# How to optimize treatment in G1 naive patients?

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# Diagnosis

- A 57-year old male patient naive to treatment
- First diagnose CHC in 2005 but choose to ignore VHC Ab positive
- Now remarried for the 6th time and preparing for in-vivo fertilization
- Not sure he wants treatment ?!

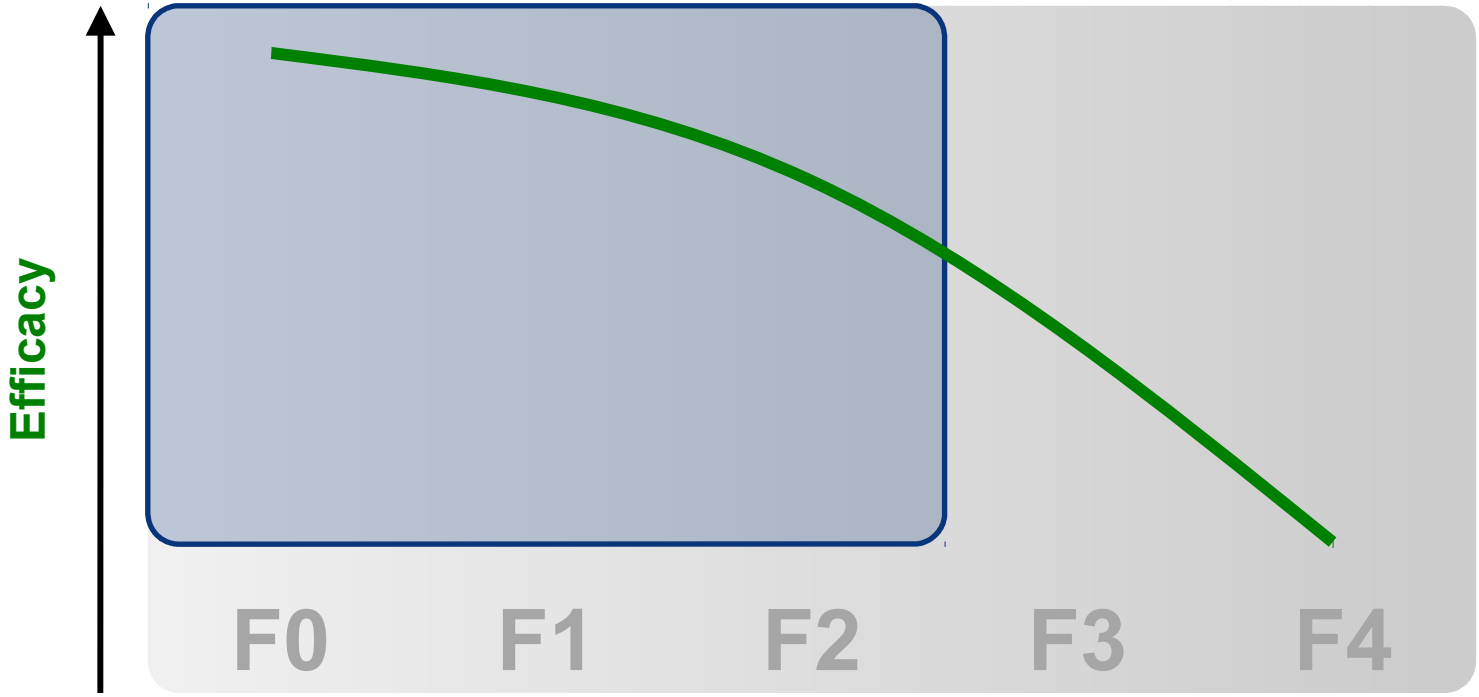
- HCV genotype: 1b
- HCV RNA: 7.9 log10 IU/mL
- Fibromax: F2, A3, NASH N2, ASH H0

# Question

Would you offer treatment to this patient ?

- A: Yes, why not !?
- B: Defer treatment  wait for IFN free treatment
- C: Start Peg and Riba

# Higher chances of cure in mild liver disease



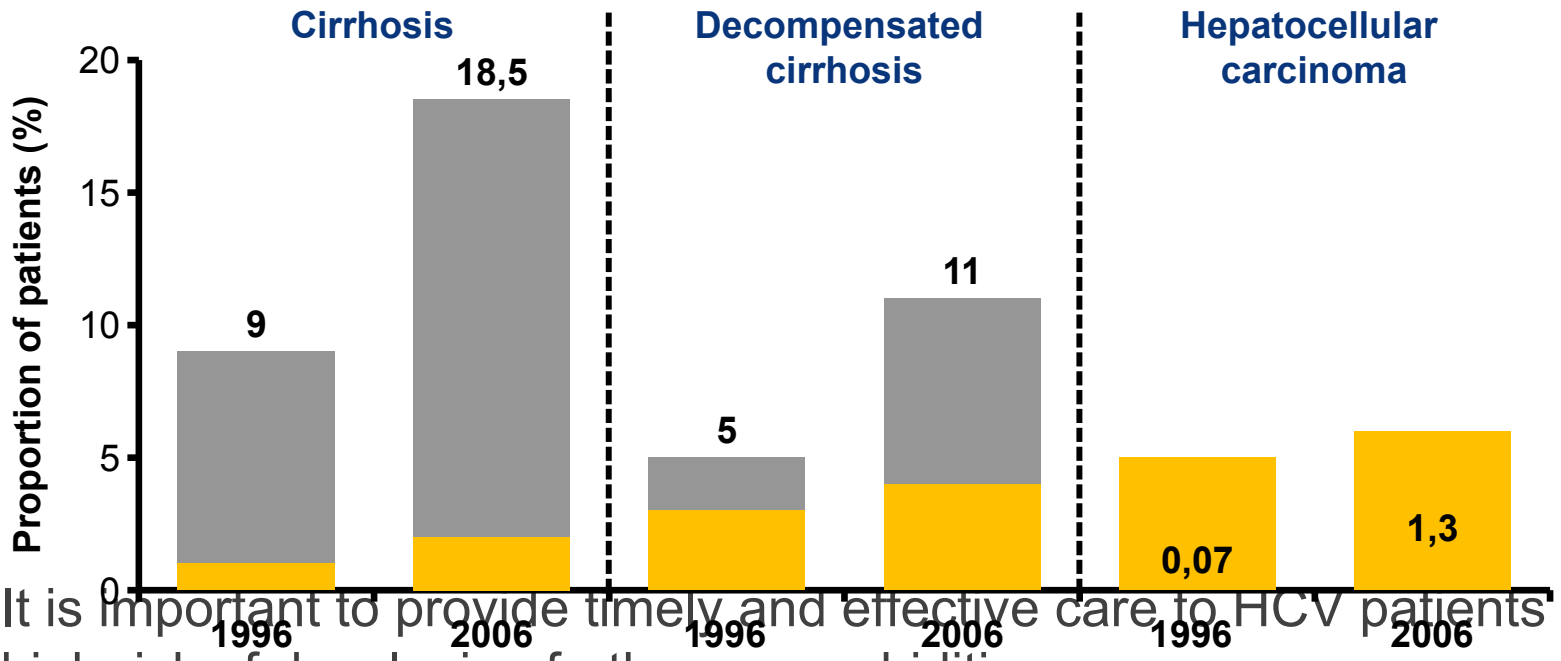

- Higher SVR rates in milder disease stage
- Viral eradication is the only way to prevent disease progression
- Unpredictability of fibrosis progression in the presence of co-morbidities

# Our patient has

- Comorbidites: Heart problems: HTA, Obesity, alter insulin tolerance…
- Concomitent medication
- DDI

# Importance of Early Treatment: Increasing Prevalence of HCV and Associated Co-morbidities

- The prevalence of HCV and associated co-morbidities is increasing
  - In one cohort, the number of individuals with HCV was 17,261 in 1996 compared with 106,242 in 2006



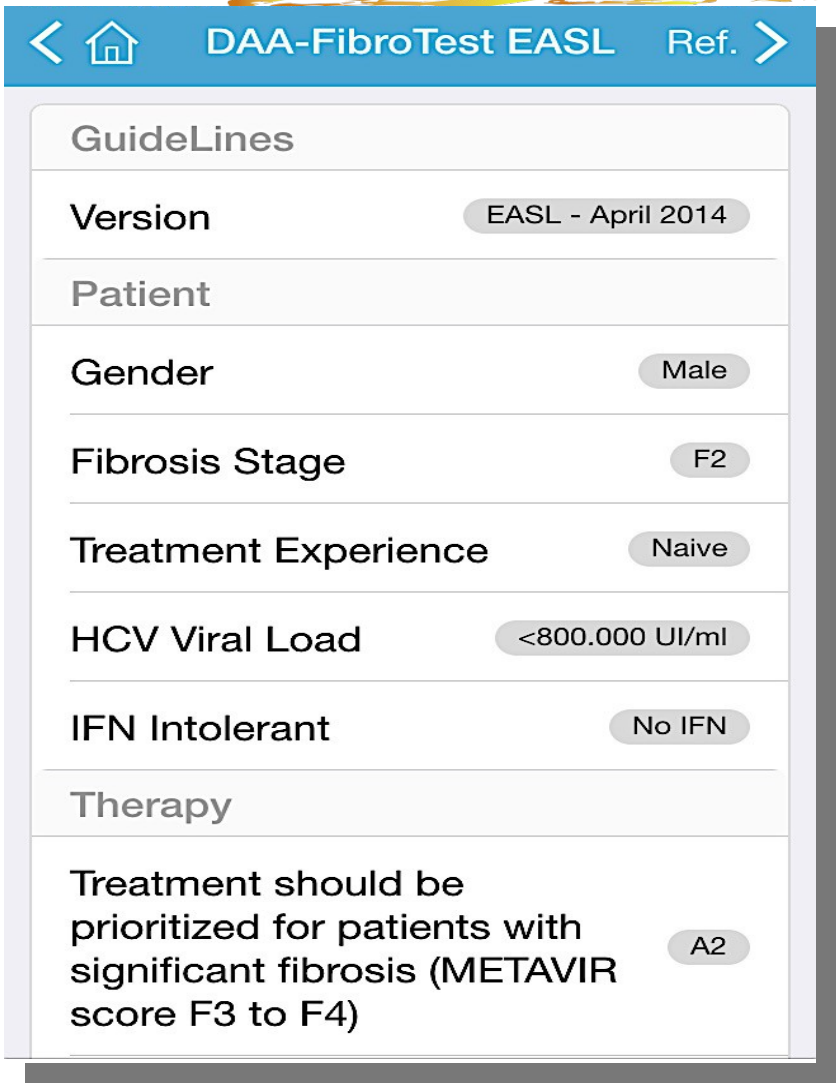

- It is important to provide timely and effective care to HCV patients at high risk of developing further co-morbidities

Kanwal F, et al. Gastroenterology 2011;140; 1182–88

EASL
European Association for the Study of the Liver

## Recommendations

- All treatment-naïve and -experienced patients with compensated disease due to HCV should be considered for therapy **(Recommendation A1)**
- Treatment should be prioritized for patients with significant fibrosis (METAVIR score F3 to F4) **(Recommendation A1)**
- Treatment is justified in patients with moderate fibrosis (METAVIR score F2) **(Recommendation A2)**
- In patients with no or mild disease (METAVIR score F0-F1), the indication for and timing of therapy can be individualized **(Recommendation B1)**
- Patients with decompensated cirrhosis who are on the transplant list should be considered for IFN-free, ideally ribavirin-free therapy **(Recommendation A1)**



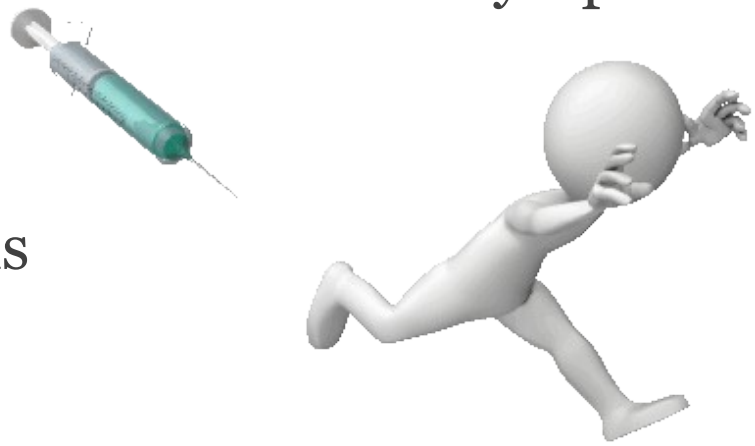

For our patient according to the EASL guidelines 2014

- 6 treatment options:
  - ✓ 3 IFN
  - ✓ 3 IFN free

EASL RECOMMENDATION ON TREATMENT OF HEPATITIS C APRIL 2014
USING FIBROEST APP ACCSED JAN 2015

# Side Effects of IFN Treatment

- Flu-like symptoms
  - Headache
  - **Fatigue or asthenia**
  - Myalgia, arthralgia
  - Fever, chills
- Nausea
- Anorexia
- Diarrhoea
- Psychiatric symptoms
  - **Depression**
  - Insomnia
- Alopecia
- Injection-site reaction
- Leucopenia
- Thyroiditis
- Autoimmunity
- Thrombocytopenia



# Side Effects of RBV Treatment

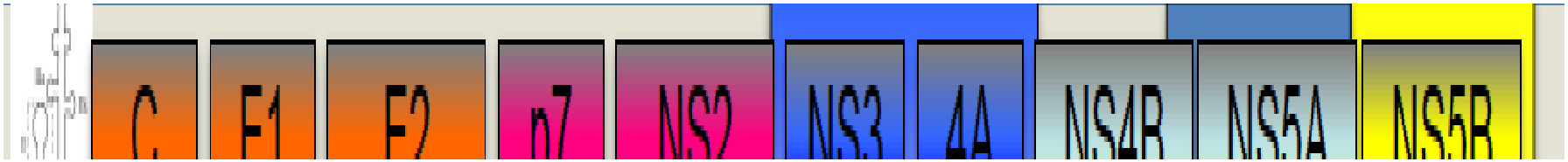
- Haemolytic anaemia
- Teratogenicity
- Cough and dyspnoea
- Rash and pruritus
- Insomnia
- Anorexia

# Our patient 57 years old

- HCV genotype: 1b
- HCV RNA: 7.9 log10 IU/mL
- Fibromax: F2, A3, NASH N2, ASH H0
- Il28B CC
- Resistance test

# DEC 2014

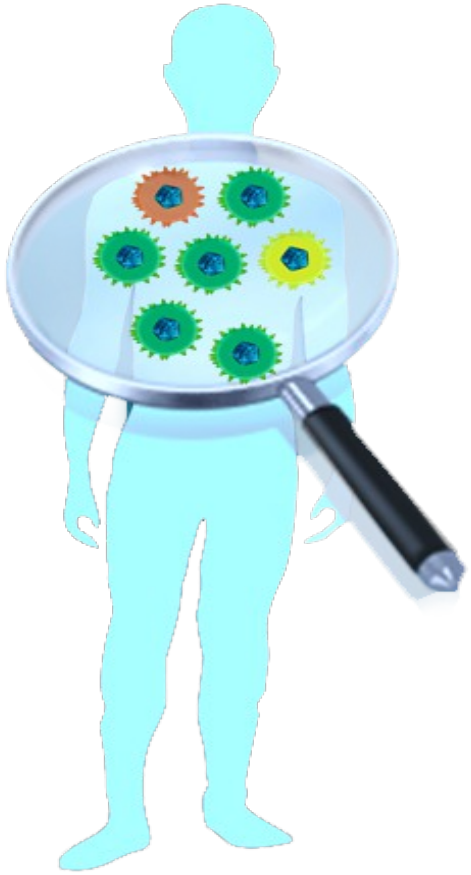
| | |
|---|---|
| NS3 region (w.r.t.D90208) | D30E,V35MV,V48I,Y56F,P86Q,M94L,V114I,R117C,I132V, V150A,I170V |
| NS3 region (w.r.t.H77) | A7S,135MV,742S,Y56F,T61S,R62K,I64L,S68G,V71I, Q89P,S91A,R117C,I132V,A147S,L153I,I170V,N174S |




| drug | prediction | | Scored mutations | Fold change |
|---|---|---|---|---|
| boceprevir | Mutation on scored position | | 36V, 117C, 170V | - |
| telaprevir | Posssible resistent | | 36V, 117C, 132V, 170V | 1.8 |
| simeprevir | susceptible | | none | - |

Resistance test provided by the National Institute of Infectious Diseases Matei Bals Bucharest

# Resistant variants are present before treatment



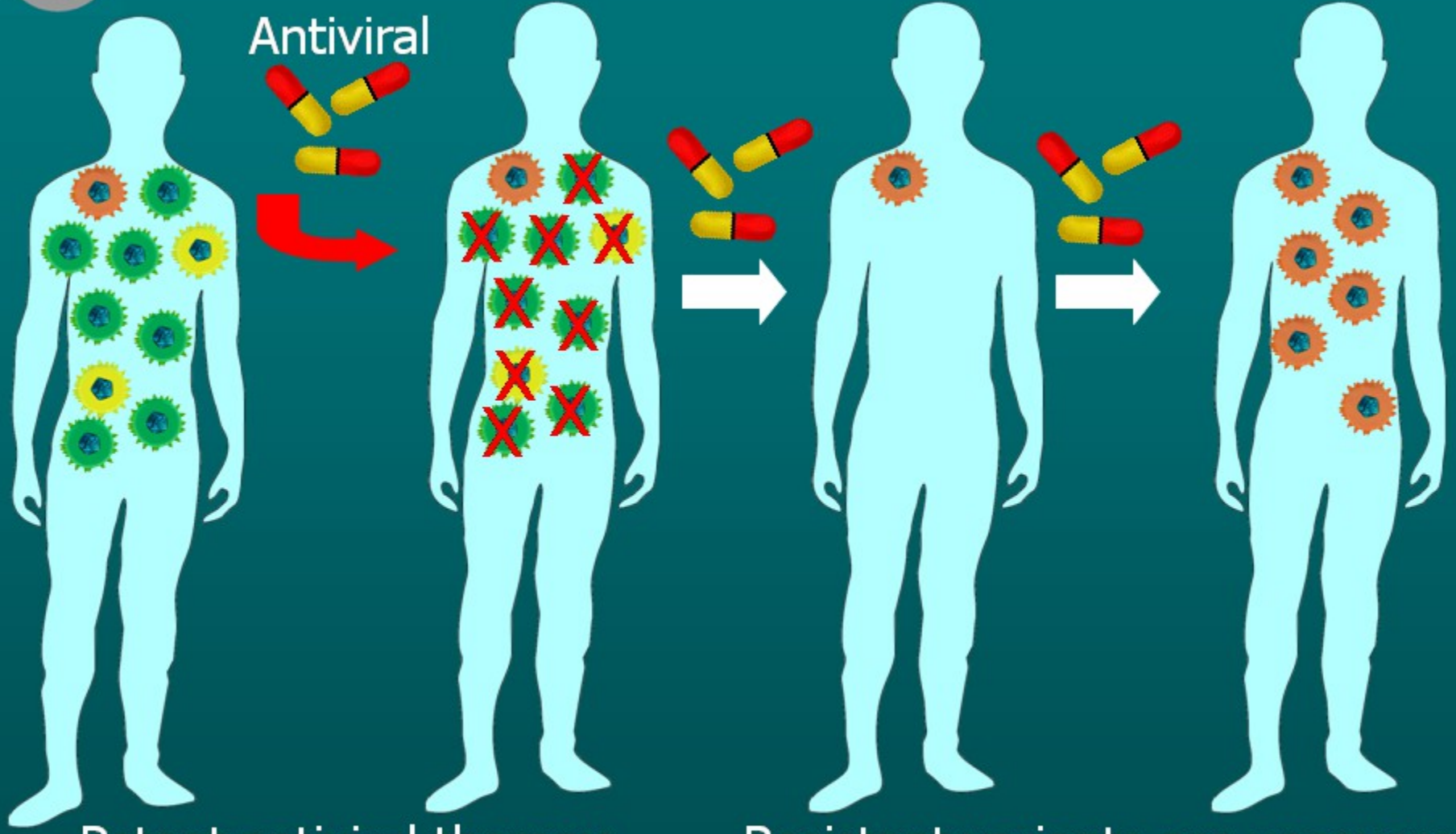
HCV is present as a mixture of populations of genetically distinct, but closely related, virions in every patient

- 1012 virions produced per day
- 1 nucleotide mutation produced per virus produced
- All possible single nucleotide mutant virus, and all combinations of duble nucleotide mutant viruses, are though to preexist before treatment in most patients2

- Most resistant variant are relatively unfit and are undetectable prior to therapy with current tehnologies3,4

1. Pawlotsky JM. *Clin Liver Dis*, 2003; 7:45-66; 2. Rong L. *Sci Transl Med* , 2010: 2 (30):30ra32; 3. Kuntzen. *Hepatology* , 2008; 48(6): 1769-78; 4. Bartels DJ. *J I nfec Dis*, 2008; 198: 797-9

# Resistant variants can be selected during treatment




Potent antiviral therapy eliminates sensitive variants

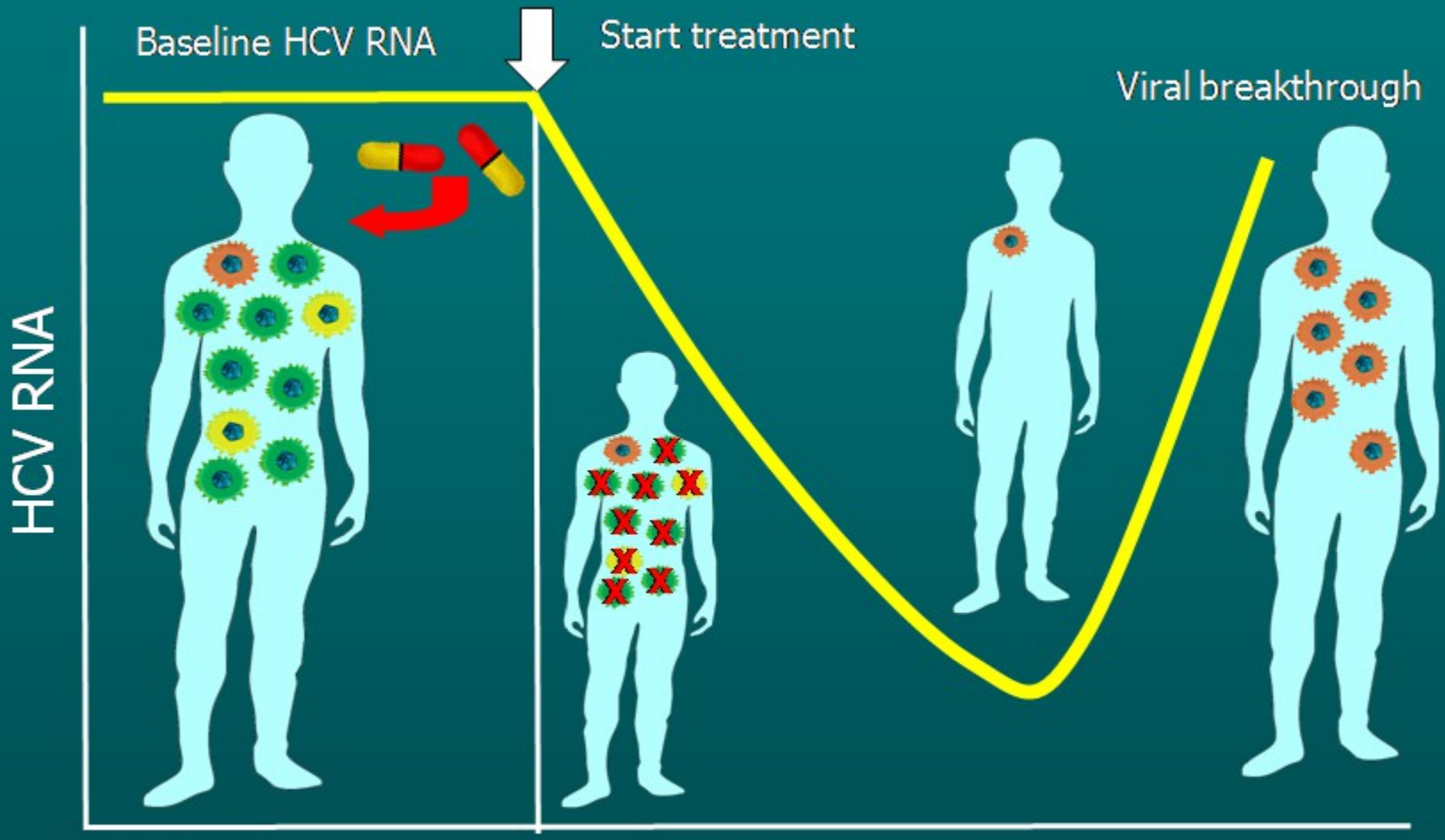
Resistant variants are uncovered which can then expand



Resistant virus

Sensitive virus

# Frequent monitoring of HCV RNA levels can detect treatment failure and resistance




Patients have viral variants with different levels of resistance to a drug

Resistant virus

Sensitive virus

## Genotype 1, Option 1

### Treat for 12 weeks

PEG IFN-α + ribavirin + sofosbuvir

- **PEG IFN-A** — PEG IFN-α weekly — 12 weeks
- **RIBAVIRIN** — ribavirin 1200 mg — 12 weeks
- **SOFOSBUVIR** — sofosbuvir 400 mg — 12 weeks

### Explanations

Patients infected with HCV genotype 1 can be treated with a combination of weekly pegylated IFN-α, daily weight-based ribavirin 1200 mg, and daily sofosbuvir (400 mg) 12 weeks — A1

DAA-FibroTest EASL Ref.

## Genotype 1, Option 2

### Treat for 24 or 48 weeks

PEG IFN-α + ribavirin + simeprevir

- **PEG IFN-A** — PEG IFN-α weekly — 24 or 48 weeks
- **RIBAVIRIN** — ribavirin 1200 mg — 24 or 48 weeks
- **SIMEPREVIR** — simeprevir 150 mg — 12 weeks

### Explanations

Patients infected with HCV genotype 1 can be treated with a combination of weekly pegylated IFN-α, daily weight-based ribavirin 1200 mg, and daily simeprevir (150 mg) — A1

Simeprevir should be administered 12 weeks in combination with pegylated IFN-α and ribavirin. Pegylated IFN-α and ribavirin should then be administered alone for an additional 12 weeks (total treatment duration 24 weeks) in treatment-naive and prior relapser patients, including cirrhotics, and for an additional 36 weeks (total treatment duration 48 weeks) in prior partial and null responders, including cirrhotics — B1

HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is — A2

DAA-FibroTest EASL Ref.

## Genotype 1, Option 3

### Treat for 24 weeks

PEG IFN-α + ribavirin + daclatasvir

- **PEG IFN-A** — PEG IFN-α weekly — 24 weeks
- **RIBAVIRIN** — ribavirin 1200 mg — 24 weeks
- **DACLATASVIR** — daclatasvir 60 mg — 12 or 24 weeks

### Explanations

Patients infected with HCV genotype 1, subtype 1b can be treated with a combination of weekly pegylated IFN-α, daily weight-based ribavirin 1200 mg, and daily daclatasvir (60 mg) 24 weeks — B1

This combination should not be proposed to patients infected with HCV genotype 1, subtype 1a, given the preliminary data available, pending results of on-going large-scale studies — B1

Daclatasvir should be administered 12 weeks in combination with pegylated IFN-α and ribavirin

## Genotype 1, Option 1

### Treat for 12 weeks

PEG IFN-α + ribavirin + sofosbuvir

| | | |
|---|---|---|
| PEG IFN-A | PEG IFN-α weekly | 12 weeks |
| RIBAVIRIN | ribavirin 1200 mg | 12 weeks |
| SOFOSBUVIR | sofosbuvir 400 mg | 12 weeks |

### Explanations

Patients infected with HCV genotype 1 can be treated with a combination of weekly pegylated IFN-α, daily weight-based ribavirin 1200 mg, and daily sofosbuvir (400 mg) 12 weeks — A1



## Genotype 1, Option 2

### Treat for 24 or 48 weeks

PEG IFN-α + ribavirin + simeprevir

| | | |
|---|---|---|
| PEG IFN-A | PEG IFN-α weekly | 24 or 48 weeks |
| RIBAVIRIN | ribavirin 1200 mg | 24 or 48 weeks |
| SIMEPREVIR | simeprevir 150 mg | 12 weeks |

### Explanations

Simeprevir should be administered 12 weeks in combination with pegylated IFN-α and ribavirin. Pegylated IFN-α and ribavirin should then be administered alone for an additional 12 weeks (total treatment duration 24 weeks) in treatment-naive and prior relapser patients, including cirrhotics, and for an additional 36 weeks (total treatment duration 48 weeks) in prior partial and null responders, including cirrhotics — B1

HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is — A2



## Genotype 1, Option 3

### Treat for 24 weeks

PEG IFN-α + ribavirin + daclatasvir

| | | |
|---|---|---|
| PEG IFN-A | PEG IFN-α weekly | 24 weeks |
| RIBAVIRIN | ribavirin 1200 mg | 24 weeks |
| DACLATASVIR | daclatasvir 60 mg | 12 or 24 weeks |

### Explanations

Patients infected with HCV genotype 1, subtype 1b can be treated with a combination of weekly pegylated IFN-α, daily weight-based ribavirin 1200 mg, and daily daclatasvir (60 mg) 24 weeks — B1

This combination should not be proposed to patients infected with HCV genotype 1, subtype 1a, given the preliminary data available, pending results of on-going large-scale studies — B1

Daclatasvir should be administered 12 weeks in combination with pegylated IFN-α and ribavirin

DAA-FibroTest EASL Ref.

## Genotype 1, Option 4

### Treat for 24 weeks

ribavirin + sofosbuvir

**RIBAVIRIN**
ribavirin 1200 mg — 24 weeks

**SOFOSBUVIR**
sofosbuvir 400 mg — 24 weeks

### Explanations

Patients infected with HCV genotype 1 who are IFN-intolerant or -ineligible can be treated with daily weight-based ribavirin 1200 mg and daily sofosbuvir (400 mg) 24 weeks — B2

DAA-FibroTest EASL Ref.

## Genotype 1, Option 5

### Treat for 12 weeks

simeprevir + sofosbuvir

**SIMEPREVIR**
simeprevir 150 mg — 12 weeks

**SOFOSBUVIR**
sofosbuvir 400 mg — 12 weeks

### Explanations

Patients infected with HCV genotype 1 can be treated with an interferon-free combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg) for 12 weeks — B1

Preliminary results do not indicate a major advantage of adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis — B1

DAA-FibroTest EASL Ref.

## Genotype 1, Option 6

### Treat for 12 weeks

sofosbuvir + daclatasvir

**SOFOSBUVIR**
sofosbuvir 400 mg — 12 weeks

**DACLATASVIR**
daclatasvir 60 mg — 12 weeks

### Explanations

Patients infected with HCV genotype 1 can be treated with an interferon-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) 12 weeks in treatment-naive (pending data with 12 weeks of therapy in treatment-experienced patients)

Preliminary results do not indicate a major advantage to adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis — B1

DAA-FibroTest EASL Ref.

Genotype 1, Option 4

## Treat for 24 weeks

ribavirin + sofosbuvir

RIBAVIRIN
ribavirin 1200 mg — 24 weeks

SOFOSBUVIR
sofosbuvir 400 mg — 24 weeks

Explanations

Patients infected with HCV genotype 1 who are IFN-intolerant or -ineligible can be treated with daily weight-based ribavirin 1200 mg and daily sofosbuvir (400 mg) 24 weeks B2

DAA-FibroTest EASL Ref.

Genotype 1, Option 5

## Treat for 12 weeks

simeprevir + sofosbuvir

SIMEPREVIR
simeprevir 150 mg — 12 weeks

SOFOSBUVIR
sofosbuvir 400 mg — 12 weeks

Explanations

Preliminary results do not indicate a major advantage of adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis B1

DAA-FibroTest EASL Ref.

Genotype 1, Option 6

## Treat for 12 weeks

sofosbuvir + daclatasvir

SOFOSBUVIR
sofosbuvir 400 mg — 12 weeks

DACLATASVIR
daclatasvir 60 mg — 12 weeks

Explanations

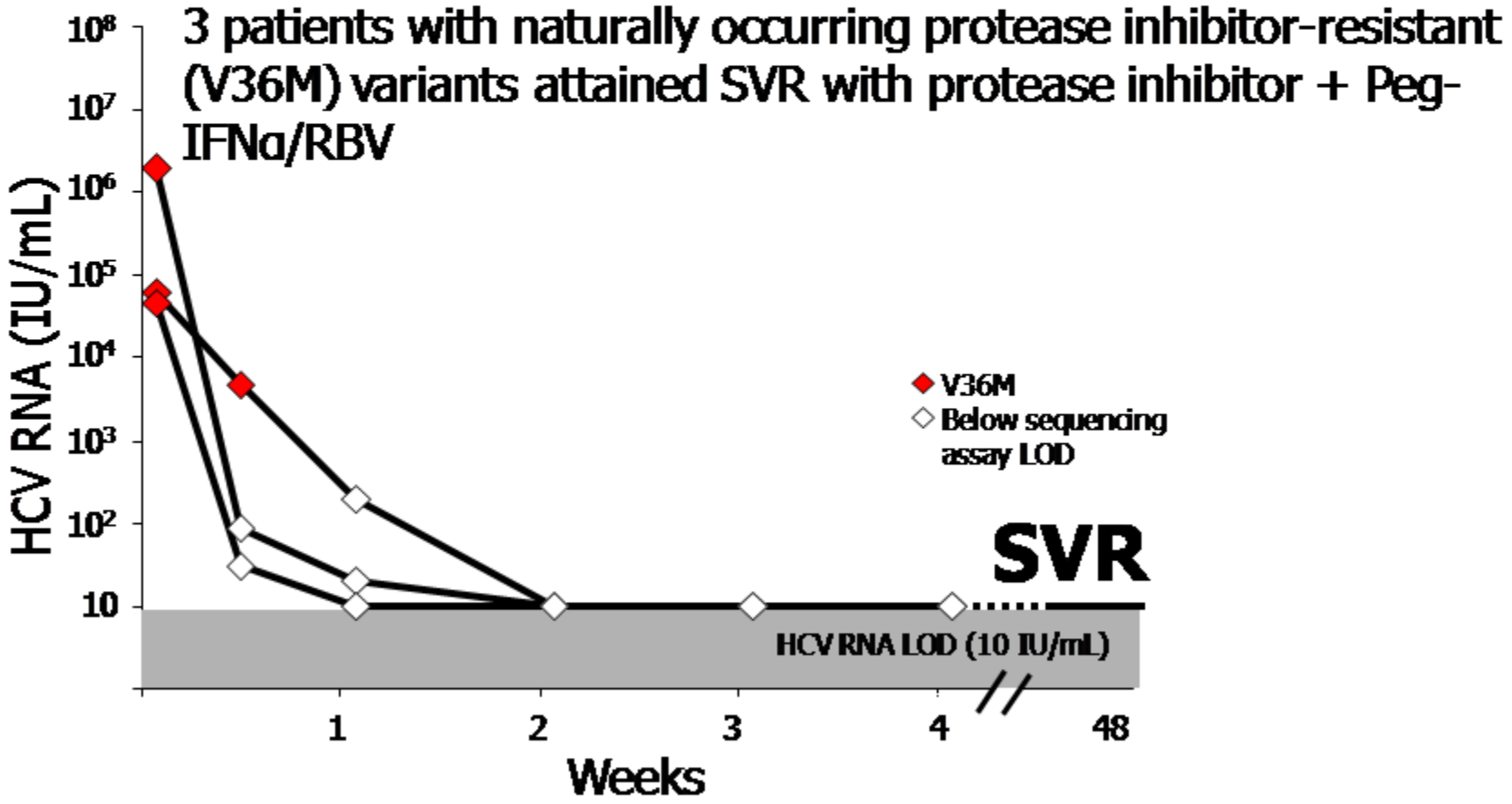
(pending data with 12 weeks of therapy in treatment-experienced patients)

Preliminary results do not indicate a major advantage to adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis B1

# What else?...

# Resistant variants can be eliminated with a combination drug regimen

| Target | Variant | NS3 Linear | NS3 Macrocyclic | NS5A inhibitor | NS5B nucleoside | NS5B Palm | NS5B Thumb | NS5B Finger | Peg-IFN | RBV |
|---|---|---|---|---|---|---|---|---|---|---|
| NS3 | V36M | R | S | S | S | S | S | S | S | S |

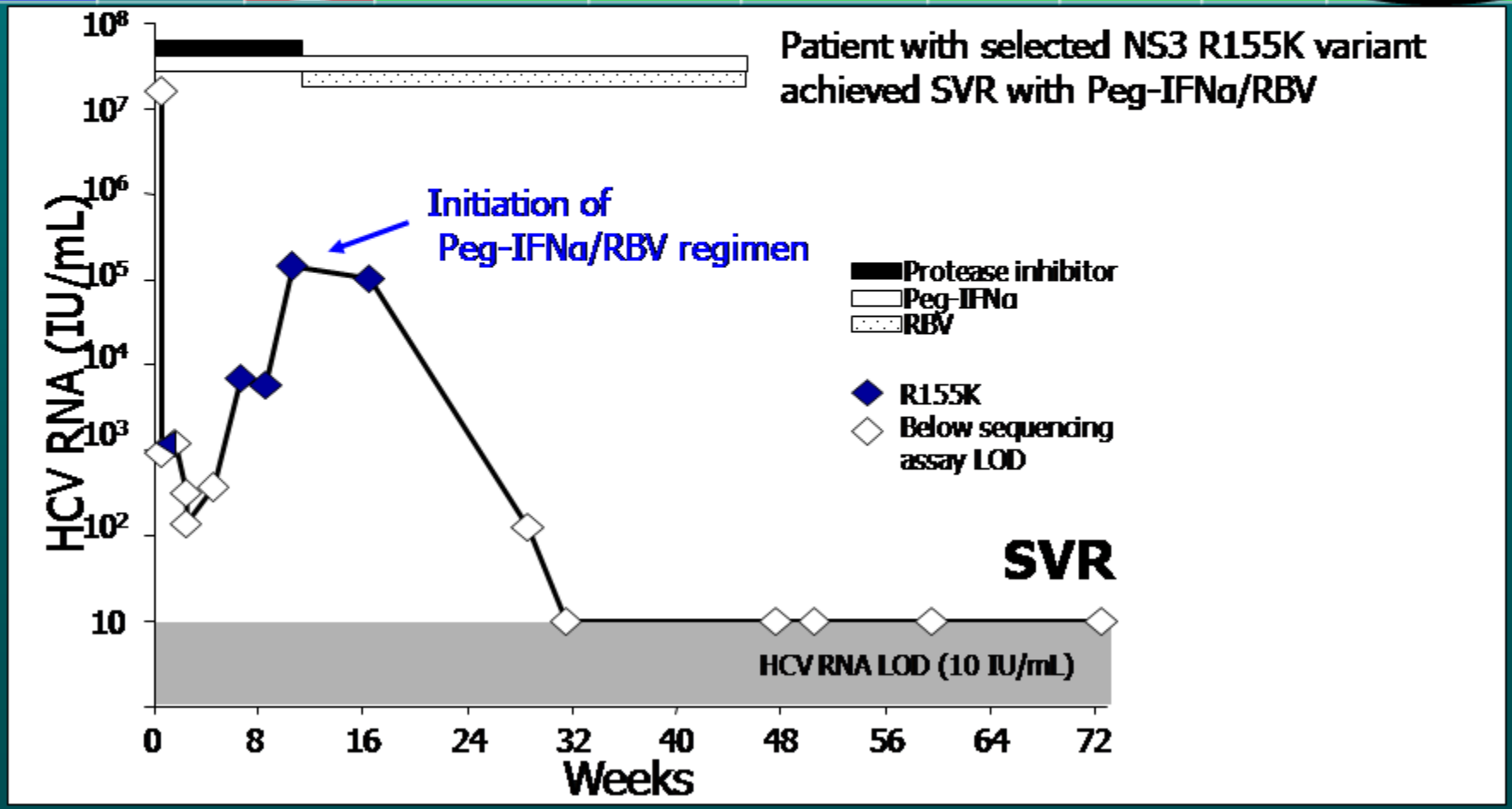





Adapted from Bartels DJ., *et al. J Infec Dis*, 2008;198(6); 800-7

# Patients with protease inhibitor-resistant variants can respond to Peg-IFNα/RBV

| Target | Variant | NS3 Linear | NS3 Macrocyclic | NS5A inhibitor | NS5B nucleoside | NS5B Palm | NS5B Thumb | NS5B Finger | Peg-IFN | RBV |
|---|---|---|---|---|---|---|---|---|---|---|
| NS3 | R155K | R | S | S | S | S | S | S | S | S |

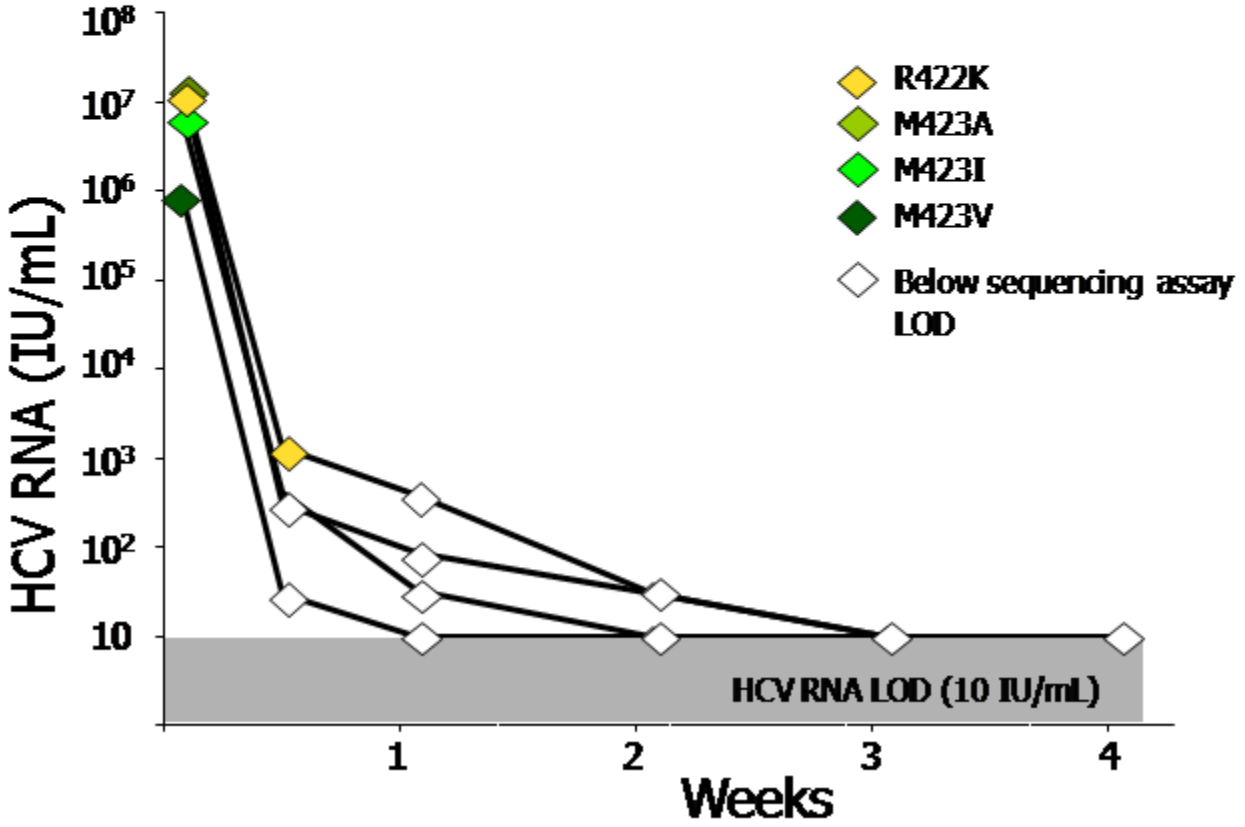




Unpublished data, example from telaprevir PROVE2 study

# Patients with naturally occurring polymerase inhibitor-resistant variants can respond to protease inhibitor + Peg-IFNα/RBV

| Target | Variant | NS3 Linear | NS3 Macrocyclic | NS5A inhibitor | NS5B nucleoside | NS5B Palm | NS5B Thumb | NS5B Finger | Peg-IFN | RBV |
|---|---|---|---|---|---|---|---|---|---|---|
| NS5B | R422K | S | S | S | S | S | R | S | S | S |
| | M423T | S | S | S | S | S | R | S | S | S |





Unpublished data, examples from telaprevir PROVE1 study

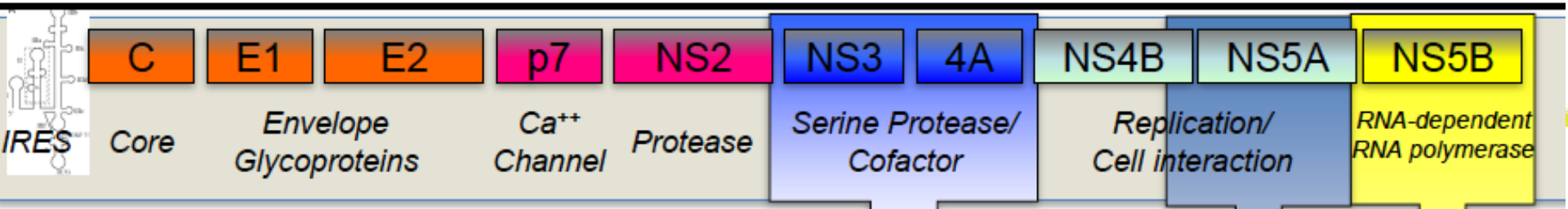
# AASLD/IDSA/IAS-USA 2014 HCV Treatment Recommendations Initial Therapy for Patients with Genotype 1 Chronic HCV

| Patients with GT 1 HCV: Initial Treatment & Retreatment of Relapsers* |
| --- |
| Not Recommended |
| Peginterferon + Ribavirin +/- [Boceprevir or Telaprevir] |
| Monotherapy with Peginterferon, Ribavirin, or a Direct Acting Antiviral Agent |
| Treatment of Decompensated Cirrhosis with Peginterferon or Simeprevir |

*Patients who experienced relapse after Peginterferon plus Ribavirin therapy

Source: AASLD/IDSA/IAS-USA (www.hcvguidelines.org). Viewed April 22, 2014

# DAA Agents Overview




**Daclatasvir**

**Ledipasvir**

**Ombitasvir**

**GS-5816,MK-8742**

**Mod to High potency**

**+/-Multi-genotypic coverage**

**Intermediate barrier to resistance**

**Telaprevir, Boceprevir, Simeprevir, Faldaprevir, Asunaprevir,**

**ABT 450/r,MK-5172**

**High potency**

**Multi-genotypic coverage**

**Low barrier to resistance ( 1a)**

**NS5B Non Nucleoside Inhibitors (NNI)**

**Low potency**

**Limited-genotypic coverage**

**Low barrier to resistance**

**Deliobuvir,Dasabuvir,BMS-791325**

**NS5B Nucleotide Inhibitors (NI)**

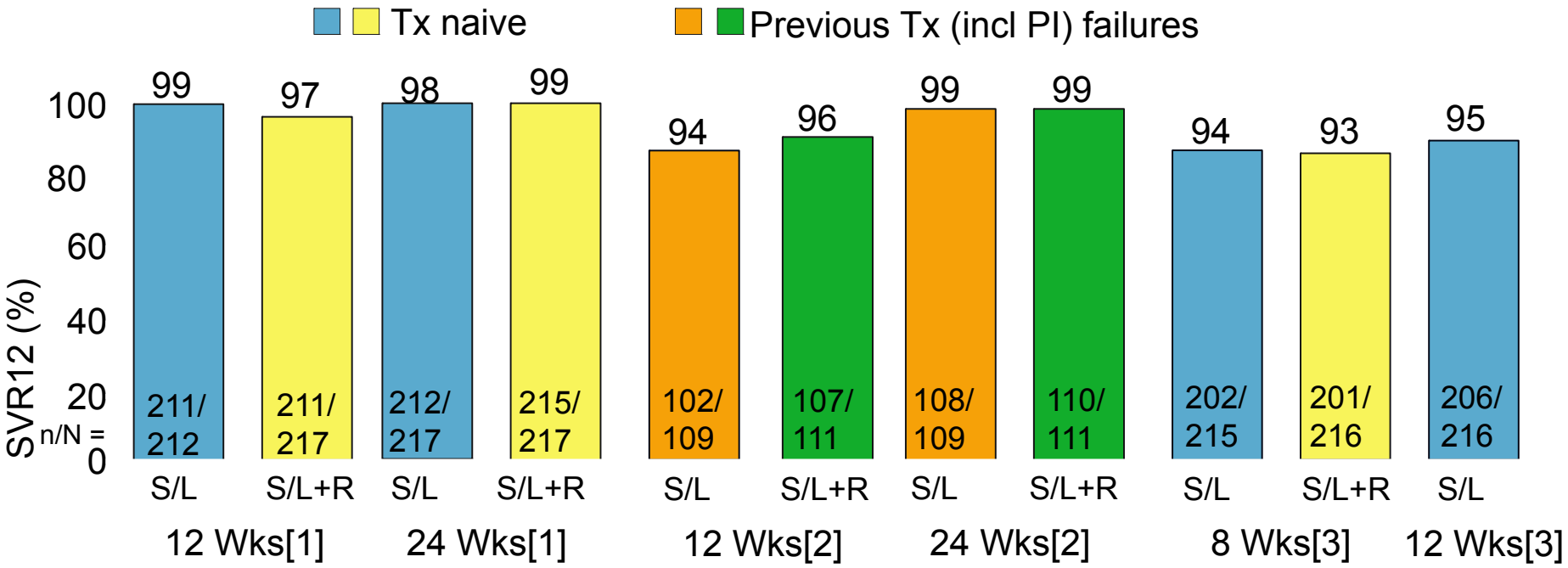
**Intermediate to high potency**

**Pan genotypic coverage**

**High barrier to resistance**

**Sofosbuvir**

# ION 1, 2, and 3: Sofosbuvir/Ledipasvir ± RBV in Tx-Naive Pts and Previous Failures




- 8 wks adequate for noncirrhotic treatment-naive pts
- RBV provides no benefit
- No SOF resistance observed; most virologic failures have LDV resistance

1. Afdhal N, et al. N Engl J Med. 2014;370:1889-1898. 2. Afdhal N, et al. N Engl J Med. 2014;370:1483-1493.
3. Kowdley KV, et al. N Engl J Med. 2014;370:1879-1888.

# Sofosbuvir/Ledipasvir: FDA-Approved Indication

| Population | Recommended Treatment Duration |
|---|---|
| Treatment naive with or without cirrhosis | 12 wks* |
| Treatment experienced† *without* cirrhosis | 12 wks |
| Treatment experienced† *with* cirrhosis | 24 wks |

*8-wk duration can be considered in treatment-naive pts without cirrhosis who have pretreatment HCV RNA < 6 million IU/mL.

†Treatment-experienced pts who have failed treatment with pegIFN/RBV ± HCV PI.

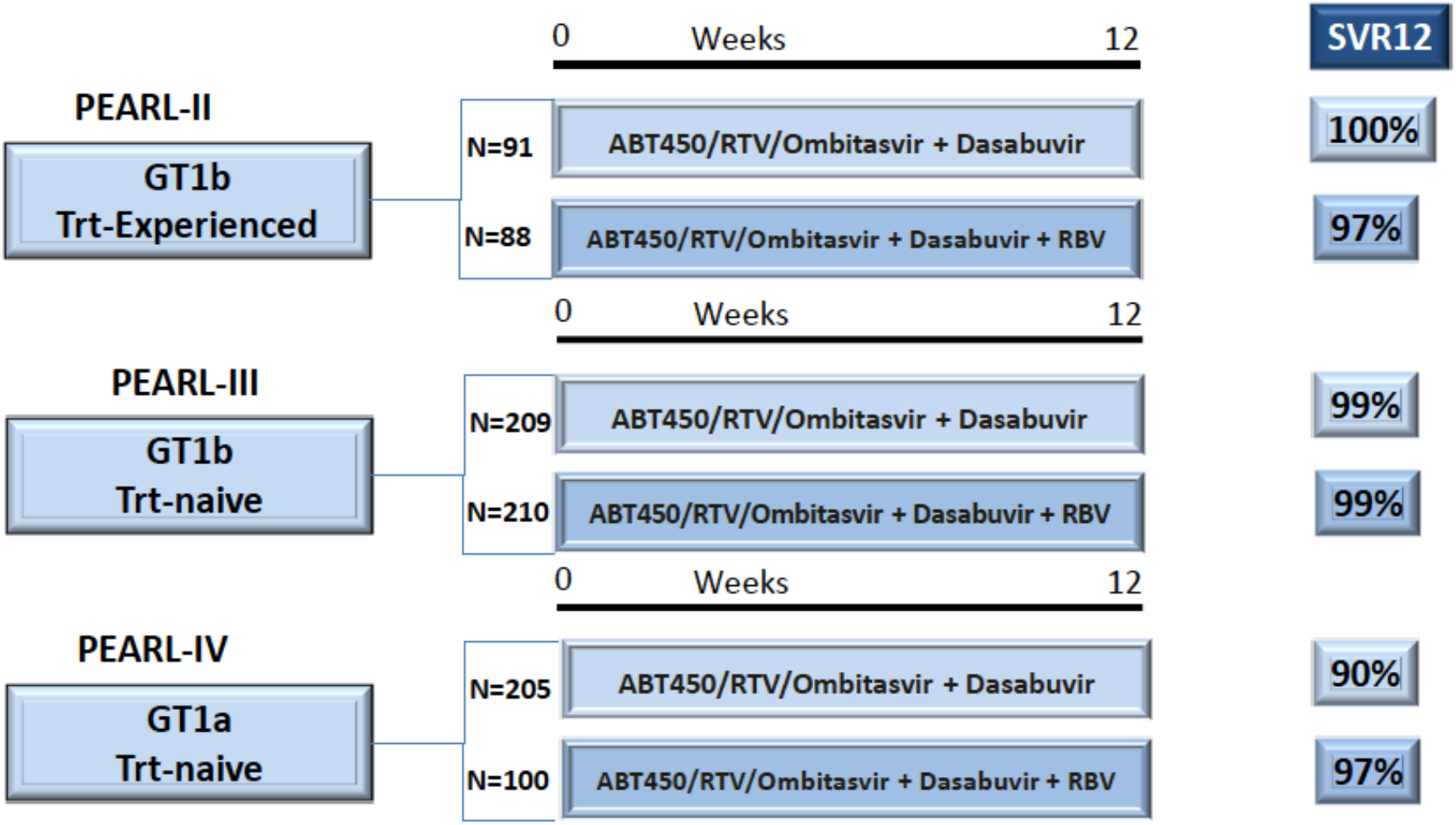
Sofosbuvir/ledipasvir [package insert]. October 2014.

# 3 Direct Acting Antiviral Regimen

- The 3D regimen includes:
  - **Co-formulated ABT-450/r/Ombitasvir with Dasabuvir**
    - ABT-450, a NS3/4A protease inhibitor (identified by AbbVie and Enanta)
    - Ritonavir (pharmacokinetic enhancer)
    - Ombitasvir (ABT-267), a NS5A inhibitor
    - Dasabuvir (ABT-333), a non-nucleoside NS5B polymerase inhibitor

[1]Feld J, et al. *N Engl J Med*. 2014:370(17);1594-603
[2]Zeuzem S, et al. *N Engl J Med*. 2014; 370(17):1604-14

# 3D regimen in HCV genotype 1a and 1b with or without ribavirin




Andreone P, et al. DDW 2014. Abstract 929e. Ferenci et al, CROI, 2014. Press release.

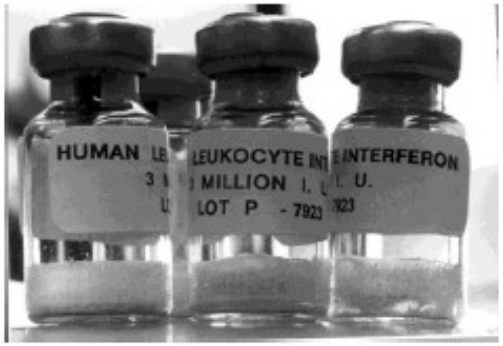
# Novel HCV Treatment Regimens in HCV

## Phase III Completed

- Sofosbuvir/Ledipasvir ± RBV
- ABT450/r + Ombitasvir + Dasabuvir ± RBV
- Daclatasvir + Asunaprevir-1b

- **Phase III in progress**
- Daclatasvir + Asunaprevir plus BMS-791325
- MK-5172 + MK8742

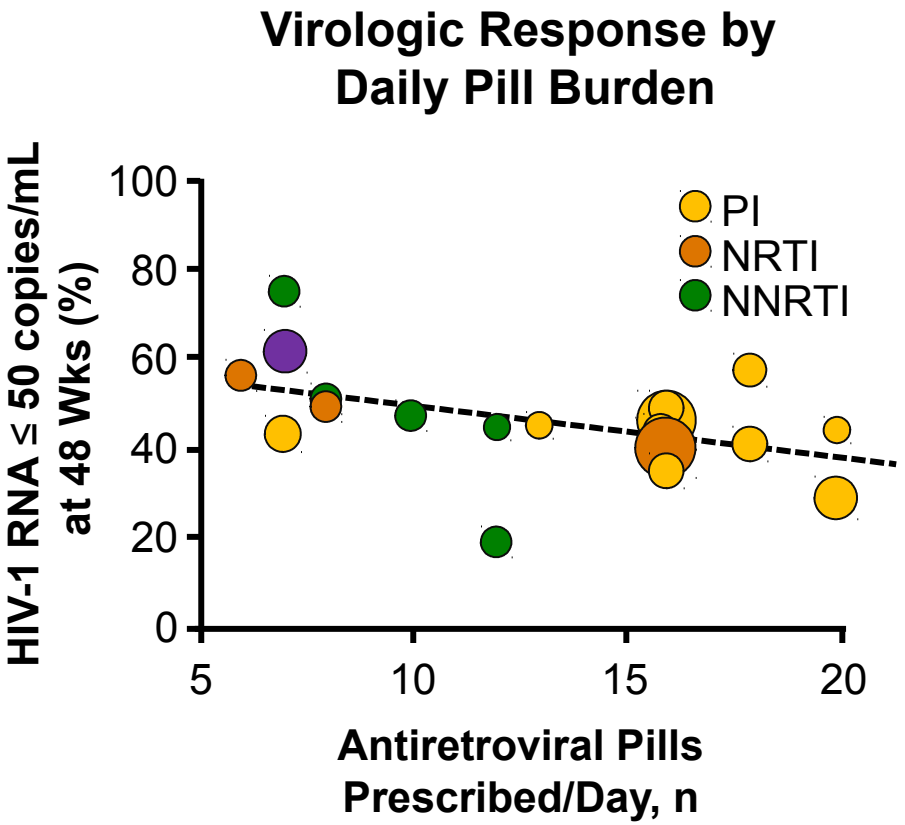
**Interferon**
**"Back bone" of HCV Therapy**




**Oral Therapy**

# Adherence Affected by Regimen Complexity and Pill Burden

- Data from HIV field illustrates virologic suppression as a function of daily pill burden[1]
- HCV triple therapy involves multiple daily pills plus injection drug
  - BOC TID: 12 pills/day
  - TVR TID: 6 pills/day
  - RBV BID: 4-6 pills/day
  - PegIFN: injection QW




Bartlett JA, et al. AIDS. 2001;15:1369-1377.

# Pill Burden in HCV Therapy

## Fixed Dose Combination

1) Ledipasvir/Sofosbuvir

2) MK-5172 and MK-5842-potentially

## 3 DAA Regimens

450r/Ombitasvir +Dasabuvir

Simeprevir plus Sofosbuvir

Daclatasvir (when approved) and Sofosbuvir

Asunaprevir+ Daclatasvir+BMS-791325

**Ribavirin 2-6 pills a day**

# Motivating Pts to Complete HCV Treatment

- Future HCV-related health problems most important factor encouraging therapy initiation
  - HCV therapy efficacy and safety also significant
- Fear of adverse events most important factor limiting initiation and completion of HCV therapy
- Pt fears can be overcome with open communication and education
- Emotional support (family, friends, support groups) important motivators for treatment initiation and adherence

Fusfeld L, et al. BMC Infect Dis. 2013;13:234.

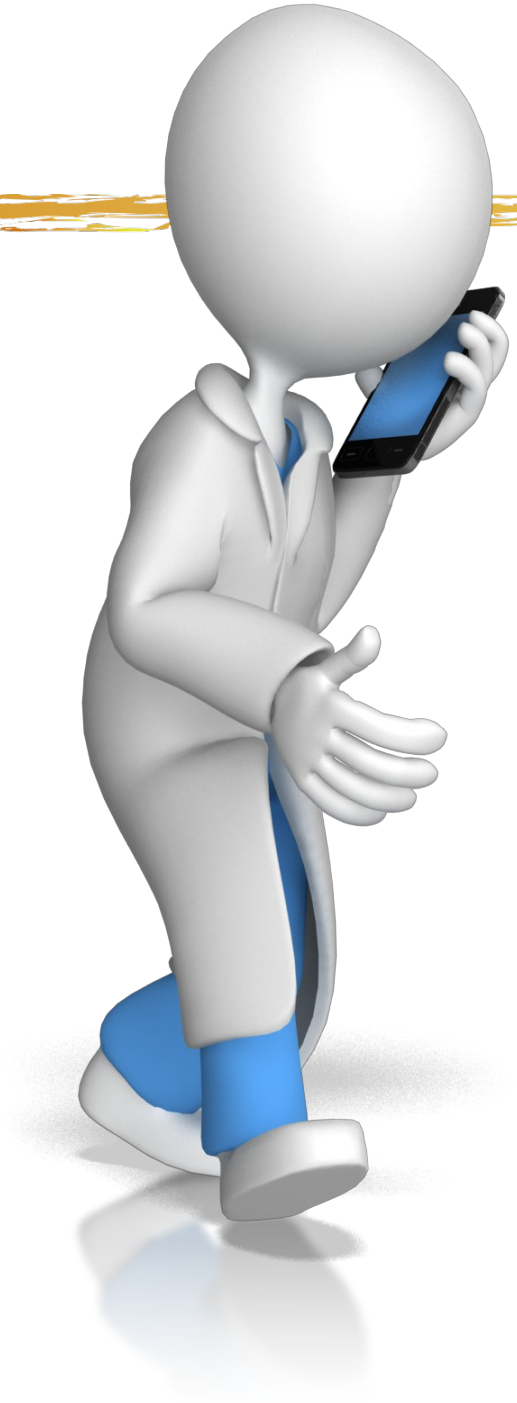
# Summary: Adherence Support Strategies

- Pill burden, regimen complexity, AEs adversely effect adherence

- Common strategies for adherence support
  - Pt education
  - Scheduling alarms (eg, cell phone)
  - Pill boxes/organizers
  - Blister packs
  - Medication worksheets

# And for second concern check  DDI…

# And ..



## *La maladie hépatique est sévère*

| | |
|---|---|
| PBH antérieure F3 ou F4 | **Traitement à court terme** |
| Ou Fibroscan ≥ 9,5 kPa | |
| Ou FibroTest ≥ 0,59 | |
| Ou FibroMètre ≥ 0,63 | |

Le bénéfice clinique à traiter rapidement le malade est important : diminution du risque de décompensation de la maladie hépatique, diminution du risque de carcinome hépatocellulaire, amélioration de la survie.

## *La maladie hépatique est peu sévère*

| | |
|---|---|
| Fibroscan < 5,6 kPa | **Surveillance annuelle. Le traitement à court terme n'est pas nécessaire.** |
| ou FibroTest < 0,27 | |
| ou FibroMètre < 0,33 | |

Le bénéfice clinique à traiter le malade dans l'année qui vient n'est pas montré. Cependant, une surveillance annuelle par l'une de ces méthodes est recommandée.

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## *La maladie hépatique est difficile à évaluer*

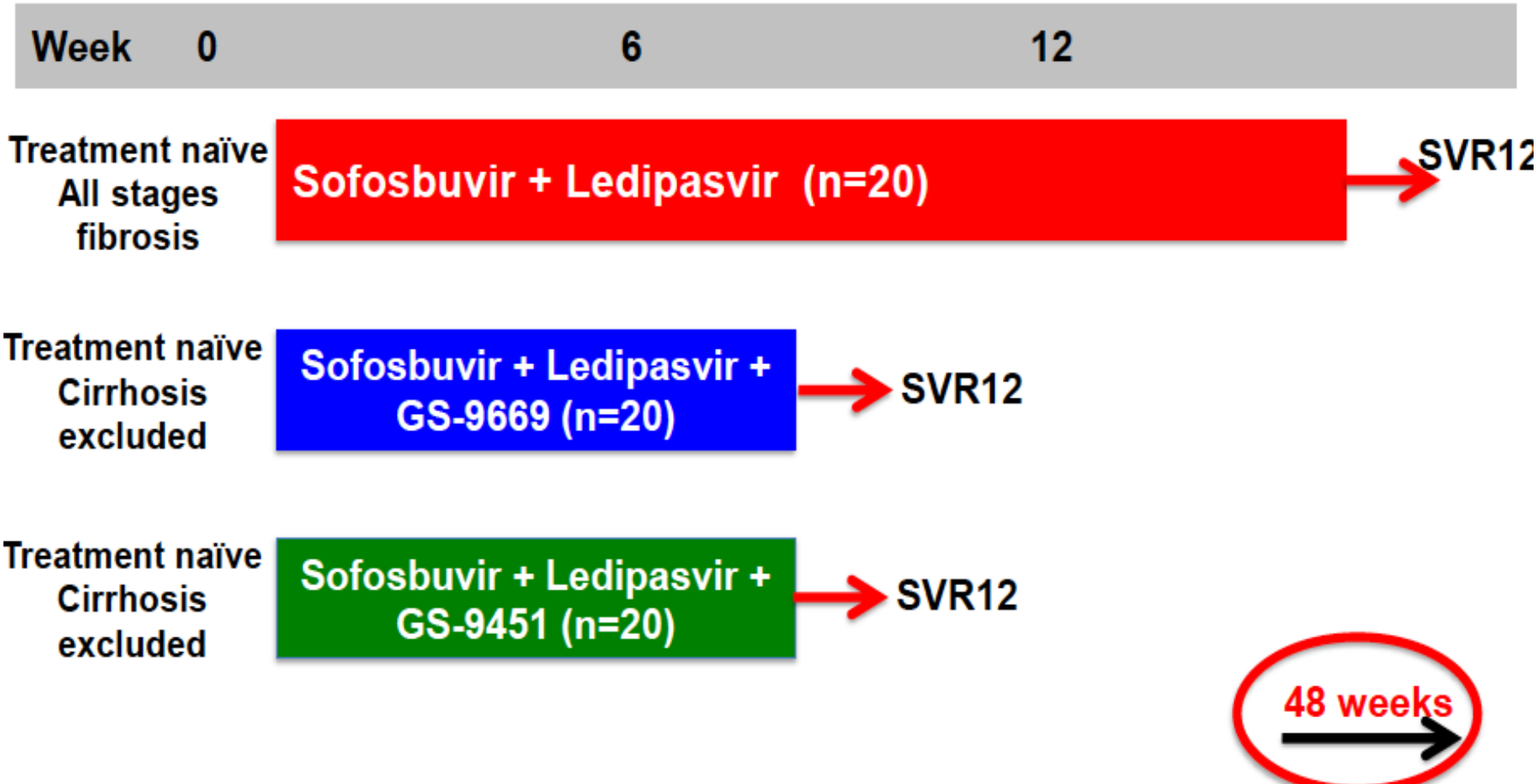
| | |
|---|---|
| Fibroscan 5,6 – 9,4 kPa<br>ou FibroTest 0,27 – 0,58<br>ou FibroMètre 0,33 – 0,62 | **Faire un deuxième test** |

Lorsque deux méthodes sont utilisées successivement, il convient d'associer une mesure de l'élasticité hépatique à un test sanguin (et non deux tests sanguins).

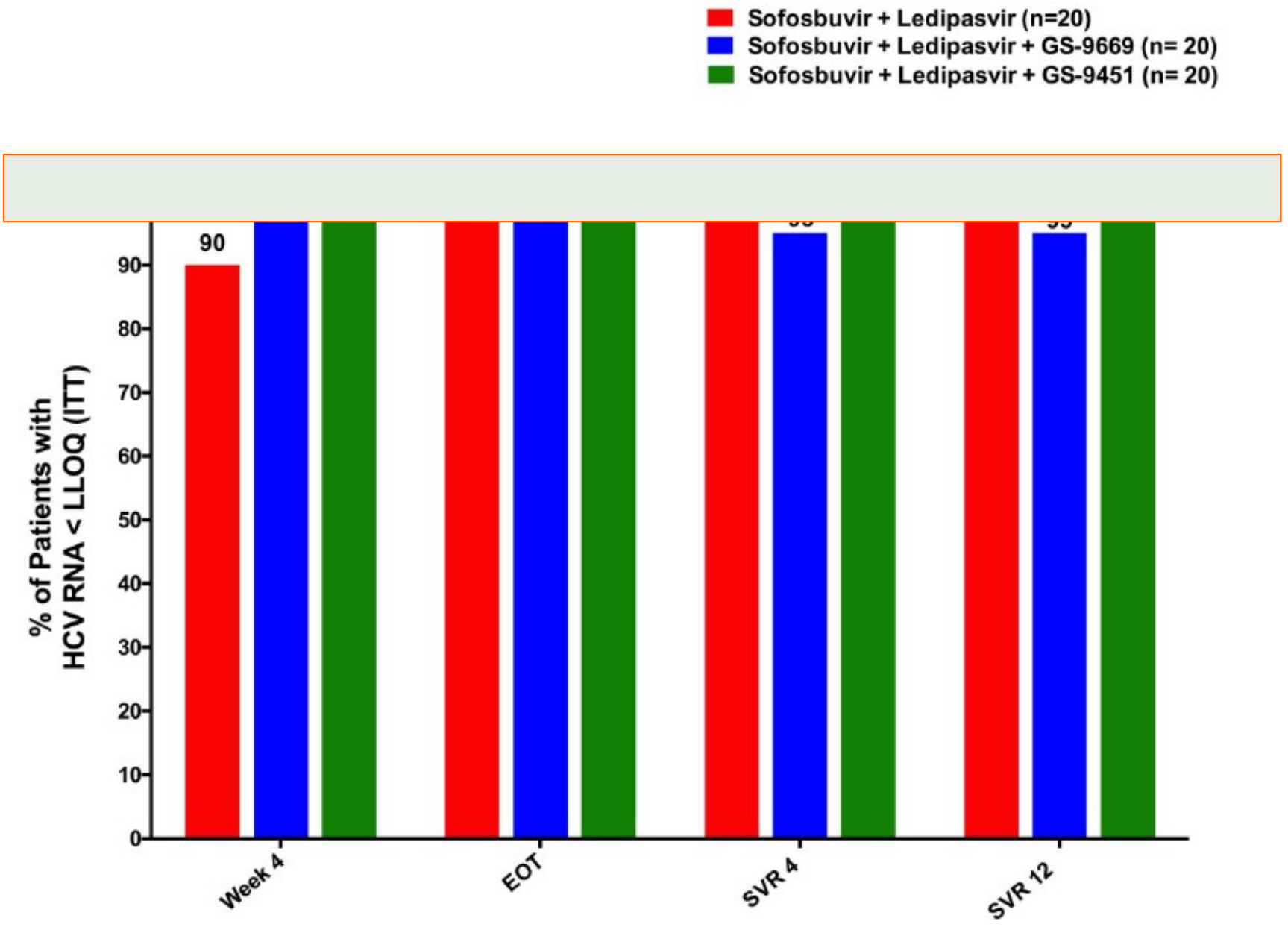
| | |
|---|---|
| Fibroscan 5,6 – 9,4 kPa et Fibrotest ≥ 0,59<br>ou Fibroscan 5,6 – 9,4 kPa et Fibromètre ≥ 0,63 | **La maladie hépatique est sévère**<br><br>**Traitement à court terme** |
| FibroTest 0,27 – 0,58 et Fibroscan ≥ 9,5 kPa<br>ou Fibromètre 0,33 – 0,62 et Fibroscan ≥ 9,5 kPa | |
| Fibroscan < 7,1 kPa et Fibrotest < 0,48<br>ou Fibroscan < 7,1 kPa et Fibromètre < 0,41 | **La maladie hépatique est peu sévère. Surveillance annuelle. Le traitement à court terme n'est pas nécessaire.** |
| Dans les autres cas | **Surveillance à un an et envisager un traitement à moyen terme (2 à 3 ans)** |

# Study Design

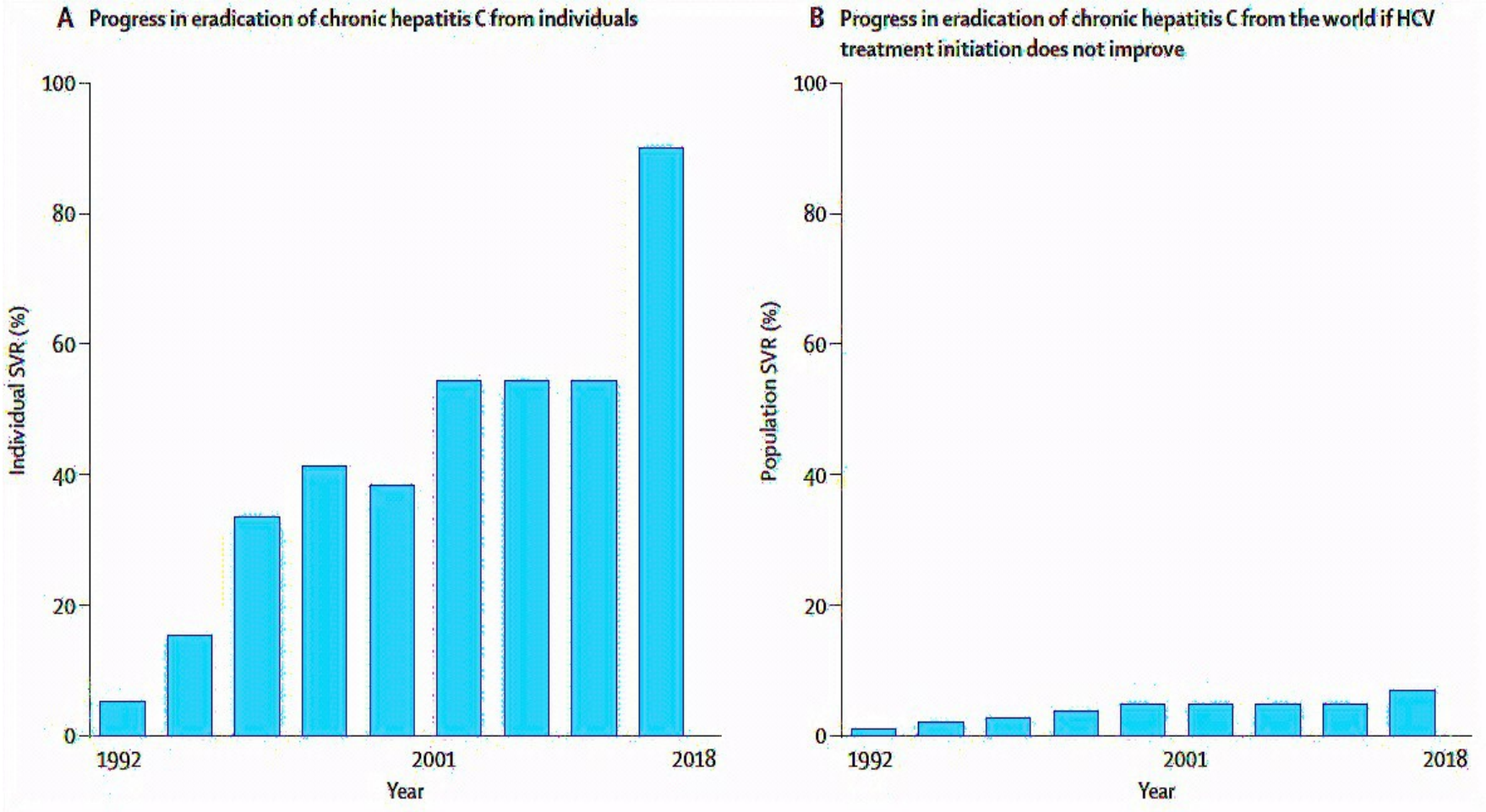
- Sofosbuvir (nucleotide NS5B inhibitor) 400 mg / ledipasvir (NS5A inhibitor) 90 mg once daily
- GS-9669 (non-nucleoside NS5B inhibitor) 500 mg once daily
- GS-9451 (a protease/ NS3/4 inhibitor) 80 mg once daily



# Treatment Response (ITT)



# Impact of improving HCV treatment




Thomas DL. Lancet 2010;376:1441-1442

# Wait and monitor..