

# HCV Treatment, Screening and Monitoring: 2015 and beyond

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# Who said?

“Never make predictions, especially about the future”

Casey Stengel

# Why predict?

“You've got to be very careful if you don't know where you are going, because you might not get there”

Yogi Berra

# My predictions

*between 2009-2015 we will..*

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- Approve first small molecules with peginterferon and RBV
- Then progressively shorten or decrease the peginterferon
- Try to eliminate RBV
- Test combinations of small molecules (starting in other countries)

# My predictions

*after 2015 we will..*

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- Use combinations of small molecules
- Use interferon-free regimens
- Expand the groups of patients receiving treatment
- Better treatments will result in more screening and identification of HCV-infected persons

# Patients for whom Peginterferon/RBV may remain Standard of Care

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- Genotype 2 and 3 (4, 5 and 6?)
- Acute hepatitis C
- Favorable genetic profile (IL28B C/C)

# Patients who may never be able to use Peginterferon/RBV

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- Medical contraindications
  - Severe depression
  - Renal insufficiency/dialysis (RBV)
  - Decompensated cirrhosis
- Social contraindications
  - Poor social background (e.g. homeless)
- Non-responders to Peginterferon/RBV who had to discontinue therapy because of severe adverse effects
- Patient choice

# Key Question

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We know that small molecules can suppress HCV replication,

*but*

Can small molecules eliminate HCV infection?

# Small Molecule Antivirals

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- Protease inhibitors (PI)
- Polymerase inhibitors
  - Nucleoside analogues (NRTI)
  - Non-nucleoside analogues (NNRTI)
- NS2 antagonists (e.g. cyclophilin antagonists)
- NS4B inhibitors
- NS5A antagonists
- others

# Possible Combinations

NRTI backbone

+

PI

+

NNRTI

+

PI  
NNRTI

Cyclophilin antagonist backbone

+

PI

+

NNRTI

+

PI  
NNRTI



# How might small molecules work without IFN?

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- Potent suppression by small molecule/s may simply end HCV replication
- Suppress replication long enough, uninfected hepatocytes may emerge
- Chronic suppressive therapy might be viable if we could prevent resistance
- Replace IFN with oral immune enhancers (e.g. TLR agonists, IFN-inducers)
- Suppression of HCV replication may allow host immunity to take over

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# Host immune mechanisms for control of HCV

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- Adaptive
  - Humoral: neutralizing Ab to E2
  - Cellular: CD4<sup>+</sup> T cells
- Innate
  - Activation TLR-3, IRF3
  - Retinoic acid inducible gene – RIG-I
  - Release of IFN  $\alpha$  and  $\beta$



# Possible challenges in developing IFN-free therapy

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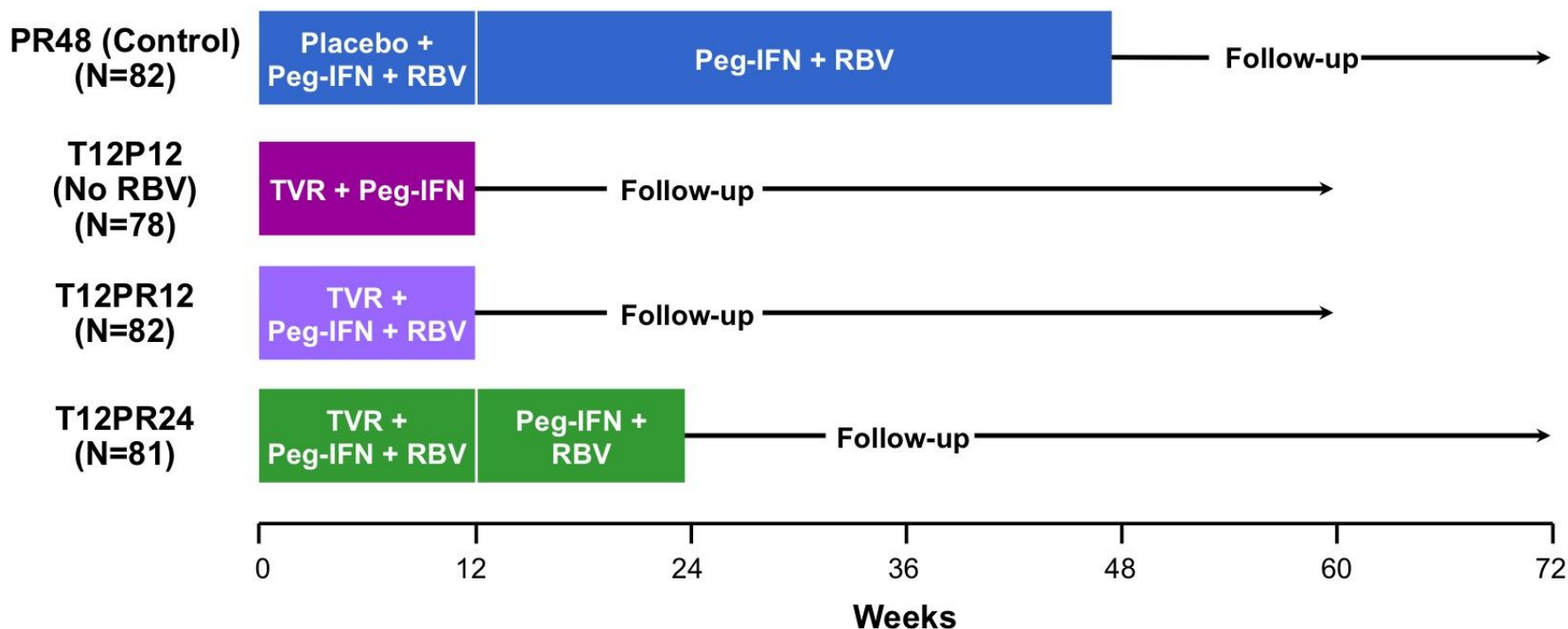
- Resistance to small molecules
- Toxicity of agents in combination
- Duration of therapy (longer? shorter?)

# What progress have we made towards IFN/RBV-free regimens?

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- Single agents tested for up to 14 days – now decreased to 3 days maximum to avoid resistance
- Tested RBV-free regimens
- Combinations of small molecules tested in animals
- First test of combination in humans (INFORM Trial)

# PROVE2: Study Design



- Patients in the TVR-based treatment groups needed to have undetectable HCV RNA levels at the last study visit before the planned end of treatment (i.e., at week 10 for the T12PR12 and T12P12 groups and at week 20 for the T12PR24 group)

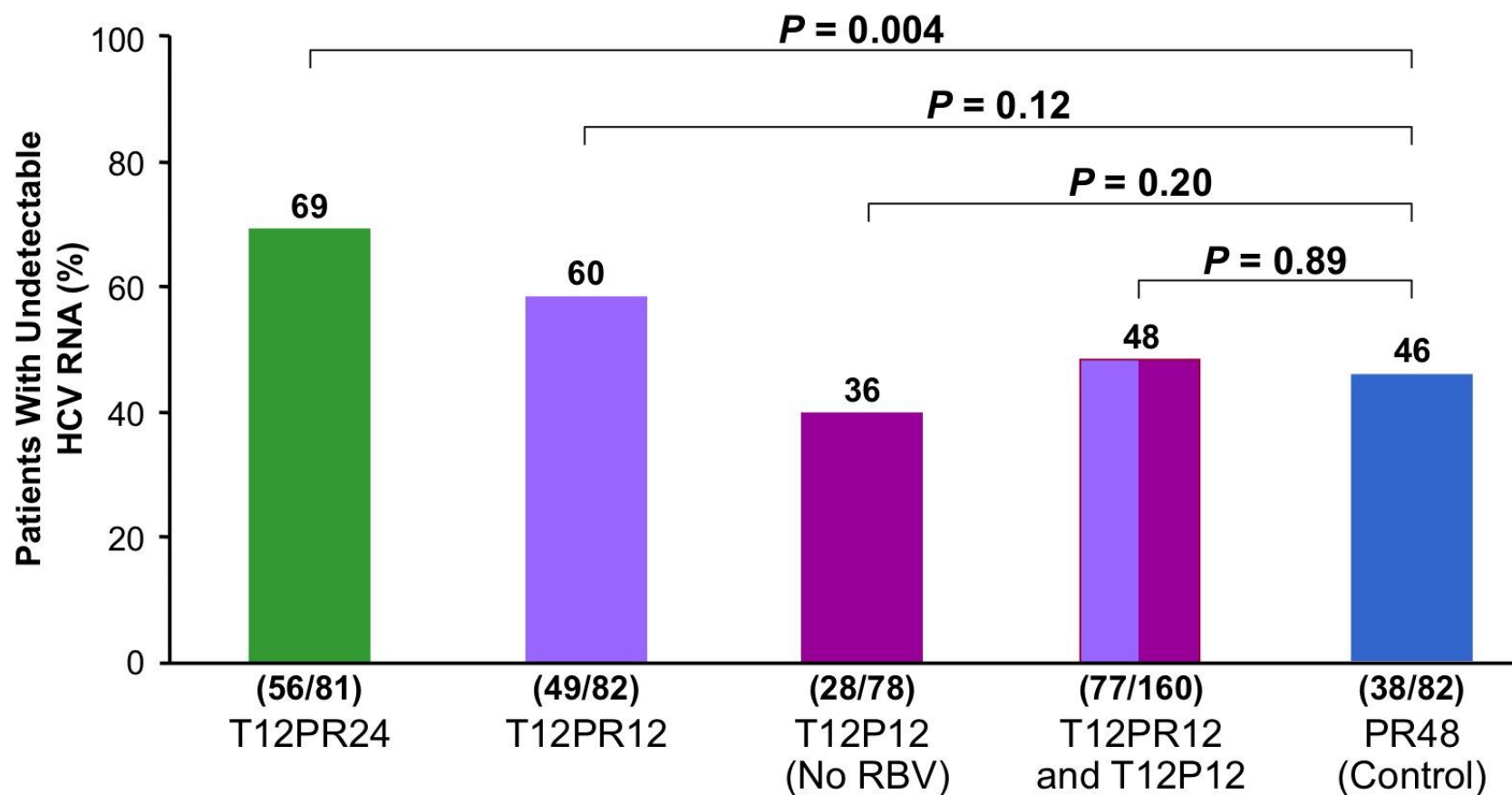
(P) Peg-IFN = pegylated interferon alfa-2a 180 µg/wk subcutaneous injection

(R) RBV = ribavirin 1000 mg/day (body weight <75 kg) or 1200 mg/day (body weight ≥75 kg)

(T) TVR = telaprevir 750 mg q8h (initial loading dose 1250 mg)

Hézode C et al, N Engl J Med 2009;360(18):1839-1850

# PROVE2: SVR Rates



2-sided Fisher's exact test.

Based on ITT (Intention to Treat) analysis

Hézode C et al, N Engl J Med 2009;360(18):1839-1850

# INFORM-1

## *Summary*

- First substantial trial of combination therapy in man
- Potent antiviral effect
- No apparent resistance after 14 days  
*but*
- Followed by Peg/RBV, so we don't know if SVR could have been achieved

# Implications of having effective IFN-free regimens

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- More patients will be treated
- Patients will not need to be treated by IFN experts, including
  - Hepatologists
  - IFN-experienced physicians
  - PAs, NPs
- Easier treatment is likely to spur screening for HCV

“The future ain't what it used to be”

Yogi Berra