Hépatite C:
l'incertitude des assertions d'experts

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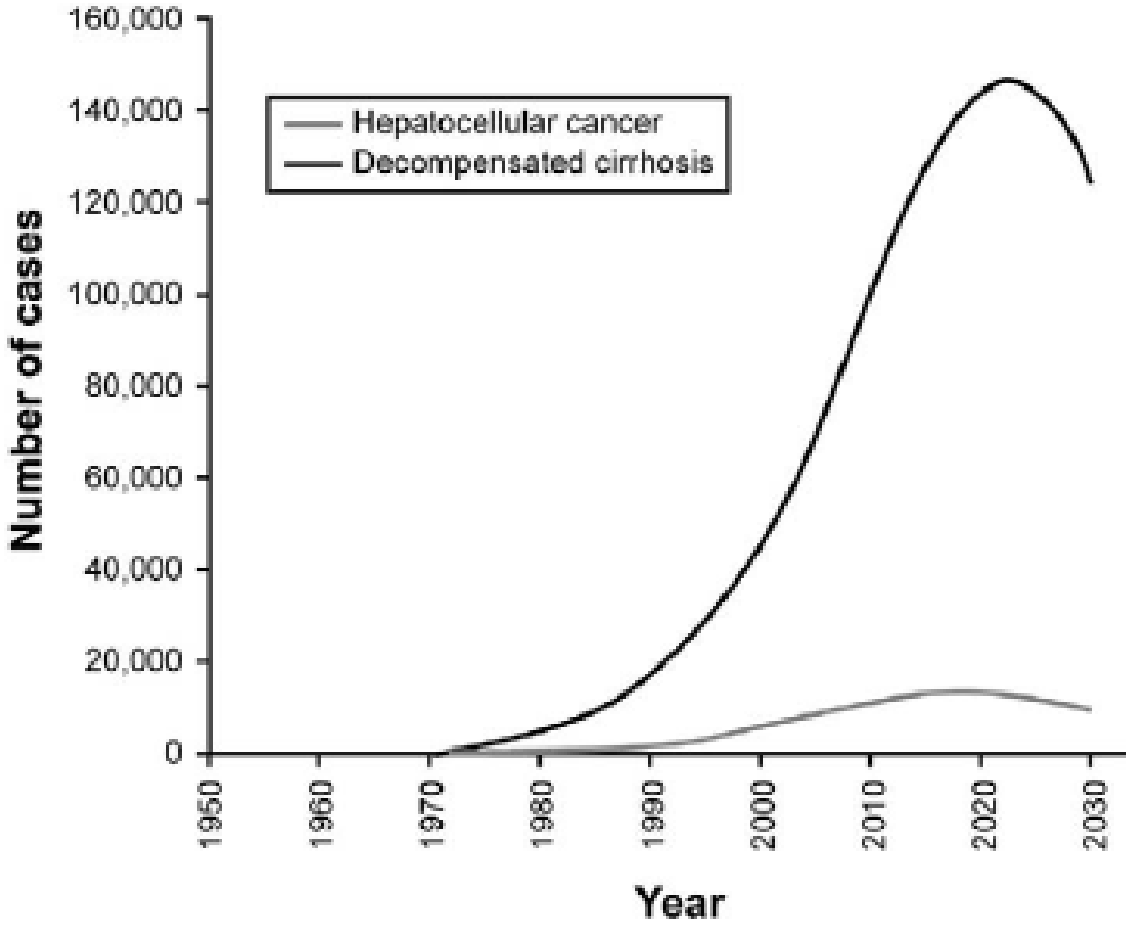
Hépatite C

Comment convertir en vies gagnées les progrès thérapeutiques?

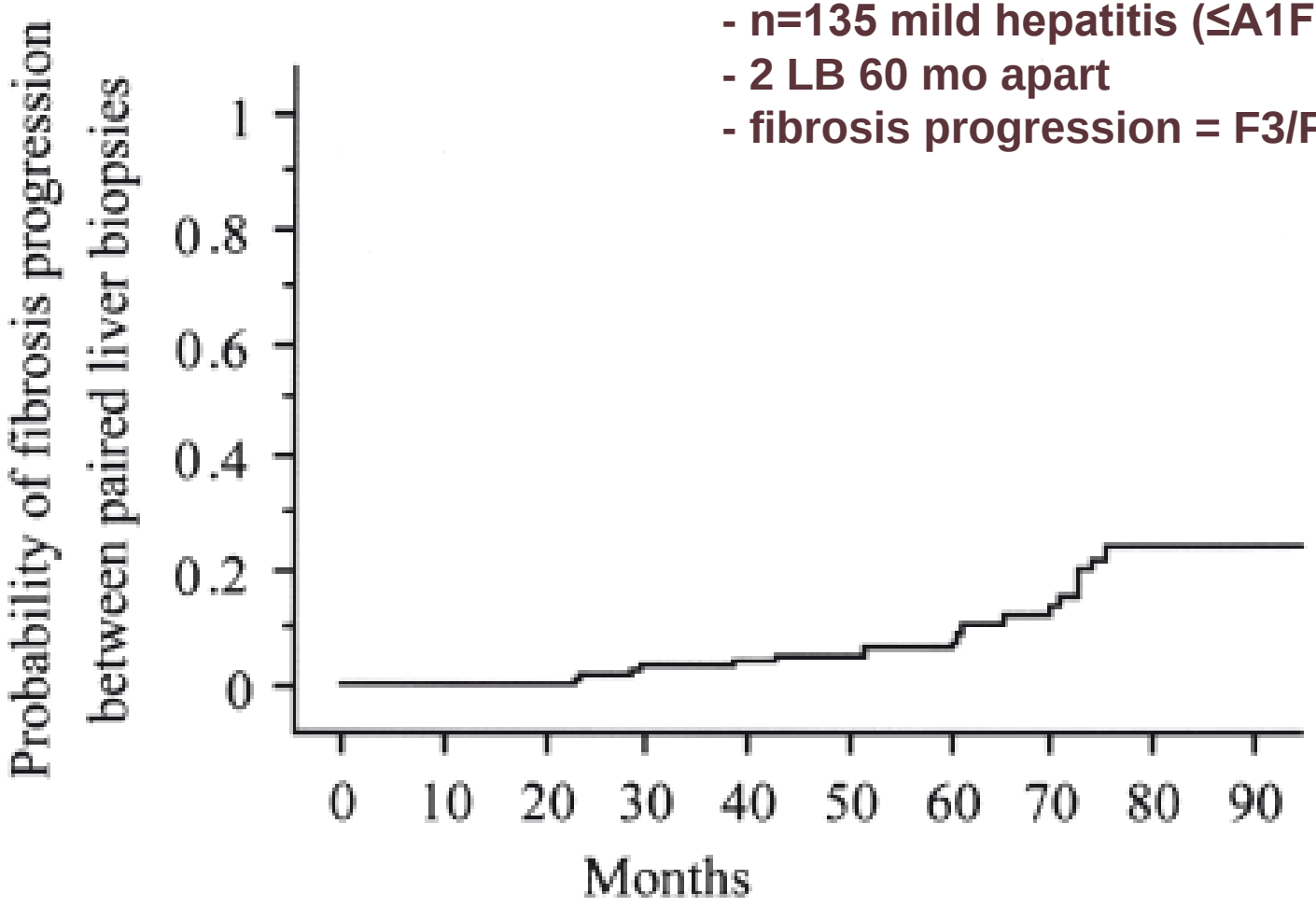
Multiple Cohort Model of HCV Prevalence and Disease Progression in USA



Davis GI et al, Gastroenterology 2010

Progression de la fibrose chez les patients ayant une hépatite minime

- n=135 mild hepatitis (≤A1F1)
- 2 LB 60 mo apart
- fibrosis progression = F3/F4



Fartoux et al. Hepatology 2005

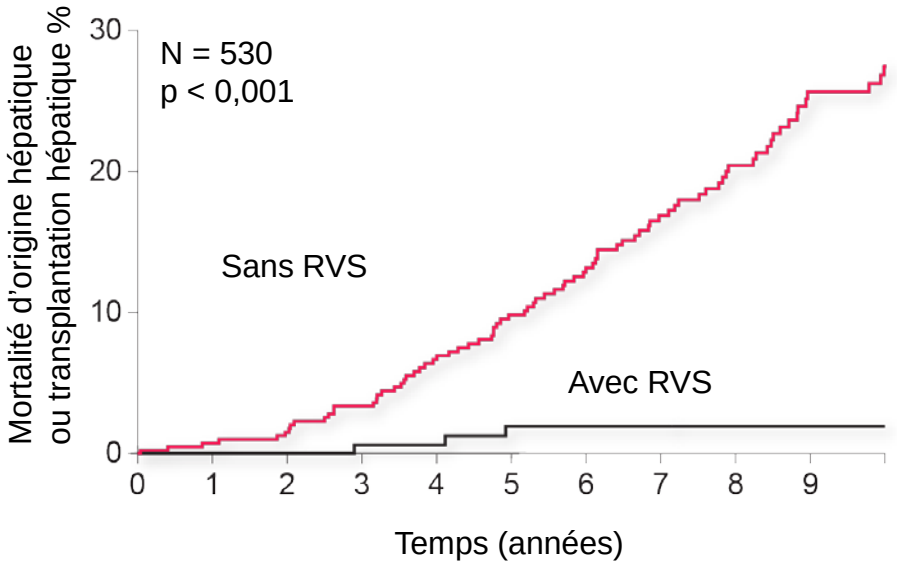
Le risque de décès lié au foie ⇑
Veteran Affairs Cohort n=24090

Liver-related outcomes: ESLD, HCC, or liver-related death			
F0	4	1396.3	2.86 (1.08-7.63)
F1	16	1568.8	10.20 (6.25-16.65)
F2	9	337.1	26.70 (13.89-51.32)
F3	5	195.9	25.52 (10.62-61.31)
F4	17	390.3	43.56 (27.08-70.07)
Total	**51**	**3888.3**	13.12 (9.97-17.26)

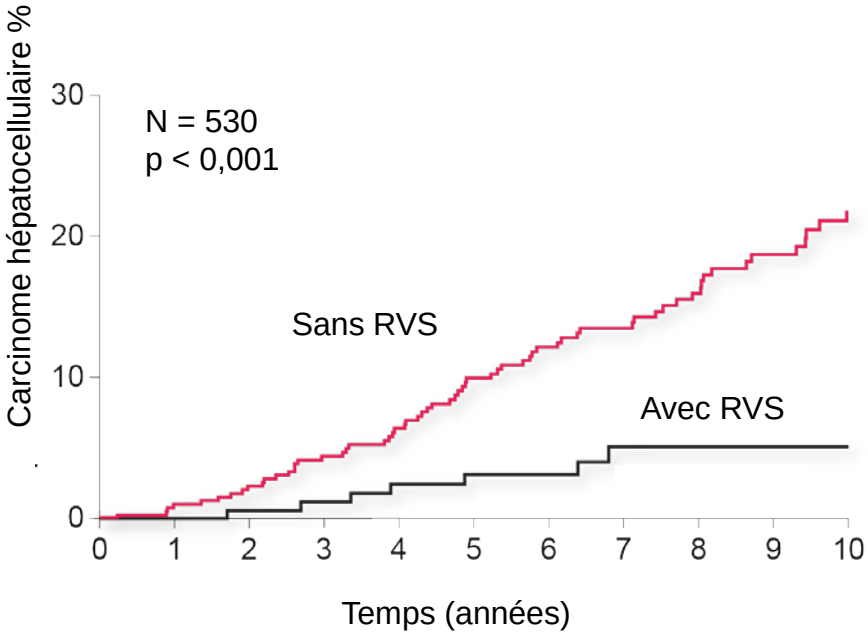
Limketkai BN, JAMA 2012

Une RVS est associée à une réduction de la mortalité d'origine hépatique et du CHC

Mortalité d'origine hépatique ou transplantation hépatique



Carcinome hépatocellulaire



Van der Meer AJ, et al. *JAMA* 2012;308(24):2584-93.

RVS : réponse virologique soutenue

- **Le problème de la cohérence des experts**

- **Les stratégies devraient être centrées sur les données de mortalité**

Reco AFEF

- *Chez les malades ayant une fibrose non sévère (F0-F1), l'indication du traitement est envisagée au cas par cas, en prenant en compte les facteurs connus de progression de la maladie hépatique (âge, sexe, syndrome métabolique, activité nécrotico-inflammatoire notamment) ainsi que les symptômes et la motivation du patient (C2, degré d'accord 94%).*

Les experts sont ils concordants avec eux-mêmes?

Characteristic	Nonblack Cohort			Black Cohort			Both Cohorts		
Metavir fibrosis score — no. (%)§									
0, 1, or 2	277 (89)	279 (88)	265 (85)	51 (98)	40 (77)	48 (87)	328 (90)	319 (87)	313 (86)
3 or 4	23 (7)	26 (8)	36 (12)	1 (2)	8 (15)	6 (11)	24 (7)	34 (9)	42 (11)

Poordad F, N Engl J Med 2011

Stage of fibrosis and cirrhosis — no. (%)			
None or minimal fibrosis	134 (37)	128 (35)	147 (41)
Portal fibrosis	156 (43)	151 (41)	141 (39)
Bridging fibrosis	52 (14)	59 (16)	52 (14)
Cirrhosis	21 (6)	26 (7)	21 (6)

Jacobson IM, N Engl J Med 2011

Les experts sont ils concordants avec eux-mêmes?

Stage of fibrosis or cirrhosis — no. (%)**			
No or minimal fibrosis	51 (19)	68 (26)	35 (27)
Portal fibrosis	83 (31)	71 (27)	38 (29)
Bridging fibrosis	60 (23)	58 (22)	29 (22)
Cirrhosis	72 (27)	67 (25)	30 (23)

Zeuzem S, N Engl J Med 2011

Metavir fibrosis score — no. (%)**			
0, 1, or 2	61 (76)	117 (72)	119 (74)
3 or 4	15 (19)	32 (20)	31 (19)
Cirrhosis — no. (%)**	10 (12)	17 (10)	22 (14)

Bacon BR, N Engl J Med 2011

- Le problème de la cohérence des experts

- **Les stratégies devraient être centrées sur les données de mortalité**

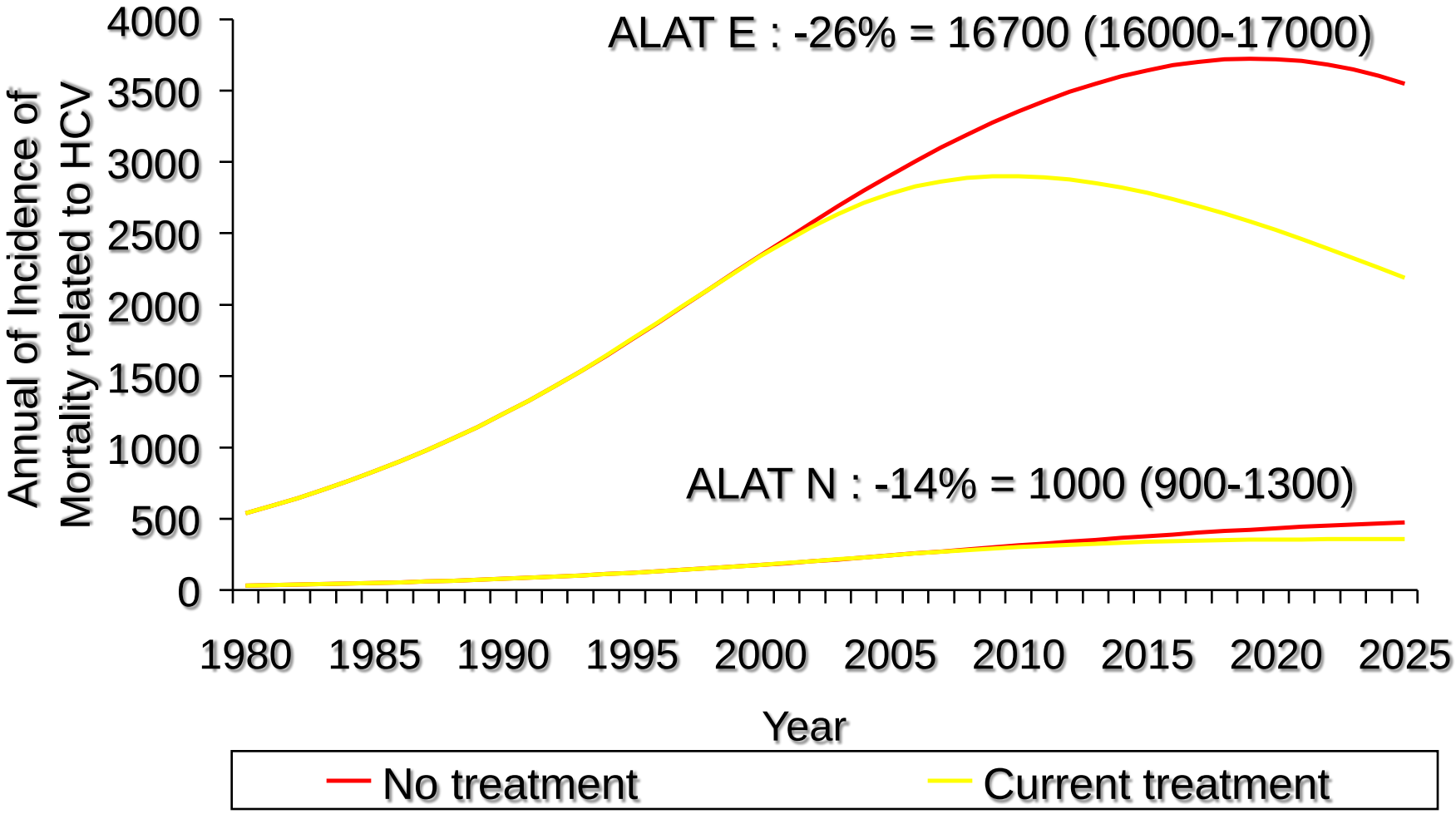
What is a Model?

Buxton and colleagues defined models in scientific disciplines:

"Models [...] are a way of representing the complexity of the real world in a more simple and comprehensible form"

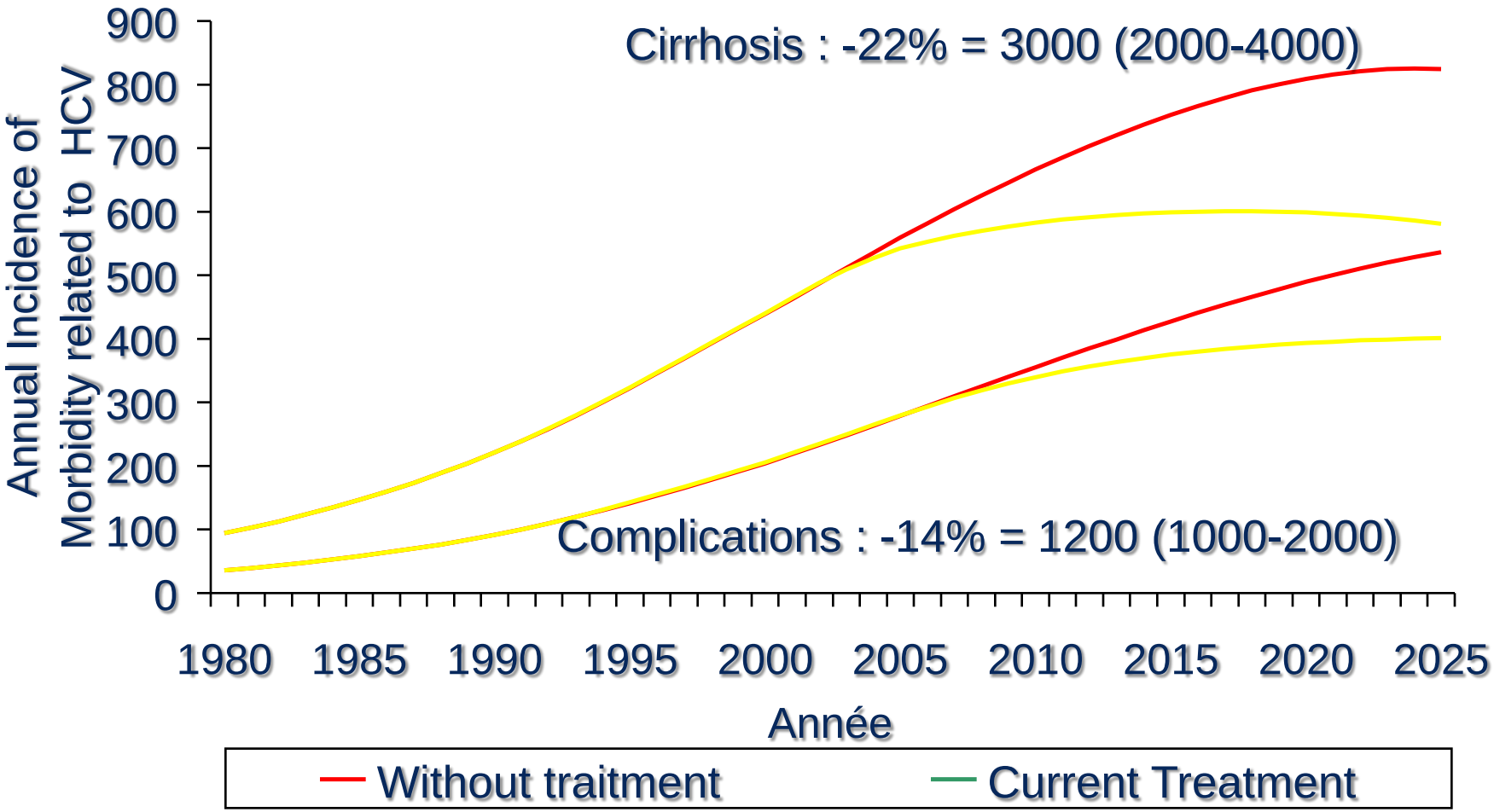
[Source: Buxton, Health Economics. 1997]

Incidence of HCV-related deaths in elevated ALT and normal ALT populations



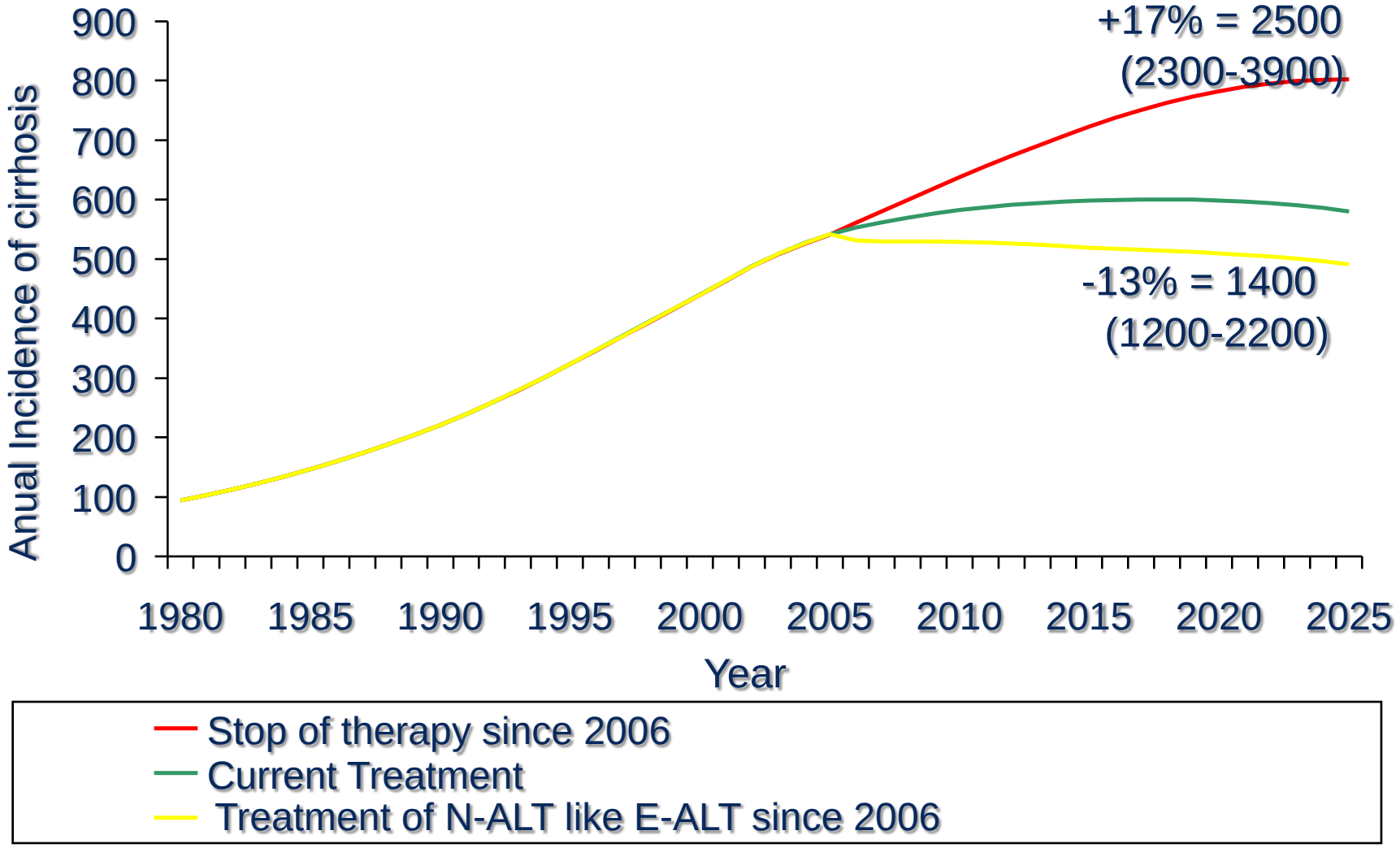
Deuffic S et al, Hepatology 2009

Incidence of cirrhosis and cirrhosis-related complications in normal ALT populations



Deuffic S et al, Hepatology 2009

Impact of alternative Scenarios on incidences of cirrhosis



Deuffic S et al, Hepatology 2009

Projection of HCV burden in Europe: objectives of a model-based analysis

Compare dynamics of infection, natural history, screening rates and treatment practices of six European countries (Belgium, France, Germany, Italy, Spain and UK)

Assess impact of dual therapy (Peg-IFN + RBV) on morbidity and mortality in HCV infection

Predict additional impact of triple therapy (PI + Peg-IFN + RBV) on morbidity and mortality rates

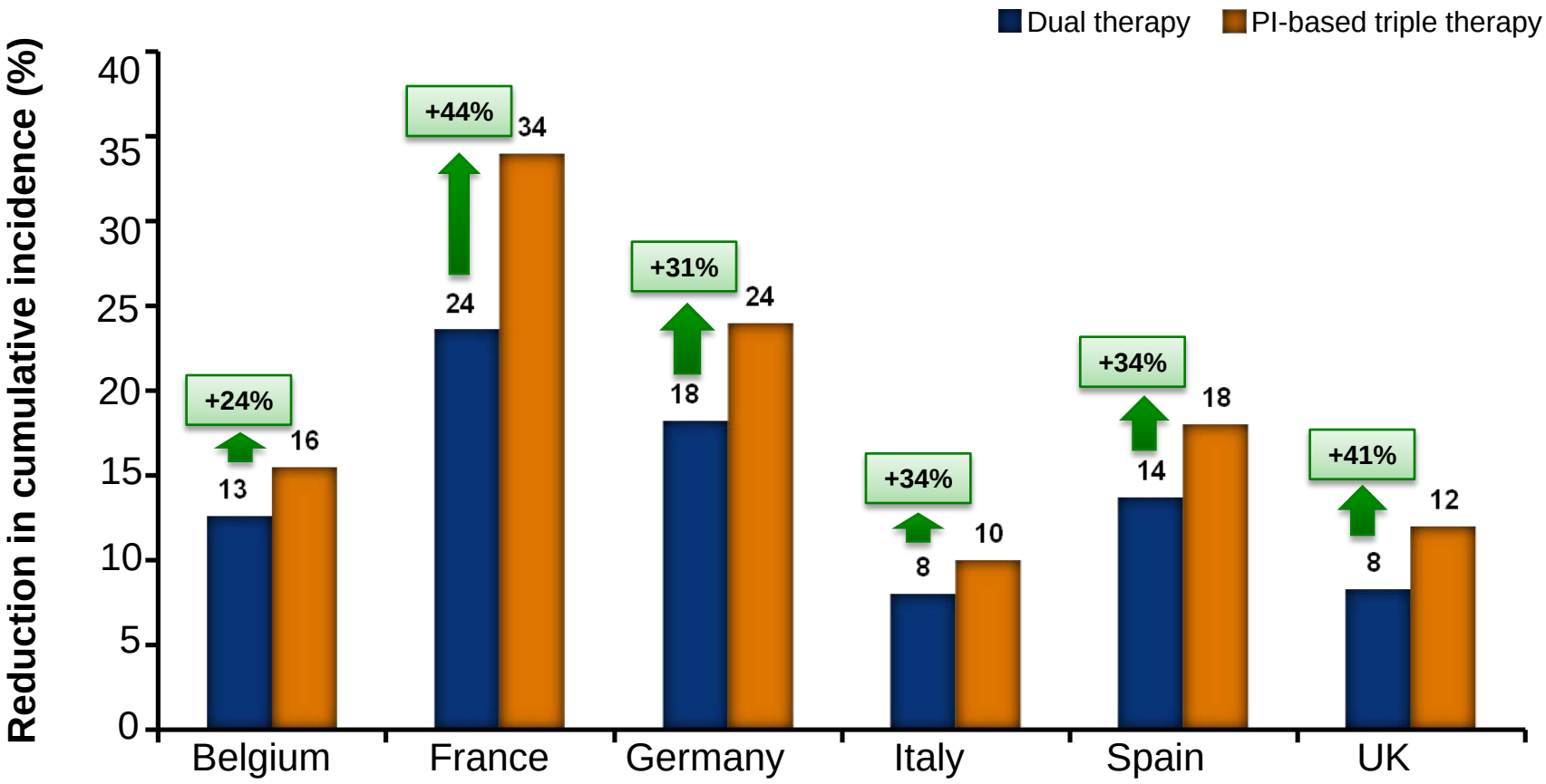
Deuffic-Burban S, et al. Gastroenterology 2012 [Epub ahead of print]

HCV Screening Rates: 2011 Estimation

	Belgium	France	Germany	Italy	Spain	UK
HCV Screening, %						
Observed, % (yr)	37 (2000)	57 (2004)	40 (2004)	40 (2005)	33 (2008–9)	30 (2004)
Estimated in 2011, %	50	64	48	46	35	34
HCV Genotype						
G1, %	60	56	60	62	65	44
G2/3, %	27	32	37	34	23	53
Other genotypes, %	13	12	3	4	12	3

Deuffic-Burban S, et al. Gastroenterology 2012 [Epub ahead of print]

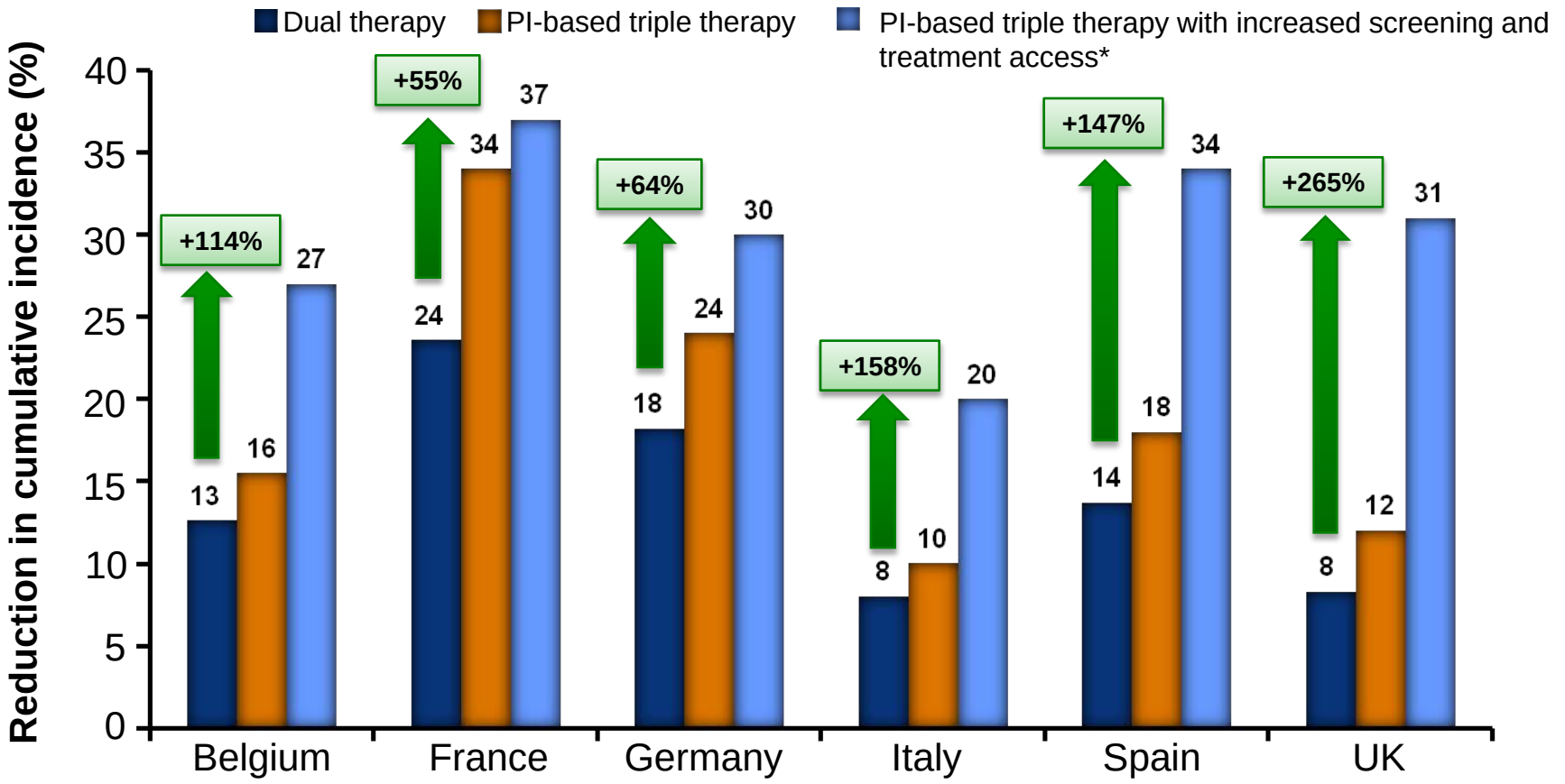
Results: reduction in cumulative incidence of genotype 1 HCV-related cirrhosis, 2012–2021



Greater reduction in HCV-related cirrhosis with PI-based triple therapy than with dual therapy

Deuffic-Burban S, et al. Gastroenterology 2012 [Epub ahead of print]

Reinforcing screening and treatment access: incidence of genotype 1 HCV-related cirrhosis, 2012–2021

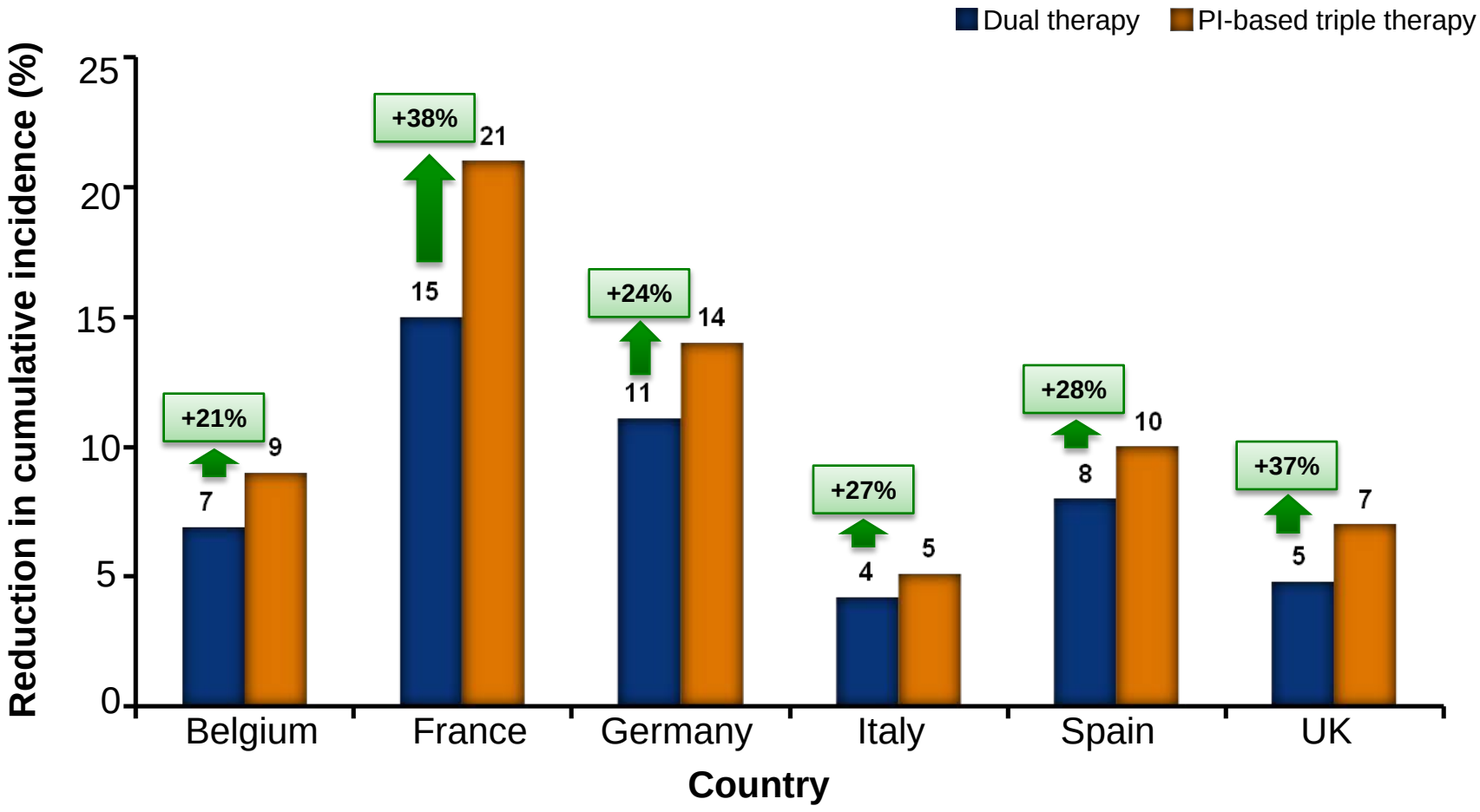


Dramatic reduction in HCV-related cirrhosis with PI-based triple therapy + reinforced screening and treatment access

*Assumes 75% of HCV-infected patients will be screened by 2015 and one G1-infected patient in 2 will be treated in 2015 with PI-based triple therapy

Deuffic-Burban S, et al. Gastroenterology 2012 [Epub ahead of print]

Results: reduction in cumulative incidence of genotype 1 HCV-related deaths, 2012–2021



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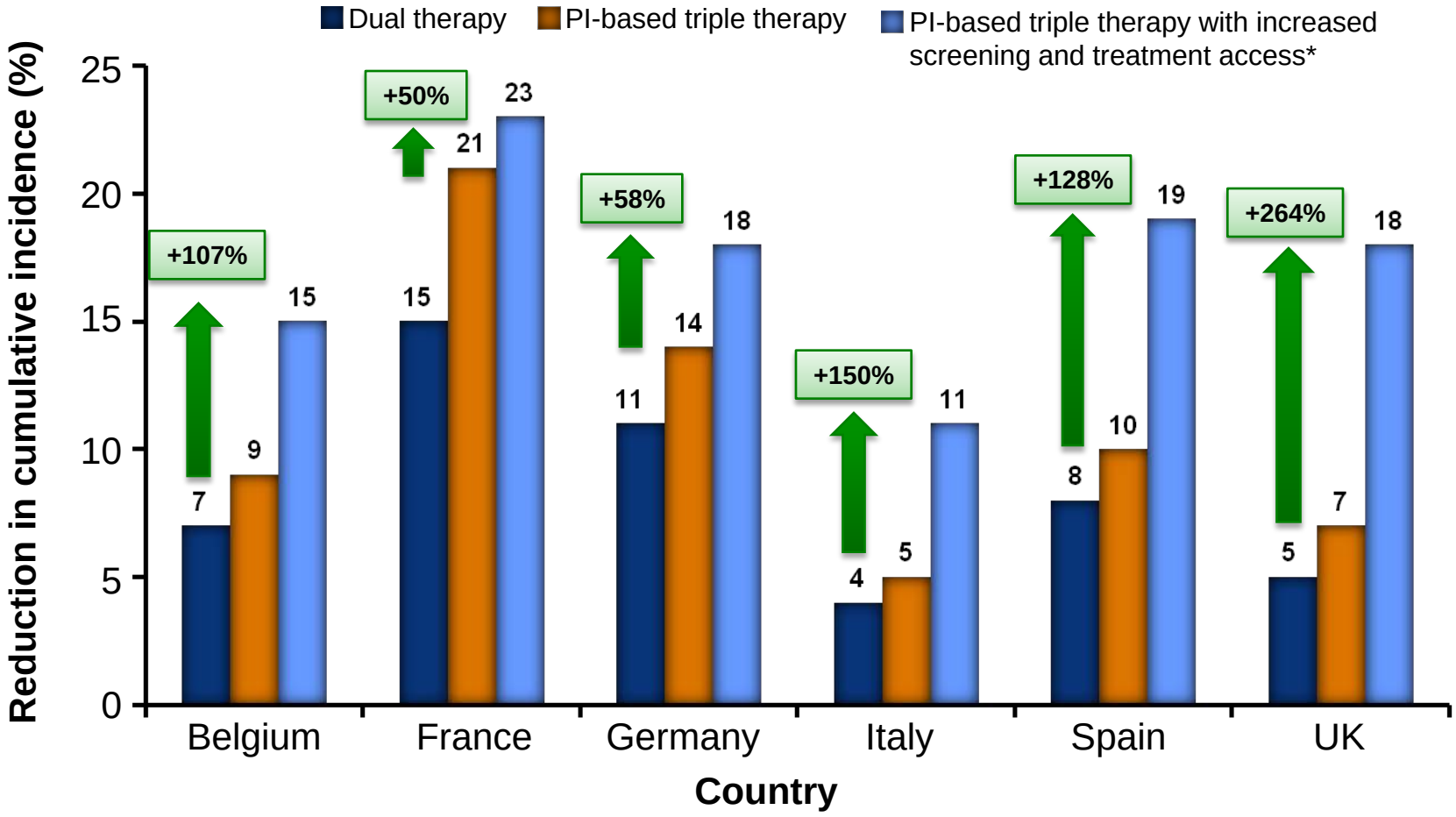


Dramatic reduction in HCV-related deaths with PI-based triple therapy + reinforced screening and treatment access

*Assumes 75% of HCV-infected patients will be screened by 2015 and one G1-infected patient in 2 will be treated in 2015 with PI-based triple therapy

Deuffic-Burban S, et al. Gastroenterology 2012 [Epub ahead of print]

Effect of treatment strategy according to fibrosis stage on HCV-related cirrhosis and deaths*

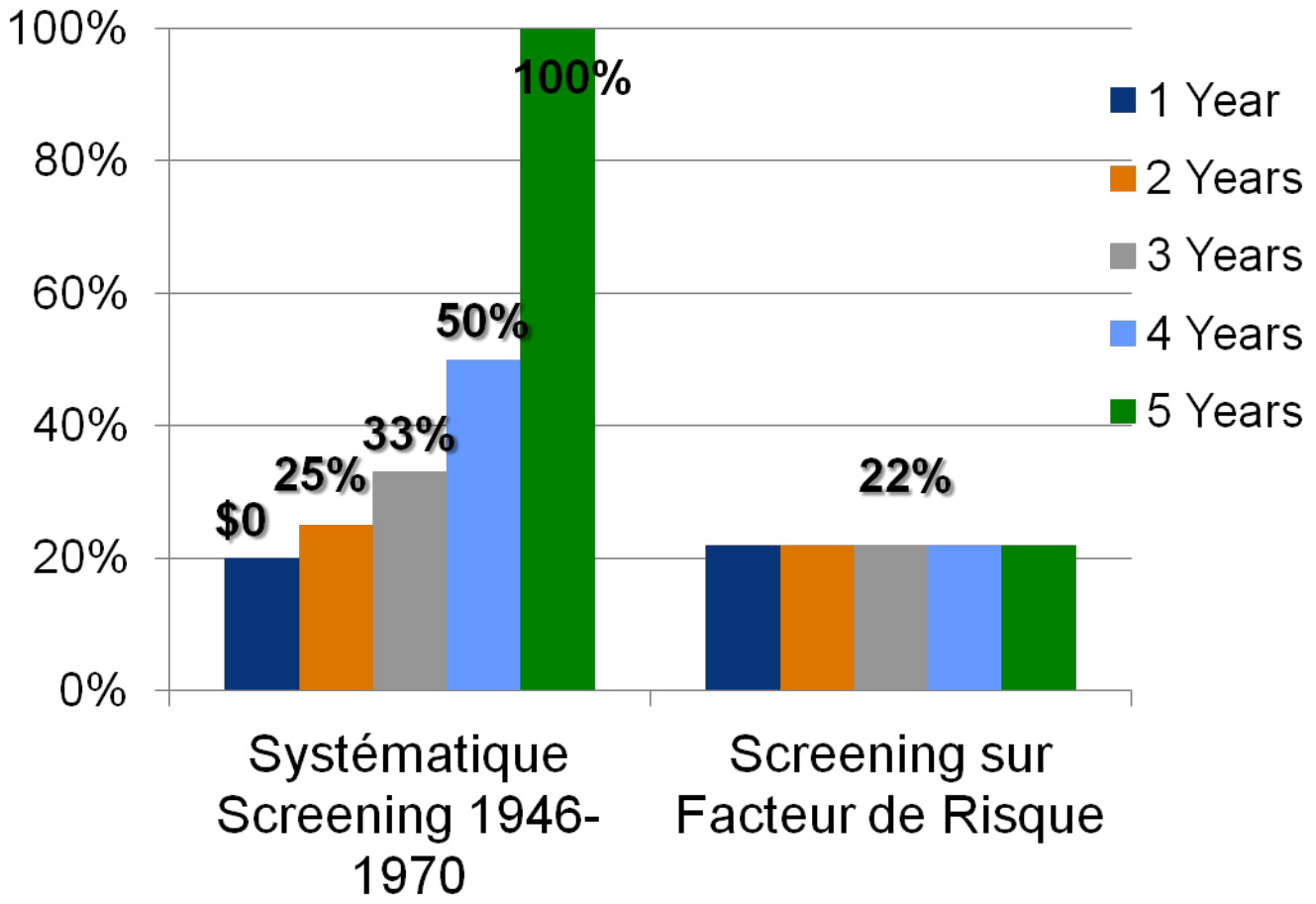
Treatment scenario	Cumulative HCV-related cirrhosis and deaths (95% CI)	
	Cirrhosis	Deaths
With treatment (baseline scenario)	**330,700 [313,200-342,000]**	**282,300 [268,600-294,200]**
Never treating patients with F0-F1	**359,300 [339,900-372,200]**	**295,000 [280,700-307,700]**
Not treating F0/F1 until F2 is reached	332,200 (314,600–343,600)	282,700 (269,000–294,600)
Not treating F0/F1 until F3 is reached	342,400 (324,100–354,300)	285,900 (272,100–298,000)

- In comparison to the baseline scenario, delaying treatment in patients with F0 or F1 is associated with an increase in mortality or in HCV-related cirrhosis regardless of the scenario
- The delaying scenario “not treating until they progress to F2” may be discussed in terms of mortality but it will necessitate efficient diagnostic testing of fibrosis to detect progression from F0/F1 to F2

* All genotypes

Deuffic-Burban S, et al. Gastroenterology 2012 [Epub ahead of print]

Dépistage ciblée vs 100% dépistage de la population américaine née entre 1946-1970



McGarry L, Hepatology 2012

Dépistage ciblée vs 100% dépistage de la population américaine née entre 1946-1970

Screening-Eligible Population	Age Group (2010) (Years)					
	40-44	45-49	50-54	55-59	60-64	All Ages (40-64)
Total*	20,922,500	22,563,700	22,065,400	19,404,800	16,593,100	101,549,300
No chronic HCV	20,703,700	22,242,900	21,685,100	19,042,800	16,289,300	99,963,700
Spontaneously cleared	127,100	195,100	225,200	197,700	153,700	898,900
Chronic HCV-infected	218,800	320,800	380,300	362,000	303,800	1,585,600
By fibrosis stage, n (% of HCV infected)						
F0	56,700 (25.9)	67,300 (21.0)	62,300 (16.4)	45,300 (12.5)	30,100 (9.9)	261,700 (16.5)
F1	82,200 (37.6)	114,300 (35.6)	121,500 (32.0)	98,200 (27.1)	69,500 (22.9)	485,800 (30.6)
F2	42,000 (19.2)	66,000 (20.6)	79,900 (21.0)	73,900 (20.4)	57,600 (19.0)	319,500 (20.1)
F3	24,400 (11.2)	44,300 (13.8)	62,700 (16.5)	67,400 (18.6)	58,800 (19.4)	257,600 (16.2)
F4	13,400 (6.1)	29,000 (9.0)	53,800 (14.2)	77,100 (21.3)	87,800 (28.9)	261,100 (16.5)

McGarry L, Hepatology 2012

Dépistage ciblée vs 100% dépistage de la population américaine née entre 1946-1970

67 % de patients screenés éligibles au traitement

Tous les patients éligibles étaient traités par bithérapie (Gén non-1) ou tri-thérapie pegylée (Gen 1)

24 % HCV connus déjà traités

Probabilité annuelle de Traitement = 10%year

Total Diagnosed: 532,496 (RBS); 1,527,937 (BCS)

Total Treated: 295,423 (RBS); 873,942 (BCS)

McGarry L, Hepatology 2012

Dépistage ciblée vs 100% dépistage de la population américaine née entre 1946-1970

Strategy	Cost/QALY
Base-case analysis	
Risk-based screening	REF
Birth-cohort screening	$37,720

It is likely to be cost-effective at U.S. and European willingness-to-pay thresholds of <$50,000 per QALY gained

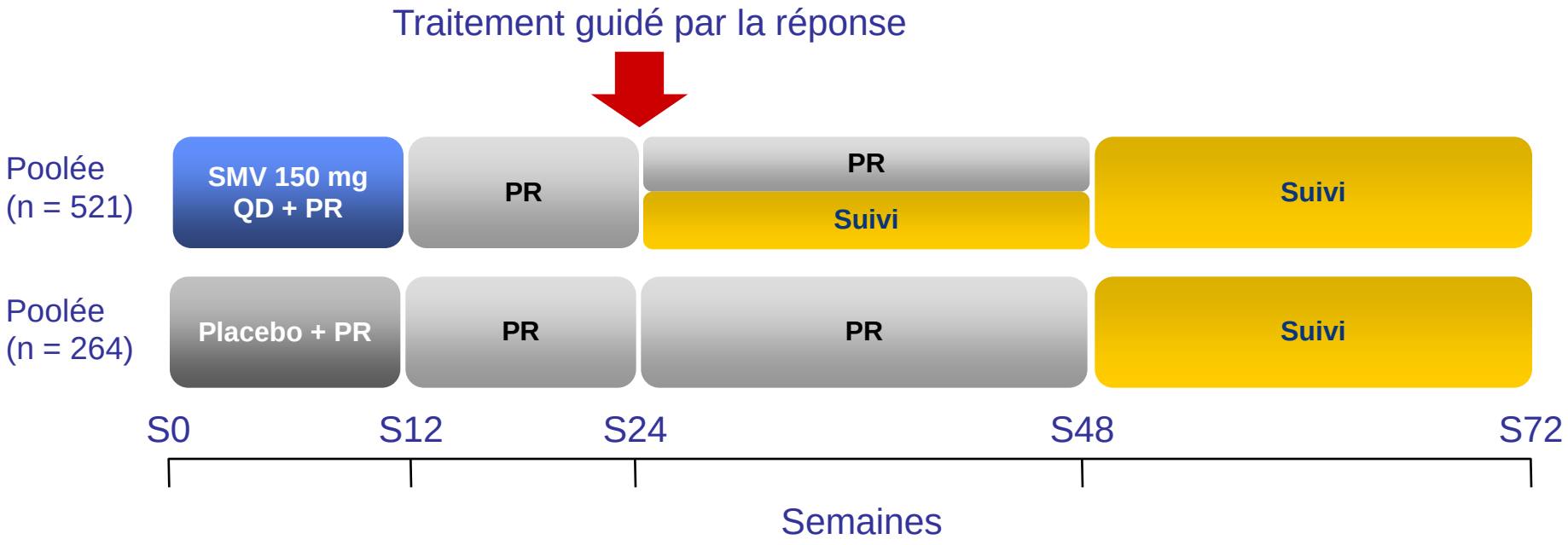
McGarry L, Hepatology 2012

Hépatite C: une nouvelle ère thérapeutique

QUEST 1 et 2 : simeprevir + PEG-IFN/RBV chez patients naïfs G1 *(1)*

- Etudes de phase III, randomisées, multicentriques, double aveugle, comparant SMV 150 mg/j + PEG-IFN/RBV versus placebo + PEG-IFN/RBV chez des patients G1, naïfs

Schéma de l'étude

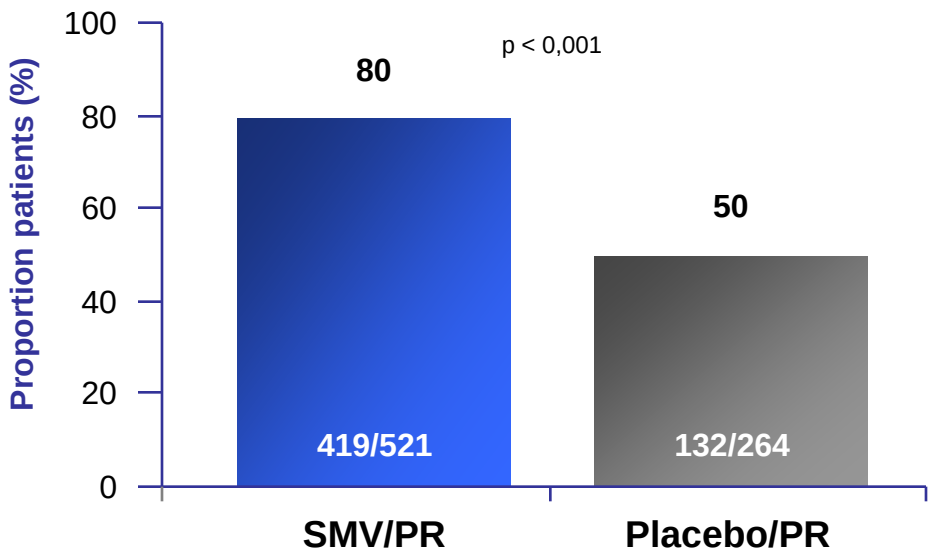


➔ Traitement guidé par la réponse : ARN VHC < 25 UI/ml détectable ou indétectable à S4 et < 25 UI/ml indétectable à S12

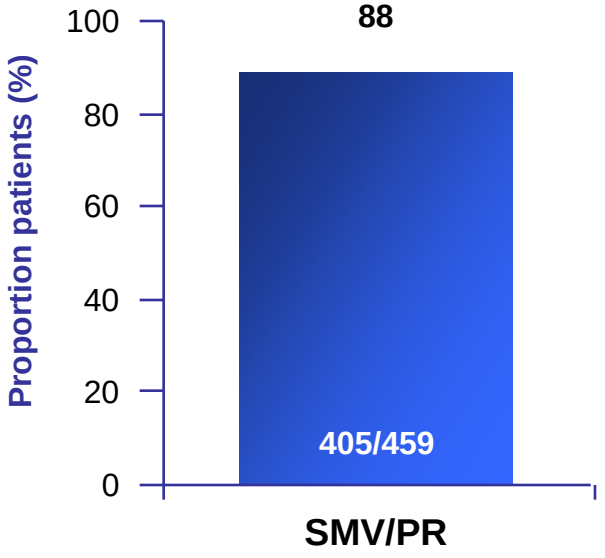
Jacobson IM, Etats-Unis, AASLD 2013, Abs. 1122, actualisé

QUEST 1 et 2 : simeprevir + PEG-IFN/RBV chez patients naïfs G1 *(2)*

RVS12
des 2 études poolées



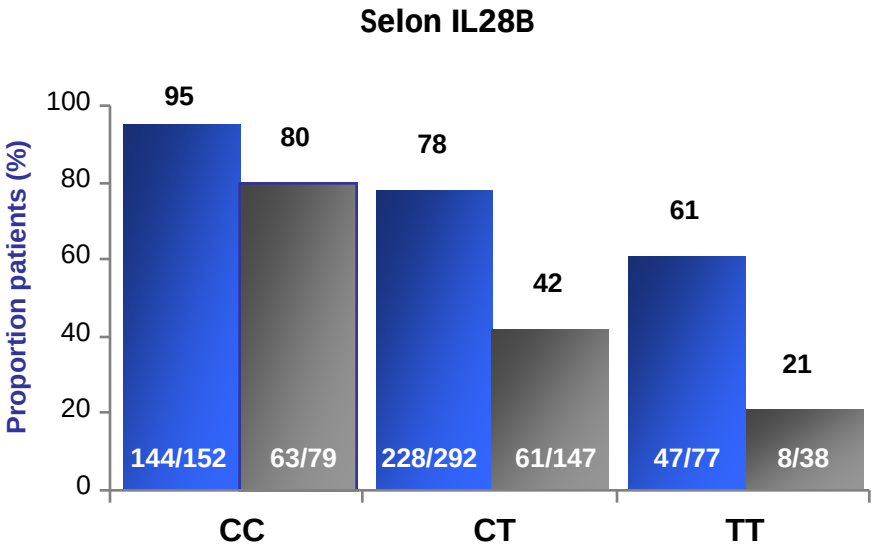
RVS12 pour les patients ayant satisfait le critère de « traitement guidé par la réponse virologique » (459/521 ; 88 %)

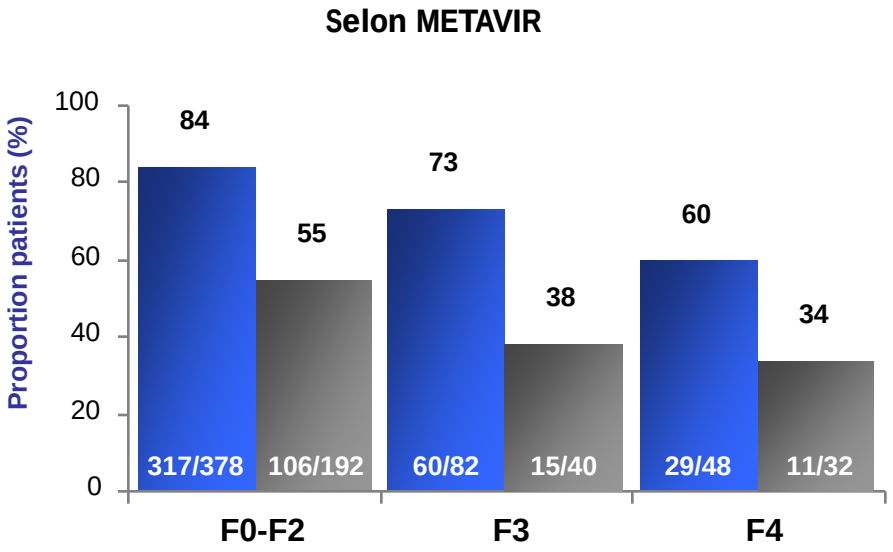


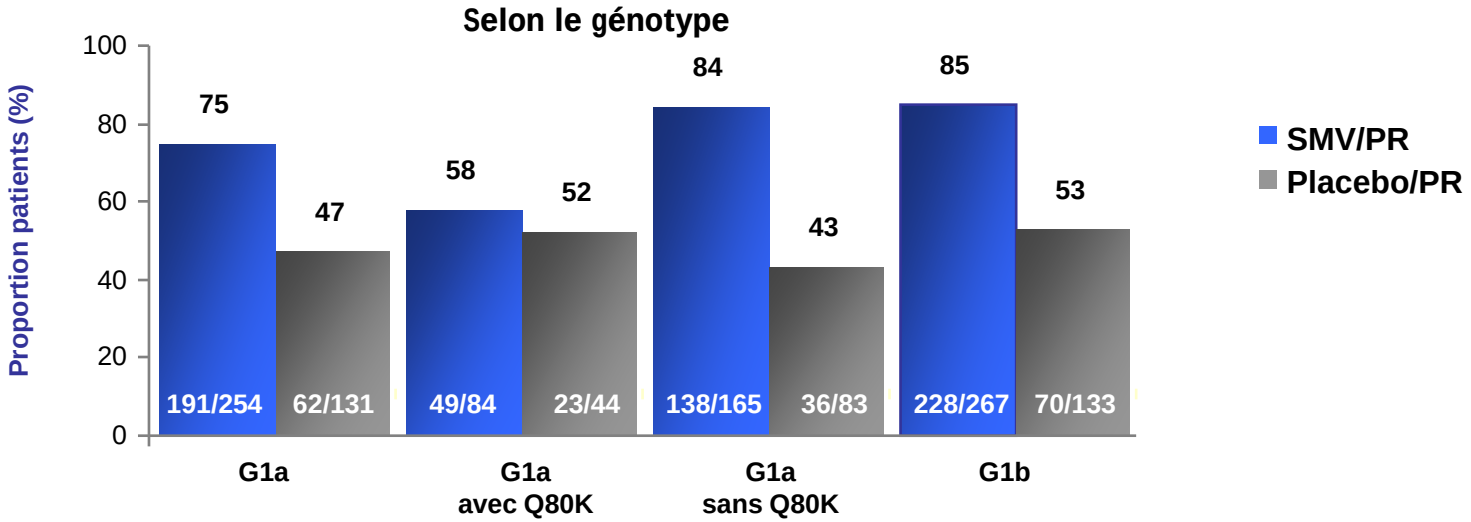
Jacobson IM, Etats-Unis, AASLD 2013, Abs. 1122, actualisé

QUEST 1 et 2 : simeprevir + PEG-IFN/RBV chez patients naïfs G1 *(3)*

Réponse virologique soutenue à 12 semaines

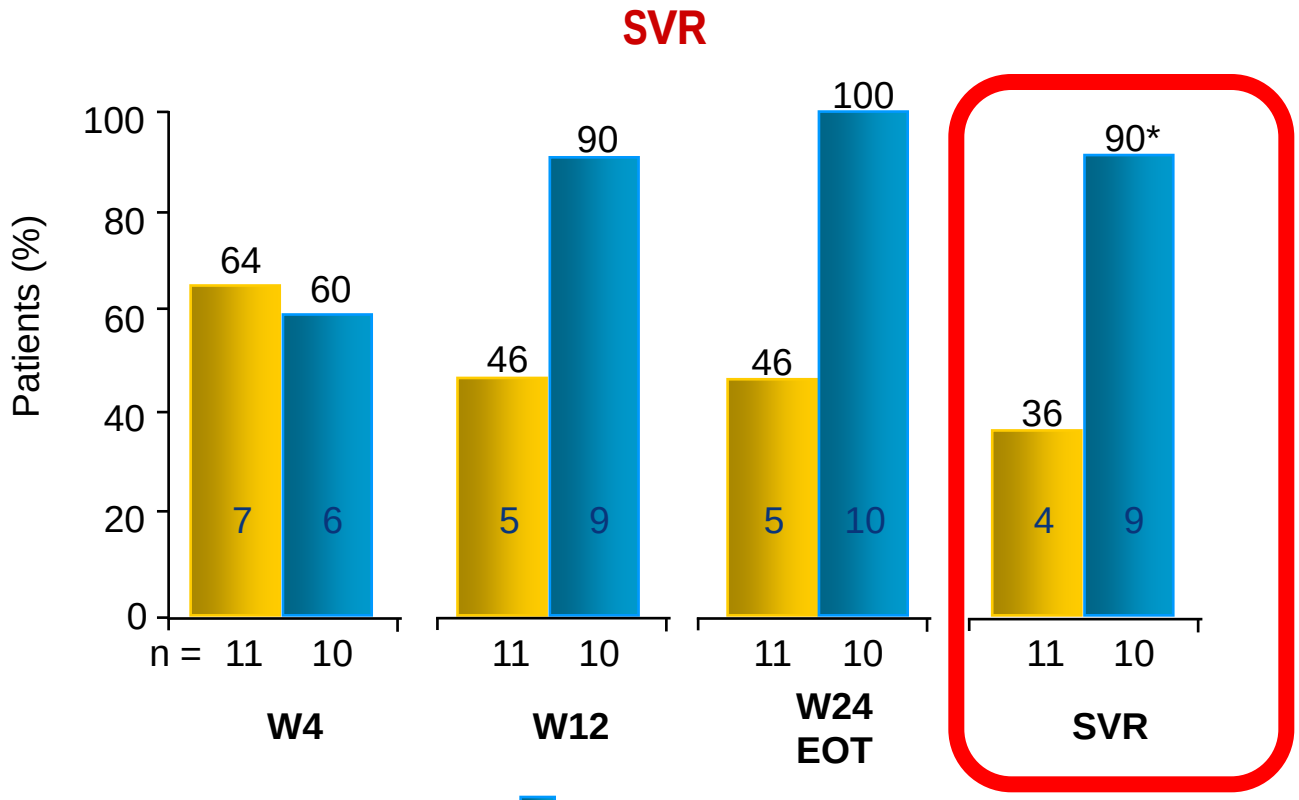






Jacobson IM, Etats-Unis, AASLD 2013, Abs. 1122, actualisé

Quadrithérapie Peg-IFN + Daclatasvir + Asunaprevir + RBV
G1 null responders



Group A : BMS-790052 + BMS-650032

Group B : BMS-790052 + BMS-650032 + PEG-IFNα/RBV

EASL 2011 – Lok A., États-Unis, Abstract LB1356
Lok A, N Engl J Med 20111

Comparaison des profils des antiviraux directs (AVD)

AVD	Pangénotypique	Efficacité	Résistance	Tolérance
Inhibiteurs protéase 1ère génération				
Nouveaux Inhibiteurs protéase Exemple Simeprivir, Asunaprevir,				
Inhibiteurs NS5A Example:Daclatasvir, Ledipasvir				
Inhibiteurs polymérase non-nuc				
Inhibiteurs polymérase nucléosidique				
Inhibiteurs polymérase nucléotidique Exemple: Sofosbuvir				

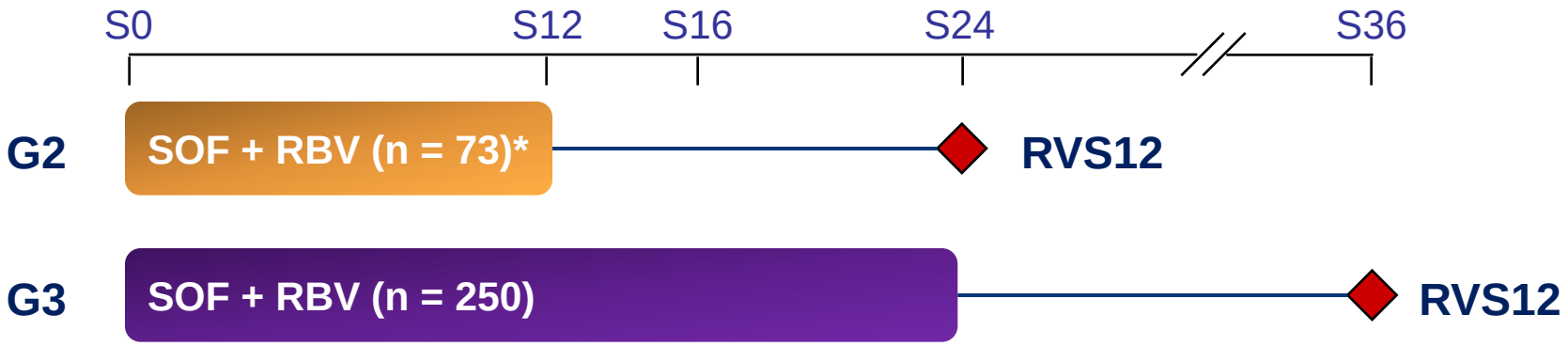
Profil favorable Profil intermédiaire Profil moins favorable

Adapté de Famik H, et al. Antivir Ther 2012;17:771-783
Bourlière M *et al. Ther Adv Infect 2013 DOI:10,1177/20499361135026*
Shah N et al. Expert Opin. Investing drugs 2013;22(9):1107-1121

Etude VALENCE : sofosbuvir chez G2/3 *(1)*

- Etude multicentrique européenne, phase III, patients G2 ou 3, SOF + RBV pendant 12 à 24 semaines

VALENCE : protocole amendé

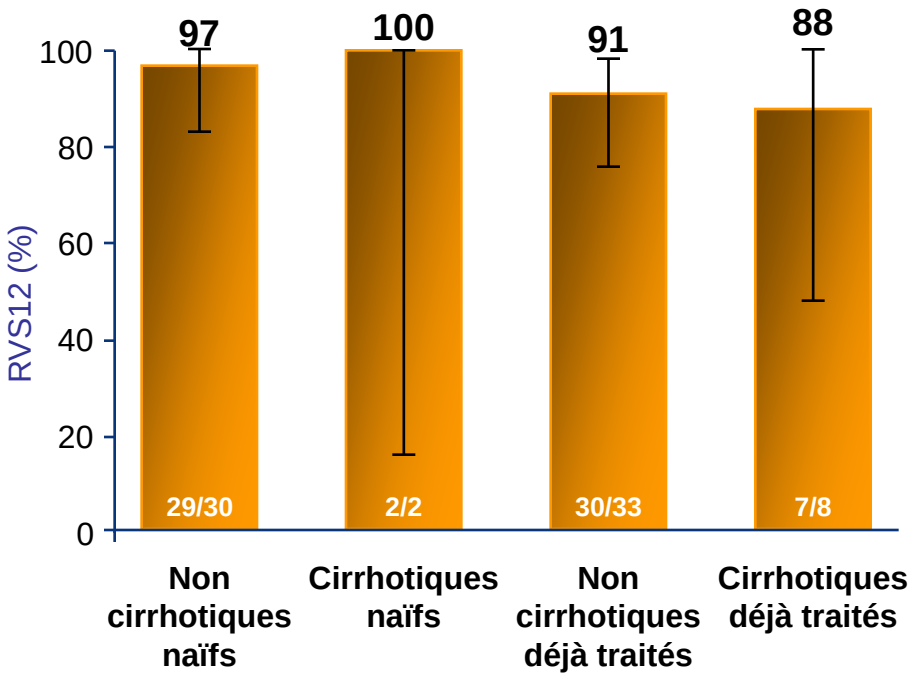


- 11 patients G3 ont eu 12 semaines de traitement. Ils étaient inclus avec G2 mais pour l'efficacité, ils étaient analysés séparément

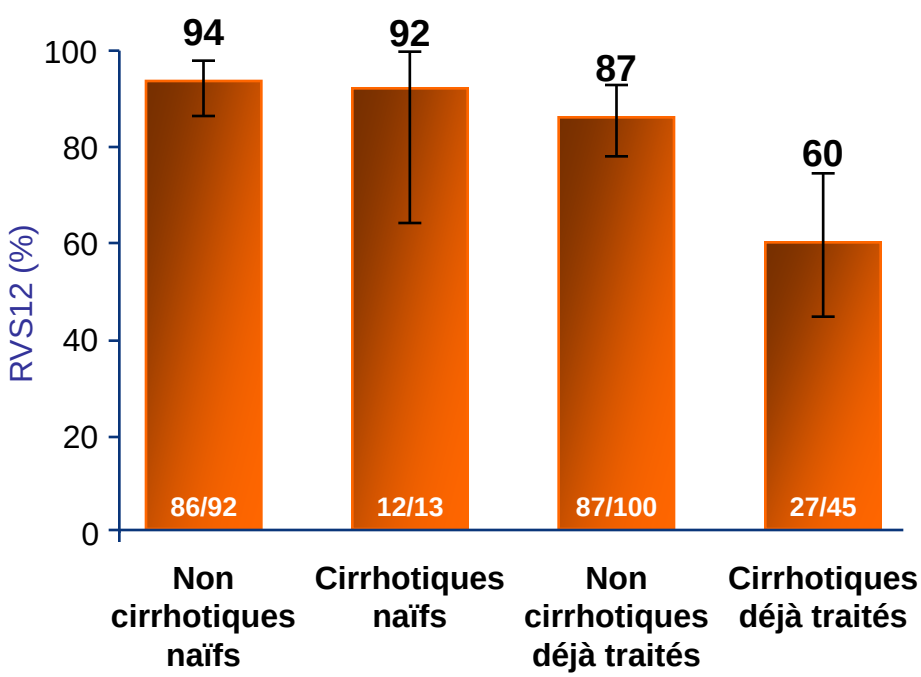
Zeuzem S, Allemagne, AASLD 2013, Abs. 1085, actualisé

Etude VALENCE : sofosbuvir chez G2/3 *(2)*

RVS12 chez patients G2 traités 12 semaines



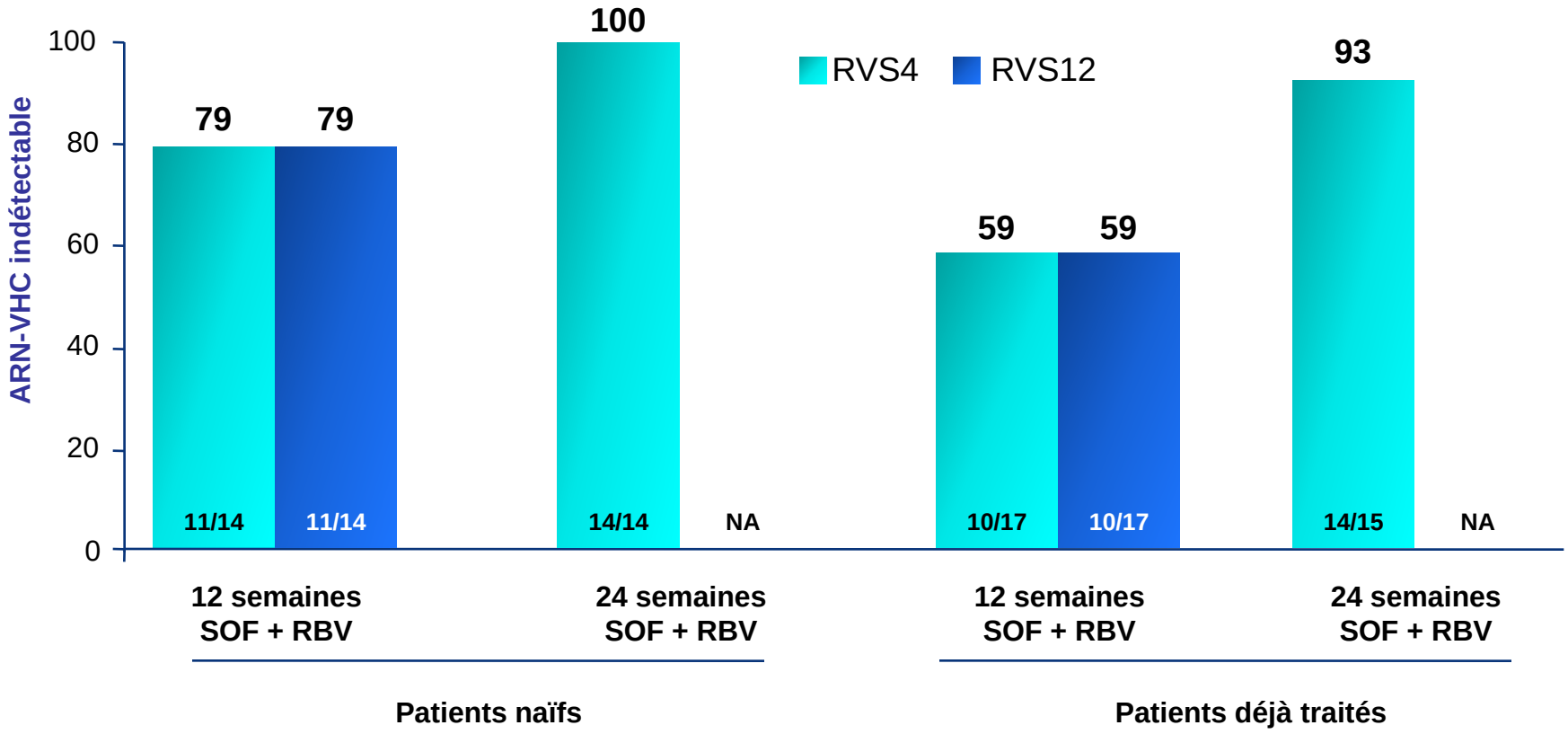
RVS12 chez patients G3 traités 24 semaines



Zeuzem S, Allemagne, AASLD 2013, Abs. 1085, actualisé

Sofosbuvir + ribavirine : patients G4 d'origine égyptienne

Réponse virologique



NA : non applicable

Ruane PJ, Etats-Unis, AASLD 2013, Abs. 1090, actualisé

Interferon-FreeRegimen-Abbvie Patients Cirrhotiques

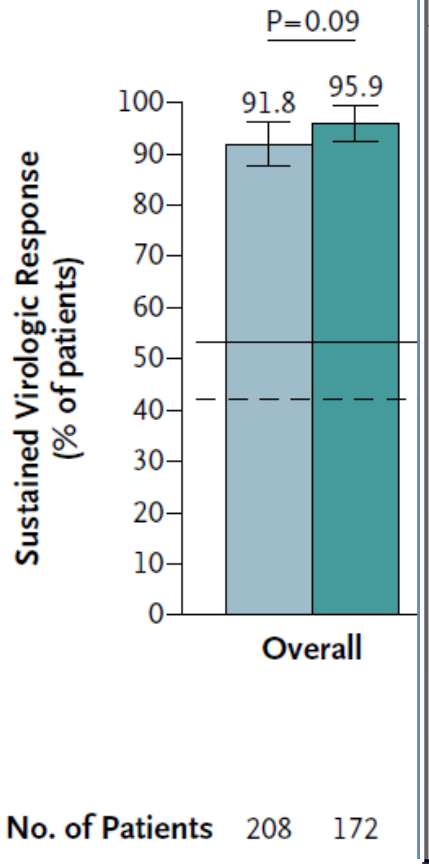


Table 2. Sustained Virologic Response at Post-Treatment Week 12 in Each Treatment Group, According to HCV Subgenotype and Status with Respect to Prior Treatment.*

Variable	12-Wk Group (N=208)	24-Wk Group (N=172)
	no./total no. (%)	
HCV genotype 1a infection		
No prior treatment	59/64 (92.2)	52/56 (92.9)
Prior treatment		
Null response	40/50 (80.0)	39/42 (92.9)
Partial response	11/11 (100)	10/10 (100)
Relapse	14/15 (93.3)	13/13 (100)
HCV genotype 1b infection		
No prior treatment	22/22 (100)	18/18 (100)
Prior treatment		
Null response	25/25 (100)	20/20 (100)
Partial response	6/7 (85.7)	3/3 (100)
Relapse	14/14 (100)	10/10 (100)

- Superiority (54%)
- Noninferiority (43%)

Poordard, New Engl J Med 2014

Protease inhibitor ABT-450 with ritonavir (ABT-450/r), NS5A inhibitor ombitasvir (ABT-267), the nonnucleoside polymerase inhibitor dasabuvir (ABT-333) + RBV

Interferon-FreeRegimen-Abbvie Patients Cirrhotiques

Table 3. Logistic-Regression Analysis of Association of Subgroup Variables with a Sustained Virologic Response at Post-Treatment Week 12.*

vs. partial response, relapse, or no prior treatment)		
HCV subgenotype (1a vs. 1b)	0.10 (0.01–0.80)	0.03

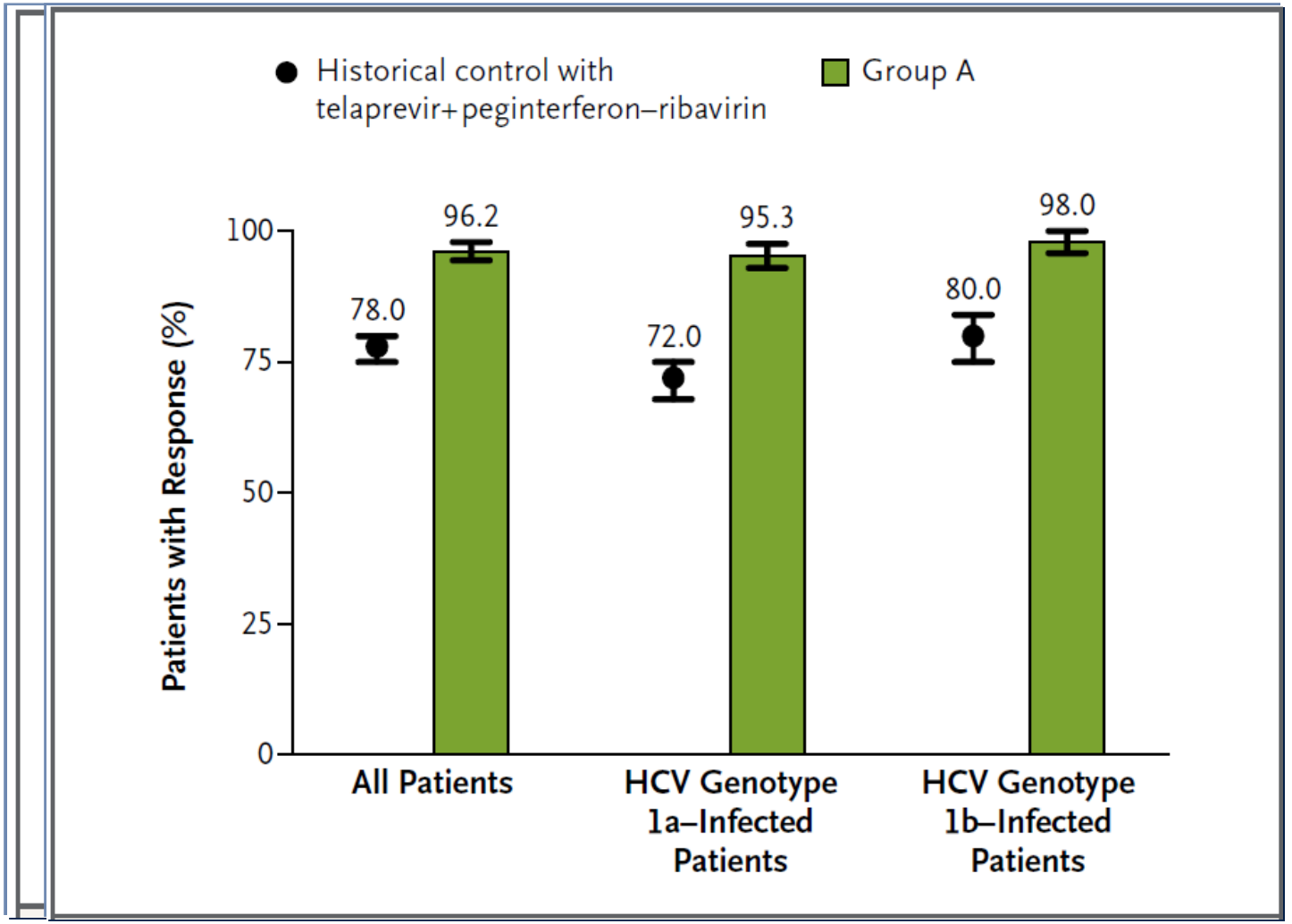
Table 4. Adverse Events and Laboratory Abnormalities.

Variable	12-Wk Group (N=208)	24-Wk Group (N=172)	Total (N=380)
	number of patients (percent)		
Any adverse event	191 (91.8)	156 (90.7)	347 (91.3)
Adverse event leading to treatment discontinuation*	4 (1.9)	4 (2.3)	8 (2.1)
Serious adverse event†	13 (6.2)	8 (4.7)	21 (5.5)

Poordard, New Engl J Med 2014

Protease inhibitor ABT-450 with ritonavir (ABT-450/r), NS5A inhibitor ombitasvir (ABT-267), the nonnucleoside polymerase inhibitor dasabuvir (ABT-333) + RBV

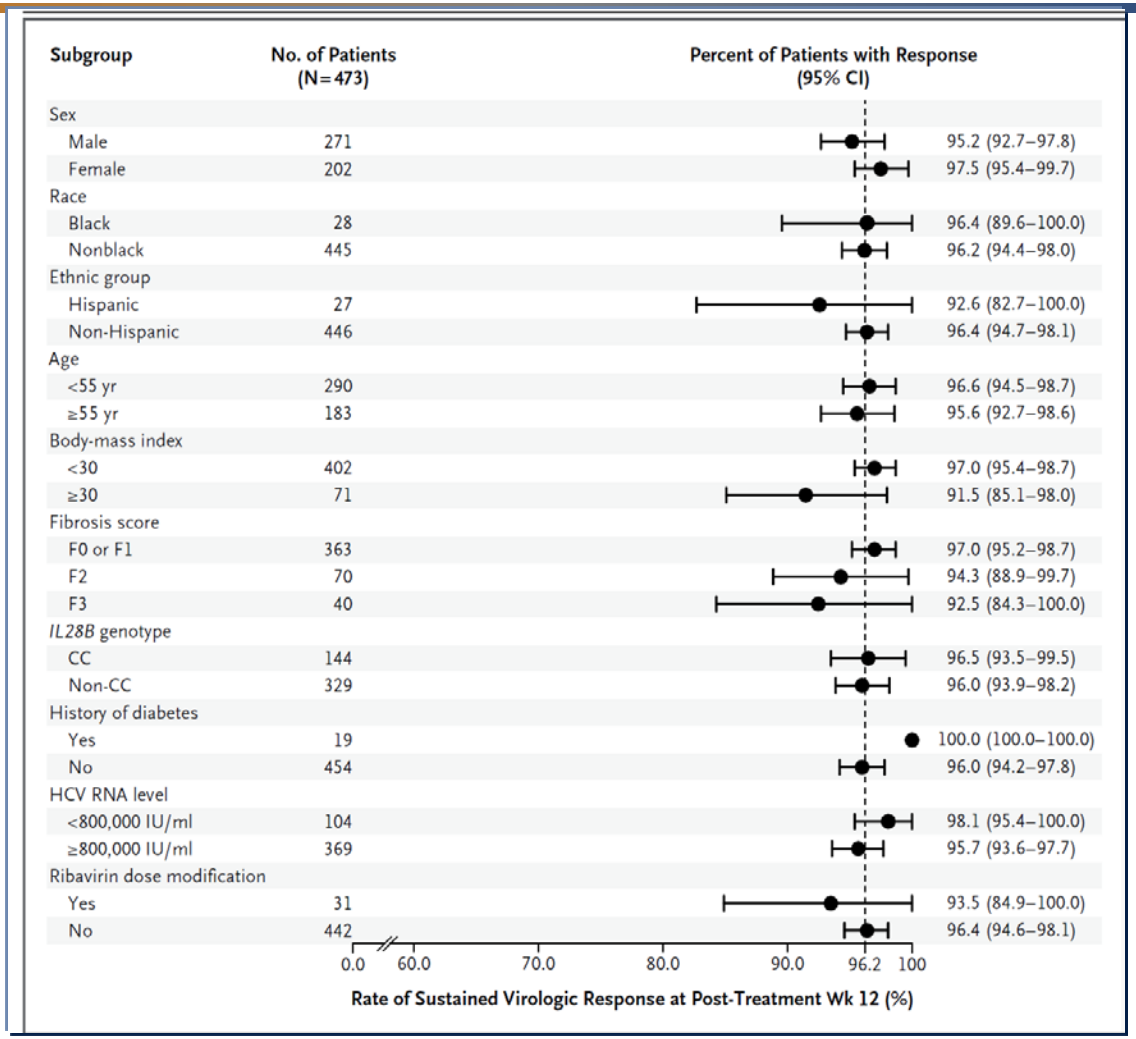
Interferon-FreeRegimen-Abbvie Patients Naifs- Etude Spahire



Feld JJ , New Engl J Med 2014

Protease inhibitor ABT-450 with ritonavir (ABT-450/r), NS5A inhibitor ombitasvir (ABT-267), the nonnucleoside polymerase inhibitor dasabuvir (ABT-333) + RBV

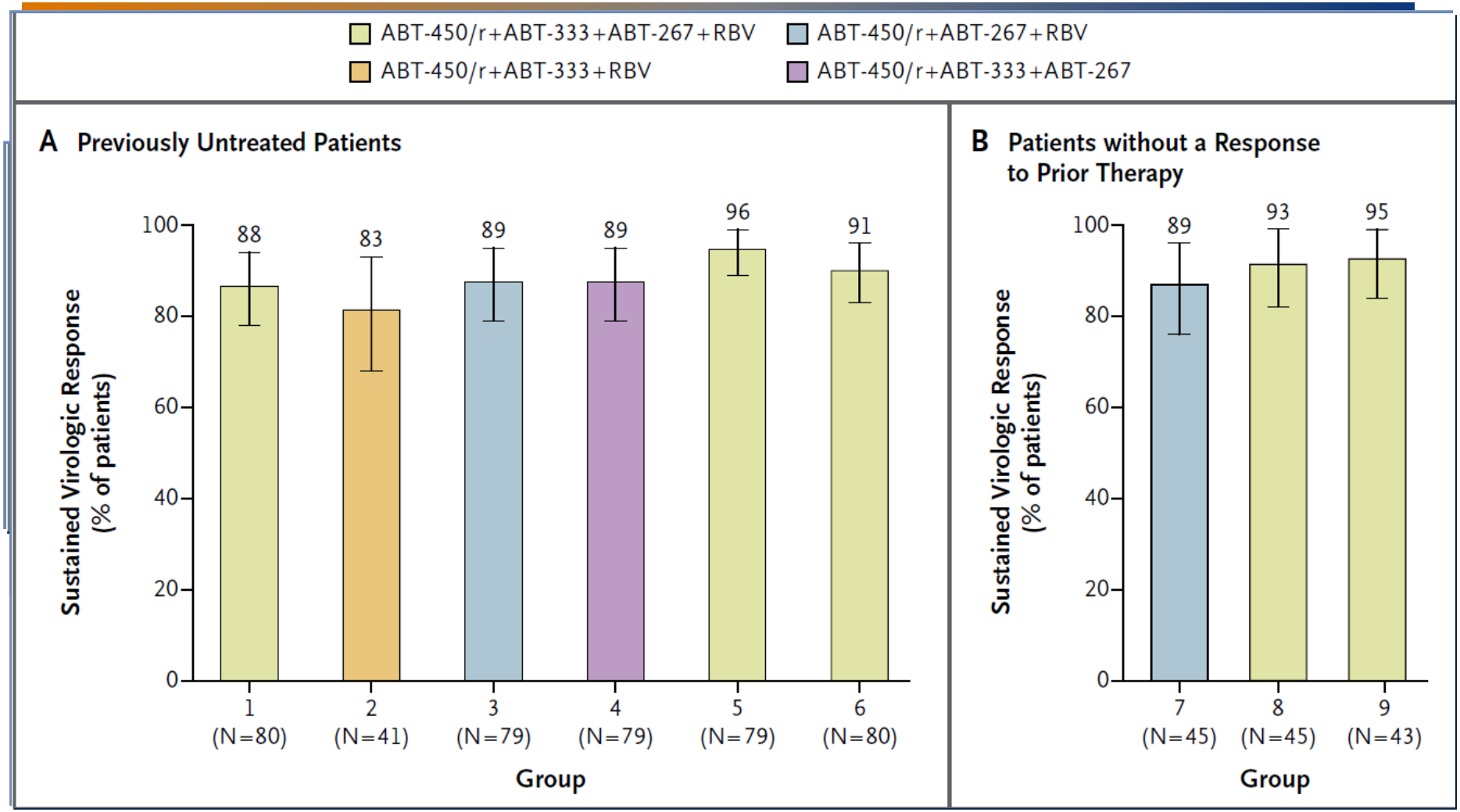
Interferon-FreeRegimen-Abbvie Patients Naifs- Etude Spahire



Feld JJ , New Engl J Med 2014

Protease inhibitor ABT-450 with ritonavir (ABT-450/r), NS5A inhibitor ombitasvir (ABT-267), the nonnucleoside polymerase inhibitor dasabuvir (ABT-333) + RBV

Interferon-FreeRegimen-Abbvie
Patients Prétraités



Kowdley KV , New Engl J Med 2014

Protease inhibitor ABT-450 with ritonavir (ABT-450/r), NS5A inhibitor ombitasvir (ABT-267), the nonnucleoside polymerase inhibitor dasabuvir (ABT-333) + RBV

Interferon-FreeRegimen-Gilead Ledipasvir-Sofosbuvir- Patients Naifs

Table 2. Response during and after Treatment.

Response	12-Wk Regimen		24-Wk Regimen	
	LDV–SOF (N=214)	LDV–SOF + RBV (N=217)	LDV–SOF (N=217)	LDV–SOF + RBV (N=217)
HCV RNA <25 IU/ml				
During treatment — no./total no. (%)*				
At week 2	174/213 (82)	181/217 (83)	179/216 (83)	180/217 (83)
At week 4	213/213 (100)	215/217 (99)	216/216 (100)	217/217 (100)
At week 12	213/213 (100)	214/214 (100)	213/214 (>99)	216/216 (100)
After end of treatment — no. (%)				
At week 4	211 (99)	213 (98)	215 (99)	215 (99)
At week 12	211 (99)	211 (97)	212 (98)	215 (99)
Virologic failure during treatment — no.	0	0	1	0

Afdhal N , New Engl J Med 2014

Interferon-FreeRegimen-Gilead Ledipasvir-Sofosbuvir- Patients Prétraités

Table 2. Response during and after Treatment.

Response	12-Wk Regimen		24-Wk Regimen	
	LDV–SOF (N=109)	LDV–SOF + RBV (N=111)	LDV–SOF (N=109)	LDV–SOF + RBV (N=111)
	number (percent)			
HCV RNA <25 IU/ml				
During treatment				
At 2 wk	89 (82)	92 (83)	89 (82)	93 (84)
At 4 wk	109 (100)	110 (99)	108 (99)	110 (99)
At end of treatment	108 (99)*	111 (100)	109 (100)	110 (99)
After end of treatment				
At 4 wk	103 (94)	107 (96)	109 (100)	110 (99)
At 12 wk	102 (94)	107 (96)	108 (99)†	110 (99)
Virologic breakthrough during treatment	0	0	0	1 (1)‡
Relapse	7 (6)	4 (4)	0	0

Afdhal N , New Engl J Med 2014

Interferon-FreeRegimen-Gilead Ledipasvir-Sofosbuvir- Patients Prétraités

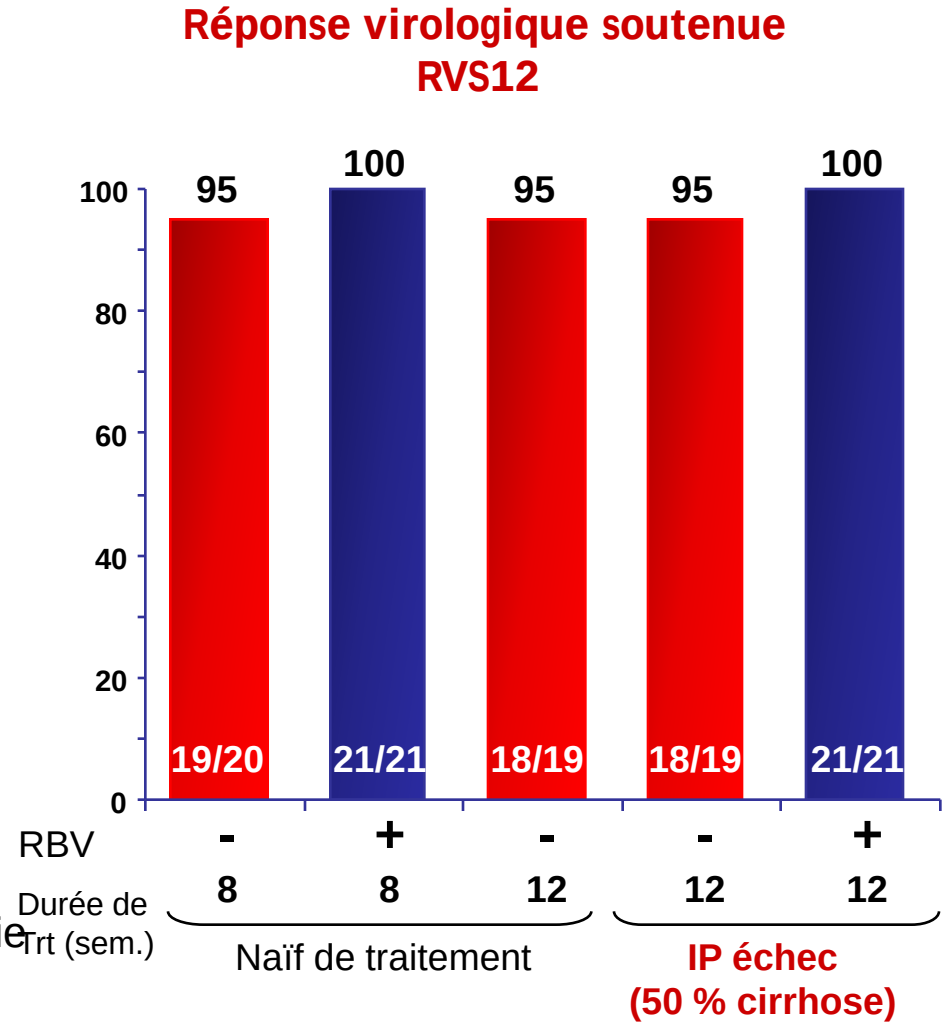
Table 3. Treatment Discontinuations, Adverse Events, and Hematologic Abnormalities.*

Variable	12-Wk Regimen		24-Wk Regimen	
	LDV–SOF (N = 109)	LDV–SOF + RBV (N = 111)	LDV–SOF (N = 109)	LDV–SOF + RBV (N = 111)
Duration of treatment — wk	12.2±0.2	12.1±0.2	23.9±1.6	24.0±1.7
Treatment discontinuation owing to adverse event — no. of patients	0	0	0	0

Afdhal N , New Engl J Med 2014

Sofosbuvir + ledipasvir ± ribavirine chez les patients de génotype 1 : LONESTAR

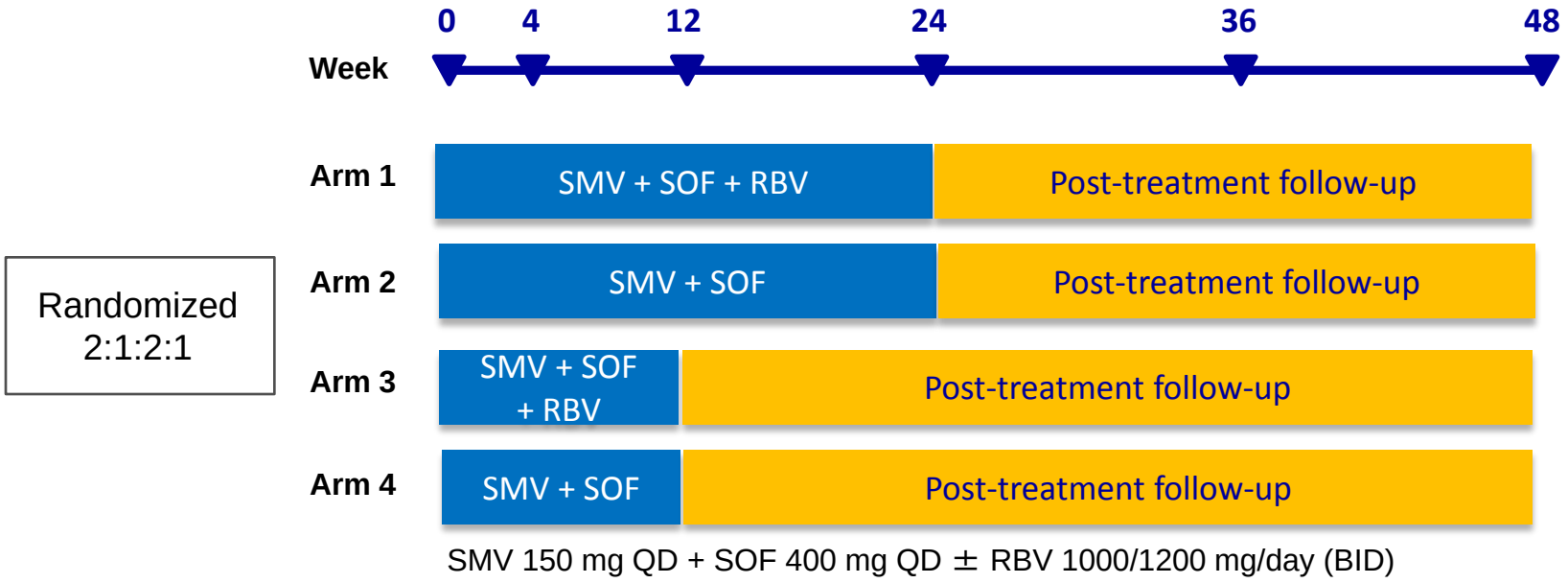
- Patients GT1 naïfs de traitement non cirrhotiques (n = 60)
  - SOF/LDV ± RBV 8 semaines ou SOF/LDV 12 semaines
- Patients non répondeurs à trithérapie avec IP, (n = 40)
  - Cirrhose, n = 22
  - SOF/LDV ± RBV pendant 12 semaines
- Sans RVS (n = 3)
  - Perdu de vue (n = 1)
  - Rechute virale (n = 2)
    - Pt naïf, traité 8 semaines
    - Pt cirrhose en échec de trithérapie avec IP sans RBV
    - Pt naïf a été retraité
- Aucun arrêt de traitement dû à EI



Lawitz E ,Etats-Unis, AASLD 2013, Abs. 215/1844, actualisés

COSMOS: Study design

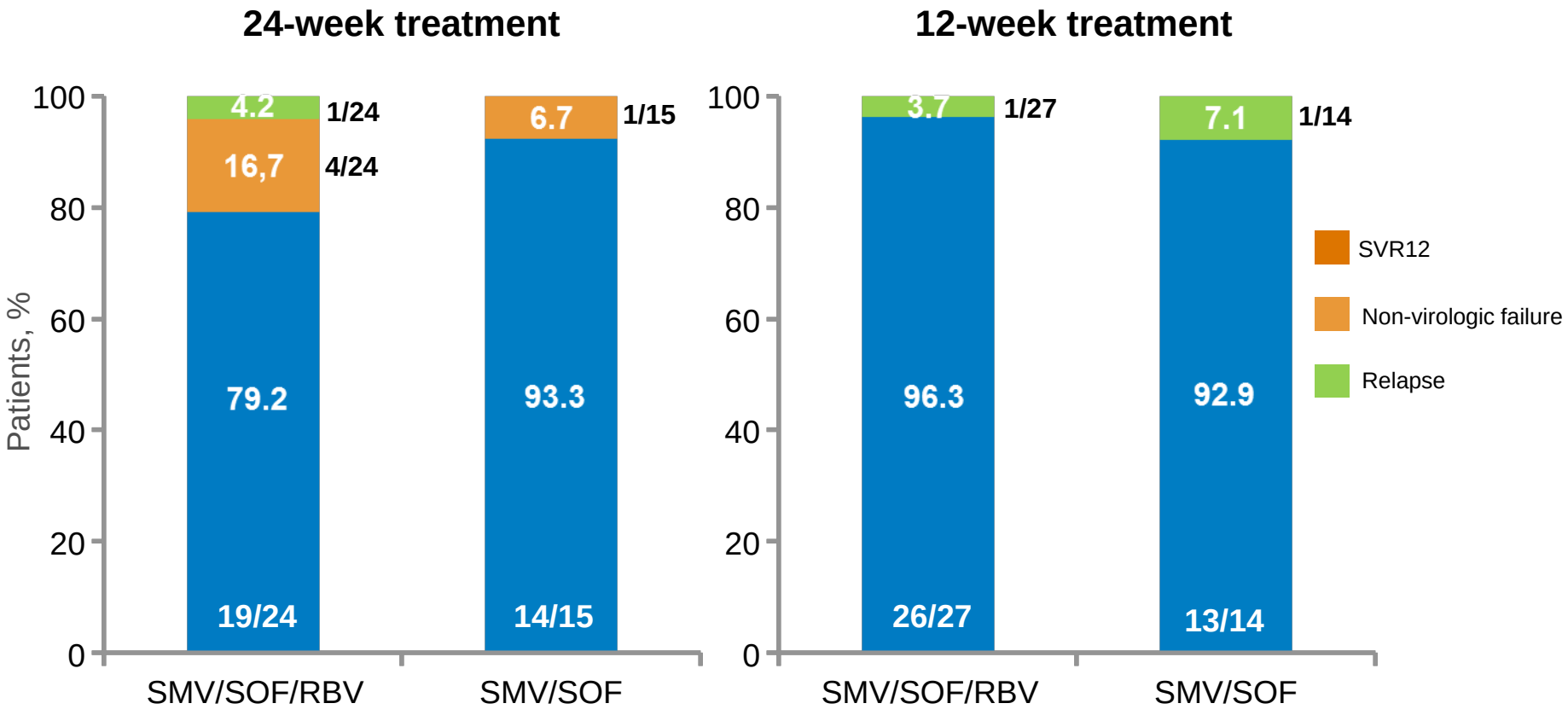
- Cohort 1: Prior null responders (METAVIR F0-F2)
- Cohort 2: Treatment-naïve and prior null responders (METAVIR F3-F4)



- Stratification: Cohort 1: HCV geno/subtype and *IL28B*
  Cohort 2: HCV geno/subtype and population (naïve/null)
- Planned interim analysis: Cohort 1: Final SVR12 for all arms
  Cohort 2: Interim SVR4 for 12 week arms

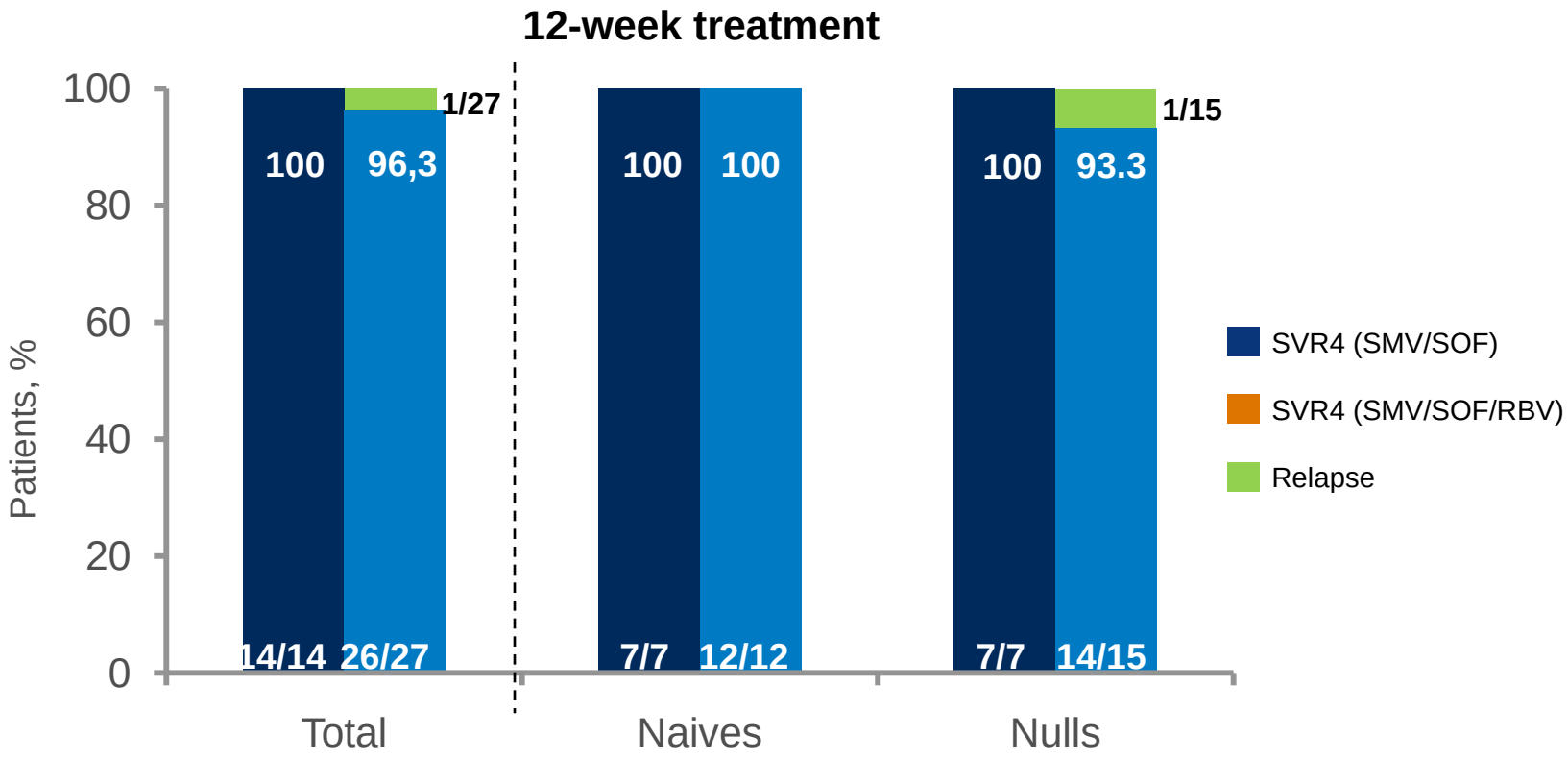
Jacobson IM, AASLD 2013

Cohort 1: Prior null responders (METAVIR F0-F2) ITT population



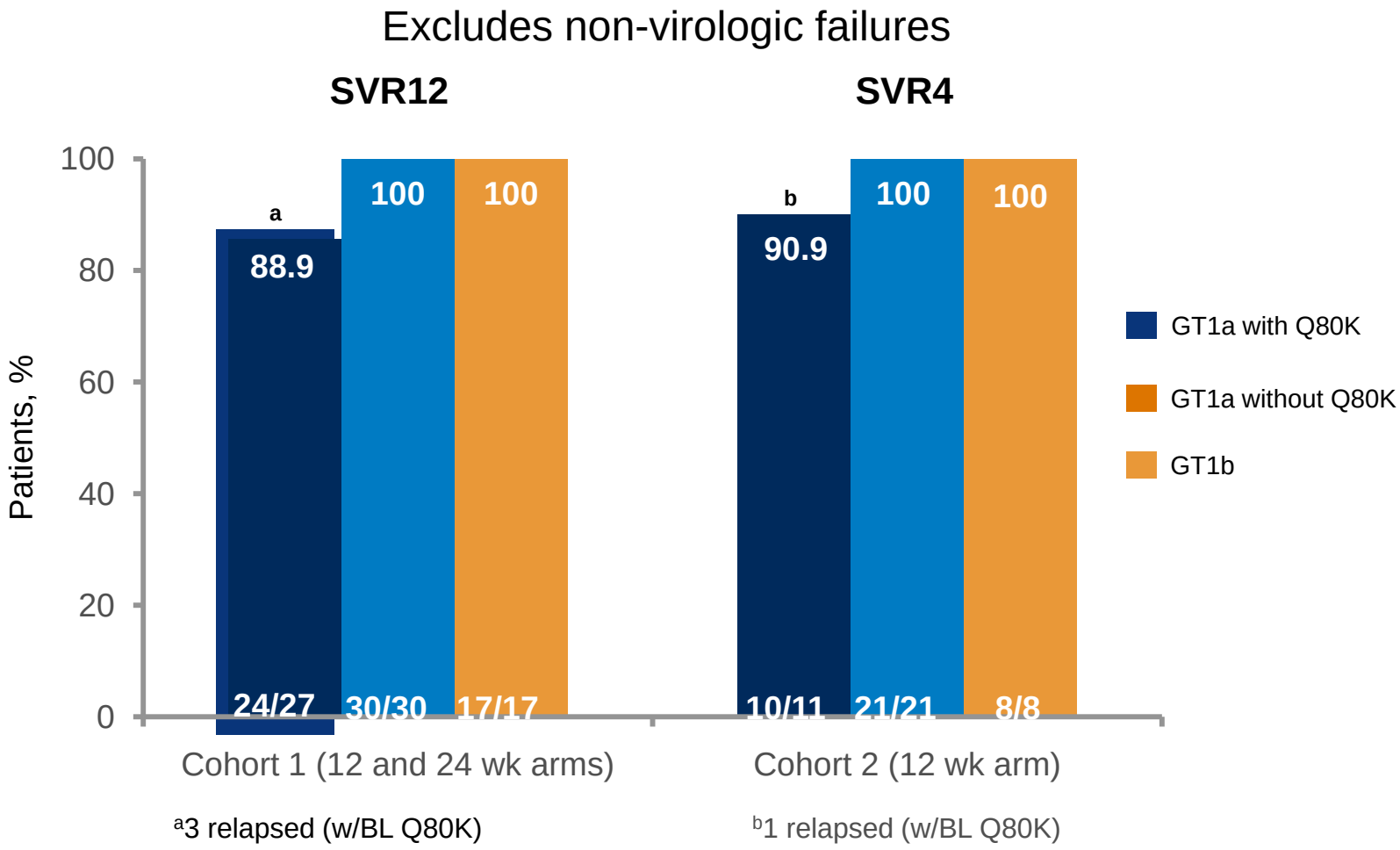
ITT, intent-to-treat; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR12, sustained virologic response 12 weeks after treatment end

Cohort 2: Naïve and prior null responders (METAVIR F3-F4) SVR4 interim analysis, ITT population



ITT, intent-to-treat; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR4, sustained virologic response 4 weeks after treatment end

SVR rates according to HCV subtype: Cohorts 1 and 2



BL, baseline; GT, genotype; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR4, sustained virologic response 4 weeks after end of treatment; SVR12, sustained virologic response 12 weeks after end of treatment

Sofosbuvir + Daclatasvir

Table 2. Virologic Response during and after Treatment.

Virologic Response	Genotype 2 or 3, Previously Untreated			
	Group B: SOF for 7 days, then SOF and DCV for 23 wk (N=16)	Group D: DCV and SOF for 24 wk (N=14)	Group F: DCV and SOF plus RBV for 24 wk (N=14)	Total: Groups B, D, and F (N=44)
	number of study participants (percent)			
Week 24				
HCV RNA <25 IU/ml	14 (88)	14 (100)	13 (93)	41 (93)
HCV RNA undetectable	14 (88)	14 (100)	13 (93)	41 (93)

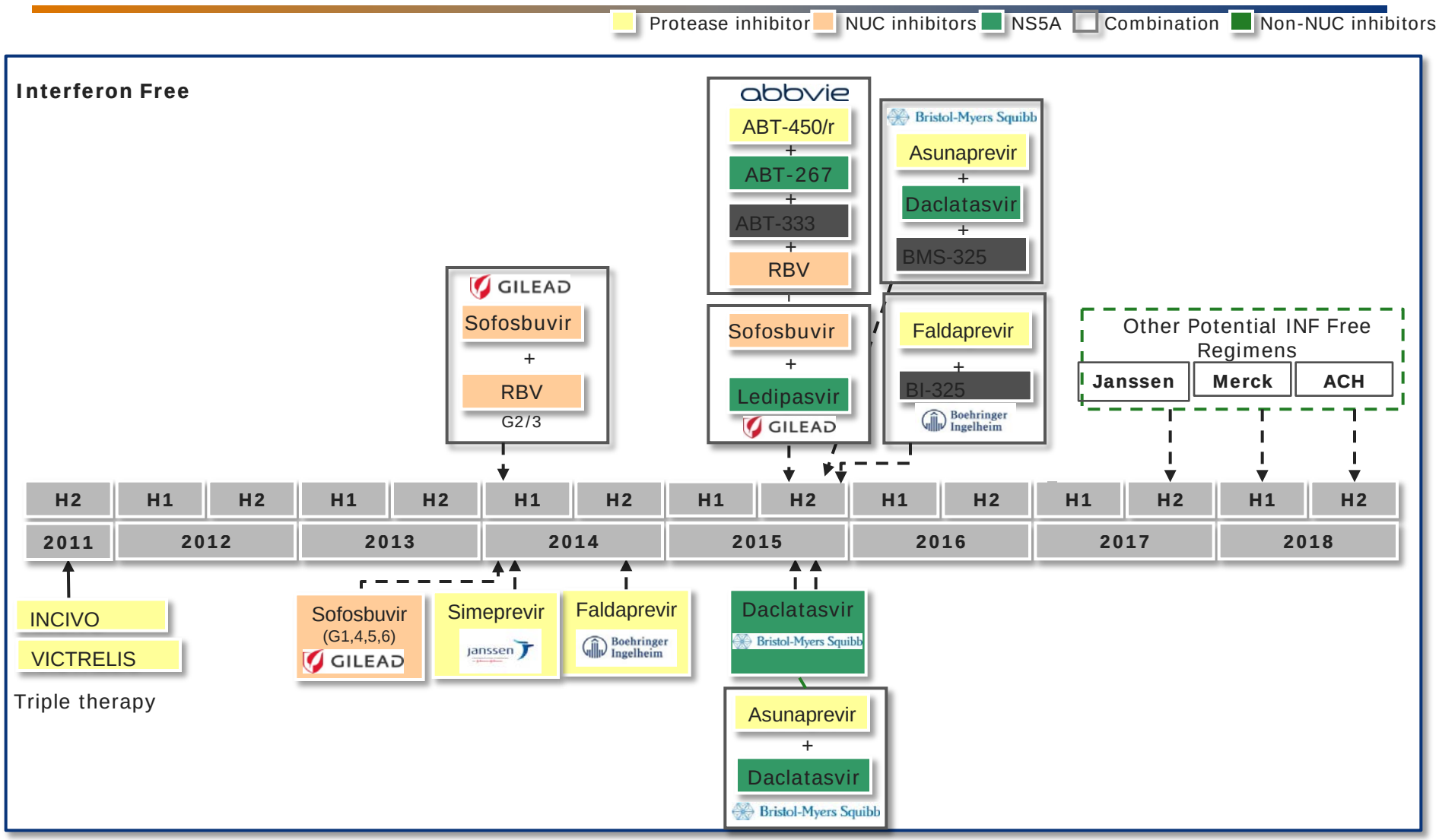
Sulkowski MS, N Engl J Med 2014

Sofosbuvir + Daclatasvir

Genotype 1, Previously Untreated						Genotype 1, Previously Treated	
Group A: SOF for 7 days, then SOF and DCV for 23 wk (N=15)	Group C: DCV and SOF for 24 wk (N=14)	Group E: DCV and SOF plus RBV for 24 wk (N=15)	Group G : DCV and SOF for 12 wk (N=41)	Group H: DCV and SOF plus RBV for 12 wk (N=41)	Total: Groups A, C, E, G, and H (N=126)	Group I: DCV and SOF for 24 wk (N=21)	Group J: DCV and SOF plus RBV for 24 wk (N=20)
number of study participants (percent)							
15 (100)	14 (100)	15 (100)	41 (100)	39 (95)§§	124 (98)	21 (100)	19 (95)¶¶
15 (100)	14 (100)	15 (100)	41 (100)	39 (95)§§	124 (98)	21 (100)	19 (95)¶¶

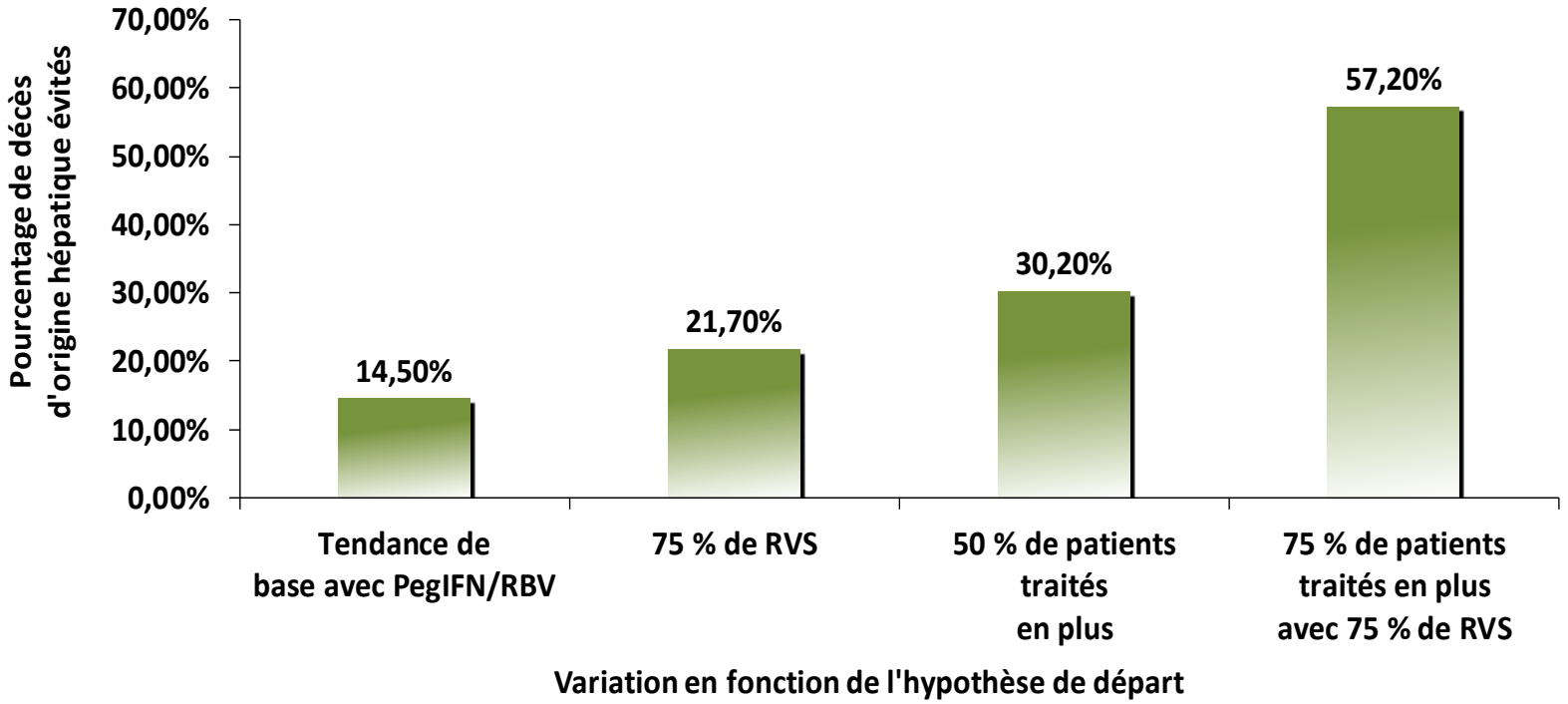
Sulkowski MS, N Engl J Med 2014

EU Competitive Launch Timeline



Accès accrue aux traitements antiviraux plus important que l'amélioration du taux de RVS

Pourcentage de décès d'origine hépatique entre 2002 et 2030 qui pourraient être évités grâce aux traitements antiviraux actuels



Volk ML Hepatology 2009

Therapy for Hepatitis C — The Costs of Success

It is hardly surprising that, despite the availability of interferon-based therapy for more than 20 years, the mortality from hepatitis C in the United States has continued to increase and now exceeds that from HIV infection

The current cost of a 12-week regimen of sofosbuvir alone is $84,000, or $1,000 per tablet.11 The addition of ledipasvir will add to the costs, and these estimates do not include expenses for diagnostic assays, monitoring, and physician visits

Public health efforts are now under way to identify persons with HCV infection and to direct them to medical care. With the present estimates of costs, however, treating even half the HCV-infected persons in the United States would add billions of dollars to an already overburdened medical care system.

Costs alone cast a pall over the stunning success in achieving the long-hoped-for goal of a safe and effective therapy for hepatitis C

Hoofnagle JH, N Engl J Med 2014

Conclusions

- Les avis d'experts devraient prendre en compte les incertitudes de leurs assertions
- Le traitement à large échelle permettra une diminution de la morbidité et de la mortalité
- Les stratégies thérapeutiques devraient être ciblées sur le bénéfice de survie en terme de population générale