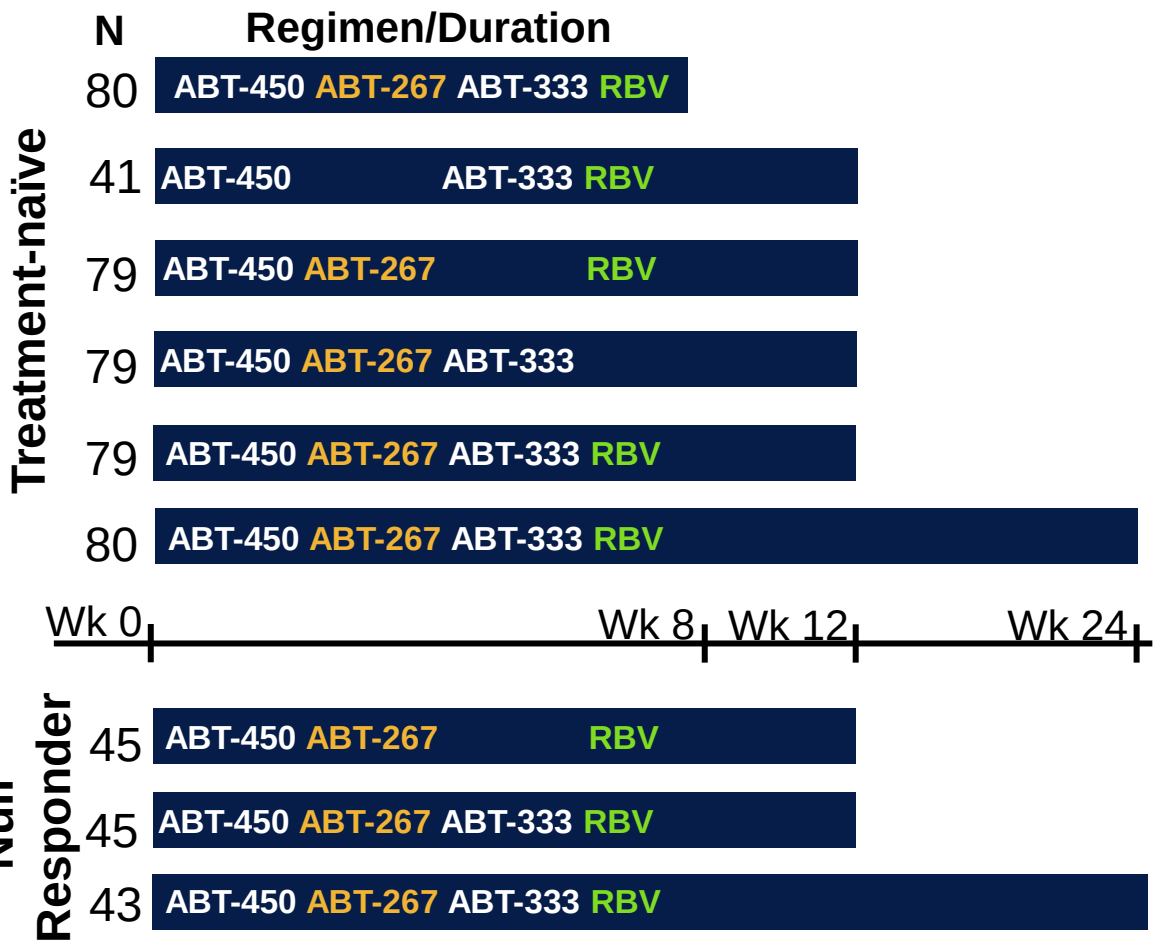
M13-102 (Long-term Follow-up)
GT1, N=500

GT = genotype; exp = experienced; RBV = ribavirin; RTV = ritonavir; PegINF = pegylated interferon

3D PROVIDES HIGH ACHIEVEMENT OF SVR-12/24

Phase 2 data demonstrate consistently high SVR and low relapse rates among all patient types

M11-652: Response Rates, All Groups, N=571



SVR_{12} %	SVR_{24}* %	Breakthrough/ Relapse
89	88	0 / 10
85	83	1 / 4
91	89	1 / 8
90	87	1 / 5
99	96	0 / 1
93	90	0 / 2
89	89	0 / 5
93	93	3 / 0
98	95	1 / 0

*8 patients with SVR_{12} have not returned for >24 weeks and are counted as virologic failures for SVR_{24}

adapted from Kowdley, et al. EASL 2013

Summary

- Chronic hepatitis C is a silent killer
- Current treatments have limitations : There is unmet need for
    - Better Tolerability
    - Better Virological response
- Future treatments fulfill current unmet need
    - Oral triple combination
    - Less side effects
    - Treatment success

Thank you for listening

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