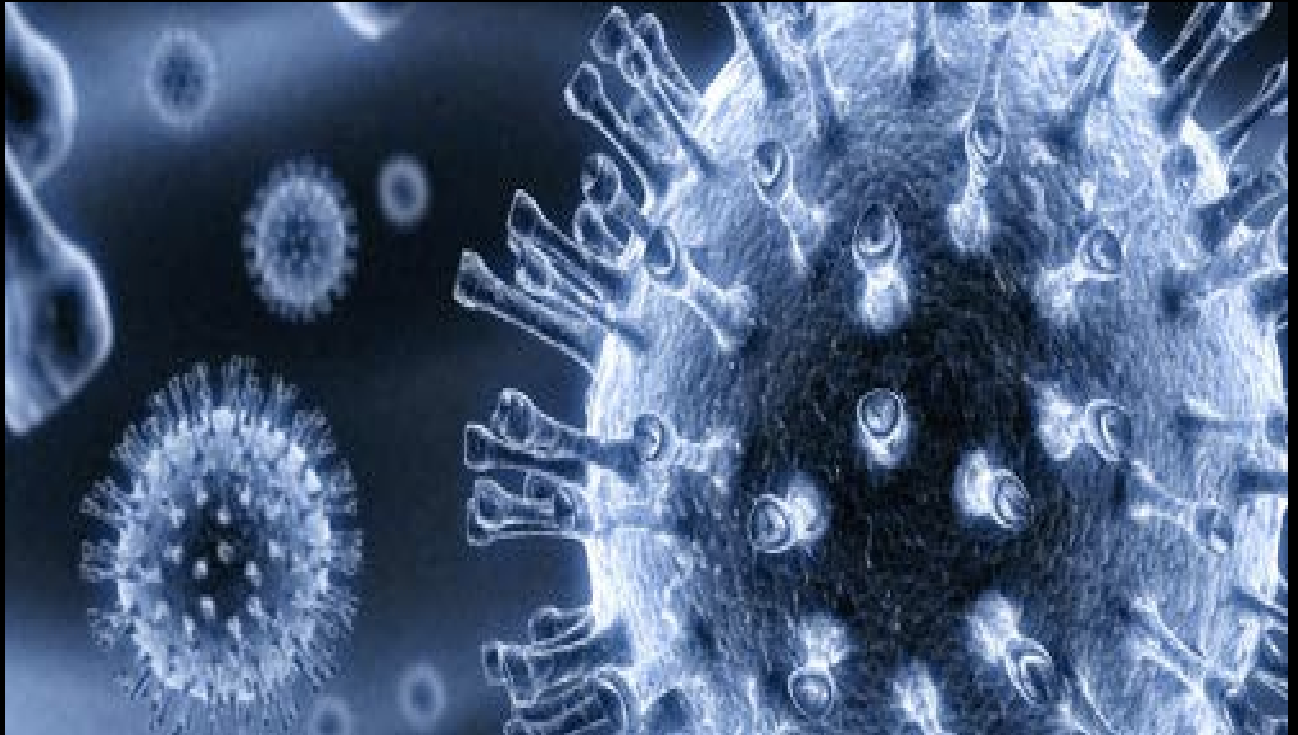


Best of Hépatites B & C

**Gilles
PIALOUX**

**APHP(Tenon)
UPMC
SFLS
CMIT
Corevih idf Centre**



**vih
.org**

Best Of - JN1 Lille 2016

Déclaration de liens d'intérêts

Membre de board, d'un conseil scientifique, investigateur d'essai ou intervenant pour un **laboratoire pharmaceutique** :

Abbvie, BMS, Gilead, MSD, Nephrotec/AAZ, Tibotec/Janssen, ViiVHealthcare.

Parts sociales ou actions dans un laboratoire pharmaceutique : Aucune.

Membre du Comité d'Orientation Stratégique (COS) de **AIDES** , Investigateur de l'essai **ANRS-IPIRGAY**

« Choisir c'est renoncer »

Epidémiologie 2016

SVR & recontamination

Modélisation du TasP VHC

Optimiser le dépistage

Risk of Late Relapse or Reinfection With Hepatitis C Virus After Achieving a Sustained Virological Response: A Systematic Review and Meta-analysis

Bryony Simmons,¹ Jawaad Saleem,¹ Andrew Hill,² Richard D. Riley,³ and Graham S. Cooke¹

¹Division of Medicine, Imperial College London, ²Pharmacology and Therapeutics, Liverpool University, and ³Research Institute of Primary Care and Health Sciences, Keele University, Staffordshire, United Kingdom

HCV Recurrence After Therapy-induced SVR • CID 2016:62 (15 March)

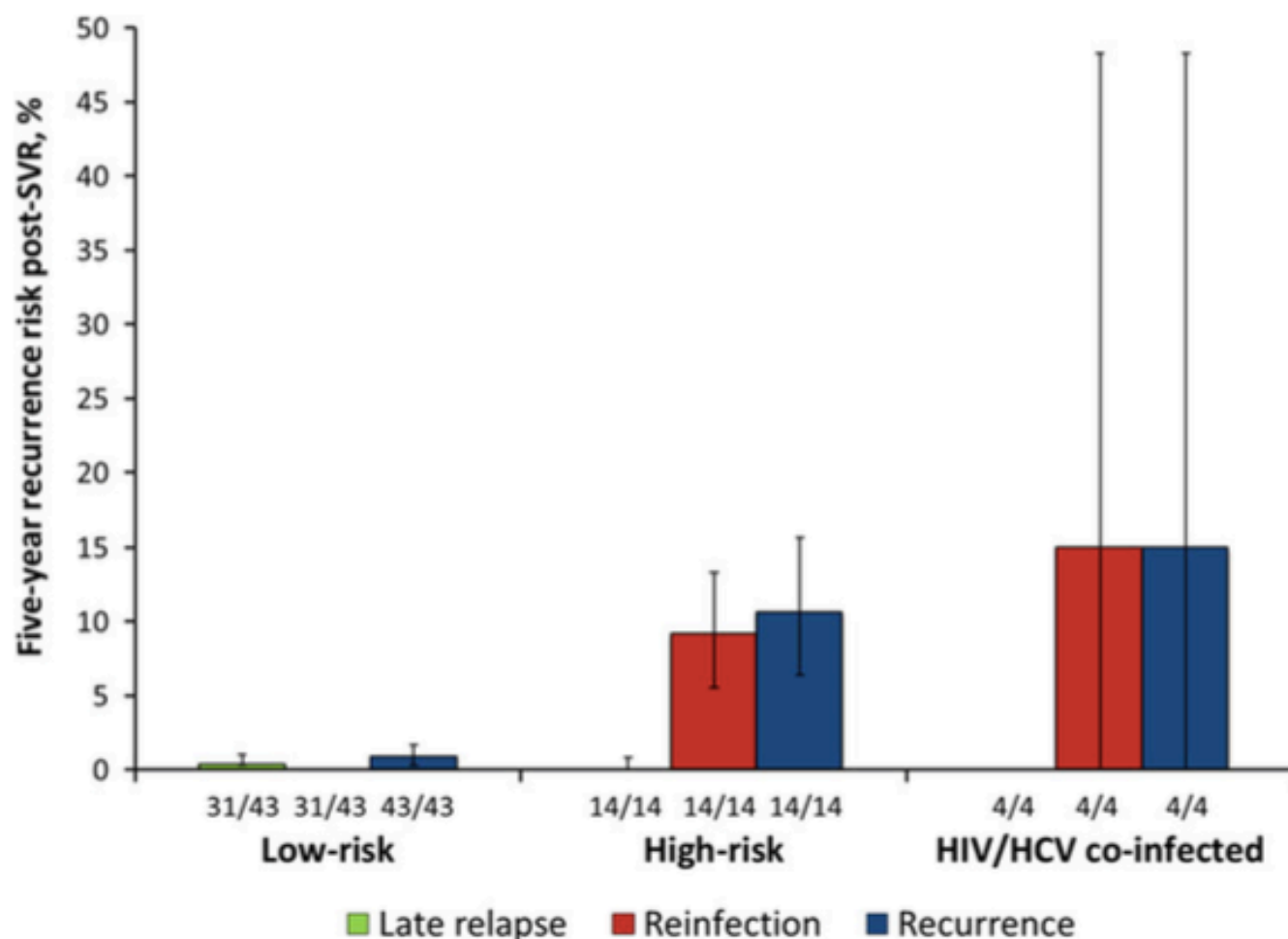


Figure 2. Summary 5-year risk (95% confidence interval) of recurrence post-sustained virological response (SVR), by risk group. Presented are the pooled estimates for the 5-year risk of recurrence after achieving an SVR. Also shown are the number of studies that were included to derive each estimate. Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Can Hepatitis C Virus (HCV) Direct-Acting Antiviral Treatment as Prevention Reverse the HCV Epidemic Among Men Who Have Sex With Men in the United Kingdom? Epidemiological and Modeling Insights

Natasha K. Martin,^{1,2,a} Alicia Thornton,^{3,a,b} Matthew Hickman,² Caroline Sabin,³ Mark Nelson,⁴ Graham S. Cooke,⁵ Thomas C. S. Martin,¹ Valerie Delpech,⁶ Murad Ruf,⁷ Huw Price,⁸ Yusef Azad,⁹ Emma C. Thomson,^{5,10} and Peter Vickerman²

¹Division of Global Public Health, University of California San Diego; ²School of Social and Community Medicine, University of Bristol, ³University College London, ⁴Chelsea and Westminster Hospital, ⁵Imperial College, ⁶Public Health England, Colindale, ⁷Medical Affairs, Gilead Sciences Ltd, London, ⁸Mid Essex Hospital Services NHS Trust, Chelmsford, ⁹National AIDS Trust, London, and ¹⁰MRC University of Glasgow Centre for Virus Research, United Kingdom

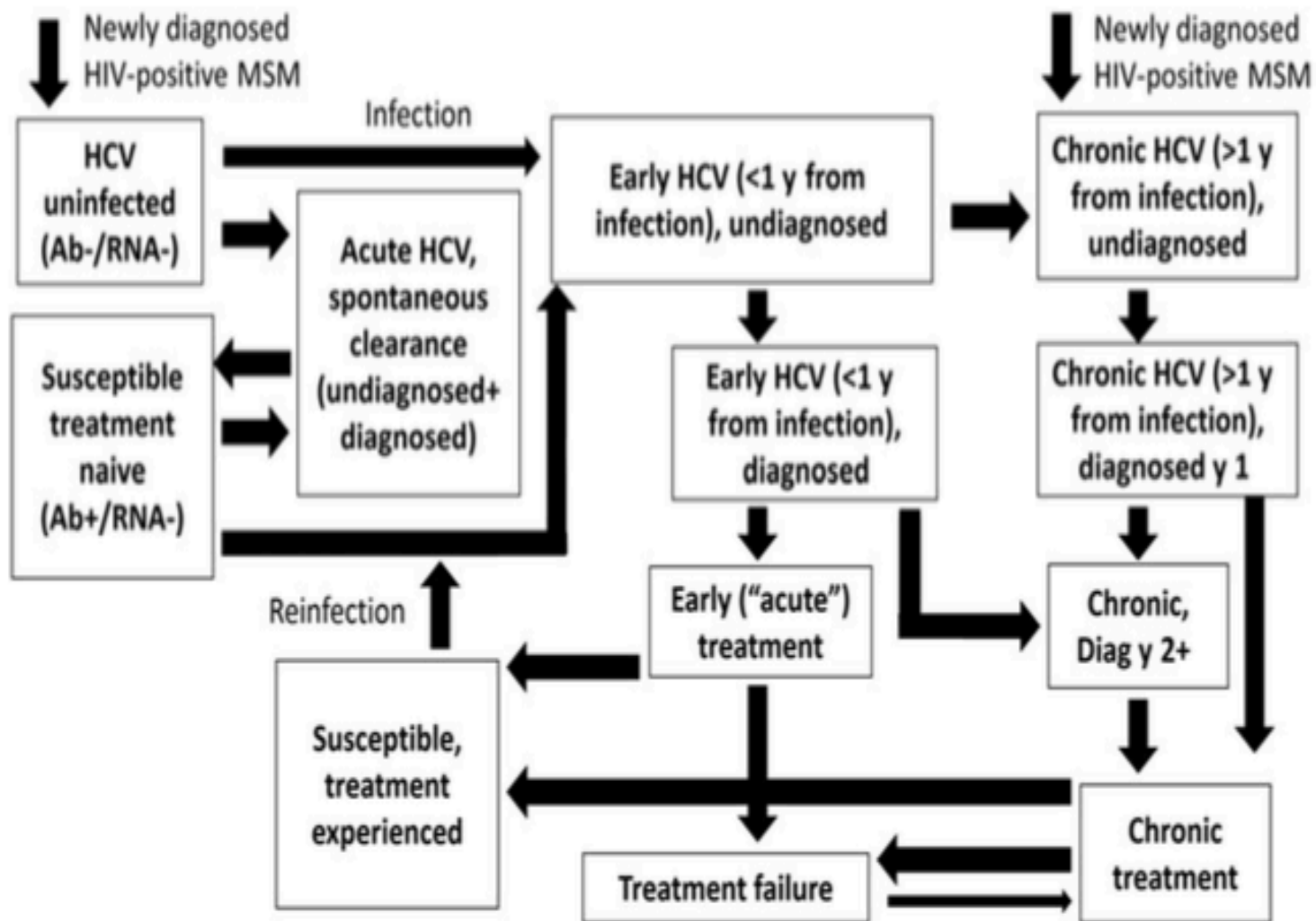
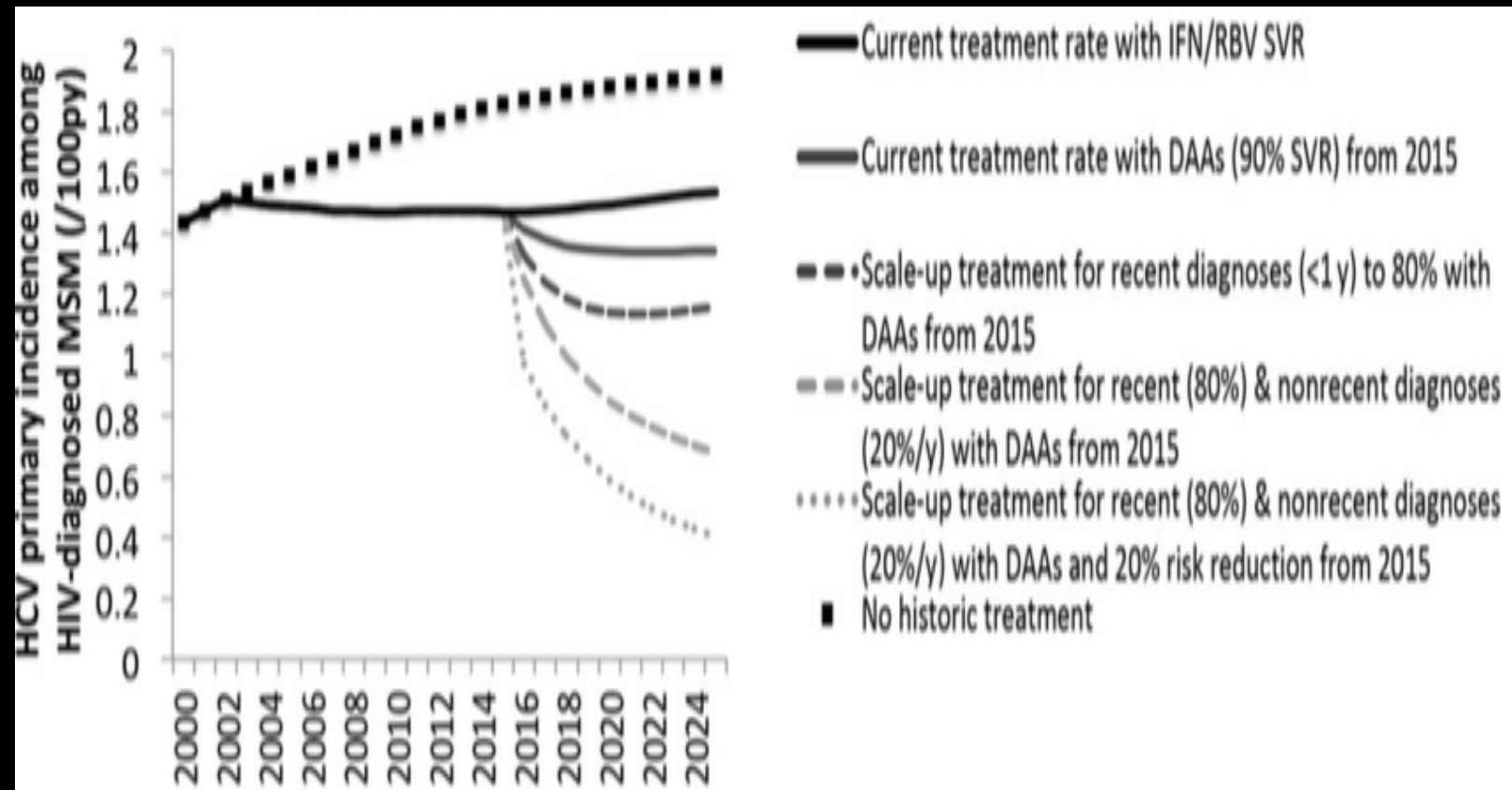


Figure 1. Mathematical model schematic. The model is also stratified by treatment-naïve, interferon-experienced, direct-acting antiviral-experienced, and low-/high-risk states. Human immunodeficiency virus (HIV) and non-HIV death occurs from all states. Abbreviations: Ab, antibody; HCV, hepatitis C virus; MSM, men who have sex with men.



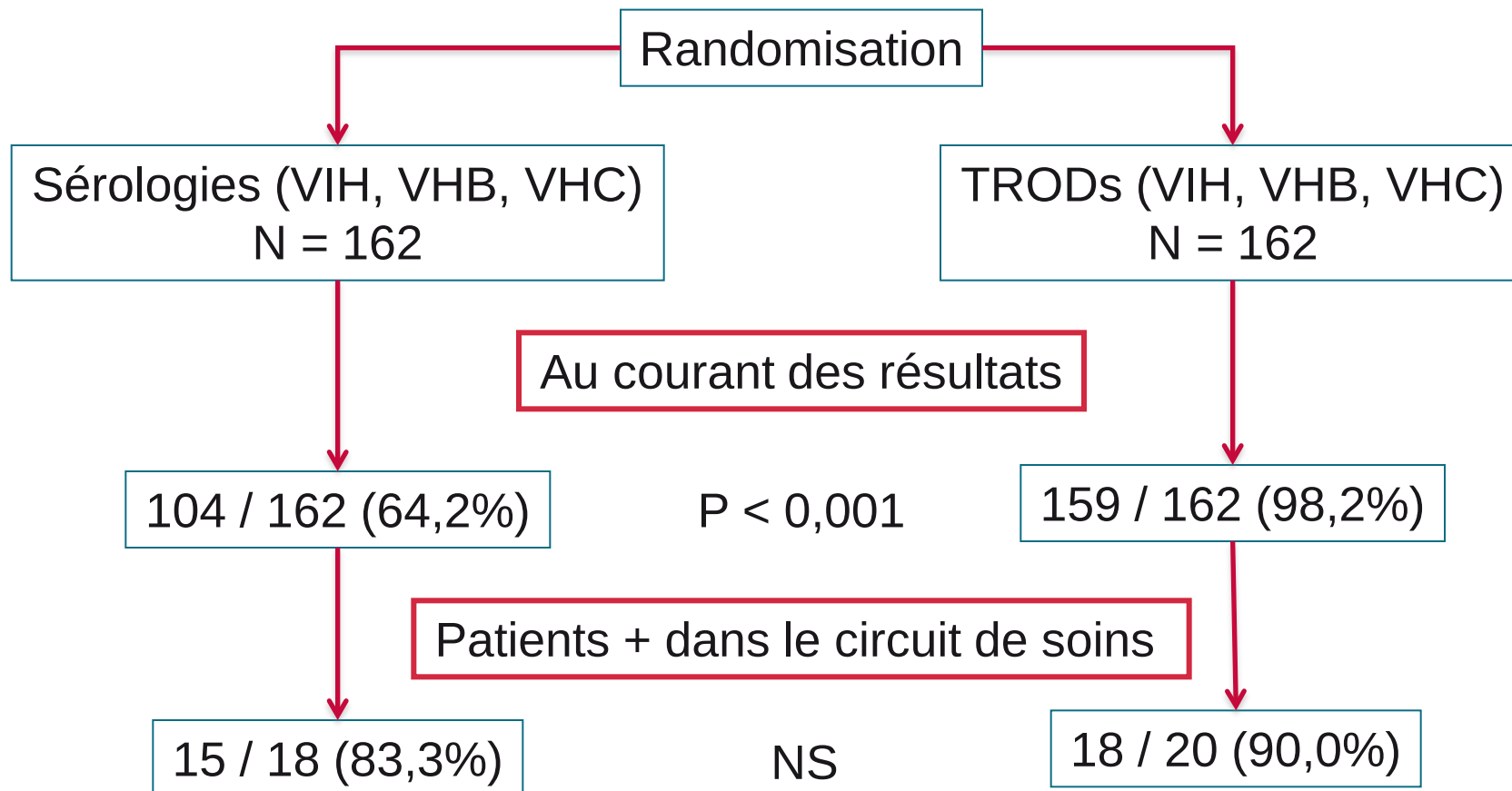
Simultaneous Human Immunodeficiency Virus-Hepatitis B-Hepatitis C Point-of-Care Tests Improve Outcomes in Linkage-to-Care: Results of a Randomized Control Trial in Persons Without Healthcare Coverage

Julie Bottero,^{1,2} Anders Boyd,¹ Joel Gozlan,^{3,4} Fabrice Carrat,^{1,5} Jean Nau,⁶ Marie-Dominique Pauti,⁷ Hayette Rougier,² Pierre-Marie Girard,^{1,2} and Karine Lacombe^{1,2}

¹Sorbonne Universités, Université Pierre-et-Marie-Curie Paris 06, Institut National de la Santé et de la Recherche Médicale (INSERM), Institut Pierre Louis d'Épidémiologie et de Santé Publique, ²Service de Maladies Infectieuses, Centre Hospitalier Universitaire (CHU) St. Antoine, ³Laboratoire de Virologie, CHU St. Antoine, ⁴INSERM U1135 Centre d'Immunologie et des Maladies Infectieuses, ⁵Département de Santé Publique, Hôpital St-Antoine, Assistance Publique-Hôpitaux de Paris, and ⁶Médecins du Monde, Centre d'Accueil de Soins et d'Orientation, and ⁷Médecins du Monde, Direction des Missions France, Paris, France

Pratique combinée des TRODs

Étude OptiScreen III (Médecins du Monde, Paris) (majorité migrants d'Afrique sub-saharienne)

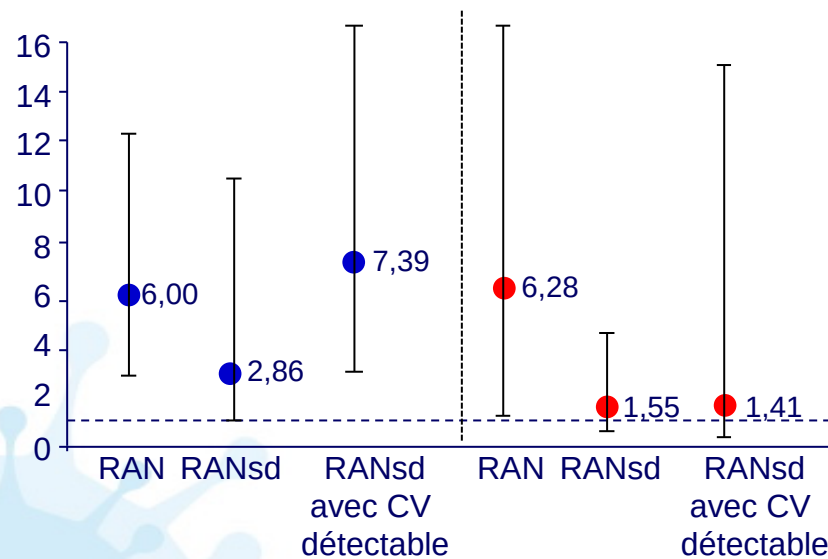


NDS & HSH

Chemsex chez les HSH au Royaume-Uni

- Au cours de l'année écoulée : parmi les 292 HSH VIH sexuellement actifs :
77 % ont eu des RAN, 46 % des RANsd et 9,2 % des RANsd avec CV ≥ 50 c/ml
- Nombre moyen de partenaires dans l'année : 30,3 si chemsex vs 9,5

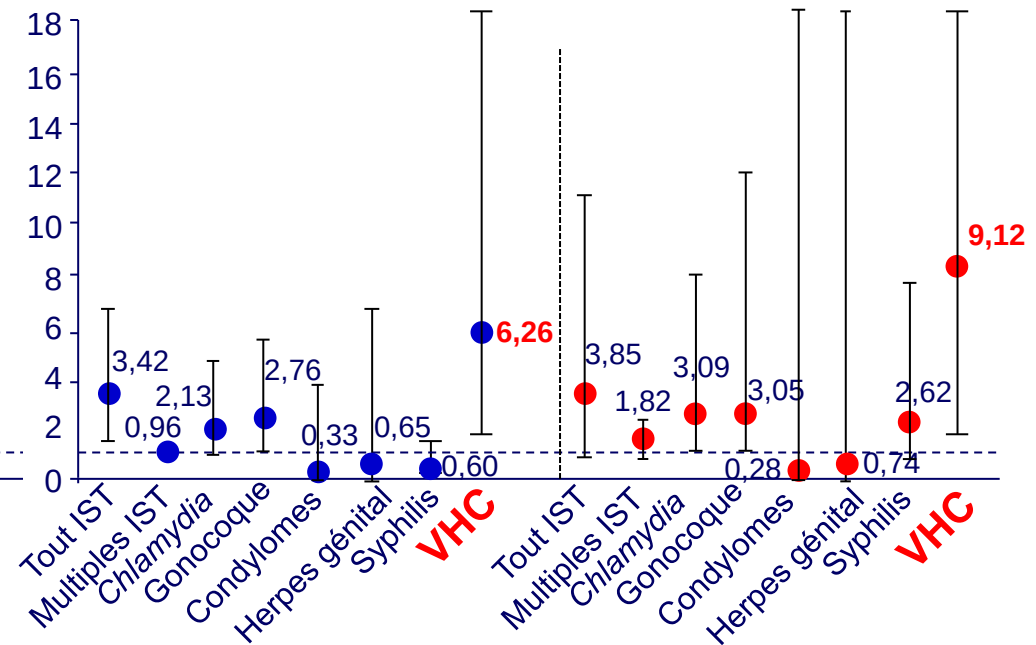
Association entre chemsex, slamsex et rapports non protégés par le préservatif (odds ratio ajusté)



Chemsex

Slamsex

Association entre chemsex, slamsex et diagnostic auto-déclaré des IST (odds ratio ajusté)



Chemsex

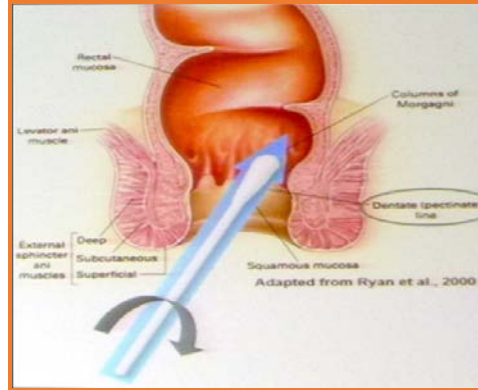
Slamsex

RAN : rapports anaux non protégés ; RANsd : rapports anaux non protégés séro-différents

**Revisiter le risque de
transmission sexuelle du VHC**

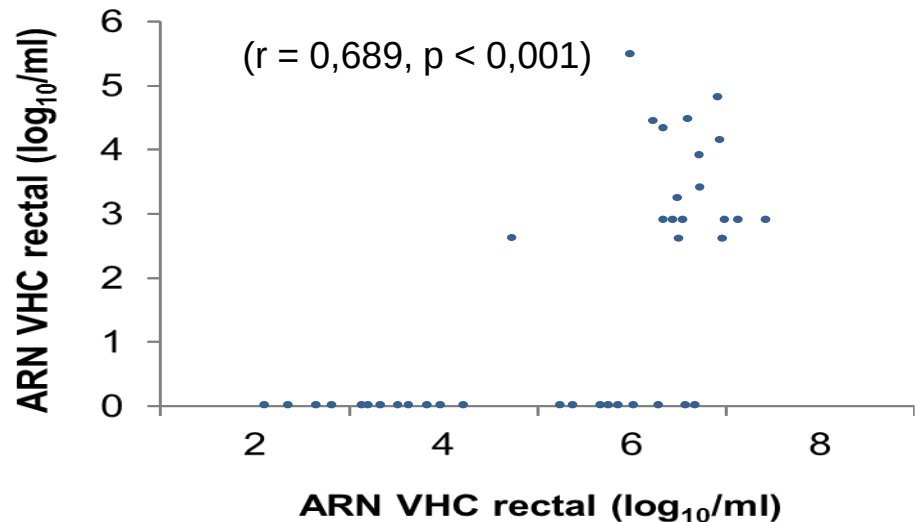
VHC dans le fluide rectal chez les hommes infectés par le VIH

- Étude de 45 homosexuels masculins avec une infection VHC aiguë (n = 33) ou chronique (n = 12)
- Recueil du fluide rectal par écouvillonnage du canal anal



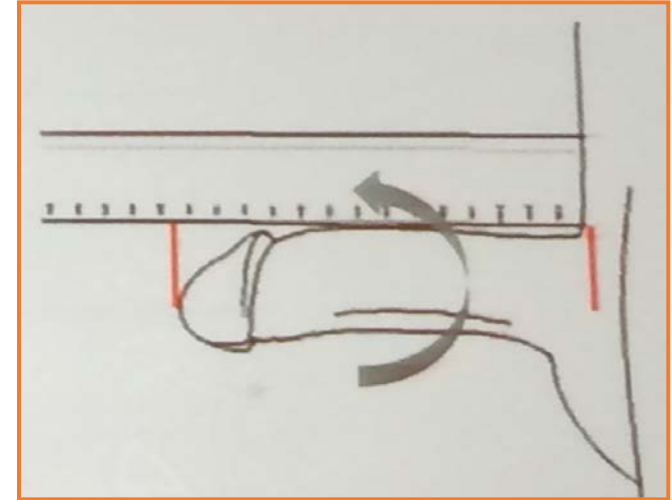
- ARN VHC détecté dans 47 % des prélèvements anaux
- ARN rectal médian 2,92 log₁₀ UI/ml
- ARN VHC détecté dans le fluide rectal quand ARN sérique > 5 log₁₀ UI/ml

Corrélation entre ARN VHC dans le sang et le fluide rectal



VHC dans le fluide rectal chez les hommes infectés par le VIH

- La dose infectieuse de VHC dans le sang est de 10 à 20 particules
- Compte tenu de l'ARN VHC médian dans le fluide rectal, la surface d'un pénis moyen circoncis* (185 cm²) serait exposée à 2 496 UI de VHC au cours d'un rapport anal



- Le VHC présent dans le fluide rectal pourrait être source d'infection mais aussi infecter le pénis et contribuer à une transmission passive du virus

Herbenick D et al J Sex Med. 2014.

*AASLD 2015 - D'après Foster AL et al., abstr. OP89,
Diapositive Eric Rosenthal (Nice)*

DAA anti HCV (suite)

Toujours plus fort, plus court ?

Peg Ifn free >> Riba Free

Cà pousse vers la pangénotypisme

RVS n'est pas le end point

Et le prix ?

ORIGINAL ARTICLE

Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis

M.P. Curry, J.G. O'Leary, N. Bzowej, A.J. Muir, K.M. Korenblat, J.M. Fenkel,
K.R. Reddy, E. Lawitz, S.L. Flamm, T. Schiano, L. Teperman, R. Fontana, E. Schiff,
M. Fried, B. Doehle, D. An, J. McNally, A. Osinusi, D.M. Brainard,
J.G. McHutchison, R.S. Brown, Jr., and M. Charlton,
for the ASTRAL-4 Investigators*

Table 1. Demographic Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N = 116)	Sofosbuvir–Velpatasvir (N = 624)
Mean age (range) — yr	53 (25–74)	54 (18–82)
Male sex — no. (%)	68 (59)	374 (60)
Mean body-mass index (range)†	26 (18–40)	27 (17–57)
Race — no. (%)‡		
White	90 (78)	493 (79)
Black	11 (9)	52 (8)
Asian	11 (9)	62 (10)
Other	4 (3)	14 (2)
Missing data	0	3 (<1)
Region — no. (%)		
North America	52 (45)	289 (46)
Europe	60 (52)	316 (51)
Hong Kong	4 (3)	19 (3)
HCV genotype		
1a	46 (40)	210 (34)
1b	19 (16)	118 (19)
2	21 (18)	104 (17)
4	22 (19)	116 (19)
5§	0	35 (6)
6	8 (7)	41 (7)
HCV RNA		
Mean — log ₁₀ IU/ml	6.3±0.58	6.3±0.66
≥800,000 IU/ml — no. (%)	87 (75)	461 (74)
IL28B genotype — no. (%)		
CC	36 (31)	186 (30)
CT	53 (46)	339 (54)
TT	26 (22)	94 (15)
Missing data	1 (1)	5 (1)
Compensated cirrhosis — no. (%)¶	21 (18)	121 (19)
Previous HCV treatment — no./total no.(%)		
No	83/116 (72)	423/624 (68)
Yes	33/116 (28)	201/624 (32)
Protease inhibitor, peginterferon, and ribavirin	6/33 (18)	56/201 (28)
Peginterferon and ribavirin	24/33 (73)	122/201 (61)
Nonpegylated interferon with or without ribavirin	3/33 (9)	23/201 (11)

* Plus-minus values are means ±SD. There were no significant differences between the groups.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race was self-reported.
§ Patients with genotype 5 HCV did not undergo randomization but were enrolled in the sofosbuvir–velpatasvir group.
¶ Cirrhosis was defined as one of the following: liver-biopsy results with a Metavir score of 4 or an Ishak score 5 or more, a FibroTest score of more 0.75 and a ratio of aspartate aminotransferase to platelets of more than 2, or a FibroScan value of more than 12.5 kPa. Patients with clinical evidence of decompensation (ascites, encephalopathy, or variceal hemorrhage) were excluded.

Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection

J.J. Feld, I.M. Jacobson, C. Hézode, T. Asselah, P.J. Ruane, N. Gruener, A. Abergel, A. Mangia, C.-L. Lai, H.L.Y. Chan, F. Mazzotta, C. Moreno, E. Yoshida, S.D. Shafran, W.J. Towner, T.T. Tran, J. McNally, A. Osinusi, E. Svarovskaia, Y. Zhu, D.M. Brainard, J.G. McHutchison, K. Agarwal, and S. Zeuzem, for the ASTRAL-1 Investigators*



Table 2. Response during and after Treatment.*

Response	Sofosbuvir–Velpatasvir (N = 624)
HCV RNA <15 IU/ml	
During treatment period — no. (%)	
At wk 2	355 (57)
At wk 4	564 (90)
At 12 wk after treatment period — no./total no. (%)	
Any genotype	618/624 (99)
1a	206/210 (98)
1b	117/118 (99)
2	104/104 (100)
4	116/116 (100)
5	34/35 (97)
6	41/41 (100)
Virologic failure — no. (%)	
During treatment	0
After treatment	2 (<1)
Other reason for classification as failure — no. (%)	
Loss to follow-up	2 (<1)
Withdrawal of consent	1 (<1)
Death	1 (<1)

**Once-daily
sofosbuvir–
velpatasvir for 12
weeks provided
high rates of
sustained virologic
response
among both
previously treated
and untreated
patients infected
with HCV genotype
1, 2, 4, 5, or 6,
including those
with compensated
cirrhosis**



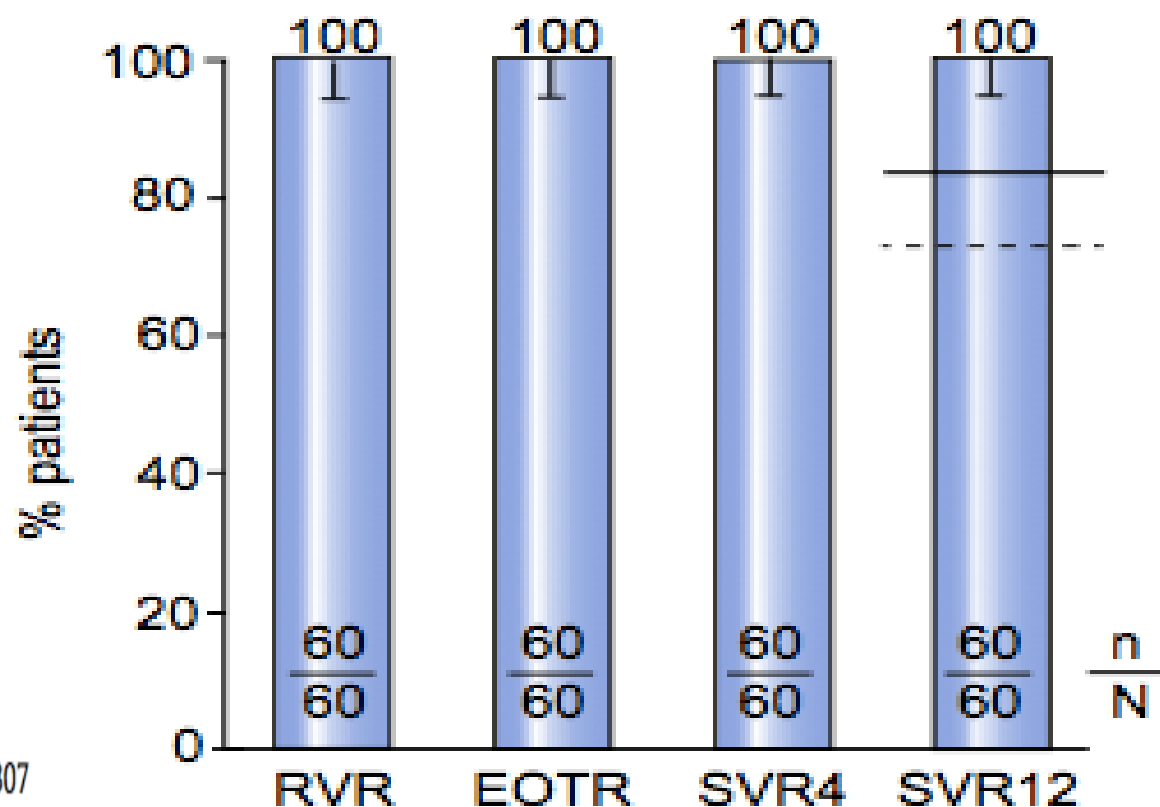


Fig. 1. Virologic response during and after treatment with OBV/PTV/r + DSV for 12 weeks. The percentage of patients achieving HCV RNA <25 IU/ml response at different time points is plotted with 95% CI using the Wilson score method. The horizontal dashed line indicates the non-inferiority margin for the historical rate achieved with sofosbuvir plus PegIFN/RBV (72.7%), and the horizontal solid line indicates the superiority threshold (83.2%). RVR, rapid virologic response at treatment week 4; EOTR, end of treatment response at week 12; SVR4, sustained virologic response at post-treatment week 4; SVR12, sustained virologic response at post-treatment week 12.

Table 2. Virologic Response Rates During and After Treatment

	12-Week 3D Plus Ribavirin (n = 31)	24-Week 3D Plus Ribavirin (n = 32)
Response, No. (%) [95% CI] ^a		
Rapid virologic response	31 (100) [89-100]	32 (100) [89-100]
End-of-treatment response	30 (97) [84-99]	31 (97) [84-100]
SVR4	29 (94) [79-98]	30 (94) [80-98] ^b
SVR12	29 (94) [79-98]	29 (91) [76-97] ^{b,c}
Reasons for not achieving SVR12, No. (%)		
Consent withdrawn	1 (3)	0
Virologic breakthrough during treatment	0	1 (3)
Virologic relapse after treatment	1 (3)	0
HCV reinfection after treatment	0	2 (6) ^{b,c}

CONCLUSIONS AND RELEVANCE In this open-label, randomized uncontrolled study, treatment with the all-oral, interferon-free 3D-plus-ribavirin regimen resulted in high SVR rates among patients co-infected with HCV genotype 1 and HIV-1 whether treated for 12 or 24 weeks. Further phase 3 studies of this regimen are warranted in patients with co-infection.

Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial



Jürgen K Rockstroh, Mark Nelson, Christine Katlama, Jay Lalezari, Josep Mallolas, Mark Bloch, Gail V Matthews, Michael S Saag, Philippe J Zamor, Chloe Orkin, Jacqueline Gress, Stephanie Klopfer, Melissa Shaughnessy, Janice Wahl, Bach-Yen T Nguyen, Eliav Barr, Heather L Platt, Michael N Robertson, Mark Sulkowski

Lancet HIV 2015; 2: e319–27

	All patients	HCV genotype 1a	HCV genotype 1b	HCV genotype 4
SVR12 (95% CI)	210/218* (96.3%, 92.9–98.4)	139/144 (96.5%, 92.1–98.9)	42/44 (95.5%, 84.5–99.4)	27/28 (96.4%, 81.7–99.9)
Lost to follow-up or other non-virological failure	1†	0	1	0
Virological breakthrough	0	0	0	0
Virological relapse	5	4	0	1
Reinfection	2	1	1	0

Data are n/N (%; 95% CI) or number of patients. Sustained virological response (SVR) defined as hepatitis C virus (HCV) RNA less than lower limit of quantitation (<15 IU/mL) at follow-up week 12. *Two patients with HCV genotype 6 infection were also included; both patients achieved SVR12. †Prohibited concomitant medication.

Table 2: Rates of sustained virological response after 12 weeks of follow-up (full analysis set)

Table 2. Predicted Minimum Costs of Selected HCV DAAs for 12 Weeks of Treatment

Agent	Patent Expiry	Daily Dose (mg)	Overall Dose Per 12-wk (g)	Estimated cost/g (US\$)	Predicted Cost (US\$)
Ribavirin	Generic	1,200	100.8	0.34*	\$48
Daclatasvir	2027	60	5.0	4.00	\$20
MK-8742	2028	50	4.2	10.50	\$44
Sofosbuvir	2029	400	33.6	3.00	\$101
MK-5172	2030	100	8.4	8.75	\$74
Ledipasvir	2030	90	7.6	12.25	\$93

*Current mid-point cost of API from 3 Chinese suppliers.⁵

Abbreviation: wk, week.

HBV

New therapeutic agents for chronic hepatitis B



Mayur Brahmania, Jordan Feld, Ambreen Arif, Harry L A Janssen

The treatment goal for chronic hepatitis B is true eradication of the hepatitis B virus, but this is rarely achieved with first-line treatment regimens because of an inability to disrupt covalently closed circular DNA and an inadequate host immune response. Therefore, new antiviral agents are needed to target various stages of the hepatitis B virus lifecycle and modulation of the immune system. This Review provides a summary of available regimens with their strengths and limitations, and highlights future therapeutic strategies to target the virus and host immune response. These new agents can hopefully lead to a finite duration of treatment, and provide a functional and durable cure for chronic hepatitis B infection.

Lancet Infect Dis 2016;
16: e10–21

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January 12, 2016
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Toronto Centre for Liver
Diseases, Toronto Western

- ***Lancet Infect Dis* 2016; 16: e10–21**

Eradication Strategies for Chronic Hepatitis B Infection

Eleanor M. P. Wilson, Lydia Tang, and Shyam Kottilil

Division of Clinical Care and Research, Institute of Human Virology, University of Maryland School of Medicine, Baltimore

Chronic hepatitis B infection affects >300 million people worldwide and is a leading cause of liver failure and cancer. Current approaches to treatment for chronic hepatitis B involve suppression of hepatitis B virus (HBV) DNA with the use of nucleoside analogues. Chronic suppressive therapy rarely results in a “functional cure” or absence of detectable HBV DNA in plasma and loss of detectable hepatitis B surface antigen after cessation of therapy. The major obstacles to achieving a functional cure are the presence of covalently closed circular DNA and ineffective/exhaustive immune system. This review focuses on novel approaches to target viral life cycle and host immunity to achieve a functional cure.

Keywords. HBV; eradication; exhaustion.

Table 1. Novel Therapeutics Against Hepatitis B Virus

Drug Name	Class	Phase	Company	Clinical Trials Registration
Viral targets				
Niuliva HBV	HBV immunoglobulin	3	Institute Ginfols, S.A.	NCT01131065
Myrcludex-B	Entry inhibitor	Preclinical	Stephan Urban, DKFZ	
TAF	Nucleotide analogue	3	Gilead Sciences, Inc	NCT02296853 NCT01940341 NCT01940471 NCT02071082
ANA380	Nucleotide analogue	2	Anadys	NCT02300688
CMX157	Nucleotide analogue	1	ContraVir	NCT01080820
ARC-520	RNAi	2a	Arrowhead Research	NCT01872065
Bay 41-4109	Capsid formation inhibitor	Preclinical	AiCuris	
NVR 3-778	HBV core inhibitor	1b	Novira Therapeutics	NCT02112799 NCT02401737
REP 2139-Ca	Blocks HBsAg release	1b	REPLICor Inc	NCT02233075
Host targets				
Interferon γ -1b (Actimmune)	IFN immune enhancer: immunomodulatory	. . .	Huntington Medical Research Institute	Approved in US NCT00753467
GS-9620	TLR-7 agonist	1	Gilead Sciences, Inc	NCT02166047 NCT01591668 NCT01590654 NCT01590641
Nivolumab	PD-1 antibody	1	Bristol-Myers Squibb	NCT01658878
DV-601	Therapeutic vaccine: viral antigen complex based	1b	Dynavax	NCT01023230
Hi-8 HBV	Therapeutic vaccine: viral antigen complex based	2	Oxxon	
ePA-44	Therapeutic vaccine: viral antigen complex based	2	Chongqing Jiachen Biotechnology Ltd	NCT00869778 NCT01326546
HB-110	Therapeutic vaccine: DNA based	1	Genexine	
HBV-DNA plasmid pdpSC18 vaccine	Therapeutic vaccine: DNA based	1	PowderMed/Pfizer	
GS-4774	Therapeutic vaccine: Tarmogen based	2	Gilead Sciences, Inc	NCT02174276
TG1050	Therapeutic vaccine: Adenovirus based	1/1a	Transgene	NCT02428400

Abbreviations: HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IFN, interferon; RNAi, RNA interference; TAF, tenofovir alafenamide; TLR, Toll-like receptor.

Tableau

Répartition des expositions à risque au cours des 6 mois précédant le diagnostic d'hépatite B aiguë, déclaration obligatoire (DO), 2012-2014, France

	Nombre de cas (N=260)	%
Aucune exposition à risque rapportée	97	37,3
Exposition sexuelle	100	38,5
<i>Partenaire sexuel Ag HBs positif*</i>	24	9,2
<i>Hommes ayant des rapports sexuels avec des hommes</i>	42	21,0 ^a
<i>Partenaires sexuels multiples*</i>	59	22,7
Voyage en zone d'endémie du VHB*	56	21,5
Soins invasifs (dialyse, chirurgie, greffe...)*	14**	5,4
Porteur chronique de l'Ag HBs dans l'entourage familial*	12	4,6
Tatouage, piercing	13	5,0
Séjour en institution*	6	2,3
Usage de drogues*	12	4,6
Exposition professionnelle*	5	1,9

