The long term impact of treatment on the outcome of liver disease?

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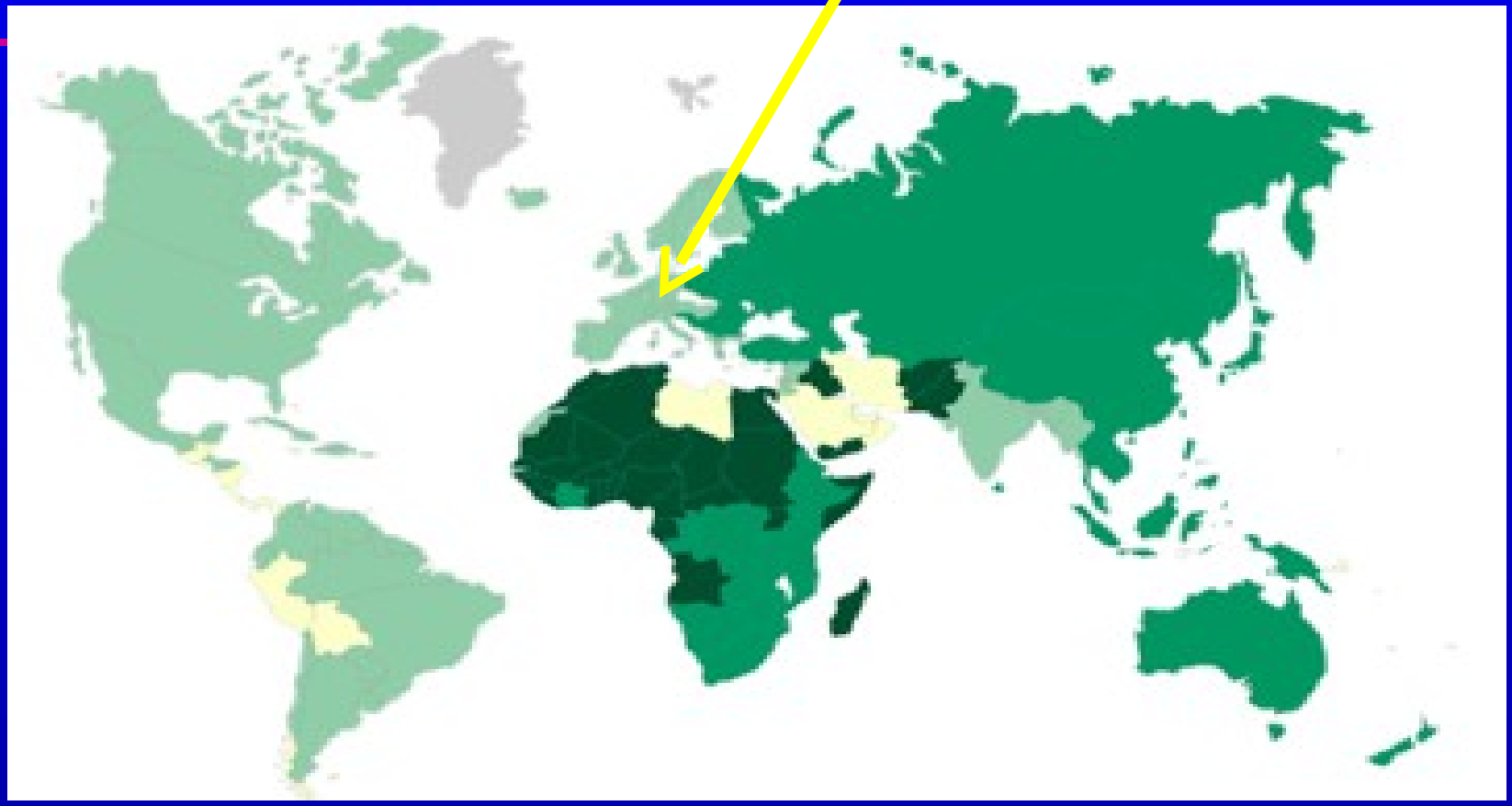
Conflicts of Interest

- Expert board, presentation at workshops and travel grants : Abbott, BMS, Gilead, MSD, Janssen, ViiV health care

Isabelle a 49 years old woman



≥ 2,9 %
2,0 % - 2,9 %
1,0 % - 1,9 %
≤ 1,0 %

Isabelle a 49 years old woman,

2012: chronic HCV infection is diagnosed

Medical History
IDU in 1984 for two years

Currently no alcohol consumption (and for the last 20 years)
No active medications

No other cormobidities

December 2012 - First outpatient visit

Total bilirubin	1 mg/dL
AST	81 UI/L
ALT	105 UI/L
Hb	14 g/dl
Platelets	200.000/mm^3
HBsAg, anti-HIV	neg/neg
HCV-RNA, Genotype	350.000 IU/ml, Ia

December 2012 - First outpatient visit

Physical Examination: nl

BMI: 21.2 (65 Kg x 1.75 m)

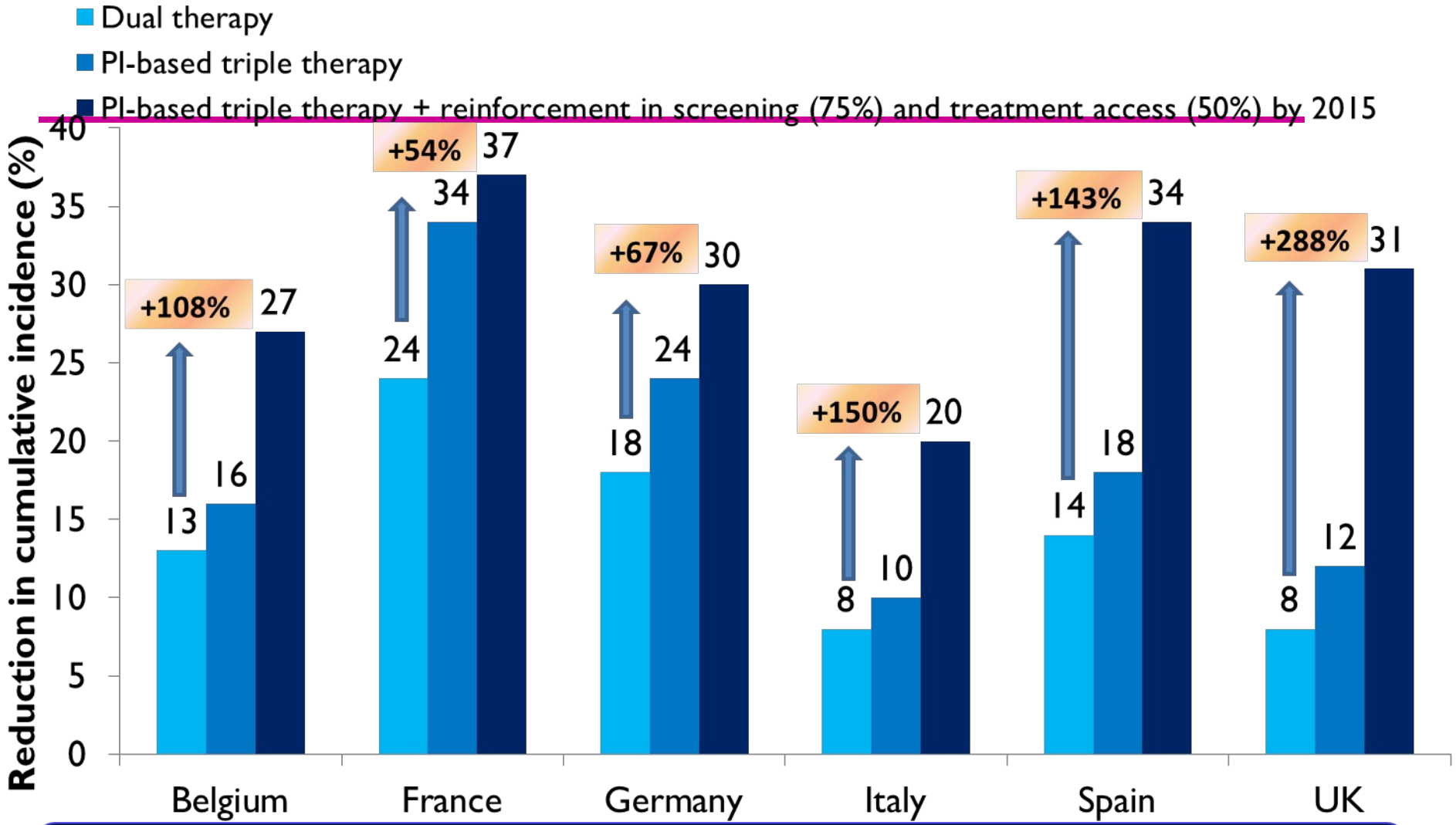
US: nl

Fibroscan: 5.5 KPa, IQR 1.4, SR 95%

The long term impact of treatment on the outcome of liver disease?

Mathematical Modelling

Specific reduction in cumulative incidence of genotype 1 HCV-related cirrhosis, **2012-2021**



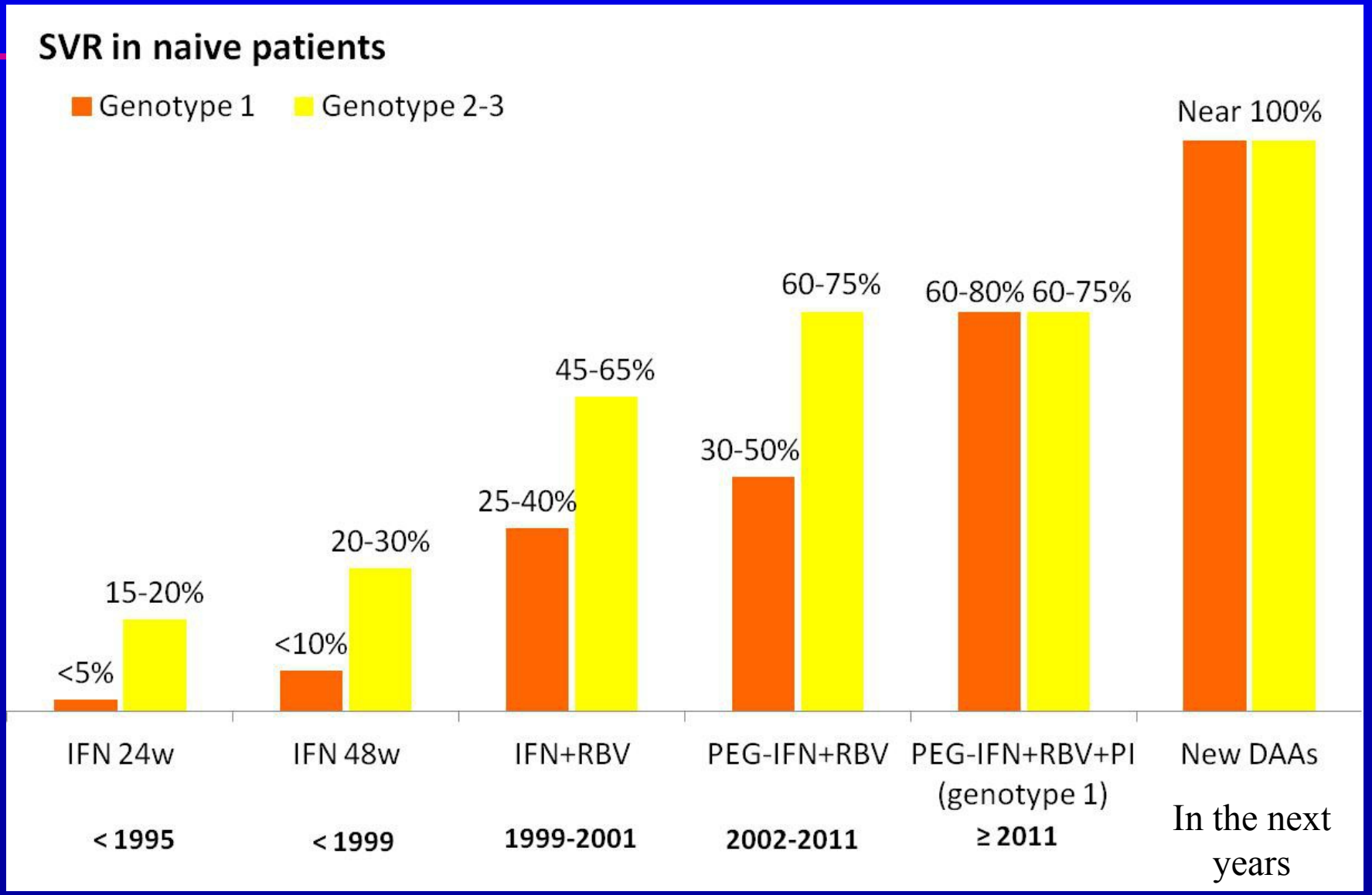
Dramatic reduction in HCV-related cirrhosis with PI-based triple therapy + reinforced screening and treatment access

Deuffic-Burban et al, Gastroenterology 2012

Would you treat this patient?

- With the current standard-of-care triple therapy combining a protease inhibitor, telaprevir **or** boceprevir, PEG-IFN and RBV?
- Wait IFN-based new DAAs?
- Wait IFN-free regimens?

Effectiveness, cost, and cost-effectiveness


SVR in naive patients
Genotype 1
Genotype 2-3
<5%
15-20%
<10%
20-30%
25-40%
45-65%
30-50%
60-75%
60-80%
60-75%
Near 100%
IFN 24w
IFN 48w
IFN+RBV
PEG-IFN+RBV
PEG-IFN+RBV+PI
(genotype 1)
New DAAs
< 1995
< 1999
1999-2001
2002-2011
≥ 2011
In the next years

ORIGINAL ARTICLE

Sofosbuvir for Previously Untreated Chronic Hepatitis C Infection

Eric Lawitz, M.D., Alessandra Mangia, M.D., David Wyles, M.D.,

Table 2. Response during and after Treatment Period.

Response	NEUTRINO Study SOF+PEG+RBV for 12 Wk (N=327)
HCV RNA <25 IU/ml — no./total no. (%)	
During treatment	
At 2 wk	299/327 (91)
At 4 wk	321/325 (99)
At last observed measurement	326/327 (>99)
After end of treatment	
At 4 wk	302/327 (92)
At 12 wk	295/327 (90)
Virologic breakthrough during treatment — no. (%)	0

Genotype 1 = 89%
Non–CC IL28B genotype = 71%
Cirrhosis = 17%

ORIGINAL ARTICLE

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Eric Lawitz, M.D., Alessandra Mangia, M.D., David Wyles, M.D.,

Table 3. Adverse Events, Discontinuation of Treatment, and Hematologic Abn

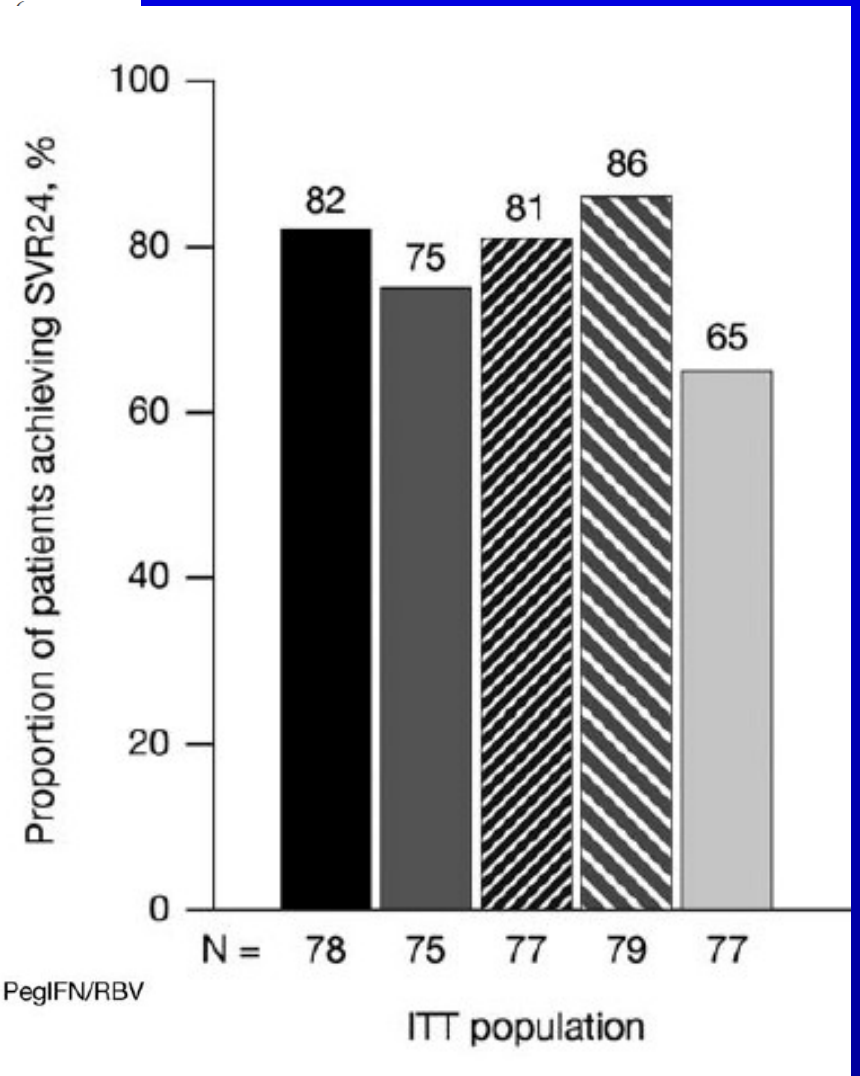
Event	NEUTRINO Study
	SOF+PEG+RBV for 12 Weeks (N=327)
Mean duration of treatment — wk	12±1
Discontinuation because of an adverse event — no. (%)	5 (2)
Any serious adverse event during treatment — no. (%)	4 (1)

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Once-Daily Simeprevir (TMC435) With Pegylated Interferon and Ribavirin in Treatment-Naïve Genotype 1 Hepatitis C: The Randomized PILLAR Study

Michael W. Fried,[1] Maria Buti,[2] Gregory J. Dore,[3] Robert Flisiak,[4] Peter Ferenci,[5] Ira Jacobs
Patrick Marcellin,[7] Michael Manns,[8] Igor Nikitin,[9] Fred Poordad,[10] Morris Sherman,[11]
Stefan Zeuzem,[12] Jane Scott,[13] Leen Gilles,[14] Oliver Lenz,[14] Monika Peeters,[14] Vanitha Sekar,
Goedele De Smedt,[14] and Maria Beumont-Mauviel[14]

- Single once daily tablet,
- No special diet
- No no significant drug-drug interactions.
- No adverse events with greater frequency than PEG-IFN and RBV



What about cost?

Resource constraints
In particular in the time of crisis

How best to utilize the resources that are available ?

Treatment costs (in France)

- Peg Inf + Ribavirine = 312€ / week
- Boceprevir* = 828€ / week
- Telaprevir* = 2,210€ / week

- Sofosbuvir* ? 5,000€ Expanded access price

*different treatment duration

Cost-effectiveness analysis

- Cost-effectiveness has two outcomes*
  - Cost ($, Euros, rand)
  - Effectiveness (YLS or QALY or DALY)
- Cost-effectiveness ratio
  - $/YLS or $/QALY gained
- The *value* of resources spent

*A cost analysis that has only one outcome ($ or rand)

Peg+RBV+SOF vs Previr-containing regimens SOF regardless of fibrosis vs. when > F2

Diagnosis at stage F0-1 (49 years)	Cost (€)	QALY	ICER (€/QALY)
Treat with « previr » when ≥ F2	26 978	19,3481	
Treat with « PEG+RBV+SOF » when ≥ F2	43 296	19,7469	**40918**
Treat with « PEG+RBV+SOF » regardless of fibrosis	64 157	19,9434	106,165

Deuffic Burban et al.

The Commission on Macroeconomics and Health

- CE ratios < GDP/capita = "very cost-effective"
- CE ratios < 3 x GDP/capita = "cost-effective"

- French GDP/capita = 30 000 euros

Intervention	$/ QALY
Streptokinase in acute myocardial infarction, age 60	1,300
Neonatal intensive care, 1000-1499g	5,500
Coronary artery bypass, three vessel	7,200
Long-term beta-blockers post myocardial infarction	7,300
Treatment of severe diastolic hypertension (>105 mmHg)	11,400
Implantable defibrillator	17,400
Treatment of mild diastolic hypertension (95-104 mmHg)	23,200
Heart transplant	26,900
Estrogen replacement therapy post-menopause	33,700
Percutaneous coronary angioplasty, two vessel	49,000
Hospital hemodialysis	59,500
HMG-CoA reductase inhibitor for high cholesterol	93,000
Annual mammography, age 40-49	94,500
Prophylactic IV immune globulin in chronic leukemia	6,000,000

- Results sensitive to
  - Comorbidities
  - Previr efficacy
  - DAAs Costs

Would you treat this patient?

- With the current standard-of-care triple therapy combining a protease inhibitor, telaprevir **or** boceprevir, PEG-IFN and RBV?
- Wait IFN-based new DAAs?
- Wait IFN-free regimens?

Table 1. Interferon free all oral therapies for patients with HCV genotype 1 drugs that are expected to be available in 2015

Company	Protease inhibitor	Polymerase inhibitor	NS5A replication complex inhibitor	Non-nucleotide polymerase inhibitor	Anticipated approval
Abbvie	ABT-245/r		ABT-267	ABT-333	4Q/2014
Gilead		Sofosbuvir	Ledipisvir		1Q/2015
Boehringer-Ingelheim	Faldeprevir		Deleobuvir		2Q/2015
Bristol-Myers-Squibb	Asunapravir		Daclatasvir	791325	3Q/2015

Liver International (2014)

Exploratory Study of Oral Combination Antiviral Therapy for Hepatitis C

Fred Poordad, M.D., Eric Lawitz, M.D., Kris V. Kowdley, M.D., Daniel E. Cohen, M.D., Thomas Podsadecki, M.D., Sara Siggelkow, R.N., Michele Heckaman, M.S., Lois Larsen, Ph.D., Rajeev Menon, Ph.D., Gennadiy Koev, Ph.D., Rakesh Tripathi, M.S., Tami Pilot-Matias, Ph.D., and Barry Bernstein, M.D.

N Engl J Med 2013;368:45-53.

Response	Group 1 (N=19)		Group 2 (N=14)		Group 3 (N=17)	
	no./total no.	*% (95% CI)*	*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*
Rapid virologic response*	19/19†	100 (82–100)	13/14	93 (66–100)	15/17	88 (64–99)
Extended rapid virologic response‡	17/19	89 (67–99)	11/14	79 (49–95)	10/17	59 (33–82)
Response at week 12 of treatment	19/19†	100 (82–100)	13/14	93 (66–100)	11/17	65 (38–86)
Sustained viral response 12 wk after treatment§	18/19	95 (74–100)	13/14	93 (66–100)	8/17	47 (23–72)

ABT-333 (400 mg twice daily) + ribavirin + ABT-450/r.

December 2012 - First outpatient visit

Physical Examination: nl

BMI: 21.2 (65 Kg x 1.75 m)

US: nl

Fibroscan: 5.5 KPa, IQR 1.4, SR 95%

State transition probabilities

Variable	Women			Men		
	Age≤30	Age [31;50]	Age>50	Age≤30	Age [31;50]	Age>50
F0 to F1	0.0420	0.0550	0.0770	0.0930	0.1550	0.1938
F0 to F1 after age 50	0.0525	0.0688	0.0770	0.1163	0.1938	0.1938
F1 to F2	0.0450	0.0510	0.0714	0.0635	0.1058	0.1323
F1 to F2 after age 50	0.0563	0.0714	0.0714	0.0794	0.1323	0.1223
F2 to F3	0.0920	0.0700	0.0980	0.0904	0.1506	0.1883
F2 to F3 after age 50	0.1150	0.0875	0.0980	0.1130	0.1883	0.1883
F3 to F4	0.0700	0.0480	0.0672	0.0946	0.1577	0.1971
F3 to F4 after age 50	0.0875	0.0600	0.0672	0.1183	0.1971	0.1971
F4 to death of HCV	0.0100	0.0100	0.0100	0.0100	0.0100	0.0100
F4 to HCC	0.0040	0.0040	0.0120	0.0100	0.0100	0.0300
F4 to HCC after 10 years of cirrhosis	0.0060	0.0060	0.0180	0.0200	0.0200	0.0450
F4 to first decompensation	0.0300	0.0300	0.0300	0.0300	0.0300	0.0300
First decompensation to death of HCV	0.3900	0.3900	0.3900	0.3900	0.3900	0.3900
First decompensation to progressive decompensated state	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000
Stable decompensated state to death of HCV	0.1250	0.1250	0.1250	0.1250	0.1250	0.1250
Progressive decompensated state to death of HCV	0.1560	0.1560	0.1560	0.1560	0.1560	0.1560
HCC to death of HCV	0.8000	0.8000	0.8500	0.8000	0.8000	0.8500
HCC to death of HCV after 1 year in HCC stage	0.3500	0.3500	0.3500	0.3500	0.3500	0.3500

D'Amico et al, *Journal of Hepatology*, 2006, Davis et al, *Gastroenterology,* 2010, Thein et al, *Hepatology*, 2008

State transition probabilities

Variable	Women			Men		
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F0 to F1 after age 50	0.0525	0.0688	0.0770	0.1163	0.1938	0.1938
F1 to F2	0.0450	**0.0510**	0.0714	0.0635	0.1058	0.1323
F1 to F2 after age 50	0.0563	0.0714	0.0714	0.0794	0.1323	0.1223
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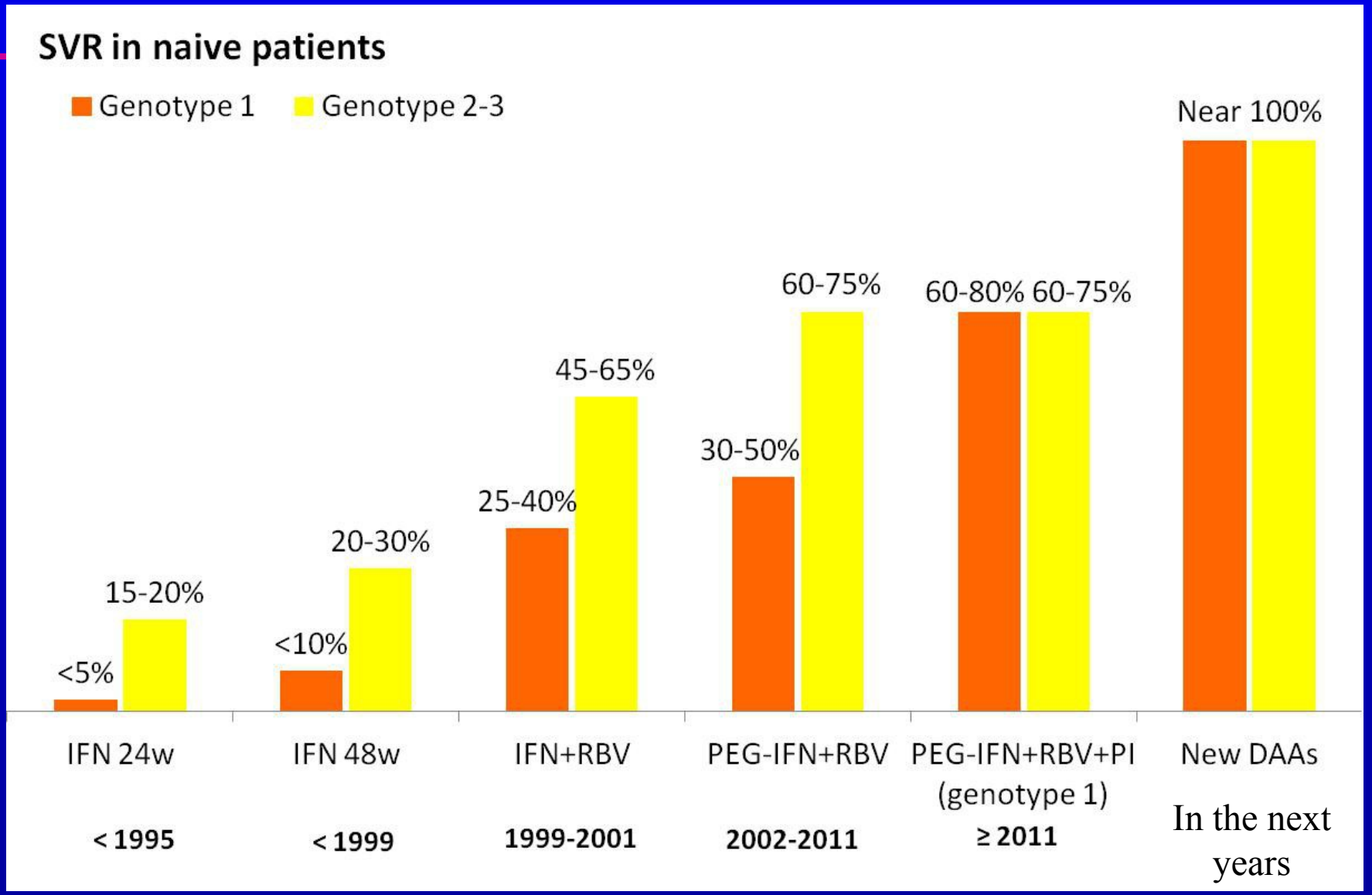
F3 to F4	0.0700	0.0480	0.0672	0.0946	0.1577	0.1971
F3 to F4 after age 50	0.0875	0.0600	0.0672	0.1183	0.1971	0.1971
F4 to death of HCV	0.0100	0.0100	0.0100	0.0100	0.0100	0.0100
F4 to HCC	0.0040	0.0040	0.0120	0.0100	0.0100	0.0300
F4 to HCC after 10 years of cirrhosis	0.0060	0.0060	0.0180	0.0200	0.0200	0.0450
F4 to first decompensation	0.0300	0.0300	0.0300	0.0300	0.0300	0.0300
First decompensation to death of HCV	0.3900	0.3900	0.3900	0.3900	0.3900	0.3900
First decompensation to progressive decompensated state	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000
Stable decompensated state to death of HCV	0.1250	0.1250	0.1250	0.1250	0.1250	0.1250
Progressive decompensated state to death of HCV	0.1560	0.1560	0.1560	0.1560	0.1560	0.1560
HCC to death of HCV	0.8000	0.8000	0.8500	0.8000	0.8000	0.8500
HCC to death of HCV after 1 year in HCC stage	0.3500	0.3500	0.3500	0.3500	0.3500	0.3500

D'Amico et al, *Journal of Hepatology*, 2006, Davis et al, *Gastroenterology,* 2010, Thein et al, *Hepatology*, 2008

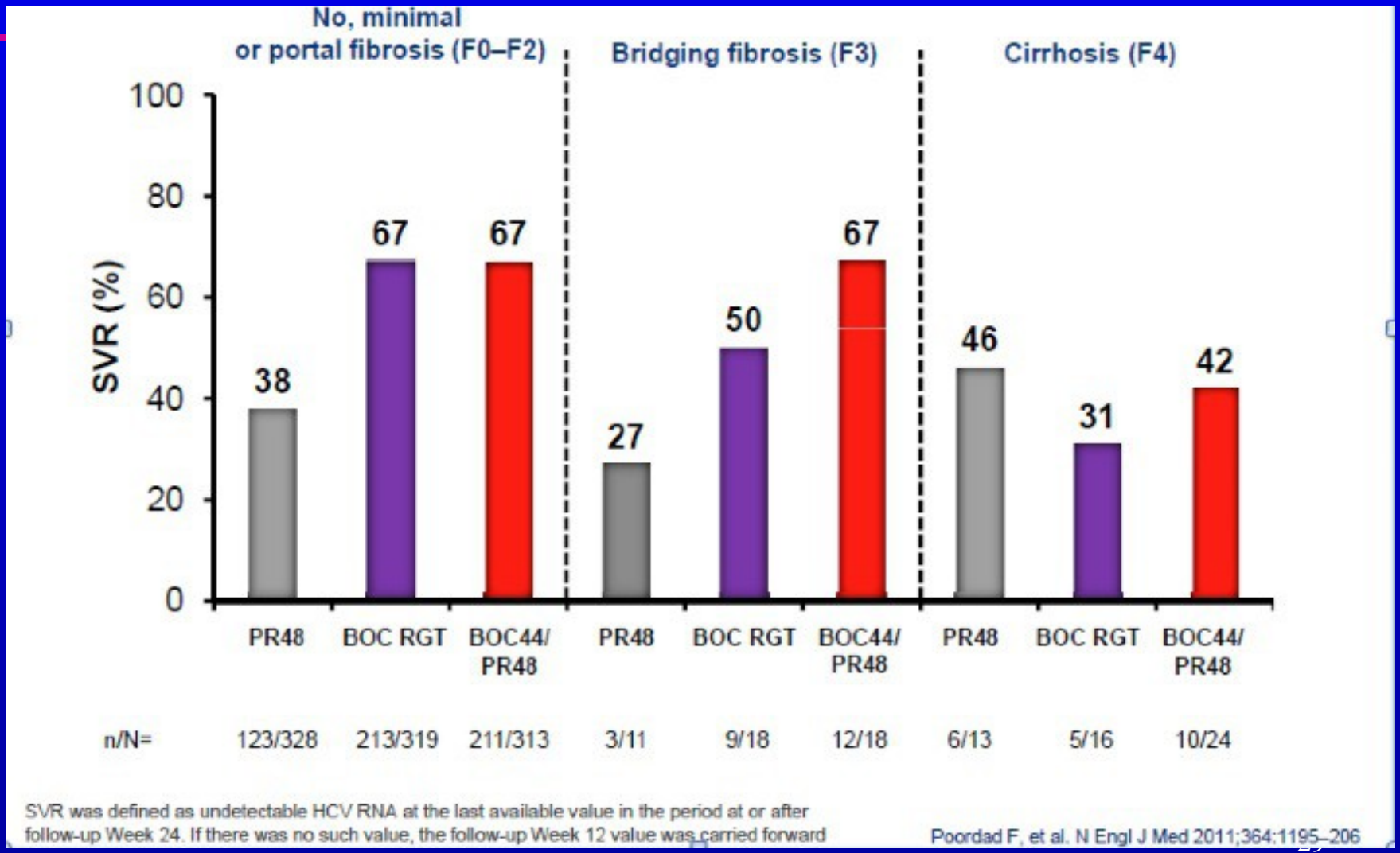
Transient elastography sensitivity and specificity

Reference	Patients (n)	F ≥2 (%)	Cut-off	Se (%)	Spe (%)
Castera 2005	183	74,3	7,1	67	89
Ziol 2005	251	64,9	8,8	56	91
Arena 2008	150	56,0	7,8	83	82
Lupsor 2008	324	64,8	7,4	76,0	83,6
Sporea 2008	191	84,3	6,8	59,6	93,3
Nitta 2009	165	60,0	7,1	80,8	80,3
Petta 2009	156	76,9	6,5	61	64
Degos 2010 *	1307	57,1	7,1	66,5	70,8
Total	**2727 pts**	**63,0%**	**≈7-8 kPa**	**67,3%**	**76,6%**

Stebbing et al. J Clin Gastroenterol. 2010


SVR in naive patients
Genotype 1
Genotype 2-3
<5%
15-20%
<10%
20-30%
25-40%
45-65%
30-50%
60-75%
60-80%
60-75%
Near 100%
IFN 24w
IFN 48w
IFN+RBV
PEG-IFN+RBV
PEG-IFN+RBV+PI
(genotype 1)
New DAAs
< 1995
< 1999
1999-2001
2002-2011
≥ 2011
In the next years

Boceprevir: efficacy by fibrosis stage



SVR was defined as undetectable HCV RNA at the last available value in the period at or after follow-up Week 24. If there was no such value, the follow-up Week 12 value was carried forward

Poordad F, et al. N Engl J Med 2011;364:1195–206

What about cost?

Resource constraints
In particular in the time of crisis

How best to utilize the resources that are available ?

Treatment costs (in France)

- Peg Inf + Ribavirine = 312€ / week
- Boceprevir* = 828€ / week
- Telaprevir* = 2,210€ / week

- Sofosbuvir* ? 5,000€ Expanded access price
- IFN-free regimens ? two times higher than IFN-based new DAAs?

*different treatment duration

Inf-Free regimens vs. Peg+RBV+SOF

Diagnosis at stage F0-1 (49 years)	Cost (€)	QALY	ICER (€/QALY)
Treat with « PEG+RBV+SOF » when ≥ F2	43 296	19,7469	**40918**
Treat with « PEG+RBV+SOF » regardless of fibrosis	64 157	19,9434	106,165
Wait « IFN-free » and then treat when ≥ F2	74 764,72	19,8975	Dominated
Wait « IFN-free », then treat all	112 362,56	20,0935	272,630

Deuffic Burban et al

The Commission on Macroeconomics and Health

- CE ratios < GDP/capita = "very cost-effective"
- CE ratios < 3 x GDP/capita = "cost-effective"

- French GDP/capita = 30 000 euros

“Cost-effective doesn’t mean cheap”

Budget impact analysis

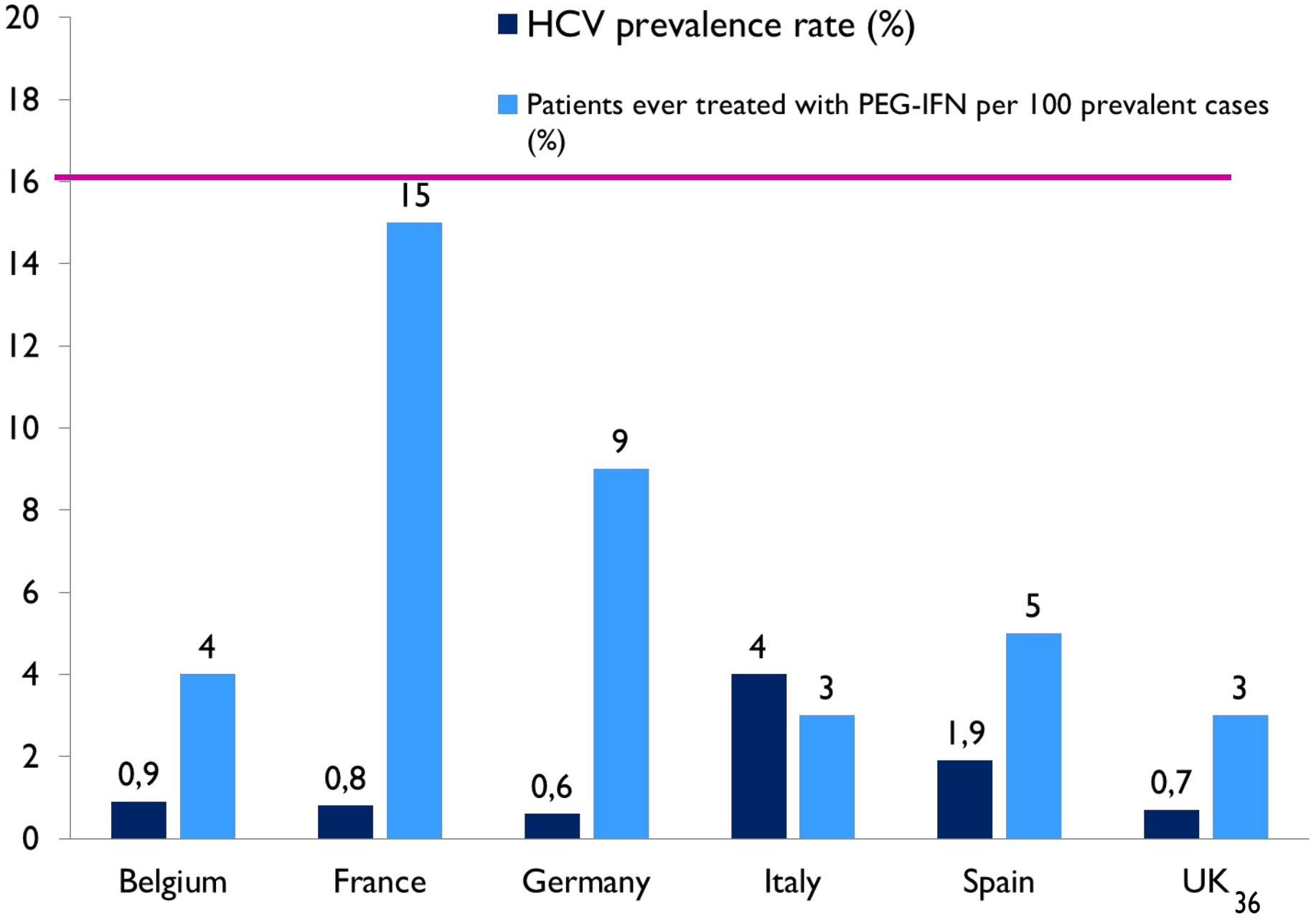
Eur J Health Econ (2011) 12:499–502
DOI 10.1007/s10198-011-0348-5

EDITORIAL

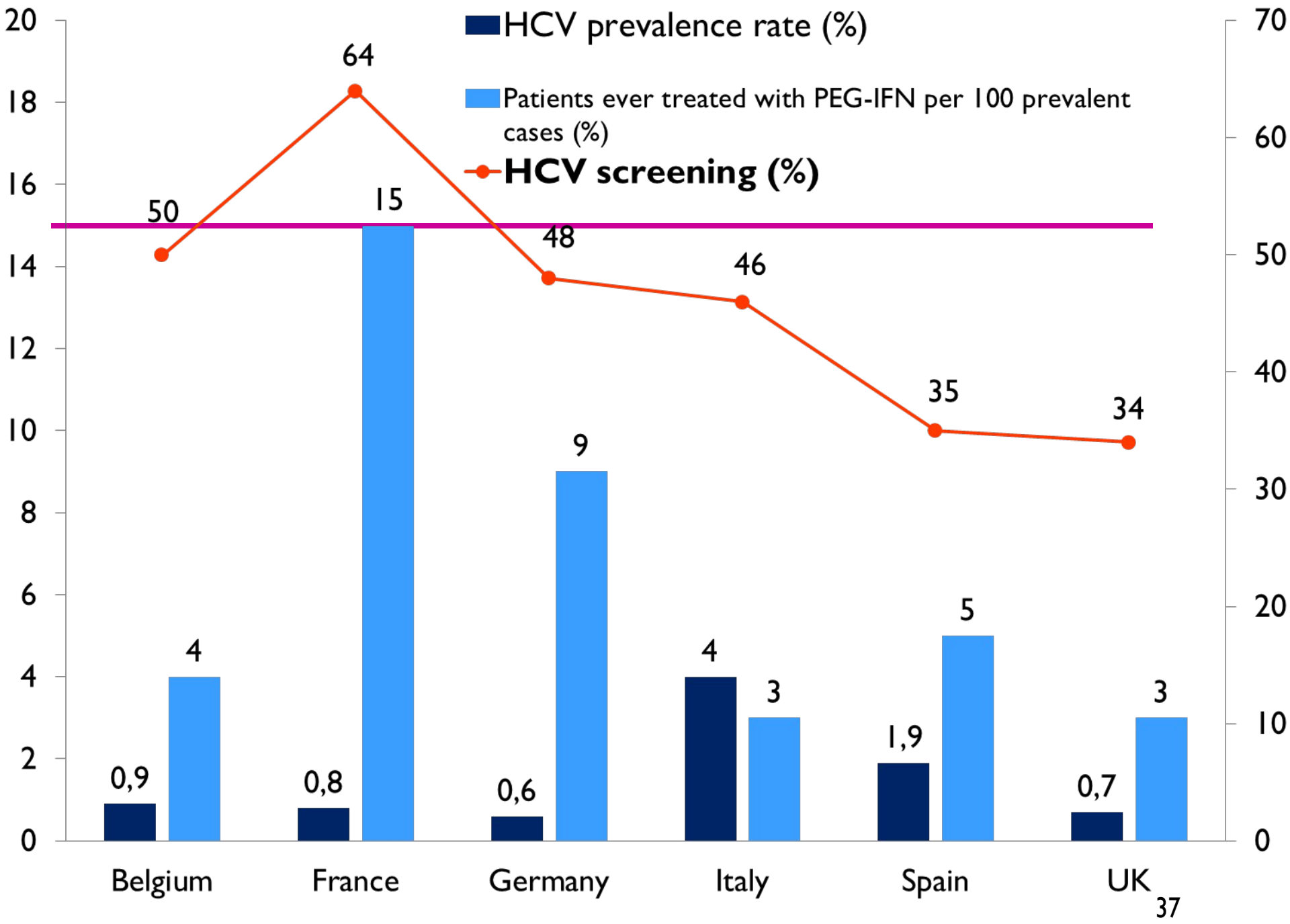
Budget impact analysis in economic evaluation: a proposal for a clearer definition

Livio Garattini · Katelijne van de Vooren

The financial consequences of introducing a new technology in a specific setting over the short to medium term : *affordability*

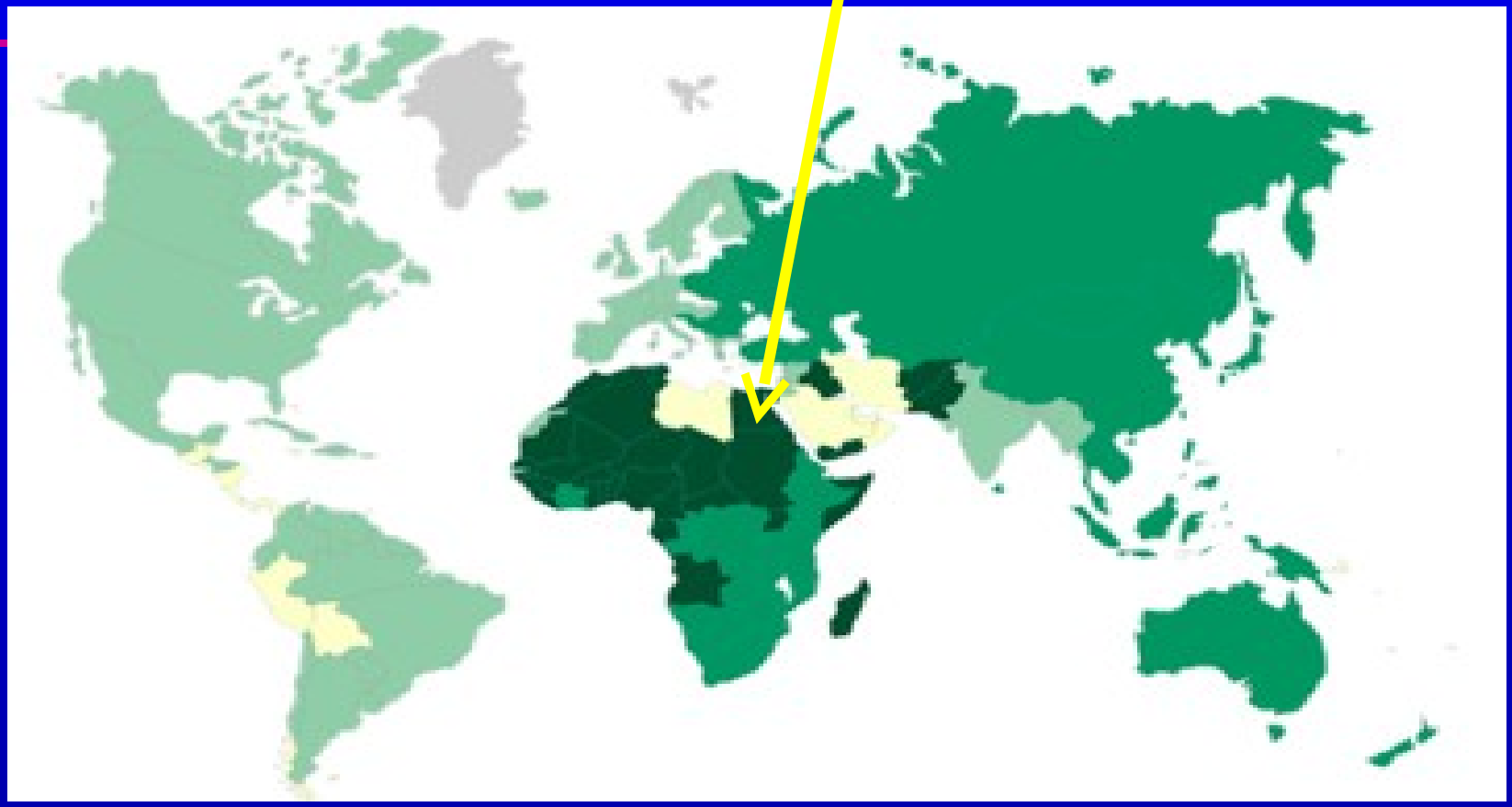


Deuffic-Burban et al, Gastroenterology 2012



Deuffic-Burban et al, Gastroenterology 2012

Fatima a 49 years old woman



≥ 2,9 %
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December 2012 - First outpatient visit

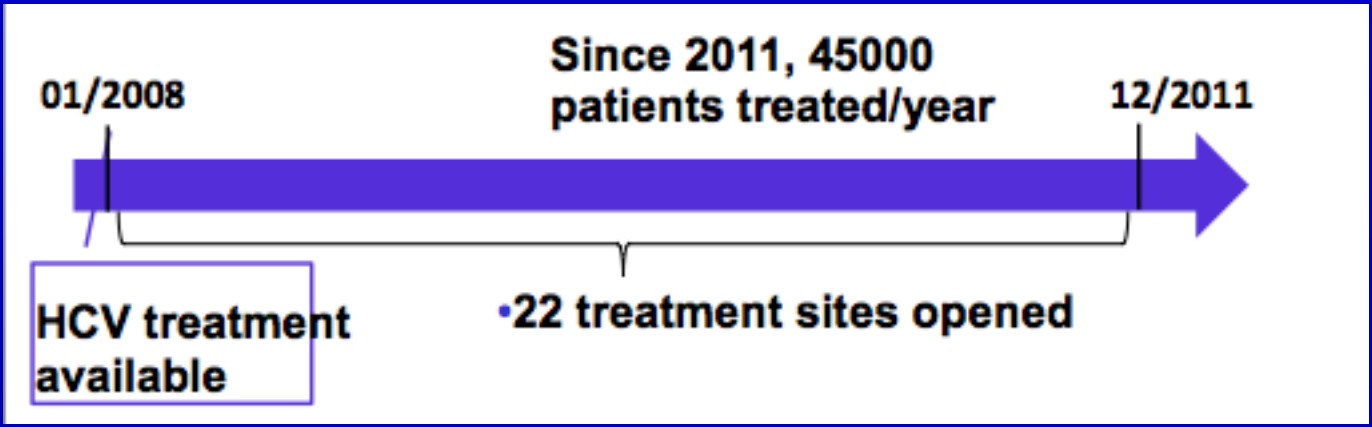
Physical Examination: nl

BMI: 21.2 (65 Kg x 1.75 m)

US: nl

Fibroscan: 5.5 KPa, IQR 1.4, SR 95% (APRI < 0.5)

- Egypt : highest HCV prevalence in the world (15% vs. <1% in France)
  - **About 4 000 000 HCV-infected patients**
-



- How should we prioritize?

Effectiveness and cost-effectiveness of immediate vs. delayed treatment of HCV-infected patients in a country with limited resources: the case of Egypt (ANRS 12215)

- In Egypt, treating HCV-infected patients with Peg-Inf and ribavirin* at fibrosis stages F2 to F4 is effective and cost-effective.
- If we consider that affordable triple therapies with new DAAs will be available in three years, treatment for patients at stage F1 should be delayed.

*Peg-Inf and ribavirin cost for 48 weeks= 2000 US$ US

Obach et al. Clin Infect Dis 2014 (In press)