«BEST OF» INFECTIOLOGIE

« *Infections Hépatiques* »

Gilles PIALOUX

APHP (Tenon)
UPMC (ParisVI)
Vice Pdt SFLS
www.vih.org

14 ème JNI – CLERMONT-FERRAND – 14 JUIN 2013

Déclaration de liens d'intérêts , Gilles Pialoux

Membre de board, d'un conseil scientifique, intervenant ou invité dans un symposium d'un laboratoire pharmaceutique :
Abbott, AbbVie, Boehringer-Ingelheim, BMS, GSK, Gilead, MSD, Pfizer, Roche, Schering-Plough, Nephrotec, Tibotec, ViiVHealthcare

Parts sociales ou actions dans un laboratoire pharmaceutique : Aucune

Membre du COS de AIDES
Investigateur de ANRS-IPERGAY

Cette présentation n'illustre pas les habitudes de prescription de l'auteur ni de son équipe mais fournit une vue des éléments scientifiques sélectifs issus de la bibliographie.

PubMed «hépatitis infection »

2012	3643* publications
Juin 2013	1712 publications

* record absolu sur 60 889 items

Liver INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE LIVER

Liver International ISSN 1478-3223

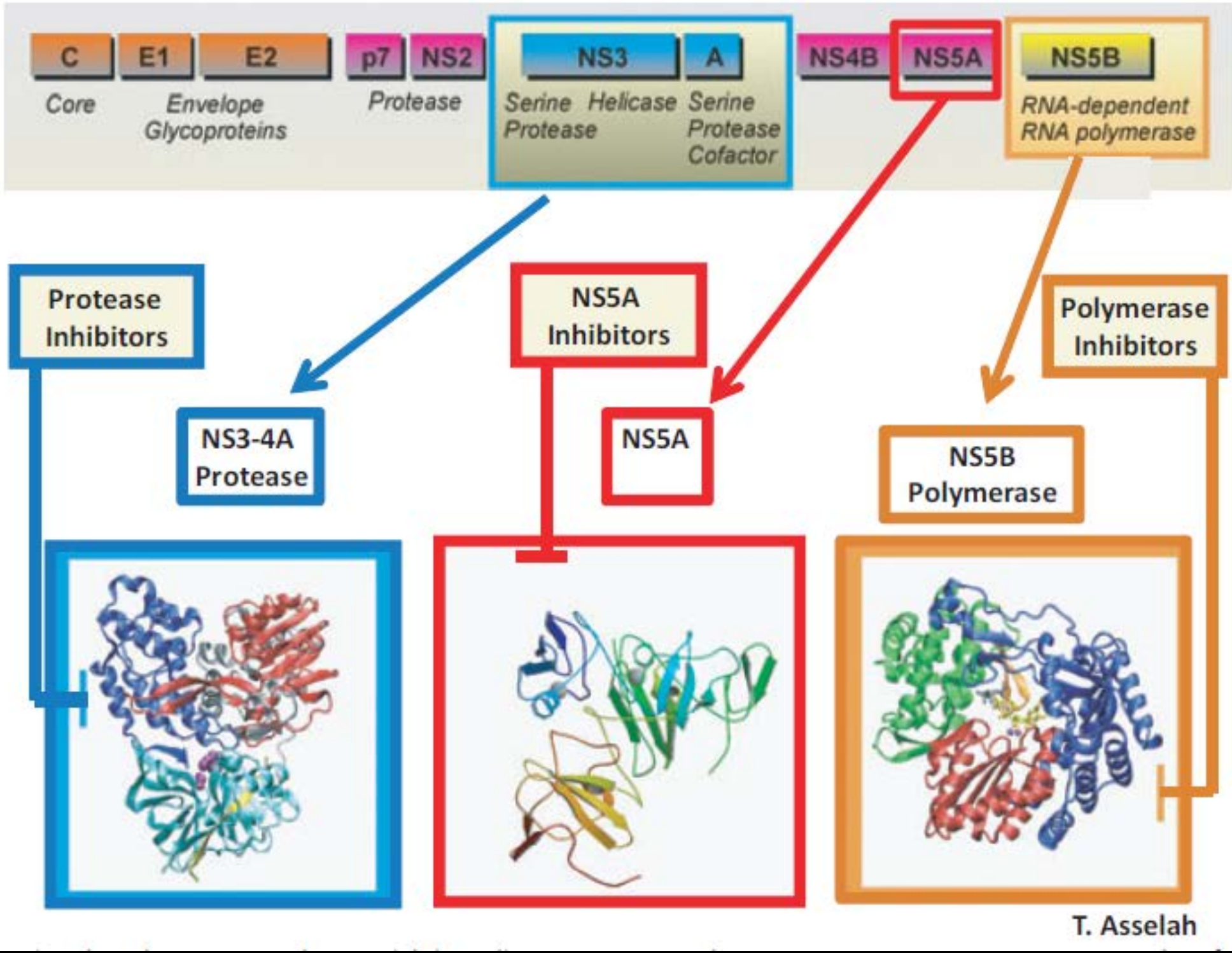
REVIEW ARTICLE

Direct acting antivirals for the treatment of chronic hepatitis C: one pill a day for tomorrow

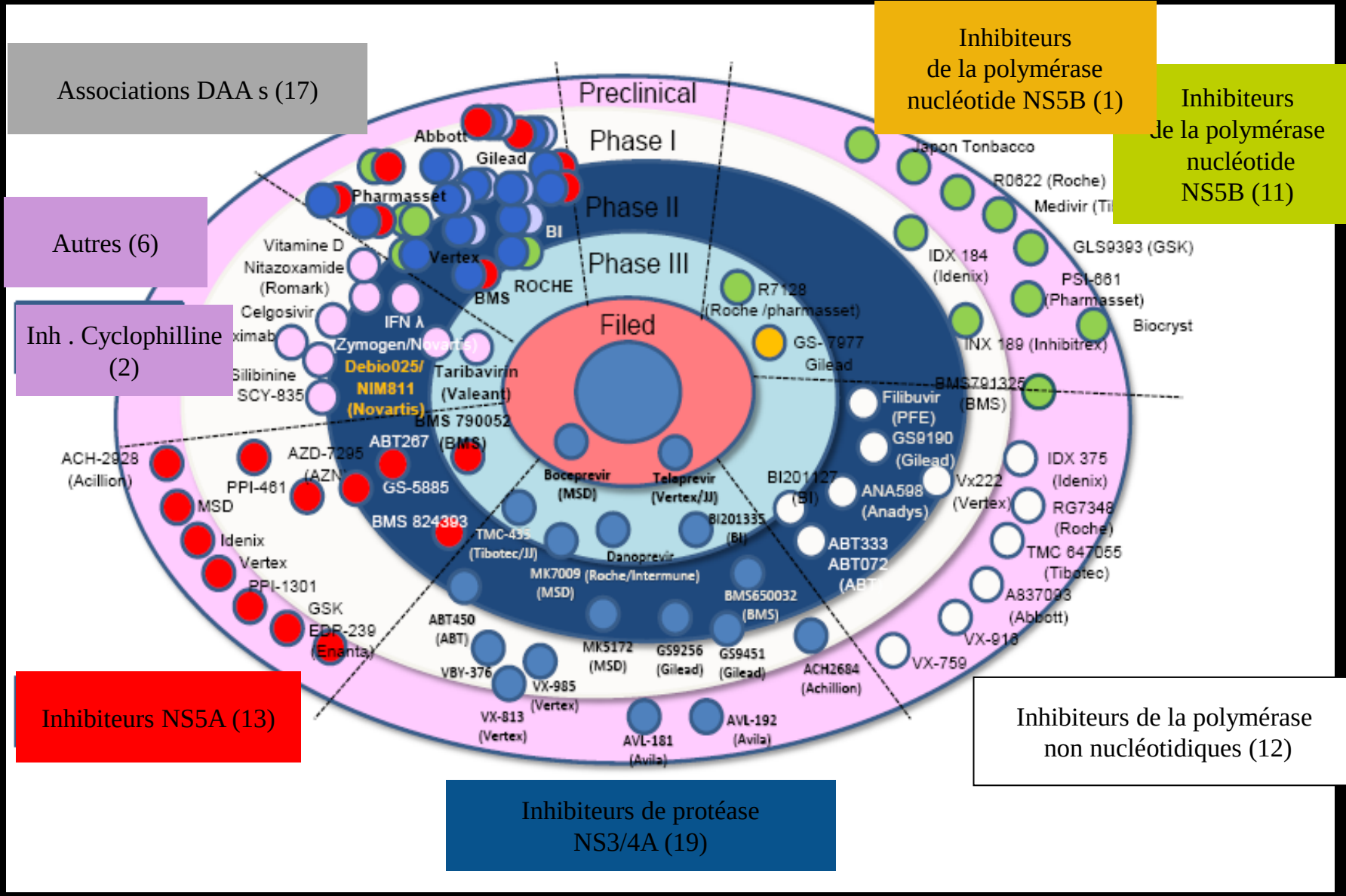
Tarik Asselah and Patrick Marcellin

Service d'hépatologie, Hôpital Beaujon, APHP, University Paris-Diderot and INSERM CRB3 Clichy, France

Liver International S1; 88-102, Feb 2012


C
E1
E2
p7
NS2
NS3
A
NS4B
NS5A
NS5B
Core
Envelope Glycoproteins
Protease
Serine Protease
Helicase
Serine Protease Cofactor
RNA-dependent RNA polymerase
Protease Inhibitors
NS5A Inhibitors
Polymerase Inhibitors
NS3-4A Protease
NS5A
NS5B Polymerase
T. Asselah

Les molécules DAA anti-VHC en développement



DiapoMarc Bourlière CROI 2013

Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial

Kris V Kowdley, Eric Lawitz, Israel Crespo, Tarek Hassanein, Mitchell N Davis, Michael DeMicco, David E Bernstein, Nezam Afdhal, John M Vierling, Stuart C Gordon, Jane K Anderson*, Robert H Hyland, Hadas Dvory-Sobol, Di An, Robert G Hindes*, Efsevia Albanis*, William T Symonds, M Michelle Berrey, David R Nelson, Ira M Jacobson

Published Online
March 15, 2013
http://dx.doi.org/10.1016/S0140-6736(13)60247-0

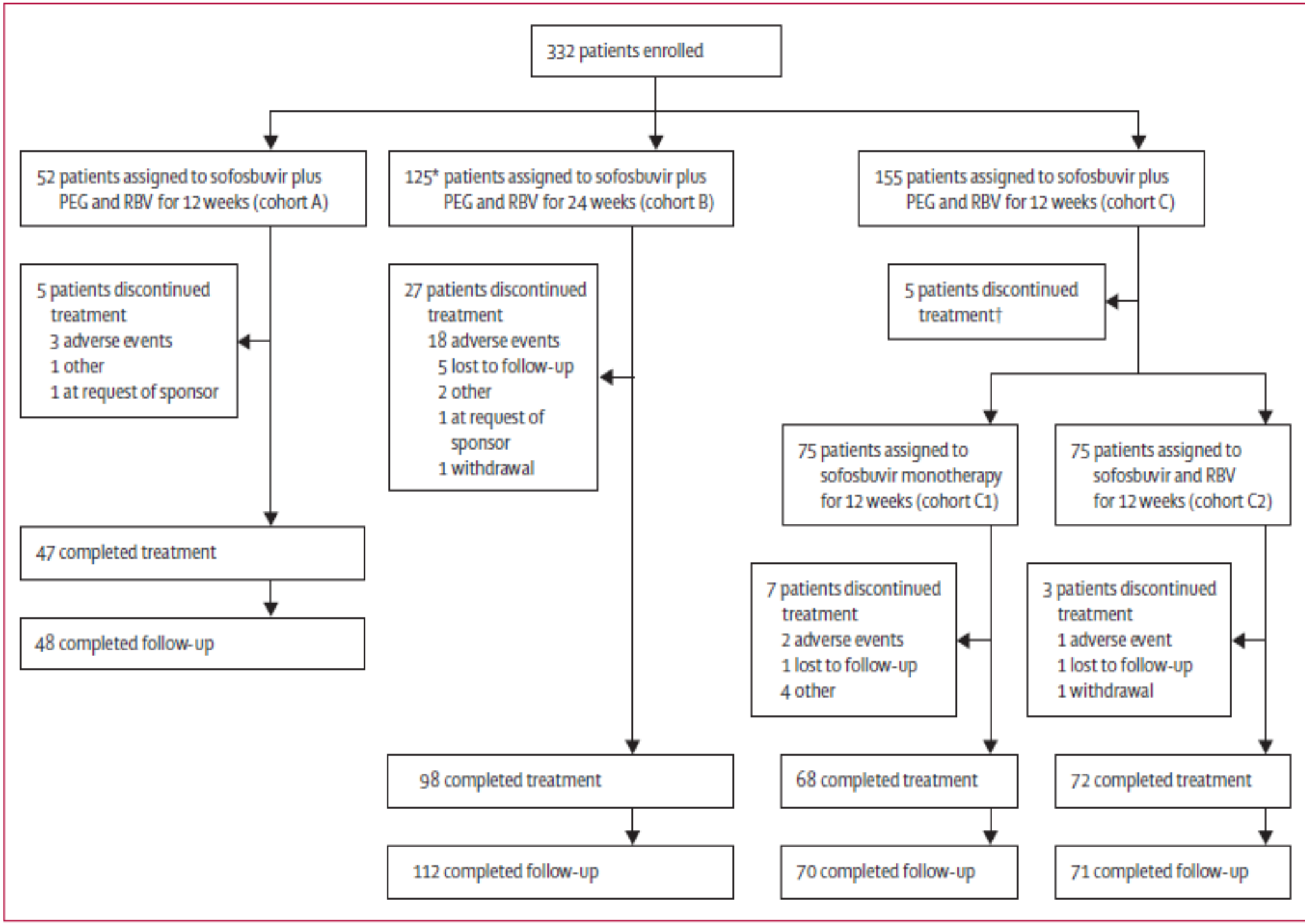


Figure 1: **Trial profile**

	Cohort A (n=52)	Cohort B (n=109)	Cohort C (n=155)
RVR	49 (94%; 84–99%)	107 (98%; 94–100%)	151 (97%; 94–99%)
SVR12	47 (90%; 79–97%)	101 (93%; 86–97%)	141 (91%; 85–95%)
SVR24 (ITT analysis)	46 (89%; 77–96%)	97 (89%; 82–94%)	135 (87%; 81–92%)
SVR24 (per-protocol analysis)*	46/48 (96%; 86–100%)	97/99 (98%; 93–100%)	135/139 (97%; 93–99%)
Virological failure			
During treatment†	0	0	0
Relapse‡	2 (4%)	1 (1%)	4 (3%)

Data are n (%; 95% CI), n/N (%; 95% CI), or number (%). RVR=rapid virological response (undetectable hepatitis C virus RNA at week 4). ITT=intention to treat. SVR12=sustained virological response at week 12 after treatment. SVR24=sustained virological response at week 24 after treatment. *Missing data were excluded from analysis. †Includes virological breakthrough, rebound, and non-response. ‡Includes only those patients who completed the full course of assigned treatment.

Table 2: Proportion of patients with HCV genotype 1 and undetectable hepatitis C virus RNA

The NEW ENGLAND JOURNAL OF MEDICINE

ESTABLISHED IN 1812 VOL. 368 NO. 20

Sofosbuvir 3 in Patients

Ira M. Jacobson, M.D., Eric M. Yoshida, M.D.,
Maribel Rodriguez, M.D., Man, M.D., Eric Lawitz, M.D.,
Gregory E. M. Tarek Al-Assi, M.D.,
G. Mani Subramanian, lly, Ph.D., Diana Brainard, M.D.,
William T. Symonds, D., Jordan Feld, M.D., M.P.H.,
M.D.

Sofosbuvir ed Chronic

Eric Lawitz, M.D., yles, M.D.,
Maribel Rodriguez, M.D., rt C. Gordon, M.D.,
Michael Schiff, M.D., id Kayali, M.D.,
K. Rajender Reddy, M.D., owdley, M.D.,
Lisa Nyberg, M.D., G. Mani Subramanian, M.D., Ph.D., Robert H. Hyland, D.Phil.,
Sarah Arterburn, M.S., Deyuan Jiang, Ph.D., John McNally, Ph.D.,
Diana Brainard, M.D., William T. Symonds, Pharm.D.,
John G. McHutchison, M.D., Aasim M. Sheikh, M.D.,
Zobair Younossi, M.D., M.P.H., and Edward J. Gane, M.D.*

Études Sofosbuvir de Phase III	Population	Groupes de traitement	Taux SVR12
NEUTRINO	Génotype 1/4/5/6 naïf de traitement	Sofosbuvir + RBV + Peg-IFN pendant 12 semaines	90 % (295/327)
FISSION	Génotype 2/3 naïf de traitement	Sofosbuvir + RBV pendant 12 semaines ou	67 % (170/253)
		Peg-IFN + RBV pendant 24 semaines	67 % (162/243)
POSITRON	Génotype 2/3, intolérant à l'IFN, inéligible ou réticent	Sofosbuvir + RBV pendant 12 semaines ou	78 % (161/207)
		Placebo pendant 12 semaines	0 % (0/71)
FUSION	Génotype 2/3 prétraités	Sofosbuvir + RBV pendant 12 semaines ou	50 % (50/100)
		Sofosbuvir + RBV pendant 16 semaines	73 % (69/95)

RBV = Ribavirine

IFN = Interferon

SVR12 = Réponse virologique soutenue 12 semaines après l'arrêt du traitement

INTERNATIONAL MEDICAL PRESS

Antiviral Therapy

Faldaprevir (BI 201335), BI 207127 and ribavirin oral therapy for treatment-naive HCV genotype 1: SOUND-C1 final results

Stefan Zeuzem, Tarik Asselah, Peter Angus, Jean-Pierre Zarski, Dominique Larrey, Beat Müllhaupt, Ed Gane, Marcus Schuchmann, Ansgar W Lohse, Stanislas Pol, Jean-Pierre Bronowicki, Stuart Roberts, Keikawus Arasteh, Fabien Zoulim, Markus Heim, Jerry O Stern, Gerhard Nehmiz, George Kukolj, Wulf Otto Böcher, Federico J Mensa

Antiviral Therapy 2013; 10.3851/IMP2567

Submission date 30th January 2013
Acceptance date 17th March 2013
Publication date 4th April 2013

Dual Therapy With the Nonstructural Protein 5A Inhibitor, Daclatasvir, and the Nonstructural Protein 3 Protease Inhibitor, Asunaprevir, in Hepatitis C Virus Genotype 1b–Infected Null Responders

Kazuaki Chayama,[1] Shoichi Takahashi,[1] Joji Toyota,[2] Yoshiyasu Karino,[2] Kenji Ikeda,[3] Hiroki Ishikawa,[4] Hideaki Watanabe,[4] Fiona McPhee,[5] Eric Hughes,[6] and Hiromitsu Kumada[3]

(HEPATOLOGY 2012;55:742-748)

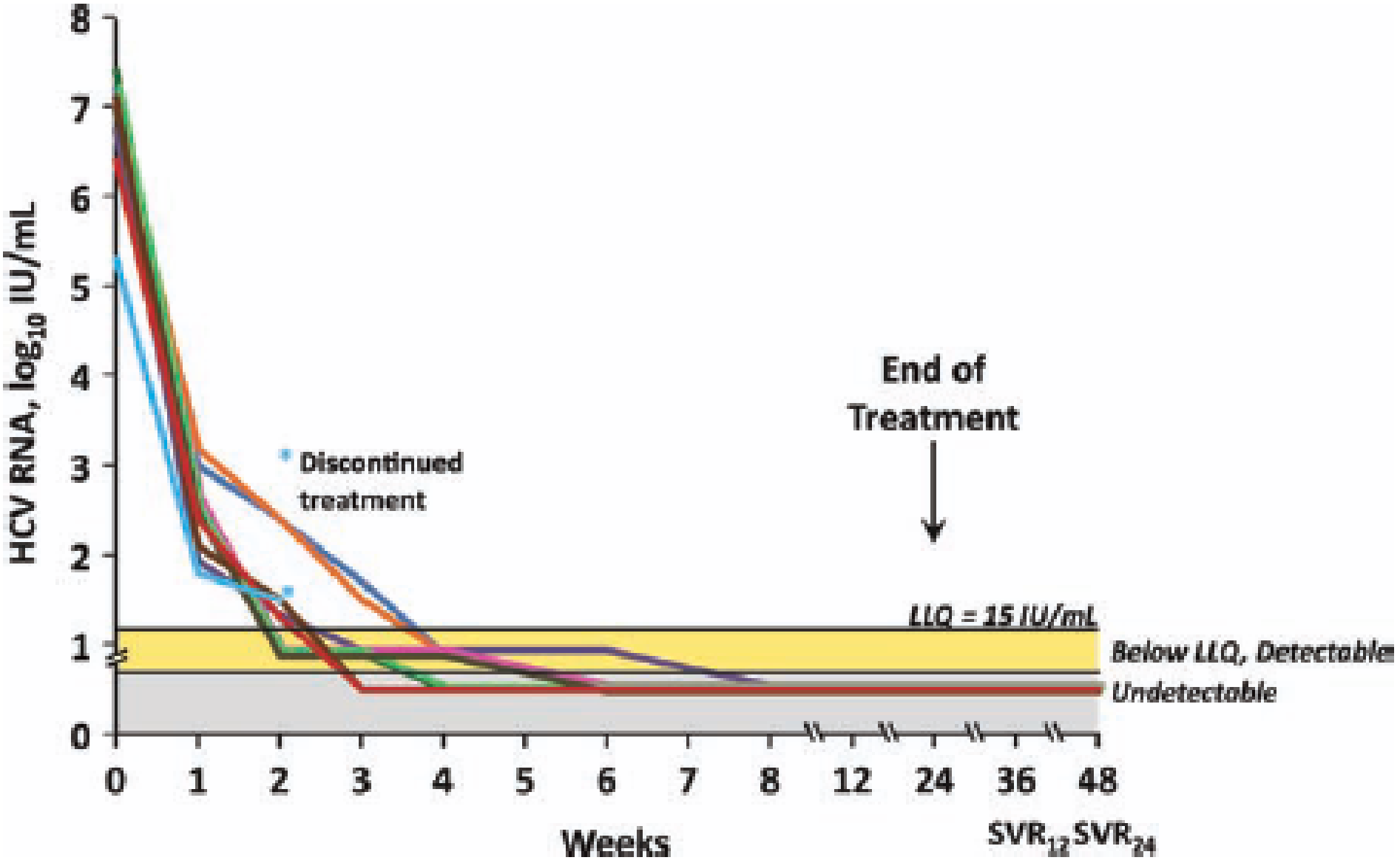


Fig. 2. HCV RNA levels: individual patients. Individual patient plasma HCV RNA levels during 24 weeks of treatment and through 24 weeks post-treatment (week 48) are shown. LLQ = 15 IU/mL.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of HCV Infection by Targeting MicroRNA

Harry L.A. Janssen, M.D., Ph.D., Hendrik W. Reesink, M.D., Ph.D., Eric J. Lawitz, M.D., Stefan Zeuzem, M.D., Maribel Rodriguez-Torres, M.D., Keyur Patel, M.D., Adriaan J. van der Meer, M.D., Amy K. Patick, Ph.D., Alice Chen, B.A., Yi Zhou, Ph.D., Robert Persson, Ph.D., Barney D. King, M.D., Sakari Kauppinen, Ph.D., Arthur A. Levin, Ph.D., and Michael R. Hodges, M.D.

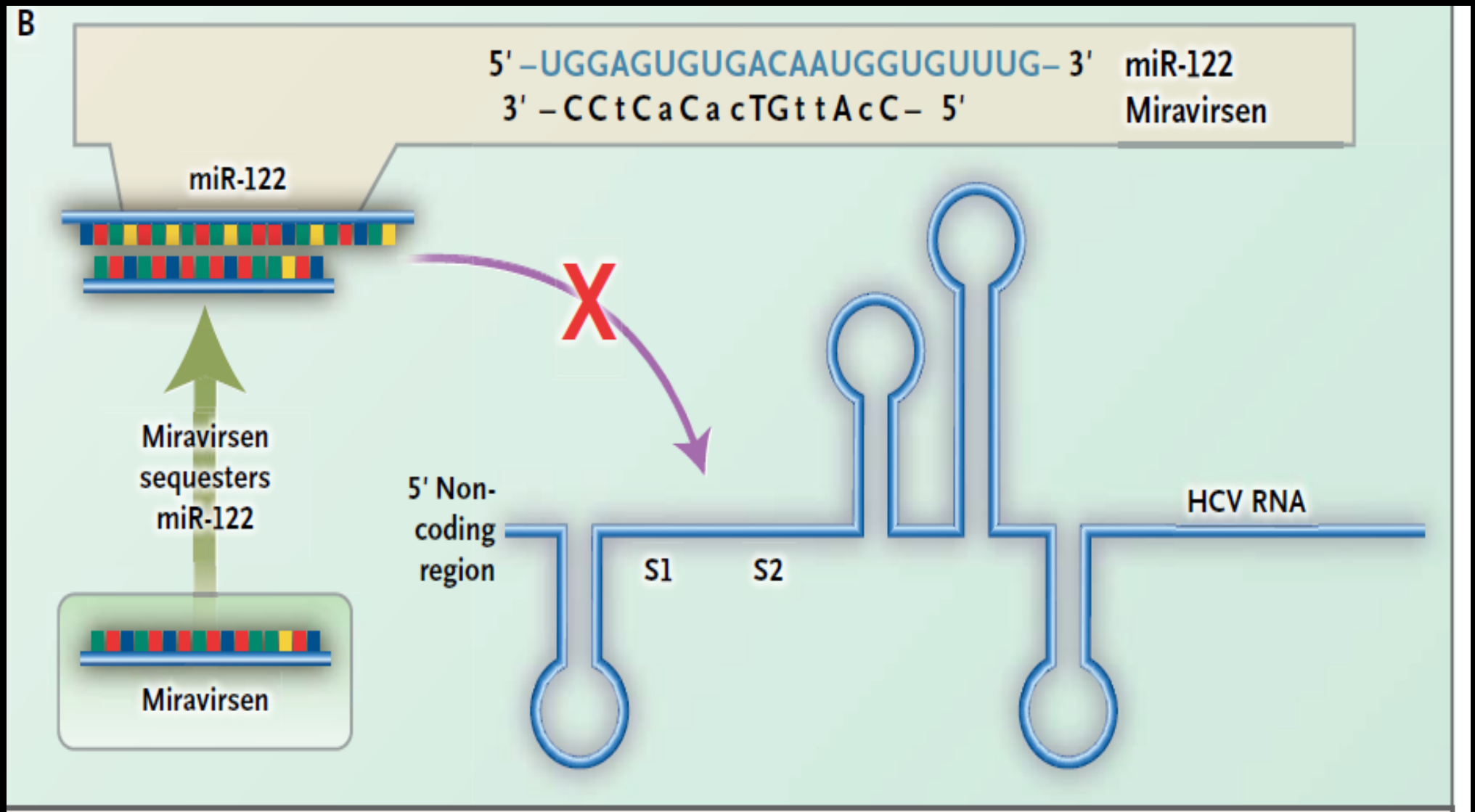


Figure 1. Mechanism of Action of Miravirsen.

In Panel A, microRNA-122 (miR-122) binds to two closely spaced target sites (S1 and S2) in the 5′ noncoding region of the HCV genome and thereby promotes the propagation of HCV RNA.[13] In Panel B, miravirsen, a locked nucleic acid–modified antisense oligonucleotide, sequesters mature miR-122 in a highly stable heteroduplex, which results in the functional inhibition of miR-122.

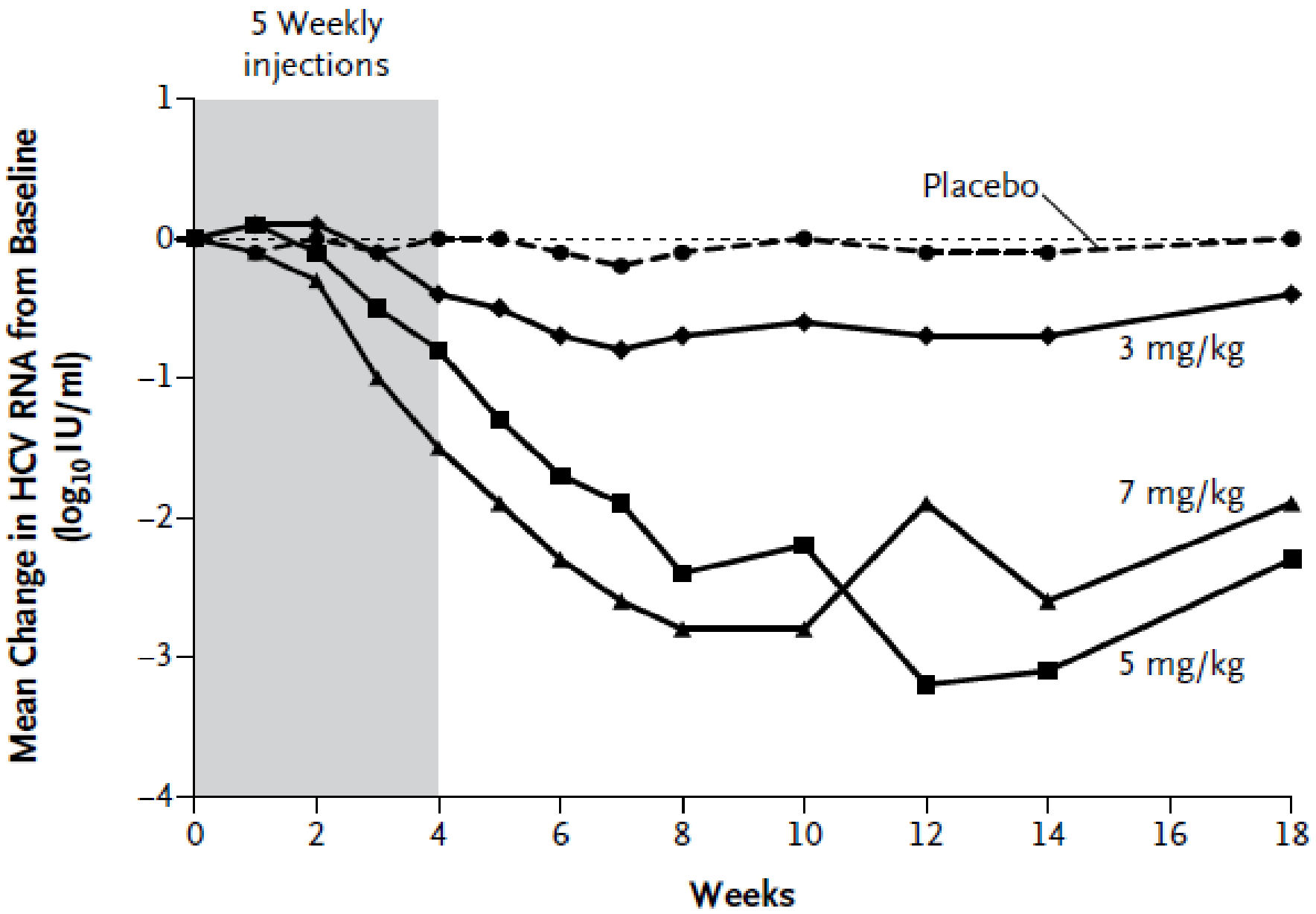


Figure 2. Change from Baseline in HCV RNA Levels.

L'infection à VHC
Maladie de système !

MAJOR ARTICLE

Chronic Hepatitis C Virus Infection Increases Mortality From Hepatic and Extrahepatic Diseases: A Community-Based Long-Term Prospective Study

Mei-Hsuan Lee,[1] Hwai-I. Yang,[1,2,3] Sheng-Nan Lu,[4] Chin-Lan Jen,[1] San-Lin You,[1] Li-Yu Wang,[5] Chih-Hao Wang,[6] Wei J. Chen,[7] Chien-Jen Chen,[1,7] and for the R.E.V.E.A.L.-HCV Study Group[a]

Table 3. Multivariate-Adjusted Hazard Ratios of Dying From Selected Causes of Death by Serostatus of Antibodies Against Hepatitis C Virus (Anti-HCV) and Serum HCV RNA Level at Study Entry

		Multivariate-adjusted Hazard Ratio[a] (95% CI)		
Causes of Death	Anti-HCV Seronegative	Anti-HCV Seropositive With Undetectable Serum HCV RNA Level	Anti-HCV Seropositive With Detectable Serum HCV RNA level	*P* Value (For Trend)
All causes	1.00 (referent)	0.97 (.70–1.35)	2.20 (1.90–2.55)	<.0001
Hepatic diseases	1.00 (referent)	2.19 (.81–5.97)	16.36 (12.09–22.13)	<.0001
Liver cancer	1.00 (referent)	4.70 (1.68–13.11)	28.02 (18.96–41.41)	<.0001
Chronic liver disease and cirrhosis[b]	1.00 (referent)	—	7.37 (4.22–12.87)	<.0001
Extrahepatic diseases	1.00 (referent)	0.90 (.64–1.28)	1.47 (1.23–1.77)	.0002
Circulatory diseases	1.00 (referent)	1.16 (.62–2.17)	1.53 (1.05–2.23)	.026
Nephritis, nephrotic syndrome, and nephrosis	1.00 (referent)	1.66 (.40–6.81)	2.98 (1.43–6.22)	.0032
Esophagus cancer[b]	1.00 (referent)	—	5.86 (1.98–17.35)	.0014
Prostate cancer[b]	1.00 (referent)	—	5.83 (1.64–20.77	.0065
Thyroid cancer[b]	1.00 (referent)	—	7.07 (.73–68.35)	.09

Table 2. Frequency and Rate of Events During Follow-up in 1599 HIV/Hepatitis C Virus–Coinfected Patients With or Without Sustained Virological Response After Therapy With Interferon Plus Ribavirin

	Frequency of Events, No. (%)			Rate of Events/100 Person-Years (95% CI)		
Event	No SVR (n = 973)	SVR (n = 626)	*P*	No SVR	SVR	*P*[a]
Loss to follow-up	114 (11.7)	56 (8.9)	.079	2.32 (1.89–2.75)	1.82 (1.35–2.3)	.139
Liver-related events						
Any event	135 (13.9)	10 (1.6)	<.001	2.87 (2.39–3.36)	0.32 (.12–.53)	<.001
Liver decompensation[b]	113 (11.6)	6 (1.0)	<.001	2.39 (1.95–2.83)	0.19 (.04–.35)	<.001
Hepatocellular carcinoma	28 (2.9)	3 (0.5)	.001	0.57 (.36–.78)	0.10 (.00–.21)	.001
Liver transplantation	21 (2.2)	4 (0.6)	.017	0.43 (.24–.61)	0.13 (.00–.26)	.024
HIV-related events						
New AIDS-defining conditions	41 (4.2)	9 (1.4)	.002	0.84 (.59–1.10)	0.29 (.10–.48)	.003
Mortality						
Deaths overall	90 (9.2)	8 (1.3)	<.001	1.82 (1.45–2.20)	0.26 (.08–.44)	<.001
Liver-related deaths	55 (5.7)	3 (0.5)	<.001	1.11 (.82–1.41)	0.10 (.00–.21)	<.001
Non–liver-related deaths	32 (3.3)	5 (.8)	.001	0.65 (.42–.87)	0.16 (.02–.30)	.002
AIDS-related	5 (0.5)	0 (0.0)	.072	0.10 (.01–.19)	0	.071
Non–liver-related, non–AIDS-related	27 (2.8)	5 (0.8)	.006	0.55 (.34–.75)	0.16 (.02–.30)	.002
Unknown	4 (0.4)	0 (0.0)	…	…	…	…

Traitement de l'hépatite C aigüe

Delayed versus immediate treatment for patients with acute hepatitis C: a randomised controlled non-inferiority trial

Katja Deterding, Norbert Grüner, Peter Buggisch, Johannes Wiegand, Peter R Galle, Ulrich Spengler, Holger Hinrichsen, Thomas Berg, Andrej Potthoff, Nisar Malek, Anika Großhennig, Armin Koch, Helmut Diepolder, Stefan Lüth, Sandra Feyerabend, Maria Christina Jung, Magdalena Rogalska-Taranta, Verena Schlaphoff, Markus Cornberg, Michael P Manns, Heiner Wedemeyer, for The Hep-Net Acute HCV-III Study Group

Lancet Infect Dis 2013;
13: 497–506

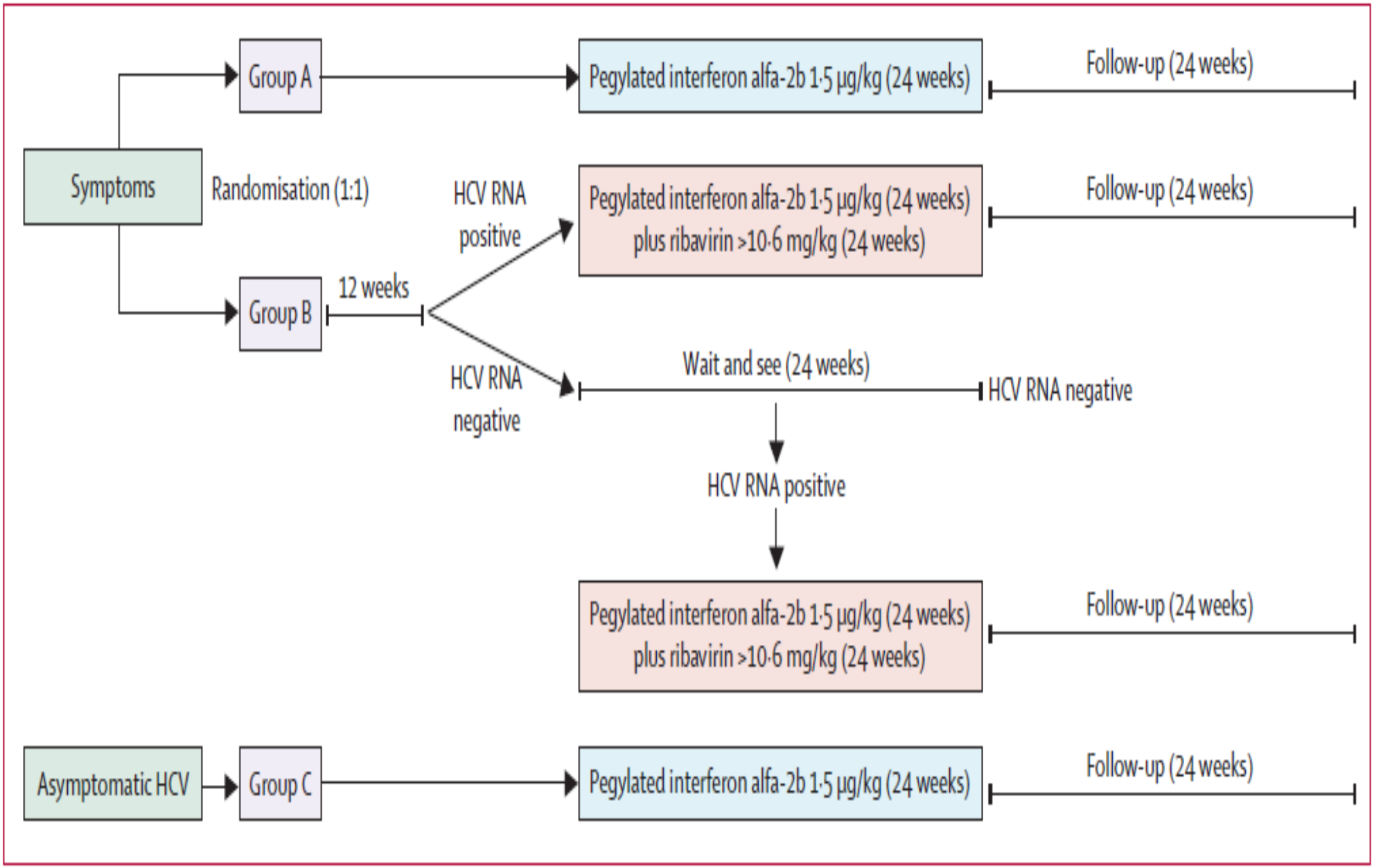


Figure 1: Study design

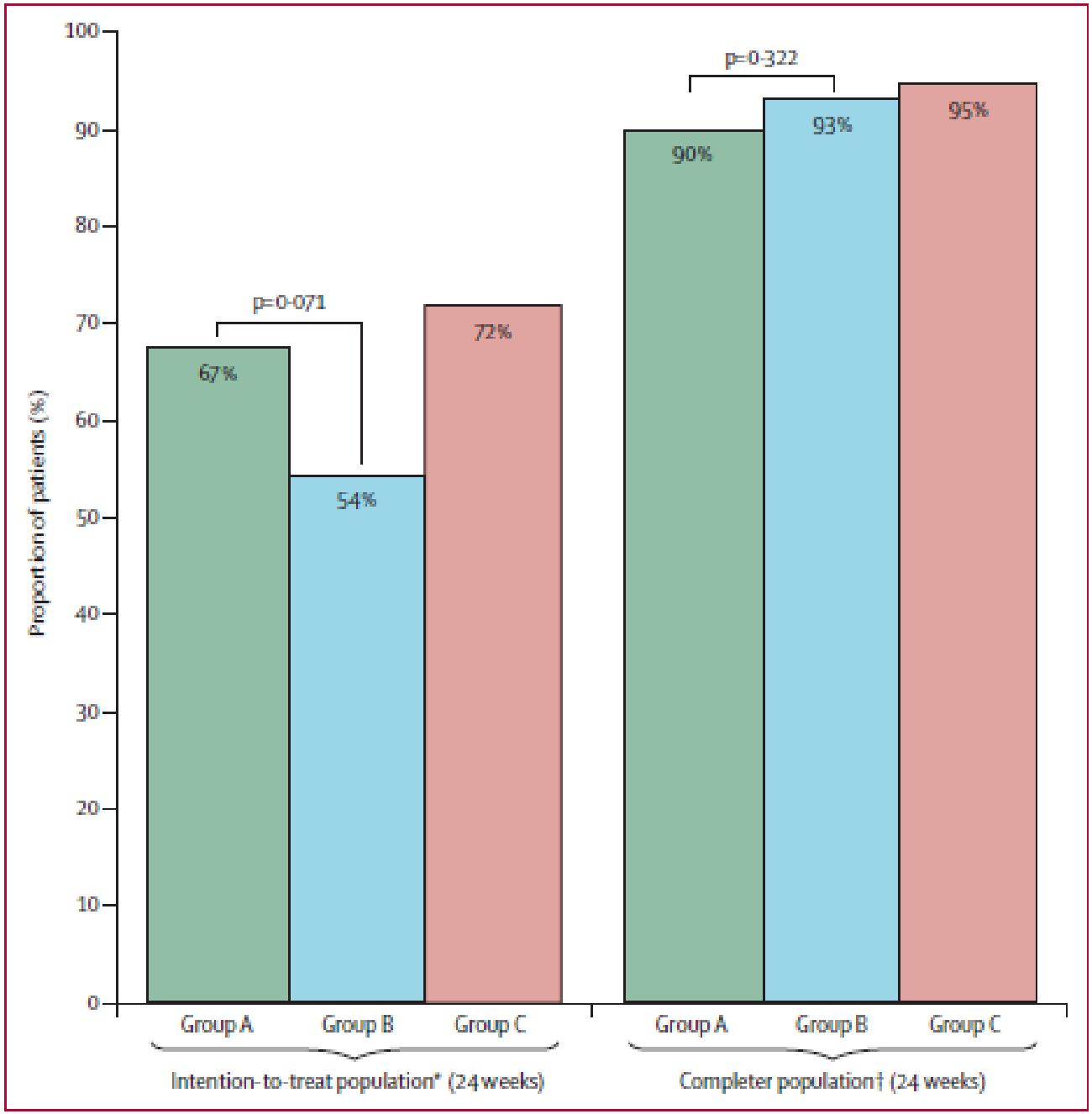


***Figure 3*: Sustained virological response rates after early or delayed treatment**

Percentages show patients who were HCV RNA negative at follow-up week 24 or study week 60. *All randomly allocated patients minus three screening failures. †Patients who completed 24 weeks of follow-up after end of pegylated interferon alfa-2b treatment, pegylated interferon alfa-2b plus ribavirin treatment, or who completed 60 weeks of observation.

CONCLUSIONS tt/VHC/aigüe

- **107 hépatites C aigues asymptomatiques et 25 recrutées entre 2004 et 2010**
- **37/55 (65%) des symptomatiques ayant un traitement immédiat ont obtenu une SVR; 28/52 (54%) des symptomatiques ayant un traitement différé ont obtenu une SVR (différence 13,7%; IC 95% = -4,6 – 32; p = 0,71)**
- **21% de clairance spontanée dans le groupe différé**
- **25 % (immédiat) et 42 % (différé) (p = 0,37) de non rétention >> traitement immédiat ?!**

Traitement du VHC et Usagers de Drogues

MAJOR ARTICLE

Determinants of Hepatitis C Virus Treatment Completion and Efficacy in Drug Users Assessed by Meta-analysis

Rositsa B. Dimova,[1] Marija Zeremski,[1] Ira M. Jacobson,[1] Holly Hagan,[2] Don C. Des Jarlais,[3] and Andrew H. Talal[1,4]

[1]Weill Cornell Medical College, [2]New York University College of Nursing, [3]Beth Israel Medical Center, New York, New York; and [4]State University of New York at Buffalo

- **36 études**
- **2866 patients**
- **La taux de rétention chez les UD était de 83.4% (95%CI: 77.1%; 88.9%).**
- **Apres ajustement pour HIV/HCV co-infection, genre, et traitemements de substitution = la taux poolé de SVR était de 55.5% (95%CI: 50.6%; 60.3%).**
- **Le genotype 1/4 (p=0.0012) et la proportion de HIV co-infectés UD (p=0.0173) influencent le taux de SVR.**
- **Après ajustement sur le genotype 1/4 et l' HIV/HCV co-infection, le taux de SVR est favorablement influençé par la prise en charge pluridisciplinaire (p<0.0001).**

VHB et régression de la fibrose sous tenofovir

Articles

Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study

Patrick Marcellin, Edward Gane, Maria Buti, Nezam Afdhal, William Sievert, Ira M Jacobson, Mary Kay Washington, George Germanidis, John F Flaherty, Raul Aguilar Schall, Jeffrey D Bornstein, Kathryn M Kitrinos, G Mani Subramanian, John G McHutchison, E Jenny Heathcote

Lancet 2013; 381: 468–75

641 patients received randomised treatment
634 with available baseline liver biopsy data

26 (4%) discontinued during the 48-week double-blind phase without liver biopsy
9 lost to follow-up
7 safety, tolerability, or efficacy reason
7 withdrew consent
3 protocol violation

615 (96%) completed the 48-week double-blind phase

30 (5%) did not enter open-label phase (10 with a biopsy)
4 declined participation in extension phase
3 lost to follow-up
2 seroconversion
21 withdrew consent

585 (91%) entered open-label phase

96 (15%) discontinued before year 5
25 lost to follow-up
15 safety, tolerability, or efficacy reason
10 investigator's discretion
4 protocol violation
8 seroconversion
33 withdrew consent
1 study discontinued by sponsor

489 (76%) completed year 5 of open-label phase

141 (22%) completed year 5 without liver biopsy

348 (54%) with biopsy samples at year 5 (week 240)

Figure 1: **Study disposition and availability of liver biopsy samples**

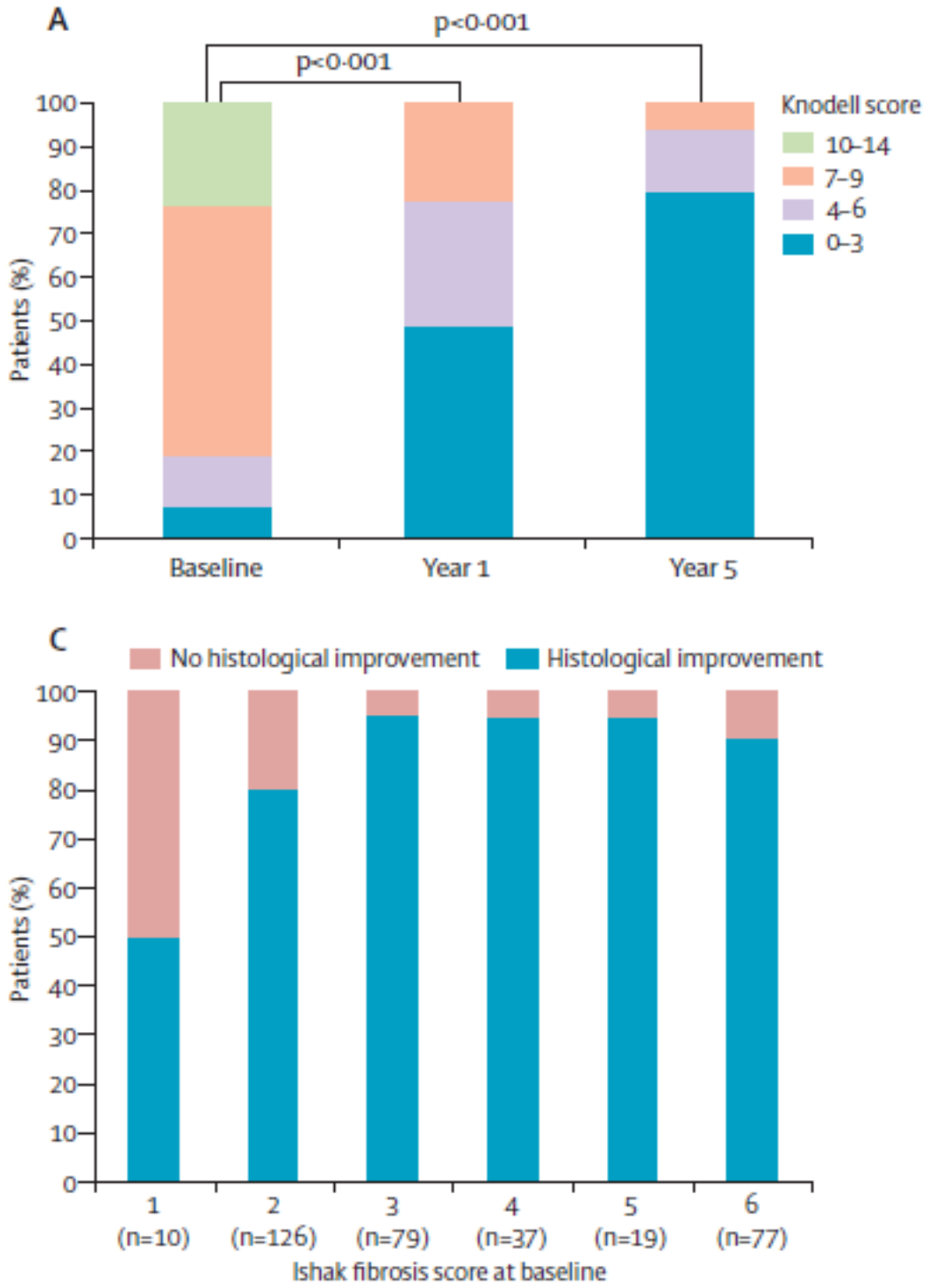


Figure 2: **Histology results over 5-year treatment phase**

CONCLUSIONS teno/histo

- **Au delà de l'objectif virologique (neg PCR, puis neg Ag Hbs (11 % à 5 ans pour les Hbe+ puis ac anti Hbs (8%) l'amélioration histologique sous tenofovir est une réalité.**
- **304/348 (87%) avec PBH ont une amélioration de la fibrose à S 240**
- **176/348 (51%) ont une régression de la fibrose à S240**
- **71/96 (74%) avec cirrhose n'ont plus de cirrhose (> 1 pt Knodell)**
- **91/348 (16%) d'AE et 9 SAE**

Recherche vaccin désespérément (1)

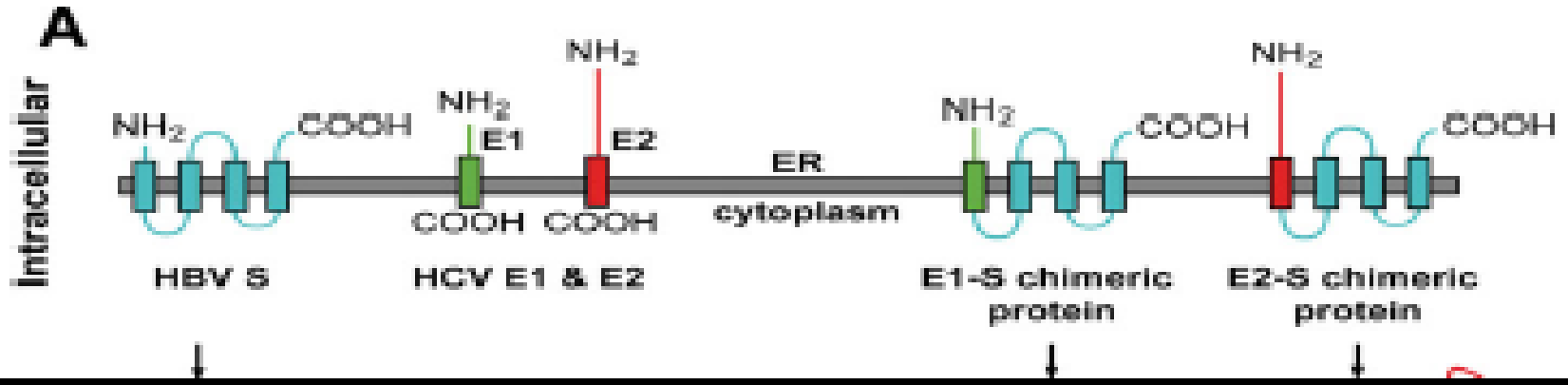
HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

VIRAL HEPATITIS

Chimeric Hepatitis B Virus/Hepatitis C Virus Envelope Proteins Elicit Broadly Neutralizing Antibodies and Constitute a Potential Bivalent Prophylactic Vaccine

Elodie Beaumont,[1] Romuald Patient,[1] Christophe Hourioux,[1]
Isabelle Dimier-Poisson,[2] and Philippe Roingeard[1]

HEPATOLOGY, Vol. 57, No. 4, 2013



Modèle de protéines chimériques produites par des cellules ovariennes de hamster et utilisées pour immuniser des lapins de Nouvelle Zélande.

Les Ac anti-E1 et anti-E2 obtenus neutralisent les pseudoparticules VHC et les cellules infectées de différentes souches hétérologues 1a, 1b, 2a et 3.

Même réponse anti VHB que les vaccins commercialisés.

RESEARCH

Laboratory-based Surveillance for Hepatitis E Virus Infection, United States, 2005–2012

Jan Drobeniuc, Tracy Greene-Montfort, Ngoc-Thao Le, Tonya R. Mixson-Hayden, Lilia Ganova-Raeva, Chen Dong, Ryan T. Novak, Umid M. Sharapov, Rania A. Tohme, Eyasu Teshale, Saleem Kamili, and Chong-Gee Teo

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 19, No. 2, February 2013

Table. Demographic, clinical, travel-related, and virologic characteristics for patients with hepatitis E, United States, 2005–2012*

Travel history and case-patient no.	Age, y/sex	Race/ ethnicity	State of residence	Transplant (organ)	Jaundice	Countries visited	Anti-HEV SCR		HEV genotype	HEV RNA viral load†
							IgM	IgG		
No recent international travel‡										
NT1	61/M	White	FL	No	Yes	NA	7.5	5.7	3	NA
NT2	45/M	White	CA	No	Yes	NA	3.7	4	–	–
NT3	63/M	White	SD	Yes (kidney)	No	NA	7.2	5.4	3	NA
NT4	61/M	South Asian	IL	Yes (liver)	No	NA	1.9	5.9	3	NA
NT5	67/M	White	FL	No	Yes	NA	6.3	1.3	–	–
NT6	44/F	Hispanic	TX	No	Yes§	NA	3.1	3.7	3	NA
NT7	21/F	Hispanic	TX	No	Yes¶	NA	2.2	1.6	–	–
NT8	67/M	White	IL	Yes (heart and lungs)	Yes	NA	3	3.3	–	–
NT9	42/M	White	WI	No	Yes	NA	6	6.6	–	–
NT10	62/F	White	IL	Yes (kidney)	No	NA	2.9	8.9	–	–
NT11	26/M	White	PA	Yes (kidney)	No	NA	5.3	8.3	3	7.8×10^2
NT12	40/F	White	NY	Yes (kidney and pancreas)	No#	NA	7.7	12.9	3	1.4×10^3
NT13	64/M	White	CT	Yes (liver)	Yes	NA	9.2	1.3	3	1.4×10^4
NT14	29/F	White	MI	No	No**	NA	6.6	9.8	–	–
NT15	62/M	White	NY	No	No	NA	Neg	9.6	3	1.5×10^3
Recent international travel‡										
T1	35/M	South Asian	DE	No	Yes	India	2.3	4.5	1	1.8×10^2
T2	14/F	South Asian	TX	No	Yes	India	7.3	5.8	–	–
T3	32/F	South Asian	TX	No	Yes	India	3.7	5.8	–	–
T4	24/M	South Asian	TX	No	Yes	India	2.3	2	–	–
T5	35/M	White	IL	No	No	India and Indonesia	2.9	8.9	–	–
T6	24/M	White	MD	No	Yes	Afghanistan and Dubai	6.9	9.4	–	–
T7	63/M	White	AL	No	Yes	China	7.9	Neg	4	2.4×10^2
T8	23/M	South Asian	ME	No	Yes	Bangladesh	7.6	10.8	–	–
T9	53/M	South Asian	MD	No	Yes††	India	9.2	9.4	–	–
T10	66/M	South Asian	TX	No	Yes	India	5.5	11.7	1	1.8×10^2
T11	22/M	South Asian	MD	No	Yes	India	9.9	10.9	1	8.3×10^5

Remerciements

PubMed,

Stanislas POL

et Jacques IZOPET