



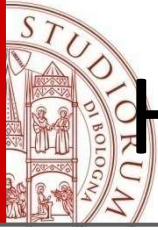
GESTIONE CLINICA DELLE EPATITI CRONICHE VIRALI

I NUOVI FARMACI PER L'EPATITE CRONICA HCV

Pietro Andreone

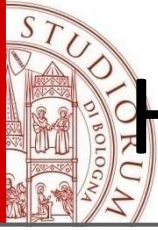
Dipartimento di Scienze Mediche e Chirurgiche
Università di Bologna

Ferrara, 2 Marzo 2013



Hep C: history of antiviral therapy

- 1990–1997: standard IFN
- 1998–2001: standard IFN + ribavirin
- 2002–2011: pegylated IFN + ribavirin
- 2012: pegylated IFN + ribavirin + DAA (PI)
- 2015 (?): pegylated IFN + ribavirin + 2nd generation DAA
- 2018 (?): IFN-free regimens



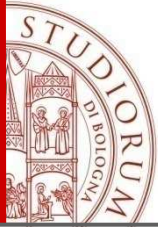
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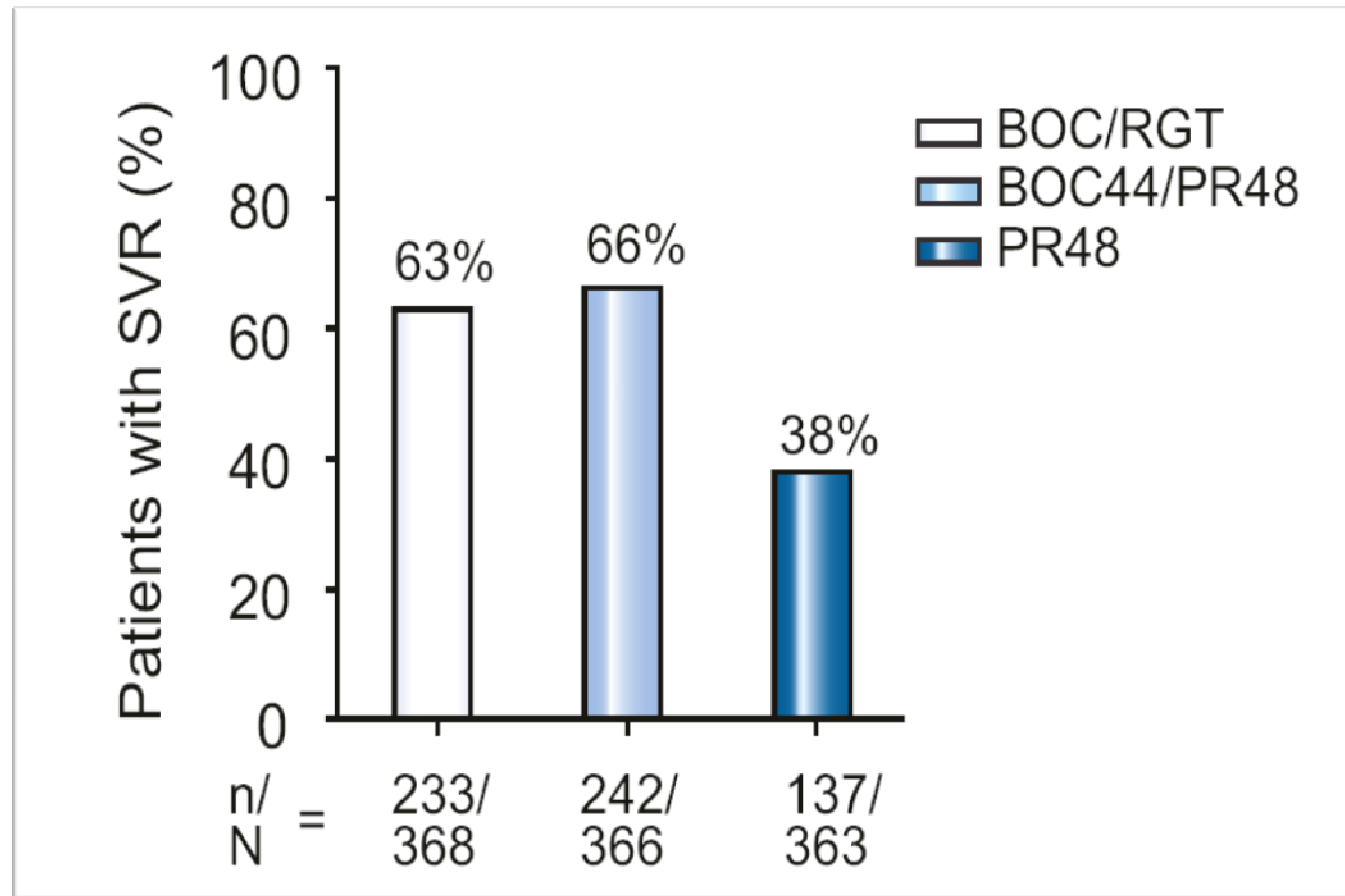


Hep C: current therapy for G1

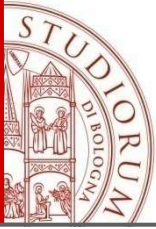
- Genotype 1a and 1b
 - Pegylated IFN α 2a (180 mg) or Pegylated IFN α 2b (1.5 mg/Kg) weekly
 - Ribavirin 800-1.400 mg/daily
 - Protease Inhibitor
 - Boceprevir 2.400 mg/daily (800 mg TID)
 - Telaprevir 2.250 mg/daily (750 mg TID/ 1.125 mg BID)
 - From 24 to 48 wks
 - **Short treatment (24-28 wks): only in RVR without cirrhosis**
 - **Prolonged treatment (36-48wks): if no RVR, advanced fibrosis, previous NR**
 - **IL28B (a predictor of IFN-sensitivity):useful in naïve, unclear in experienced**
 - **RVR best predictor of SVR**



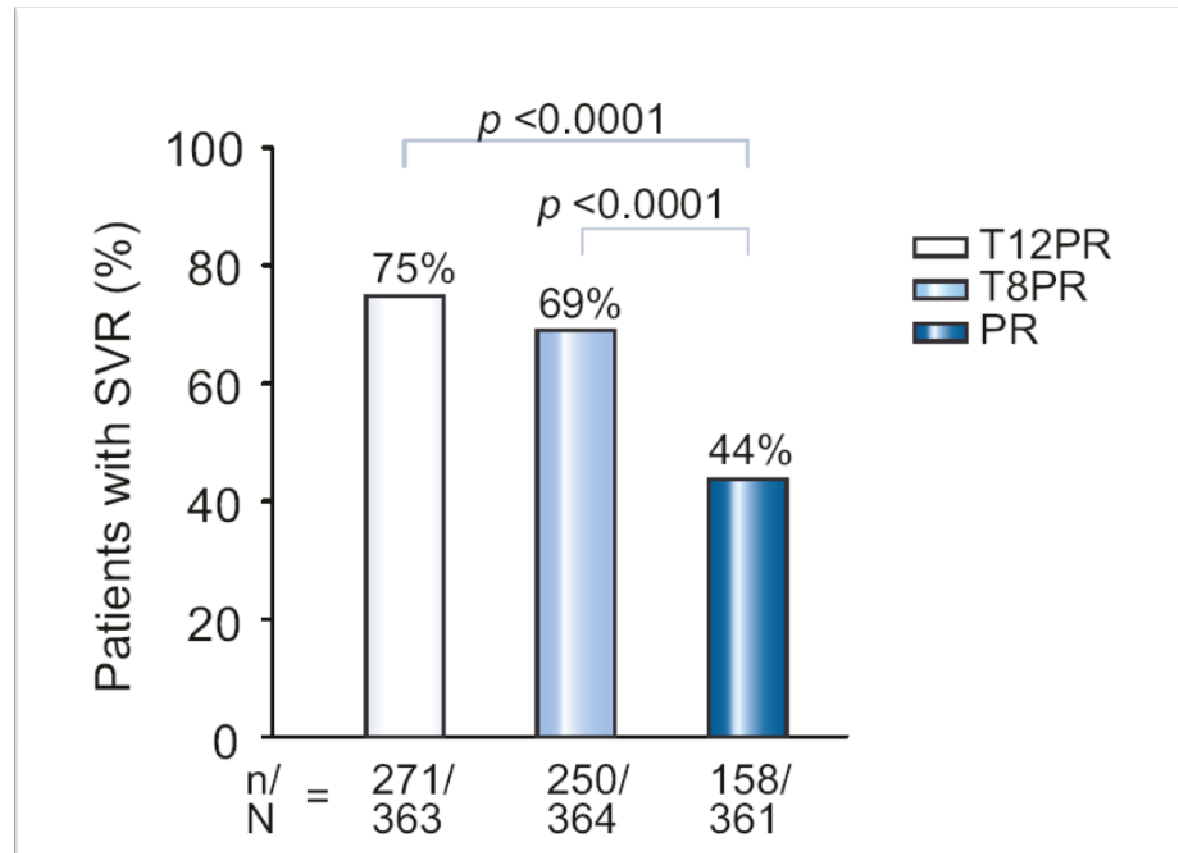
SVR rates in the SPRINT-2 trial (Boceprevir NAïVE)



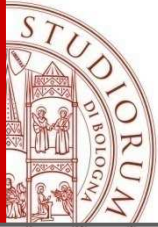
Poordad F, et al. 2011 NEJM



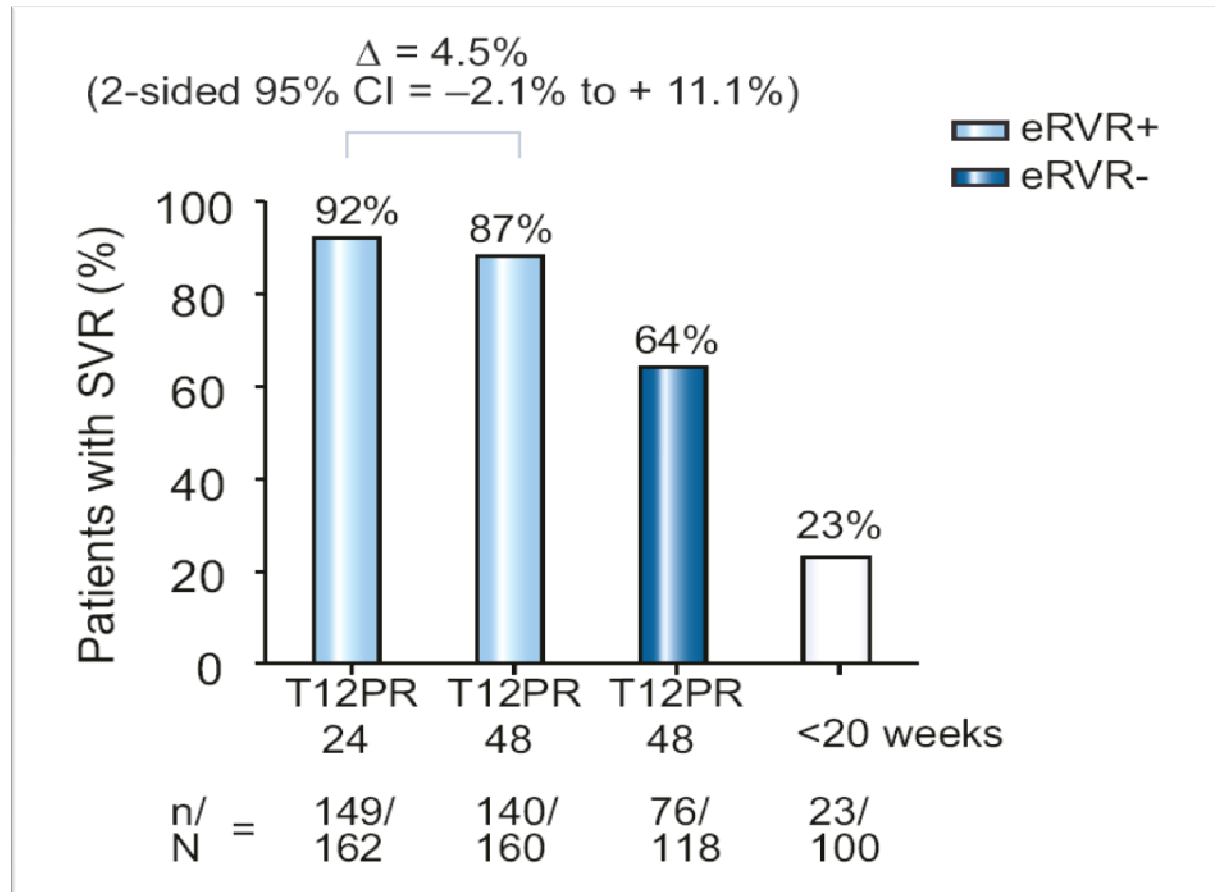
SVR rates in the ADVANCE trial (Telaprevir NAïVE)



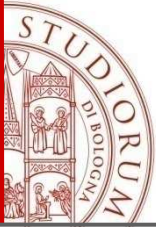
Jacobson IM, NEJM 2011



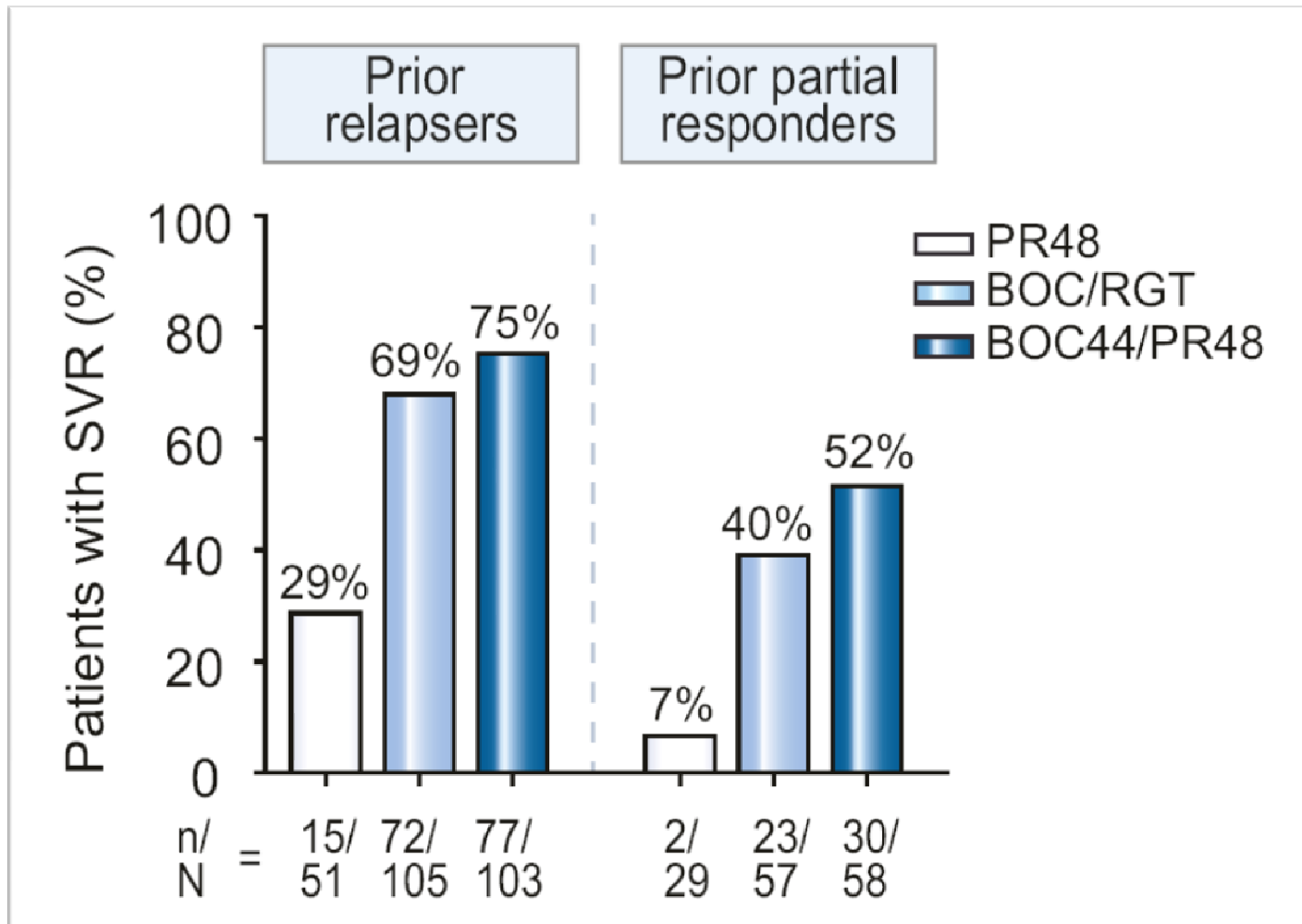
SVR rates in the ILLUMINATE trial (Telaprevir NAïVE)



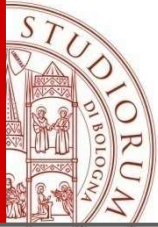
Sherman KE, Hepatology 2010



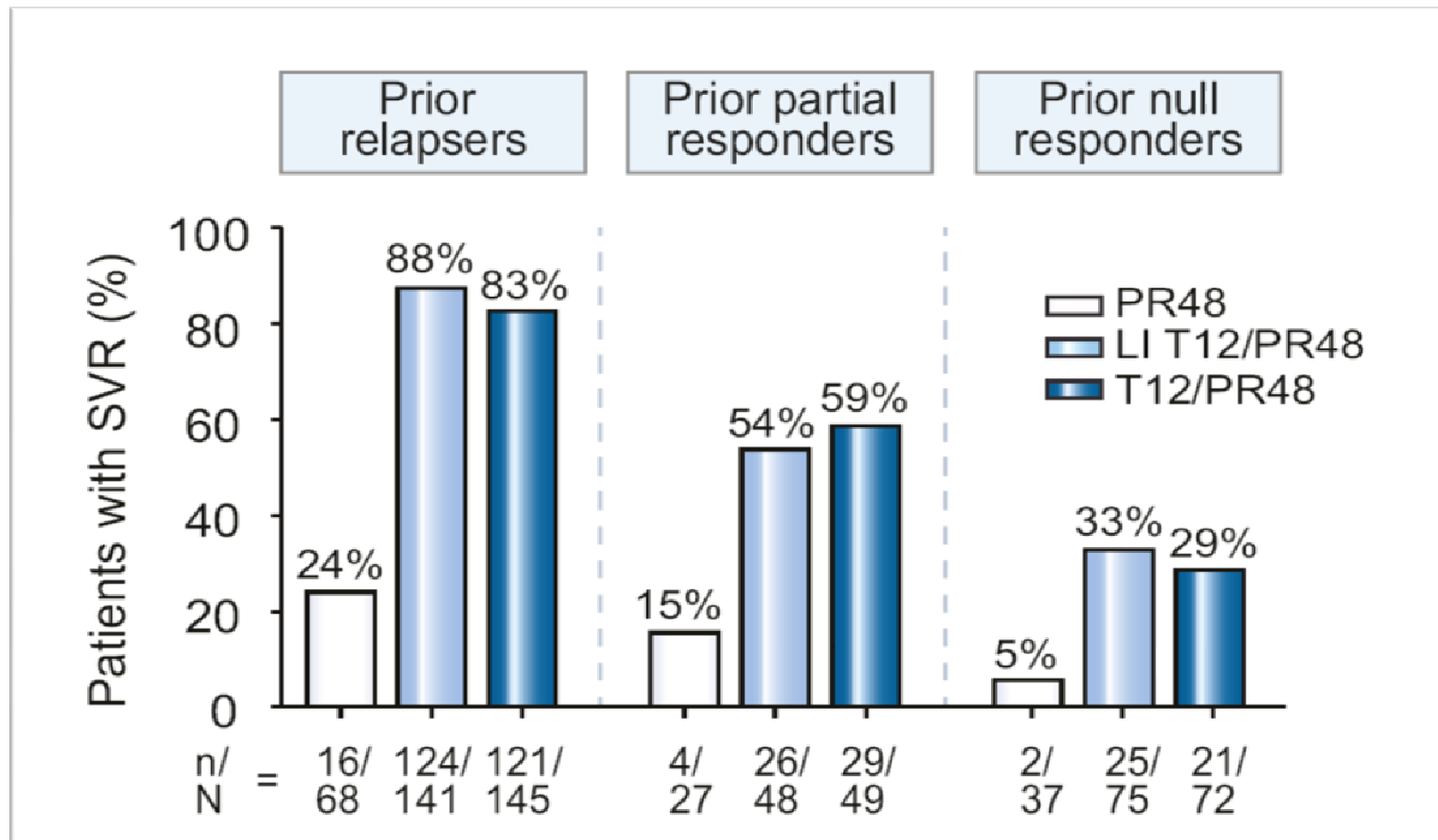
SVR rates in the RESPOND-2 trial (Boceprevir EXPERIENCED)



Bacon BR, et al. N Engl J Med 2011



SVR rates in the REALIZE trial (Telaprevir EXPERIENCED)



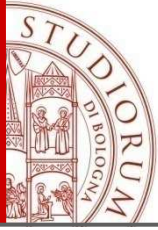
Zeuzem S, et al. N Engl J Med 2011;364:2417-28



Issues of triple therapy

- **Patient choice**
 - mild disease
 - cirrhosis
 - null responders
- **The type of drug**
 - **BOC**: lower cost but longer treatment
 - **TVR**: higher cost but shorter treatment
- **The treatment schedule**
 - lead-in
 - no lead-in
- **Predictors of response**
 - Pre-treatment (IL28B)
 - On treatment (RVR)

- Management of side effects
- Drug interactions



Major Side Effects during AVT

- **Dual therapy (Peg-IFN + RBV)**

- asthenia, headache, nausea, fever, musculo-skeletal pain
- anemia, neutropenia
- decline in mood, irritability, insomnia
- rash

- **Triple therapy (Peg-IFN + RBV + DAA)**

- **TVR**: pruritus, rash, anemia, gastro-intestinal disorders
- **BOC**: fatigue, anemia, nausea, diarrhoea, **dysgeusia**, neutropenia

Pegintron EU SmPC; Pegasys EU SmPC; Rebetol EU SmPC; Jacobson IM, et al. NEJM 2011; Sherman KE, et al. NEJM 2011; Zeuzem S, et al. NEJM 2011; Telaprevir EU SmPC; Poordad F, et al. NEJM 2011; Bacon BR, et al. NEJM 2011; Boceprevir EU SmPC

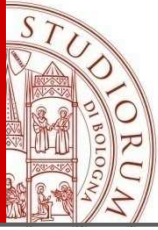


Anemia: data from registrative trials

	BOCEPREVIR (phase III)		TELAPREVIR (phase II/III)*	
	Treated	Controls	Treated	Controls
Prevalence	49%	29%	32%	15%
Premature discontinuation	0-3%	0-1%	2%	0.5%

*EPO not allowed

Jacobson IM, et al. NEJM 2011; Sherman KE, et al. NEJM 2011; Zeuzem S, et al. NEJM 2011; Telaprevir EU SmPC; Poordad F, et al. NEJM 2011; Bacon BR, et al. NEJM 2011; Boceprevir EU SmPC



Anemia management

- **Ribavirin dose reduction**

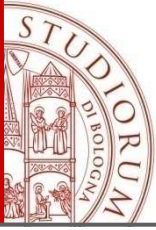
- 200 mg at a time
- Possibly when HCV-RNA negative

- **Epoetin**

- Can allow to maintain the dose of RBV
- Use if Hb <10 g/dl
- Recommended dose: 30,000 IU/week
- Halving dose if Hb increases by 1 g/week or 2 g/month
- Discontinue if Hb > 12 g/dl

- **Blood transfusion** if Hb <8 g/dl

- Do not suspend RBV and continue treatment with Peg-IFN + DAA (high risk of resistance)
- Do not reduce DAA dose (high risk of resistance)



Ano-Rectal symptoms

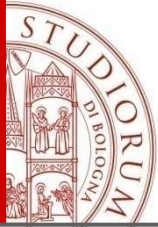
- Secondary to irritant metabolites
- Include several disorders
 - Ano-Rectal discomfort
 - Hemorrhoids
 - Anal itching
 - Rectal burning
- **Boceprevir**
 - Infrequent event in ph. 3 studies comparable to SoC (1%)
- **Telaprevir**
 - Frequent event (29% vs 7% SoC)
 - Disease severity: mild to moderate
 - Disappear with the end of treatment
 - <1% need to stop TVR
 - **Treatment:** topical steroids + anesthetics; antihistamines; high fiber diet

Jacobson IM, et al. NEJM 2011; Sherman KE, et al. NEJM 2011; Zeuzem S, et al. NEJM 2011; Telaprevir EU SmPC; Poordad F, et al. NEJM 2011; Bacon BR, et al. NEJM 2011; Boceprevir EU SmPC

Rash

- Boceprevir
 - Naïve: **14÷17% (SoC: 5%)**
 - Experienced: not reported
- Telaprevir
 - Naïve
 - ✧ All grades: **58÷61% (SoC: 48%)**
 - ✧ Grade 3: **4÷6% (SoC: 1%)**
 - Experienced
 - ✧ Grade 3: **3% (SoC: 0%)**
 - ✧ Grade 4: **0.5%**
 - ✧ Treatment discontinuation (TVR o triple): **4÷5% (SoC: 0%)**

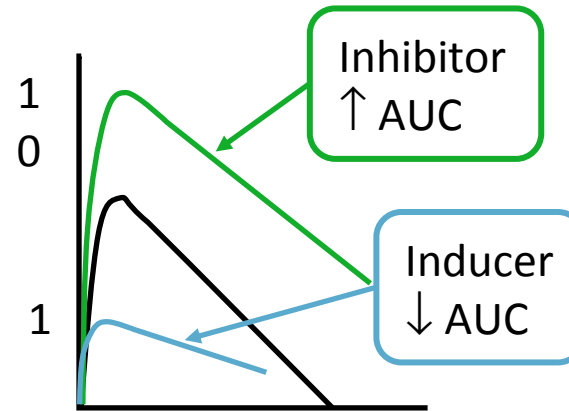
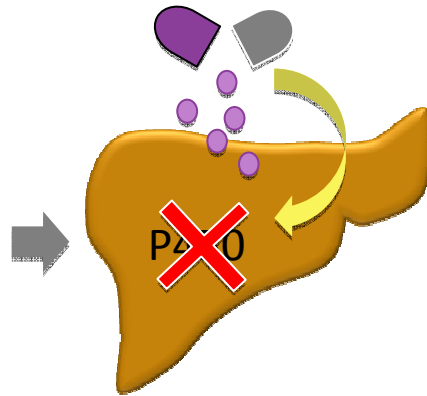




Drug Interactions

Drug + Inhibitor

Inhibitor blocks the function of the CYP enzyme



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DRUG INTERACTION CHARTS

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INTERACTIONS WITH TELAPREVIR AND BOCEPREVIR

Telaprevir & Boceprevir - INTERACTIONS NOW FULLY LISTED

Telaprevir and boceprevir were licensed by the FDA in May and have been added as columns to the interaction charts. To view the interactions, click on the drug interaction chart section above.

[CLICK HERE TO REGISTER FOR WEBSITE UPDATES](#)

Please add nicropi@hep-druginteractions.org and hepdrug@liv.ac.uk to your address book to assist in uninterrupted delivery and check your Spam or BULK folder to ensure emails are not being lost.

Antibiotici

- Rifampicina

Antidepressivi, ansiolitici, antipsicotici, neurolettici e anticonvulsivi

- Midazolam (enterale)
- Triazolam
- Pimozide

Antidolorifici. Derivati dell'ergotamina

- Diidroergotamina
- Ergotamina

Antagonisti dell'adrenorecettore-alfa-1

- Alfuzosina

Inibitori della PDE-5 (nel trattamento dell'ipertensione polmonare)

- Sildenafil
- Tadalafil

Ipolipemizzanti

- Atorvastatina
- Lovastatina
- Simvastatina



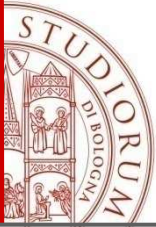
Hep C: current therapy for G non-1

- Genotype 2 & Genotype 3
 - Pegylated IFN α 2a (180 mg) or Pegylated IFN α 2b (1.5 mg/Kg) weekly
 - Ribavirin 800 mg/daily (15 mg/Kg/daily if baseline predictive factors of low response)
 - 24 wks
 - **Short treatment (12-16 wks): only in RVR with weight based RBV**
 - **Prolonged treatment (48wks) : if no RVR, advanced fibrosis, high BMI**
 - **Unclear the role of IL28B**
 - **RVR best predictor of SVR**

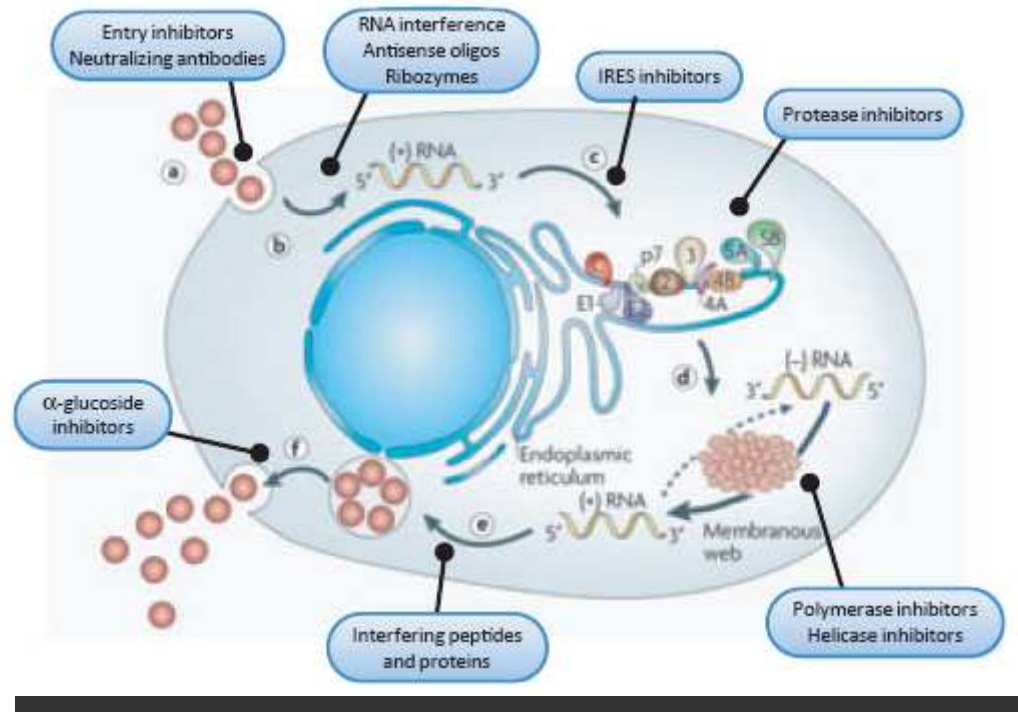


Hep C: current therapy for G non-1

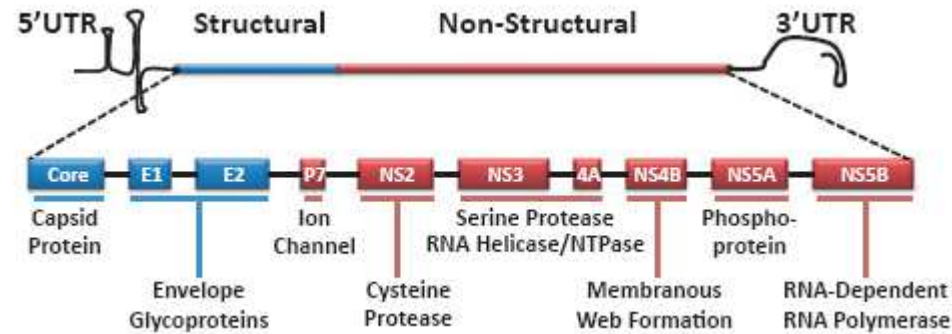
- Genotype 4
 - Pegylated IFN α 2a (180 mg) or Pegylated IFN α 2b (1.5 mg/Kg) weekly
 - Ribavirin 15 mg/Kg/daily
 - 48 wks
 - **Short treatment (24 wks): if RVR and no baseline negative predictive factors of NR**
 - **Prolonged treatment (72 wks) : if pEVR**
 - **IL28B: CC associated with SVR**
 - **RVR: best predictor of SVR**



Hep C: potential therapeutic targets



Hep C: genomic targets and new drugs



NS3/4A Protease Inhibitors (PI)

- High potency
- Multi-genotypic coverage
- Intermediate to high barrier to resistance

NS5B Nucleoside Inhibitors (NI)

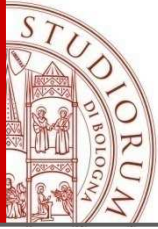
- Intermediate potency
- Pan-genotypic coverage
- High barrier to resistance

NS5A Inhibitors

- High potency
- Multi-genotypic coverage
- Low to intermediate barrier to resistance

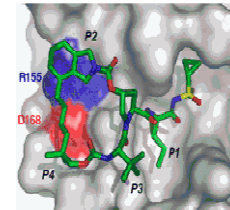
NS5B Non-Nucleoside Inhibitors (NNI)

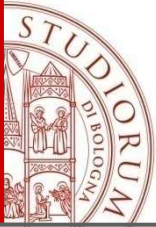
- Intermediate potency
- Limited-genotypic coverage
- Low barrier to resistance



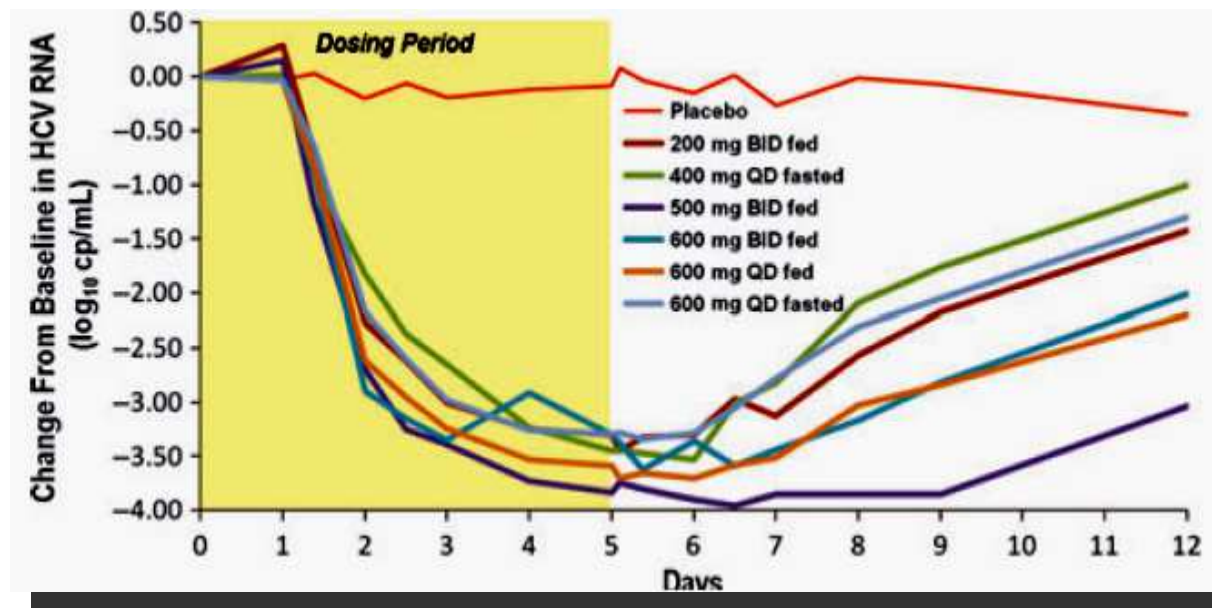
Second generation NS3-4A protease inhibitor (PI)

- **Simeprevir (TMC-435)**
 - phase 3, naïve, experienced
 - G1, G4
 - once daily
- **Asunaprevir (BMS-650032)**
 - phase 2, experienced
 - G1, G4
 - twice daily
- **Faldaprevir (BI-201335)**
 - phase 3, naïve, experienced
 - G1
 - once daily
- **Sovaprevir (ACH-1625)**
 - phase 2, naïve
 - G1
 - twice/once daily
- **Danoprevir (RG-7227)**
 - phase 2, naïve
 - G1, G4, G6
 - once daily
- **Vaniprevir (MK-7009)**
 - Development stopped
- **MK-5172**
 - G1, G2, G3, G4, G5, G6
 - phase 1
 - **active against V36,T54, R155, V36+R155 RAVs**
- **ACH-2684**
 - phase 1
 - in vitro G1, G2, G3, G4, G5, G6
 - **active against R155, A156, D168 RAVs**





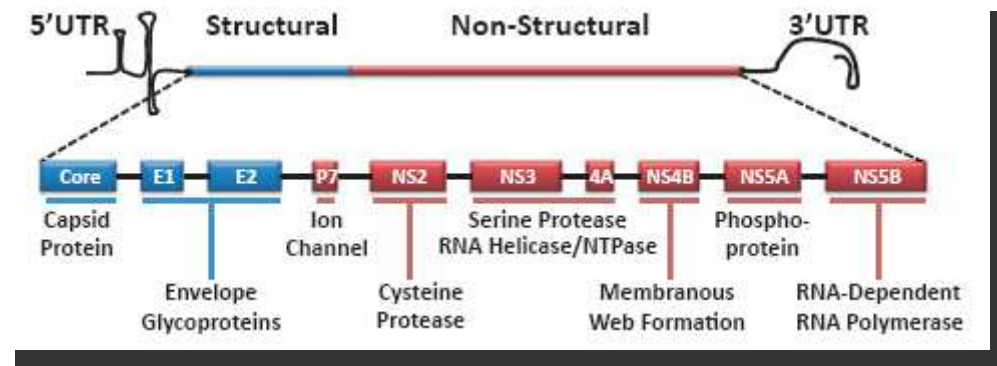
Second generation NS3-4A PI: **Sovaprevir**

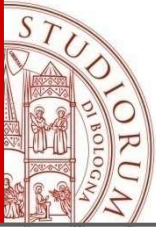


Poordad F, et al. JVH 2012

NS5A inhibitors

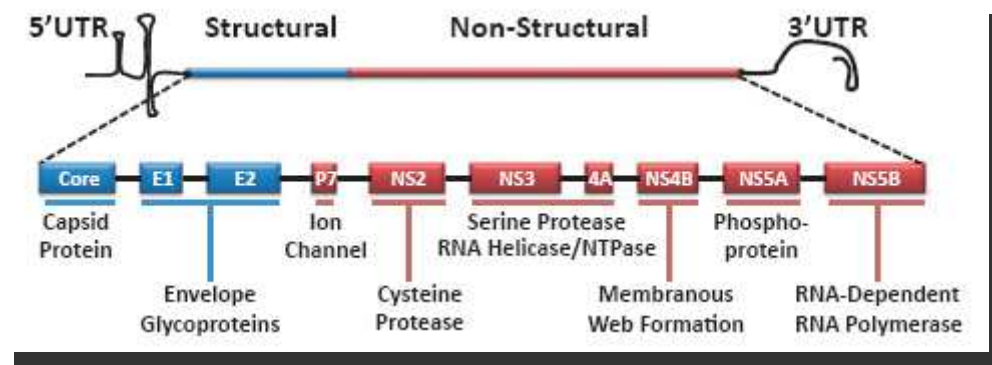
- **Daclatasvir (BMS-790052)**
 - phase 3, naïve, experienced,
 - G1, G2, G3, G4; HIV
 - once daily
- **ACH-2928**
 - phase 1, naïve
 - G1, G2, G3, G4, G5, G6
 - once daily
- **ABT-267**
 - phase 2, naïve
 - G1 CC
- **ANA-958**
 - phase 2, naïve
 - G1
 - twice daily





NS5B nucleoside/nucleotide analogue inhibitors (NI)

- **Mericitabine (RG-7128)**
 - phase 2, naïve, experienced
 - G1, G4
 - twice daily
- **Sofosbuvir (GS-7977)**
 - phase 3, naïve, experienced
 - G1, G2, G3
 - once daily
- **INX-189 (BMS-094)**
 - Development stopped



NS5B non-nucleoside inhibitors **NNI**

- **Filibuvir (PF-00868554)**

- phase 2, naïve
- G1
- twice daily

- **VX-222**

- phase 2, naïve
- G1
- twice daily

- **ABT-072**

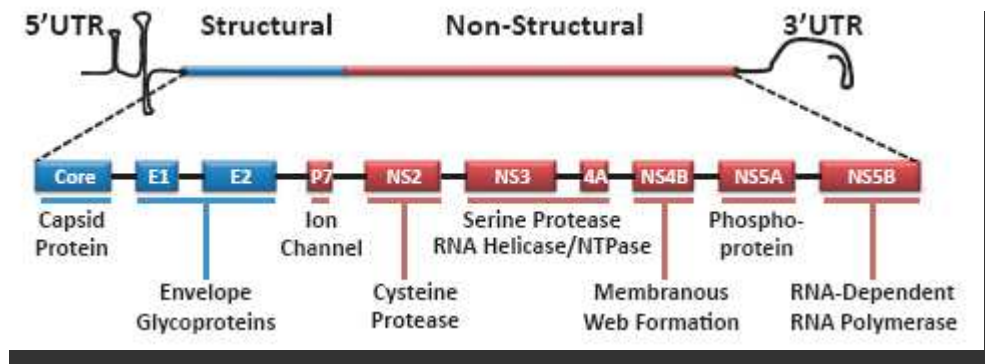
- phase 2, naïve
- G1
- once daily

- **Setrobuvir (ANA-598)**

- phase 2, naïve
- G1
- twice daily

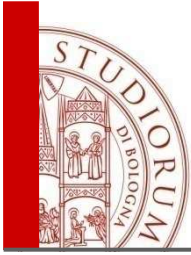
- **BI-207127**

- phase 2, naïve
- G1
- thrice daily





we try to mix the cards?



... an infinite set of combinations

- Double therapy (\pm RBV \pm Peg-IFN)
 - PI + NS5A Inhib
 - PI + NI
 - PI + NNI
 - ...
- Triple therapy (\pm RBV \pm Peg-IFN)
 - PI + NS5A Inhib + NI
 - PI + NS5A Inhib + NNI
 - PI + NI + RBV
 - ...
- Quadruple therapy
 - Peg-IFN + RBV + PI + ?



the first ...

Oral combination therapy with a nucleoside polymerase inhibitor (RG7128) and danoprevir for chronic hepatitis C genotype 1 infection (INFORM-1): a randomised, double-blind, placebo-controlled, dose-escalation trial

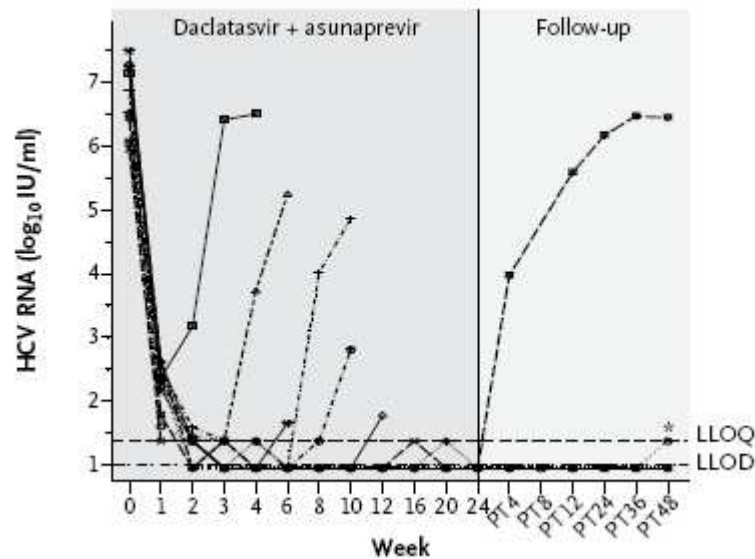


Gane E, et al. Lancet 2010

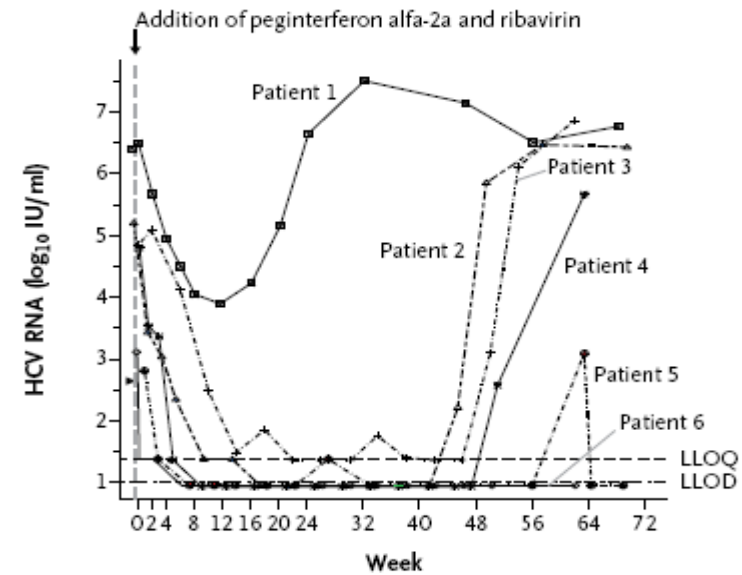
... and the last

11 null responders to Peg-IFN + RBV

A HCV RNA Levels, Group A



B HCV RNA Levels after Initiation of Rescue Therapy, Group A



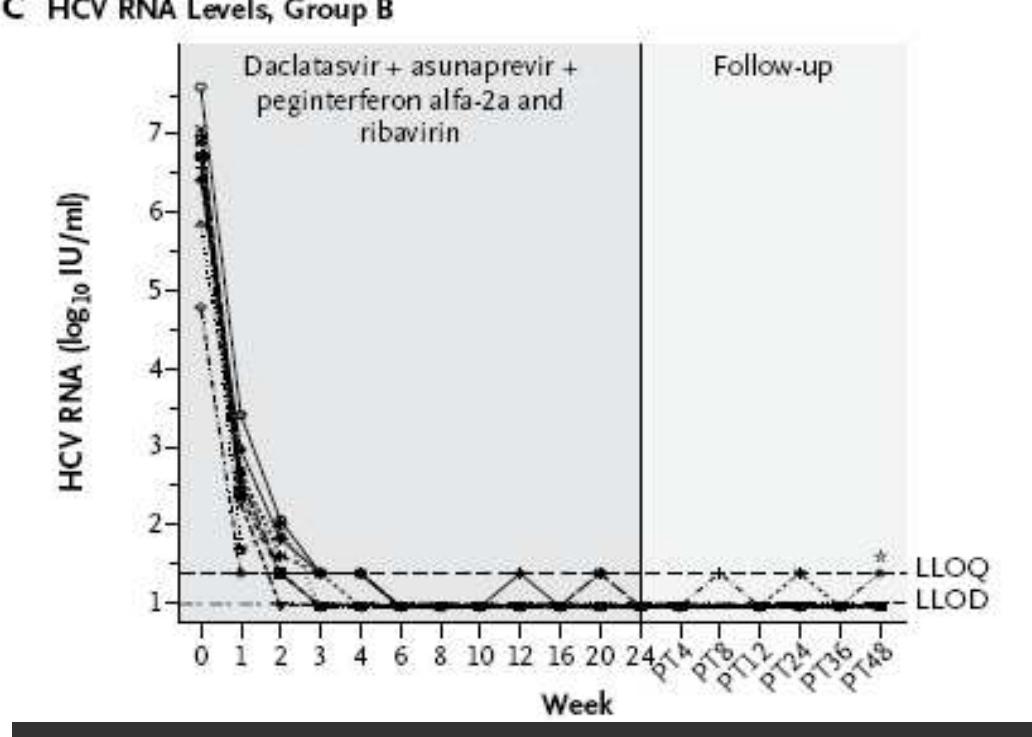
Lok ASF et al., NEJM 2012



... and the last

10 null responders to Peg-IFN + RBV

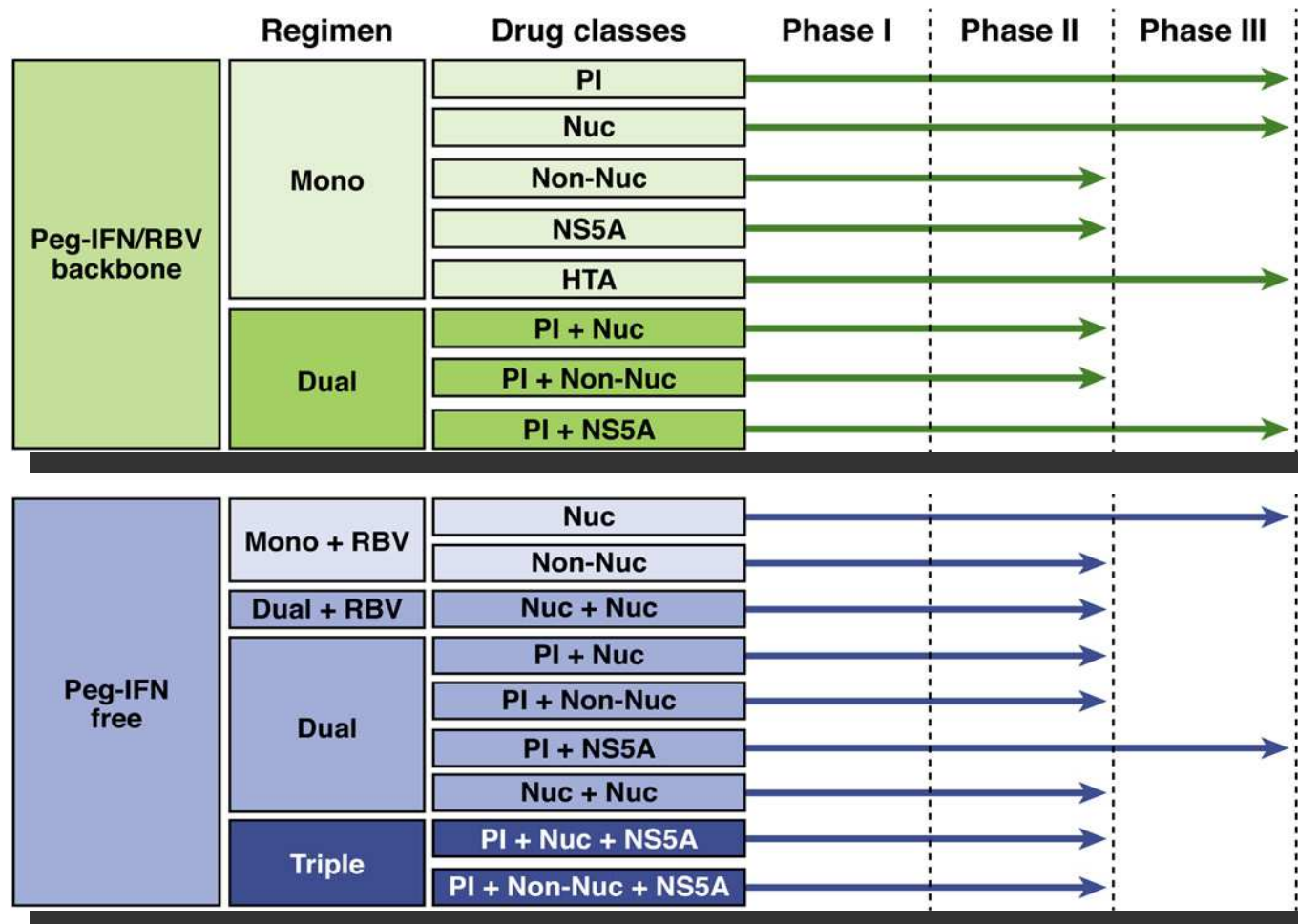
C HCV RNA Levels, Group B



Lok ASF et al., NEJM 2012



The near future



Zeuzem S, et al. Gastroenterology 2012



EPATITE CRONICA HCV: ANCORA UN PROBLEMA?