The Role of Ribavirin in the New Era of HCV Therapy

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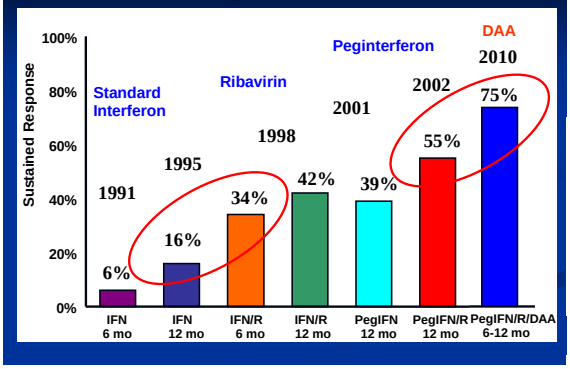
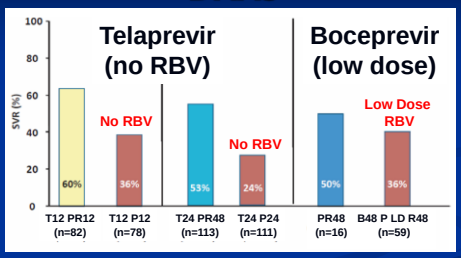
RBV as good as DAAs!



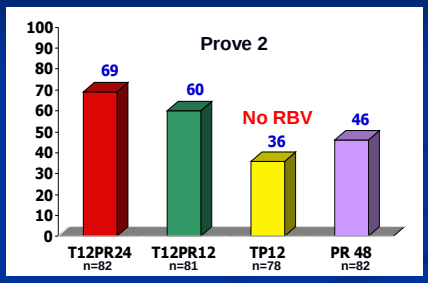
RBV Necessary with 1st Gen DAAs



- Absence of RBV → very ineffective
- Reduced dose RBV → very ineffective

Clark Liver Int 2012

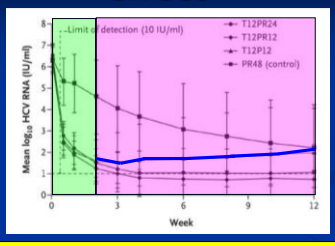
RBV Necessary with 1st Gen DAAs



Peg/TVR worse than Peg/RBV

Hézode NEJM 2009

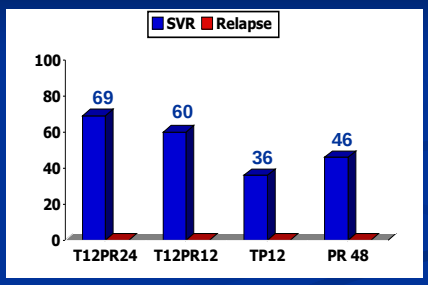
An early but not immediate effect



- No effect seen on first phase
- 24% breakthrough by week 12 with no RBV
- All resistant virus

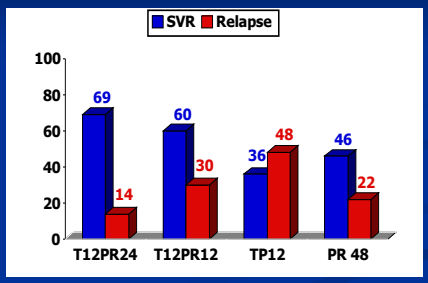
Hézode NEJM 2009
Feld Gastro 2012

A Late Effect



Hézode NEJM 2009

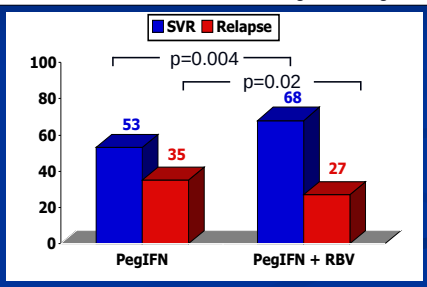
A Late Effect



Hézode NEJM 2009

Necessary Until the End

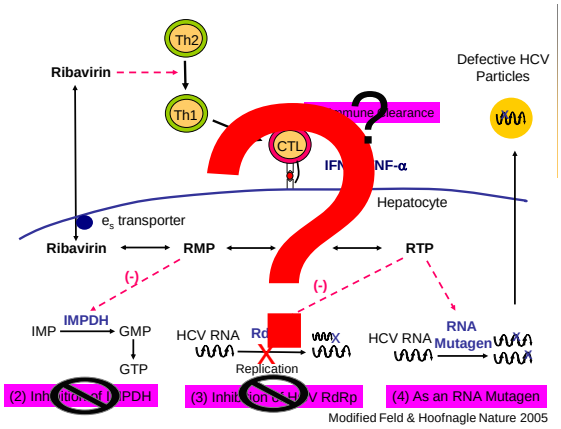
358 pts cEVR randomized at wk 24 to Peg2a vs Peg2a +RBV



Bronowicki Gastro 2006

So what does this data tell us about mechanism?

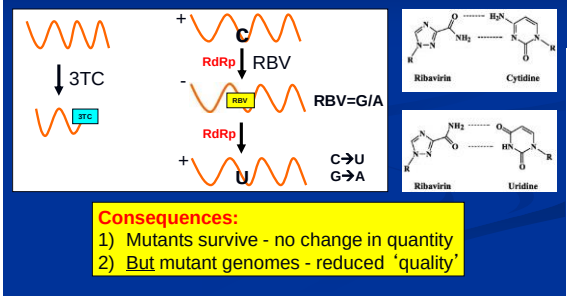
1. Ribavirin is not a typical DAA
   (cannot be replaced by more potent DAA and no obvious RBV resistance)
2. Necessary early to prevent/delay breakthrough - limits development of resistant variants
3. Necessary late to prevent relapse



Modified Feld & Hoofnagle Nature 2005

Mutagenesis

Not your average nucleotide analogue

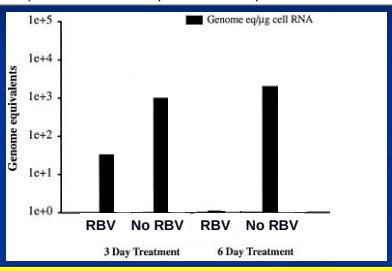


Consequences:

1) Mutants survive - no change in quantity
2) But mutant genomes - reduced 'quality'

Quality Over Quantity

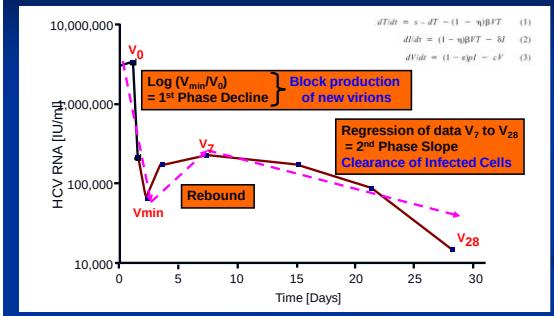
After exposure to RBV - equal GBV-B copies to infect naïve cells



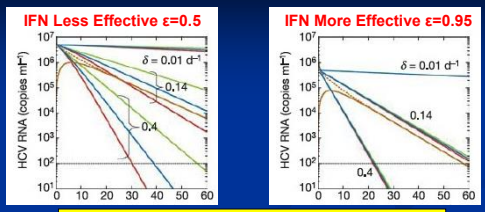
- Markedly reduced infectivity after RBV exposure
- Increased error rate in replicons exposed to RBV

Lanford J Virol 2001

Can kinetics tell us the Answer? A picture is worth 1000 Greek Letters



Kinetics Support Mutagenesis



Predictions of the Model:

1. RBV effect on 2nd phase
2. RBV effect lost if IFN very effective
3. Not immune clearance b/c dependent on ε
4. RBV most effective at low viral loads
   - increased RBV/genome

Dixit Nature 2004

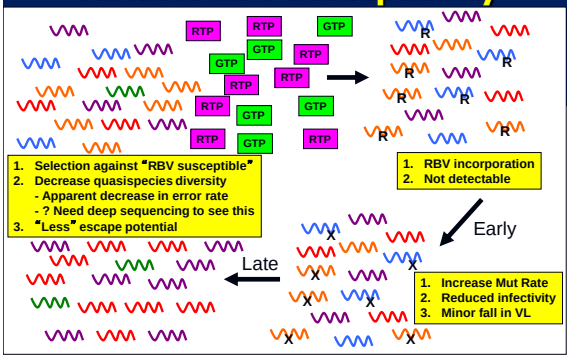
The Real Test - Patient Data

Study	Error Rate		Method	Conclusion
	RBV Mono	RBV + Peg		
Asahina J Hepatol 2005	Increased	NA	Consensus	Increased error rate associated with SVR
Lutchman Gastro 2007	Increased 4 wks No change 24 wks	NA	Consensus + Cloning	Early modest effect
Hofmann Gastro 2007	Early increase	Early decrease	~ 18 clones per pt per time-point	Increase with RBV mono Decrease with Peg/RBV
Chevaliez J Virol 2007	No effect	- No effect even at low viral load - Trend to decrease	20 clones per pt per time-point	**No effect**

1. Modest early increase in mutation rate with RBV monotherapy
2. No sustained effect
3. Possible decrease in mutation rate with combination therapy

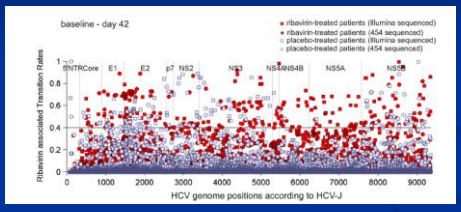
How can these data be reconciled?

A Potential Explanation…Timing & Variable RBV Susceptibility



Deep sequencing

Full genome of 4 RBV monotherapy vs placebo day 0 & 42



- No increase in overall mutation rate
- Significant increase in RBV-associated transitions G→A & C→U

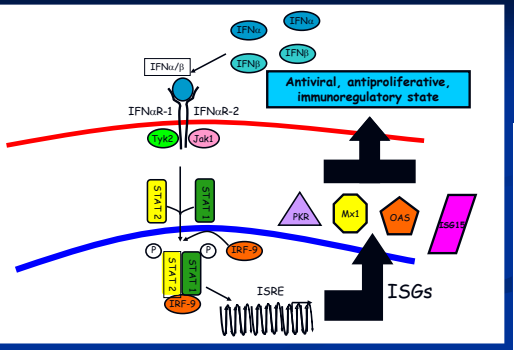
Dietz JVI 2013

Bottom Line on Mutagenesis

- Easy to see *in vitro*, hard to detect *in vivo*
- Likely more relevant if:
  1. Higher RBV concentrations
  2. Lower viral loads
  3. Lower GTP concentrations (IMPDH)
- Mutations random, do not accumulate - therefore must do cloning (miss low frequency genomes)
- Conceivably may reduce quasi-species diversity over long-term (RBV incorporation is variable):
  1. Reduced "escape" potential with pressure
     - IFN / DAA / Immune (acute)

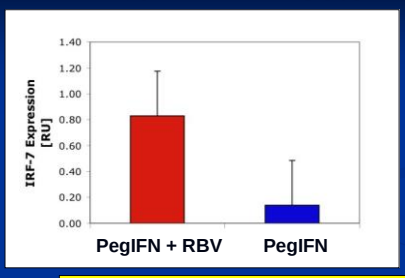
But what's the connection to IFN?

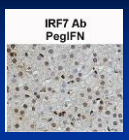
Mechanism of Action of Interferon



Modified from Gale Nature 2005

Ribavirin Affects ISGs

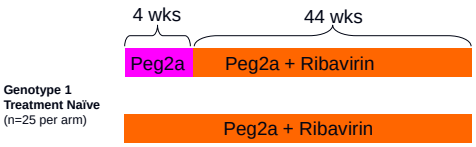




- Ribavirin induces a small subset of ISGs
- Leads to enhanced ISG induction by IFN

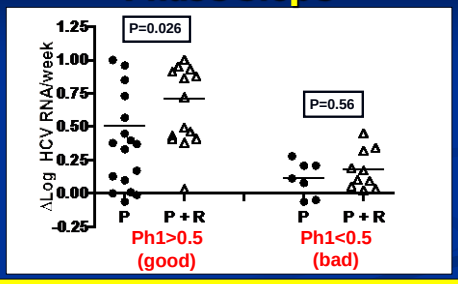
Feld Hepatology 2007
Thomas Hepatology 2010

Back to the Clinic



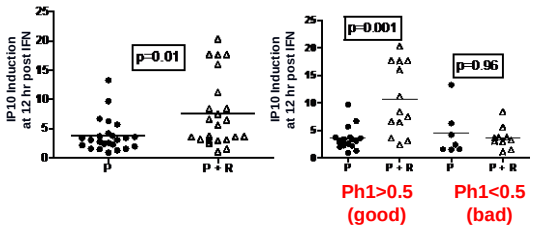
1. Compare Early Viral Kinetics
   - Phase 1 Decline
   - Phase 2 Slope
2. ISG Induction (IP10/MCP1/MIG)

RBV Improves Second Phase Slope



- RBV accelerates viral decline caused by IFN
- But - only effective if respond well, but not too well to IFN

RBV Improves ISG Induction

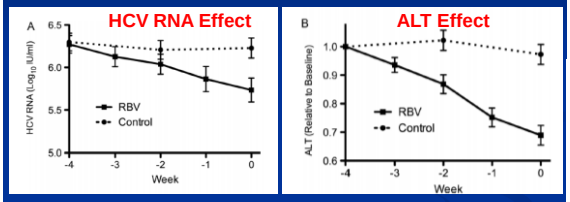


- RBV augments ISG induction
- But - only if respond well to IFN

Feld Gastro 2010

Effect of RBV Priming

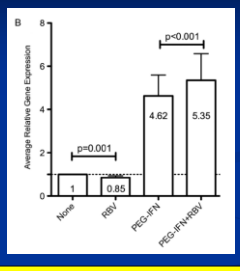
4 weeks of RBV monotherapy before Peg/RBV



- No association with IL28B genotype
- ALT but ***NOT*** HCV RNA response predictive of response to Peg/RBV

Rotman Gut 2013

Liver Biopsy Gene Expression



- RBV priming actually reduced ISG expression
- But led to greater ISG induction with Peg…reset ISG setpoint

Rotman Gut 2013

Summary on MOA

- Remains somewhat unclear
- Support for mutagenic effect
- Support for resetting of ISG set-point
  - Explains synergy with IFN
  - May explain ALT effect
- Both may be relevant

- Useful with modest IFN (or DAA) effect
- Not helpful at extremes
  - IFN null responder
  - IFN super responder (or very potent DAA combo)

Is RBV necessary with IFN-free DAA therapy?

Roles of RBV

- Limits resistance & relapse with low barrier combinations
- Issues to sort out:
  - RBV Dose
  - Does RBV resistance exist?
  - RBV tolerability in the absence of IFN

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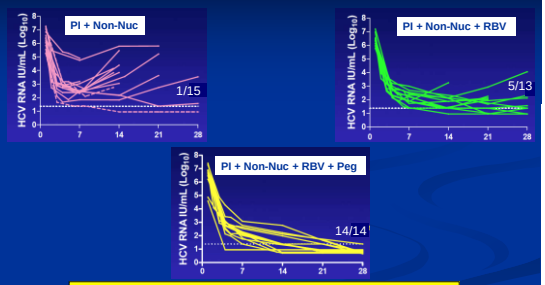
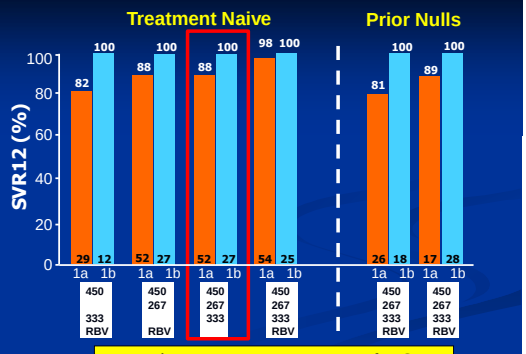
RBV prevents/delays resistance



RBV 'rescues' 2 DAAs with modest potency + low barrier to resistance

Zeuzem Hepatology 2012

AVIATOR: PI/r + NS5A + NNI + RBV x 12 wks

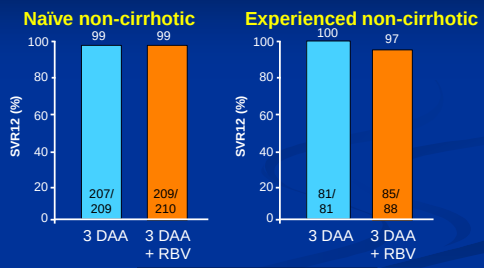


Removing RBV seems to matter for G1a

Kowdley NEJM 2012

PEARL – G1b

ABT-450/r + ABT-267 (ombitasvir) + ABT-333 (dasabuvir) +/- RBV x 12 wks

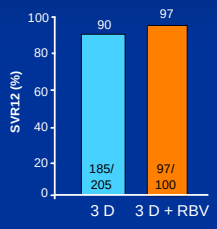


- G1b → no need for RBV

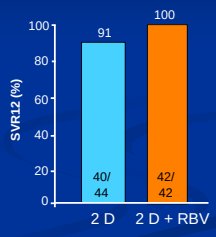
Ferenci CROI 2014

RBV helpful for G1a & G4

ABT-450/r + ombitasvir + dasabuvir +/- RBV x 12 wks



ABT-450/r + ombitasvir +/- RBV x 12 wks



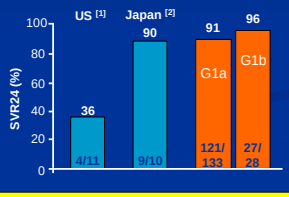
RBV adds 5-10% benefit

AbbVie Press Release/EASL 2014

Similar combo – similar results

Daclatasvir (NS5A) + asunaprevir (PI) x 24 wks (IFN-Free)

Daclatasvir (NS5A) + asunaprevir (PI) + BMS 791325 (NNI) x 12 wks



US Study
9/11 G1a

Japanese Study
10/10 G1b

- 2 drugs for 1b, 3 for 1a
- Would RBV have helped for G1a…I suspect so

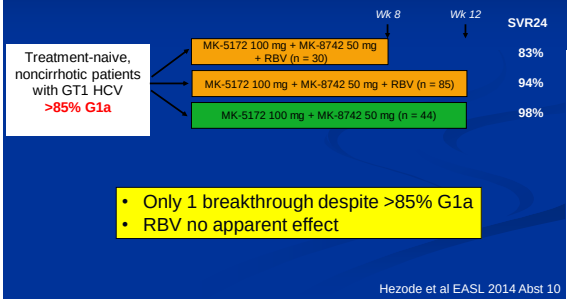
1. Lok et al NEJM 2012;366:216-24, 2. Chayama AASLD 2011 LB-4 3. Everson AASLD 2013 LB-1

A PI backbone

PI NS5A What about a 'better" PI and NS5A?

MK5172 (PI) + MK-8742 (NS5A)

Relatively pan-genotypic PI and NS5A
Will be combined as single pill

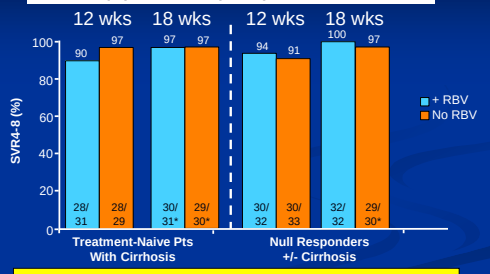


- Only 1 breakthrough despite >85% G1a
- RBV no apparent effect

Hezode et al EASL 2014 Abst 10

Tougher to cure population

MK5172 (PI) + MK-8742 (NS5A) x 12-18 wks +/- RBV

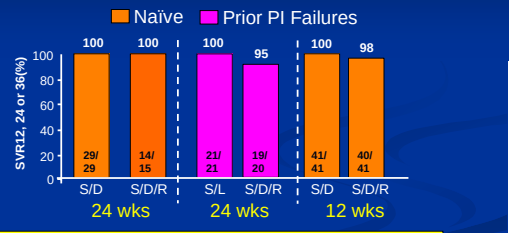


- Higher barrier PI/NS5A combo…no need for RBV

Lawitz et al EASL 2014 Abst 61

What about with even higher barrier combos?

Nuc (sofosbuvir) + NS5A (daclatasvir) +/- RBV

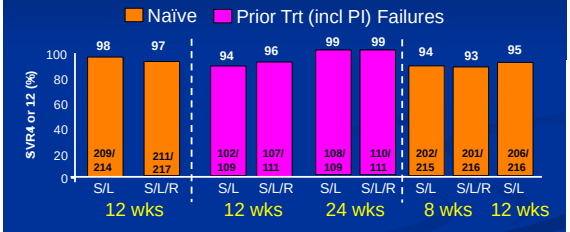


- With Nuc/NS5A combination – potent, high barrier
- RBV unnecessary

Sulkowski NEJM 2014

Similar story

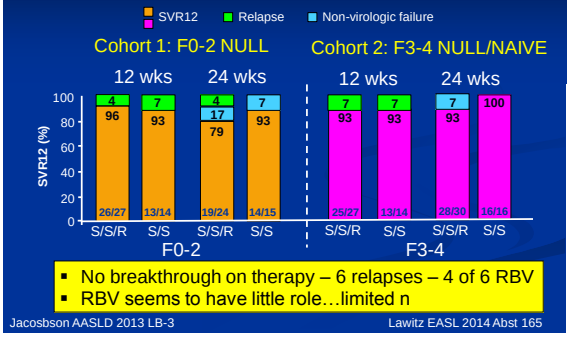
ION 1, 2 & 3: SOF (nuc) + LDV (NS5A) FDC +/- RBV



Similar result in ION trials – no need for RBV with nuc/NS5A

Mangia EASL 2014 Abst 0164, Afdahl EASL 2014 Abst 0109, Kowdley EASL 2014 Abst 056

COSMOS: Nuc (Sofosbuvir) + PI (Simeprevir) +/- RBV



- No breakthrough on therapy – 6 relapses – 4 of 6 RBV
- RBV seems to have little role…limited n

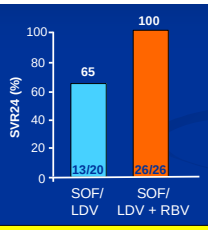
Jacosbson AASLD 2013 LB-3

Lawitz EASL 2014 Abst 165

What about with G3?

RBV apparently important

ELECTRON-2: SOF/LDV +/- RBV x 12 wks

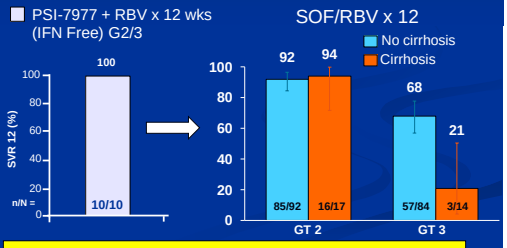


- Looks very promising
- Surprising…LDV minimal G3 activity

Gane EASL 2014

SOF/RBV for G3

- If we recall…ELECTRON 1 → 100% SVR in G2/3
- Did not hold up in Phase 3



Is there something special about G3 in New Zealand?

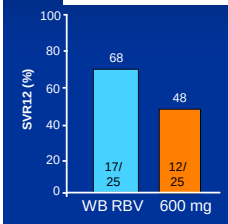
Roles of RBV

- Limits resistance with low barrier combinations
- Reduces relapse

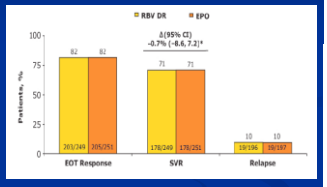
- Issues to sort out:
  - **- RBV Dose**
  - - Does RBV resistance exist?
  - - RBV tolerability in the absence of IFN

Does the dose matter?

SPARE TRIAL[1]
G1: SOF + WB vs LD RBV x 24 wks



RBV dose reduction vs EPO[2]



- Starting with a low dose of RBV is not effective
- But reducing ***FOR*** anemia is very effective – can go very low

1. Osinusi JAMA 2013 2. Poordad EASL 2012

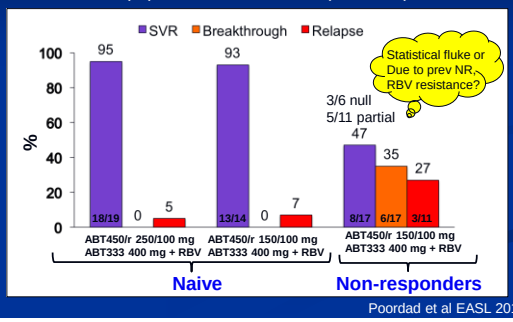
Roles of RBV

- Limits resistance with low barrier combinations
- Reduces relapse

- Issues to sort out:
  - - RBV Dose
  - **- Does RBV resistance exist?**
  - - RBV tolerability in the absence of IFN

Past treatment may affect future response…

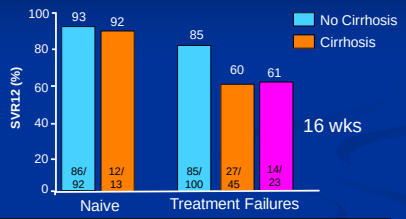
ABT-450 (PI)/ritonavir + ABT-333 (Non-nuc) + RBV



Poordad et al EASL 2012

VALENCE – more support for 'RBV resistance'?

SOF + RBV x 24 wks



- Surprisingly worse in cirrhotic prior relapsers
- Is this due to previous RBV exposure?
- No appearance of F415Y mutation

Zeuzem NEJM 2014

Roles of RBV

- Limits resistance with low barrier combinations
- Reduces relapse

- Issues to sort out:
  - RBV Dose
  - Does RBV resistance exist?
  - **RBV tolerability in the absence of IFN**

Tolerability of RBV (without Peg)

- Fairly well tolerated – no discontinuations
- But more AEs than in RBV-free arms
- Anemia: <10 g/dL → 2-10%
  <8.5 g/dL → <1%

Less of an issue without BM suppression of IFN

- But: Still an issue for cirrhotics, ESRD, Hb-opathies
- Other issues:
  - Rash rare
  - Mild GI toxicity
  - Pill burden

To summarize a lot of data

- RBV helps for regimens with
  1. Lower barrier to resistance (PI/NS5A/NNI with G1a)
  2. Higher relapse rate (SOF in G3)
  3. Including IFN (removal of RBV, worse than P/R)
- No benefit to RBV with potent, high barrier combos (nuc + NS5A/PI)
- RBV dose can be reduced for anemia (effective RBV level) but not at baseline
- Although prior exposure MAY reduce future response to RBV…very questionable, should not lead to withholding therapy

What's the future of RBV?

- **Near Future**
  - Useful with low barrier combinations:
    - 1st gen PI/NS5A/NNI (3D) for G1a
    - 2D (PI/NS5A) for G4
    - But low threshold to stop (90% SVR without RBV)
  - Not needed with 2nd gen PI/NS5A or for G1b
  - No use with SOF combo regimens (except G3?)
- **Longer Term**
  - Possibly to shorten therapy…no evidence yet
  - Possibly to use a 'cheaper' 'less effective' regimen

Does HIV matter?

- The short answer – probably not
- Currently RBV advocated in acute HCV with Peg
- IFN-free DAA combos seem to be equally effective with HIV co-infection
- Trials to date…conservatively include RBV
- RBV will likely have the same role (or lack thereof) in this population

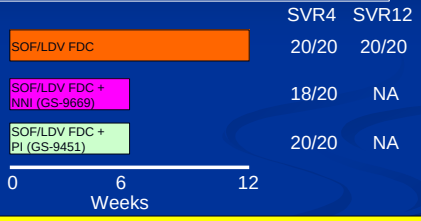
Does this tell us anything about MOA?

- Resistance effect supports mutagenesis
- But ALT effect and relapse effect may support resetting ISG set-point
- Does it matter?
  - For HCV – probably not
  - For other viral infections - perhaps → HEV, RSV

Not quite yet, but we are getting close to RBV's curtain call

More drugs…shorter therapy

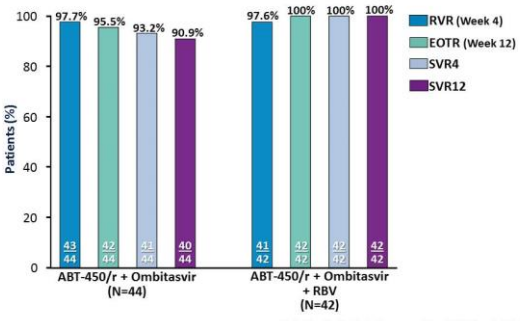
SYNERGY trial
Inner city, largely AA, IL28B non-CC population



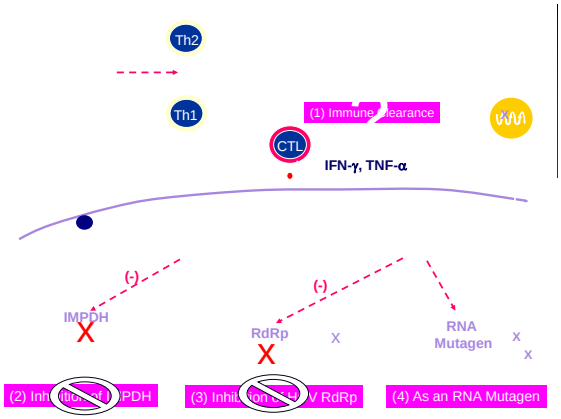
- IFN and RBV-free therapy for 6 wks or less possible
- Will increase options for treating 'difficult-to-treat'

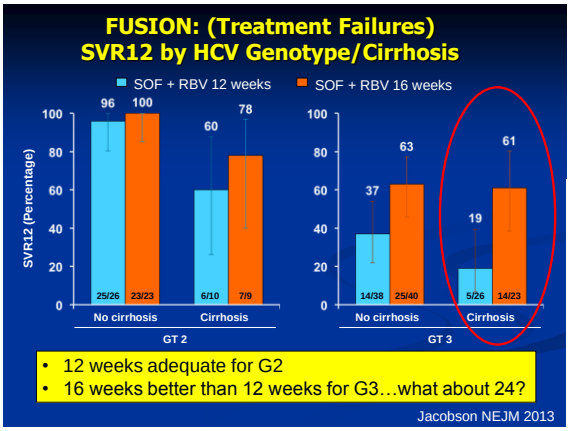
Kohli AASLD 2013

PEARL-I GT4-Infected Treatment-Naïve Patients: ITT Efficacy Analysis



Adapted from the Christophe Hezode presentation at ILC/EASL on April 11, 2014





Outline

- Mechanism(s) of action of RBV
- RBV with different classes of DAAs
- Downsides of RBV
- The future